Cochrane Library

Cochrane Database of Systematic Reviews

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

Farquhar C, Marjoribanks J

Farquhar C, Marjoribanks J.
Assisted reproductive technology: an overview of Cochrane Reviews.
Cochrane Database of Systematic Reviews 2018, Issue 8. Art. No.: CD010537.
DOI: 10.1002/14651858.CD010537.pub5.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Overview of Reviews]

Assisted reproductive technology: an overview of Cochrane Reviews

Cindy Farquhar[1], Jane Marjoribanks[1]

[1]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Contact address: Cindy Farquhar, Department of Obstetrics and Gynaecology, University of Auckland, FMHS Park Road, Grafton, Auckland, 1003, New Zealand. c.farquhar@auckland.ac.nz.

Editorial group: Cochrane Gynaecology and Fertility Group
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 8, 2018.

Citation: Farquhar C, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2018, Issue 8. Art. No.: CD010537. DOI: 10.1002/14651858.CD010537.pub5.

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 these 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) procedures.

Methods

Published Cochrane systematic reviews of couples undergoing ART procedures (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 primary outcome of the overview was live birth or the composite outcome live birth or ongoing pregnancy, as reported by the included reviews. Our secondary outcomes were clinical pregnancy, multiple pregnancy, miscarriage, and ovarian hyperstimulation syndrome. We excluded studies of intrauterine insemination and ovulation induction.

We undertook selection of systematic reviews, data extraction, and quality assessment in duplicate. We assessed review quality by using the AMSTAR tool. We organised reviews by their relevance to specific stages in the ART cycle. We summarised their findings in the text and reported data for each outcome in 'Additional tables'.

Main results

We included 68 systematic reviews published in the Cochrane Library up to May 2018. All were of high quality. These reviews identified 38 interventions that were effective (n = 23) or promising (n = 15), and they identified 19 interventions that were ineffective (n = 2) or possibly ineffective (n = 17). For 15 interventions, review authors were unable to draw conclusions owing to lack of evidence.

We identified an additional 11 protocols and four titles 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. Evidence from this

overview could be used to develop clinical practice guidelines and protocols that can be applied in daily clinical practice 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

Review question

What is the evidence on effectiveness and safety of procedures and treatment options available to couples with subfertility undergoing assisted reproductive technology (ART) procedures.

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 68 Cochrane systematic reviews on various stages of the ART cycle. All were of high quality. We included in the overview reviews of in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). We did not include reviews of intrauterine insemination (placing sperm inside a woman's uterus to facilitate fertilisation) or ovulation induction (stimulation of ovulation by medication). This overview provides the most up-to-date evidence from randomised controlled trials on ART cycles. The overview is up-to-date to May 2018.

Key results

The reviews identified 38 interventions that were effective (n = 23) or promising (n = 15), and they identified 19 interventions that were ineffective (n = 2) or possibly ineffective (n = 17). For 15 interventions, the reviews were unable to draw conclusions owing to lack of evidence. Use of 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.

Quality of the evidence

All included reviews were of high quality. The quality of the evidence for specific comparisons ranged from very low to high.

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 of an ART cycle.

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 the steps make up an ART cycle.

- 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.
- After ovarian stimulatory drugs are initiated, monitoring is undertaken at intervals to assess the growth of follicles.
- 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).
- 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.
- Next is the fertilisation process, which usually is completed by in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).
- Laboratory procedures follow for embryo culture: culture media, oxygen concentration, co-culture, assisted hatching, etc.
- 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.
- Then comes luteal phase support, for which several options are available, including administration of progesterone, oestrogen (E_2), and human chorionic gonadotrophin (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) is applied to treat 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 highlights 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 procedures.

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, or the composite outcome of live birth or ongoing pregnancy, as reported by the individual reviews.

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 on 4h May 2018, 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

We selected reviews addressing the stages or steps of ART interventions. One review author identified these reviews and a second review author confirmed them. We resolved disagreements by consensus or by discussion with a third party.

We separated reviews according to the following topics (discussed under these headings).

1. Indication for ART

2. Pre-ART and adjuvant strategies

2.1. Strategies for unselected populations

2.1.1. Lifestyle advice

2.1.2. Surgical therapy

2.1.3. Medical therapy

2.1.4. Alternative therapy

2.2. Strategies for selected populations

2.2.1. Tubal pathology

2.2.2. Endometriosis

2.2.3. Polycystic ovary syndrome (PCOS)

2.2.4. Ovarian cysts

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

9.4 Interventions for recurrent implantation failure

10. Luteal phase support

11. Prevention of ovarian hyperstimulation syndrome (OHSS)

12. Frozen embryo replacement cycles

Data extraction and management

For the 2018 update, two review authors (JM and CF) independently extracted data on the above outcomes. We resolved disagreements by consensus. When significant data were missing, we contacted the original review authors for assistance. We extracted and reported in additional tables information concerning the following.

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

We used the same effect measures as were used in 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 chance of events, the odds ratio is larger than the risk ratio, so misinterpretation will tend to overestimate the intervention effect, especially when events are common (with, say, risk of events > 20%). For interventions that reduce the chance of events, the odds ratio is 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

We assessed the quality of the included reviews using the AMSTAR tool (Shea 2007). We 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 evidence for the main comparisons. We took into account the following criteria: study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, and publication bias.

Data synthesis

We prepared a narrative description of the included trials and did not conduct a network meta-analysis.

We summarised the main results of the included reviews by categorising their findings within 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 that 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 that more evidence is needed.
- No conclusions possible due to lack of evidence: indicating that the review found insufficient evidence for review authors to comment on the effectiveness of an intervention.

Authors of the overview determined that the choice of category reflected the conclusions of the original review authors. We

resolved disagreements by discussion between overview authors to reach a consensus.

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

As of May 2018, we included in this review 68 systematic reviews published in the Cochrane Library (over 175,055 participants). See Table 1 for a summary of characteristics of the 68 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 interventions and comparisons, outcomes, and main limitations of each review). We added 9 of the 68 reviews to the 2018 update (Ata 2018; Craciunas 2016; Kalampokas 2017; Lensen 2018, Nagels 2015; Reavey 2016; Siristatidis 2018; Wong 2017; Youssef 2015).

Currently, we have identified an additional 10 protocols and four active titles in progress that will be added to the overview when they are published as full reviews and the overview is next updated. For details, see Appendix 1.

We have withdrawn one protocol identified in the previous version of this overview, as the topic is now covered by other reviews (ElDaly 2006).

Methodological quality of included reviews

Quality of systematic reviews

We rated the quality of the included reviews by using the AMSTAR tool (Shea 2007).

- All reviews had pre-specified their clinical question and inclusion criteria.
- All reviews conducted study selection and data extraction in duplicate.
- All reviews conducted a comprehensive literature search.
- All reviews included searches of grey literature.
- All reviews listed included and excluded studies.
- All reviews described the characteristics of included studies.
- All reviews assessed study quality.
- All reviews combined studies using appropriate methods.
- A total of 65 of the 67 reviews addressed the risk of reporting bias, using a statistical test when appropriate.
- All reviews addressed the potential for conflict of interest.

Only 30 of the 68 reviews (44%) had conducted a literature search within the past three years (to May 2018) or had 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.

Quality of evidence from primary studies in included reviews

We rated the quality of evidence reported by primary studies in the included reviews by 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 and Table 8 for details.

Effect of interventions

For statistical evidence from the reviews for each outcome, which will indicate the extent of any benefit or harm, please see the following additional tables. These tables present odds or risk ratios and also absolute event rates per thousand in each group.

- Table 4: live birth or live birth/ongoing pregnancy (composite outcome) per woman (data from 52 reviews).
- Table 5: clinical pregnancy per woman (data from 63 reviews).
- Table 6: ovarian hyperstimulation syndrome per woman (data from 23 reviews).
- Table 7: multiple pregnancy per woman (data from 32 reviews).
- Table 8: miscarriage per woman (data from 41 reviews).

Summary of review findings for each stage of the ART pathway

1. Indication for ART

We identified three reviews.

- Pandian 2015: "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 2015 reported that IVF may be associated with higher rates of live birth and clinical pregnancy than expectant management (very low-quality evidence), but evidence is insufficient to permit firm conclusions. IVF may also be associated with higher live birth rates than unstimulated intrauterine insemination (IUI) (low-quality evidence). In women pre-treated with clomiphene + IUI, IVF appears to be associated with higher live birth rates than IUI + gonadotropins (moderate-quality evidence). However in women who were treatment-naive, evidence was insufficient to show whether there is a difference in rates of live birth or clinical pregnancy between IVF and IUI + gonadotropins, or between IVF and IUI + clomiphene (moderate-quality evidence). We could not adequately assess adverse events associated with these interventions owing to lack of evidence.

Neither Yossry 2006 nor Siristatidis 2009 identified any randomised controlled trial evidence to address their review questions.

2. Pre-ART and adjuvant strategies

2.1. Strategies for unselected populations

We identified nine reviews.

- Anderson 2010: "Preconception lifestyle advice for people with subfertility" (KA992).
- Nastri 2015: "Endometrial injury in women undergoing assisted reproductive techniques" (WM1504).
- Showell 2014: "Antioxidants for male subfertility" (MGS1510).
- Showell 2017: "Antioxidants for female subfertility" (MGS1630).

- Duffy 2010: "Growth hormone for in vitro fertilisation" (KH291).
- Siristatidis 2016: "Aspirin for in vitro fertilisation" (VJP951).
- Cheong 2013: "Acupuncture and assisted reproductive technology" (IRS911).
- Gutarra-Vilchez 2014: "Vasodilators for women undergoing fertility treatment" (RBG1760).
- Nagels 2015: "Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction" (HEN1730).

2.1.1. Lifestyle advice

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

2.1.2. Surgical therapy

Endometrial injury

Nastri 2015 reported moderate-quality evidence showing that endometrial injury performed between day 7 of the previous cycle and day 7 of the embryo transfer (ET) cycle was associated with improvement in live birth or ongoing pregnancy rates and in clinical pregnancy rates among women with more than two previous embryo transfers. Evidence was insufficient to show whether there was a difference in rates of multiple pregnancy (very low-quality evidence), miscarriage (low-quality evidence), or bleeding. Evidence suggested that endometrial injury on the day of oocyte retrieval was associated with lower clinical and ongoing pregnancy rates (low-quality evidence).

2.1.3. Medical therapy

Antioxidants

Showell 2014 included three randomised controlled trials (RCTs) with 111 male partners of women undergoing ART, two of which reported live birth and pregnancy rates in this subgroup. The evidence suggested that antioxidant supplementation in subfertile males may improve live birth rates (low-quality evidence), but there was no clear evidence of a difference in clinical pregnancy rates (low-quality evidence).

Showell 2017 included 27 RCTs of over 3000 women undergoing ART. Evidence was insufficient to show whether antioxidant supplementation was of benefit with regard to birth rate (very low-quality evidence), and review authors found no clear evidence of a difference with regard to clinical pregnancy rates (very low-quality evidence).

Growth hormone

Duffy 2010 reported no evidence of overall benefit in fertility outcomes for growth hormone compared with placebo during an IVF protocol (moderate-quality evidence). A subgroup of women who were considered to be 'poor responders' showed an increase in rates of live birth (moderate-quality evidence) and clinical pregnancy (high-quality evidence) in favour of adjuvant growth hormone compared with placebo. Results were based on a small number of trials with relatively small sample sizes, and the review authors recommend that the evidence should be interpreted with caution.

Androgens

Nagels 2015 concluded that in women identified as poor responders undergoing ART, pre-treatment with dehydroepiandrosterone (DHEA) or testosterone may be associated with improved rates of live birth or ongoing pregnancy (moderate-quality evidence). Evidence was insufficient to permit conclusions about the safety of either androgen.

Aspirin

Siristatidis 2016 found no evidence in favour of routine use of aspirin to improve clinical pregnancy rates for a general IVF population (moderate-quality evidence).

Vasodilators

Gutarra-Vilchez 2014 found insufficient evidence to show whether vasodilators influenced the live birth rate in women undergoing fertility treatment (moderate-quality evidence). However, low-quality evidence suggests 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 evidence was insufficient to show the effect of acupuncture on live birth rate, regardless of whether acupuncture was performed around the time of oocyte retrieval or around the day of embryo transfer (low-quality evidence). No evidence suggested that acupuncture had any effect on rates of pregnancy (low- to very low-quality evidence) or miscarriage (low-quality evidence), nor that acupuncture led to significant side effects.

2.2. Strategies for selected populations

We identified four reviews.

- 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 before IVF increased the chances of clinical pregnancy (moderate-quality evidence). Review authors concluded that surgical treatment should be considered for all women with hydrosalpinges before IVF treatment. Previous evidence supported only unilateral salpingectomy for a unilateral hydrosalpinx (bilateral salpingectomy for bilateral hydrosalpinges). Johnson 2010 suggested laparoscopic tubal occlusion as an alternative to laparoscopic salpingectomy for improving pregnancy

rates among women with hydrosalpinges undergoing IVF. Evidence was insufficient to allow assessment of the value of aspiration of hydrosalpinges before or during IVF procedures (very low-quality evidence) or the value of tubal restorative surgery as an alternative (or as a preliminary) to IVF.

2.2.2. Endometriosis

Benschop 2010 reported that evidence was insufficient to show whether there was a difference in clinical pregnancy rates among those given gonadotropin-releasing hormone (GnRH) agonists and antagonists for endometrioma before ART (low-quality evidence), or whether there was a difference in clinical pregnancy outcomes between surgery (cystectomy or aspiration) before ART and expectant management (low-quality evidence), or between pre-ART ablation and cystectomy in women with endometrioma (very low-quality evidence).

2.2.3. Polycystic ovary syndrome (PCOS)

Tso 2014 found no clear evidence that metformin treatment before or during ART cycles improved live birth rates among women with PCOS (low-quality evidence). However, use of this insulin-sensitising agent increased clinical pregnancy rates (moderate-quality evidence) and decreased the risk of ovarian hyperstimulation syndrome (OHSS) (moderate-quality evidence).

2.2.4. Ovarian cysts

McDonnell 2014 found insufficient evidence to determine whether drainage of functional ovarian cysts before controlled ovarian hyperstimulation (COH) influenced clinical pregnancy rates (very low-quality evidence). None of the studies reported live birth. The review authors concluded that there was no supportive evidence for cyst drainage, in view of the requirement for anaesthesia, extra costs, psychological stress, and risk of surgical complications.

3. Down-regulation with agonists or antagonists

We identified four reviews 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 2016: "Gonadotrophin-releasing hormone antagonists for assisted reproductive technology" (HA412).
- Siristatidis 2015: "Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive treatment" (SD265).

Sallam 2006 reported that the live birth rate per woman was higher among women receiving the GnRH agonist (GnRHa) than among those given the control intervention. Administration of GnRHa for a period of three to six months before IVF or ICSI in women with endometriosis increased the odds of clinical pregnancy (very low-quality evidence). This evidence was of very low quality, and the review is being updated.

Albuquerque 2013 found insufficient evidence to determine whether there was a difference in rates of live birth (low-quality evidence) or clinical pregnancy (moderate-quality evidence) or OHSS (low-quality evidence) 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. Given that depot GnRHa requires more gonadotrophins and a longer duration of use, this approach may increase the overall costs of IVF treatment.

Al-Inany 2016 reported that use of GnRH antagonist compared with long-course GnRHa protocols was associated with a substantial reduction in OHSS without reducing the likelihood of achieving live birth (moderate-quality evidence).

Siristatidis 2015 compared long GnRHa protocols and short GnRHa protocols and found no clear evidence of a difference in live birth and ongoing pregnancy rates (low-quality evidence) but provided moderate-quality evidence showing higher clinical pregnancy rates in the long protocol group. Evidence was insufficient to show whether there was a difference in birth or pregnancy outcomes between any of the other compared protocols (low- or very low-quality evidence).

4. Ovarian stimulation

We identified 11 reviews.

- Kamath 2017: "Clomiphene citrate for controlled ovarian stimulation in women undergoing IVF" (AM1335).
- Pouwer 2015: "Long-acting FSH versus daily FSH for women undergoing assisted reproduction" (AWP1710).
- Mochtar 2017: "Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI 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).
- Farquhar 2017: "Oral contraceptive pill, progestogen or oestrogen 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).
- Kalampokas 2017: "Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI" (BKT841).
- Lensen 2018: "Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI)" (SL1977).

4.1. Medication type

Kamath 2017 found insufficient evidence to determine whether clomiphene citrate or letrozole with or without gonadotrophins differed from gonadotrophins in GnRH agonist or antagonist protocols with respect to their effects on live birth (low-quality evidence) or pregnancy rates (low- to moderate-quality evidence), either in the general population of women undergoing IVF

treatment or among women who were poor responders. Use of clomiphene or letrozole led to a reduction in the quantity of gonadotrophins required and the incidence of OHSS (low-quality evidence). However, use of clomiphene citrate or letrozole appeared to be associated with an increase in the incidence of cycle cancellations, as well as with reductions in the mean number of oocytes retrieved in both the general IVF population and among poor responders.

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

Mochtar 2017 found no clear evidence of a difference between recombinant luteinising hormone (rLH) combined with recombinant follicle-stimulating hormone (rFSH) and rFSH alone in rates of live birth (very low-quality evidence) or OHSS (low-quality evidence), but evidence suggested that use of rLH combined with rFSH may lead to more clinical pregnancies than use of rFSH alone (moderate-quality evidence). Results show little or no difference between groups in rates of miscarriage (moderate-quality evidence). The review authors concluded that the evidence was insufficient to encourage or discourage stimulation regimens that include rLH combined with rFSH in IVF/ICSI cycles.

van Wely 2011 reported insufficient evidence to show whether there was a difference in live birth rates (high-quality evidence) or in clinical pregnancy rates (moderate-quality evidence) when rFSH was compared with 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 cost, and that turther research on these comparisons was 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 COH in women undergoing ART compared with conventional COH was very uncertain (very low-quality evidence). Evidence suggested that this intervention did not influence the chance of clinical pregnancy (low-quality evidence), and that it was likely to result in an equivalent number of oocytes retrieved, with less FSH expended. The review authors suggested that more studies are needed to strengthen the evidence regarding the effect of this intervention on important reproductive outcomes.

Farquhar 2017 found that among women undergoing ovarian stimulation in antagonist protocols, pre-treatment with the combined oral contraceptive pill (COCP) was associated with a lower rate of live birth or ongoing pregnancy than no pre-treatment (moderate-quality evidence). Evidence was insufficient to show whether rates of live birth or ongoing pregnancy were influenced by pre-treatment with progestogens or oestrogens (low- to moderate-quality evidence), or by COCP pre-treatment using other stimulation protocols (low-quality evidence). Findings on adverse events were inconclusive, except that progesterone pre-treatment may reduce the risk of ovarian cysts in agonist cycles, and COCP in antagonist cycles may reduce the risk of pregnancy loss compared with no pre-treatment in agonist cycles.

Kalampokas 2017 concluded that the safety and effectiveness of glucocorticoid administration in women undergoing controlled ovarian hyperstimulation for IVF/ICSI cycle glucocorticoids were unclear owing to lack of data. Glucocorticoids may increase clinical pregnancy rates but may have little or no impact on live birth rates (low-quality evidence).

Lensen 2018 found no conclusive evidence to show that tailoring the FSH dose in any particular ovarian reserve test (ORT) population influenced rates of live birth/ongoing pregnancy (low-quality evidence). In predicted high responders, lower doses of FSH seemed to reduce the overall incidence of moderate and severe OHSS (very low-quality evidence). ORT-based individualisation was associated with live birth/ongoing pregnancy rates similar to a policy of giving all women 150 IU (moderate-quality evidence). ORT algorithms reduced the incidence of OHSS compared with standard dosing of 150 IU, but the size of the effect was unclear (low-quality evidence).

4.2. Monitoring

Kwan 2014 found no evidence to suggest that combined monitoring of ovarian stimulation by ultrasound plus serum oestradiol was more efficacious than ultrasound alone, with regard to clinical pregnancy rates and incidence of OHSS (low-quality evidence).

4.3. Interventions for poor responders

Pandian 2010 summarised the evidence from 10 RCTs and suggested that evidence is insufficient to support the routine use of any one particular intervention for the treatment of women who are 'poor responders'. Only one of the trials reported on live birth (low- to very low-quality evidence).

4.4. Natural cycle IVF

Allersma 2013 found no clear evidence of a difference between natural cycle and standard IVF in subfertile couples with regard to rates of live birth (very low-quality evidence), OHSS (very low-quality evidence), clinical pregnancy (low-quality evidence), multiple pregnancy (very low-quality evidence), or other outcomes (ongoing pregnancy, number of oocytes retrieved, number of cycles needed to conceive, cumulative pregnancy, cycle cancellation, gestational abnormalities, cancellation of treatment due to patient motivation, or adverse effects).

5. Ovulation triggering

We identified two reviews that reported on ovulation triggering.

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

- Youssef 2016a: "Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles" (HA413).

Youssef 2014 reported evidence of lower live birth rate (moderate-quality evidence), reduced ongoing pregnancy rate (low-quality evidence), and higher miscarriage rate (moderate-quality evidence) in women who received a GnRH agonist for final oocyte maturation triggering compared with women given hCG in fresh autologous cycles (women's own eggs). However, the incidence of OHSS was lower in the GnRH agonist group (moderate-quality evidence).

Youssef 2016a found no clear evidence of a difference between recombinant human chorionic gonadotrophin (rhCG) and urinary human chorionic gonadotrophin (uhCG), or between recombinant human luteinising hormone (rhLH) and uhCG, with respect to rates of live birth or ongoing pregnancy (moderate-quality evidence), clinical pregnancy (moderate-quality evidence), OHSS (low-quality evidence), or miscarriage (low-quality evidence).

6. Oocyte retrieval

We identified three reviews.

- Reavey 2016: "Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation" (IG1250).
- Kwan 2018: "Pain relief for women undergoing oocyte retrieval for assisted reproduction" (IOK971).
- Georgiou 2018: "Follicular flushing during oocyte retrieval in assisted reproductive techniques" (SW811).

Reavey 2016 found insufficient evidence to determine whether hCG priming had an effect on rates of live birth (low-quality evidence) or miscarriage (low-quality evidence) in oocyte maturation in vivo (IVM). Evidence suggested that hCG priming might reduce clinical pregnancy rates (low-quality evidence), but these findings were limited by the small quantity of data included.

Kwan 2018 compared a variety of head-to-head and placebo-controlled interventions for conscious sedation. The study reporting live birth described a higher birth rate following conscious sedation plus electroacupuncture plus paracervical block compared with conscious sedation plus paracervical block (low-quality evidence). There was no evidence of a difference in clinical pregnancy rate for the same comparison. Simultaneous use of sedation combined with analgesia such as the opiates, further enhanced by paracervical block or acupuncture techniques, resulted in better pain relief than occurred with one modality alone. The review did not support one particular method or technique over another for providing effective conscious sedation and analgesia for pain relief during and after oocyte recovery (low- or very low-quality evidence for most comparisons).

Georgiou 2018 reported that follicular flushing probably has little or no effect on live birth rates or clinical pregnancy rates compared with aspiration alone. Evidence was insufficient to permit any firm conclusions with regard to adverse events or safety.

7. Sperm retrieval

We identified two reviews.

- 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 the evidence was insufficient to allow recommendations on any specific sperm retrieval technique for azo-ospermic men undergoing ICSI. The single trial provided some evidence that microsurgical epididymal sperm aspiration (MESA) was associated with a lower pregnancy rate than the micropuncture with perivascular nerve stimulation technique (low-quality evidence).

McDowell 2014 reported that evidence was insufficient to show whether sperm selected by hyaluronic acid binding improves rates of live birth or clinical pregnancy (low-quality evidence), or whether there is a difference in efficacy between the hyaluronic acid binding methods SpermSlow and PICSI (physiological intracytoplasmic sperm injection). Review authors found no randomised evidence evaluating sperm selection by sperm apoptosis, sperm birefringence, or surface charge.

8. Laboratory phase

We identified 10 reviews.

- Carney 2012: "Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI))" (MWS391).
- Glujovsky 2014: "Vitrification versus slow freezing for women undergoing oocyte cryopreservation" (DG1352).
- Van Rumste 2003: "Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility" (MVR461).
- Bontekoe 2012: "Low oxygen concentrations for embryo culture in assisted reproductive technologies" (SB1283).
- Twisk 2006; "Preimplanation genetic screening for abnormal numbers of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection" (SMA991).
- Huang 2013: "Brief co-incubation of sperm and oocytes for in vitro fertilization techniques" (ZH1093).
- Teixeira 2013: "Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction" (WPM1800).
- Armstrong 2015: "Time-lapse systems for embryo incubation and assessment in assisted reproduction" (SCA1950).
- Youssef 2015: "Culture media for human pre-implantation embryos in assisted reproductive technology cycles" (MM1610).
- Siristatidis 2018: "Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies" (CS1968).

Carney 2012 found no evidence of an influence on live birth rates from assisted hatching compared with no assisted hatching (moderate-quality evidence). Although assisted hatching (AH) appeared to offer an increased chance of achieving a clinical pregnancy, the finding only just reached statistical significance (moderate-quality evidence). The included trials provided insufficient data to show 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 (moderate-quality evidence), but multiple pregnancy rates were increased in the AH groups (low-quality evidence).

Glujovsky 2014 found that vitrification probably increased clinical pregnancy rates compared with slow freezing (moderate-quality evidence). However the total number of women and of pregnancies was low. No data were available on live birth or adverse events.

Van Rumste 2003 reported that neither live birth nor miscarriage rates or other adverse events were reported in the single trial in their review. Evidence was insufficient to show whether there was a difference in clinical pregnancy rates between ICSI and IVF (low-quality evidence).

Bontekoe 2012 reported an increase in live birth rates associated with embryo culture using low oxygen concentrations (˜5%) compared with atmospheric oxygen concentrations (˜20%) (moderate-quality evidence). This equated to an increase from a 30% success rate to 32% to 42% success with low oxygen concentrations. Similar results were reported for ongoing and clinical pregnancy rates. Review authors found no clear evidence of an increase in adverse events (multiple pregnancy or miscarriage (low-quality evidence)) associated with embryo culture with low oxygen concentrations.

Twisk 2006 reported that live birth rates were lower following IVF or ICSI with pre-implantation genetic screening with fluorescent in situ hybridisation compared with no pre-implantation genetic screening, both in women with advanced age (moderate-quality evidence) and in those with repeated IVF failure (very low-quality evidence). For women with a good prognosis, no clear evidence suggested a difference between intervention and control groups (very low-quality evidence). Until further research findings are available for newer techniques in pre-implantation 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 ongoing pregnancy and clinical pregnancy rates for infertile women undergoing IVF cycles, although more RCTs are required (low-quality evidence).

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

Armstrong 2015 reported that evidence of any difference in rates of live birth (moderate-quality evidence), miscarriage (low-quality evidence), or stillbirth or clinical pregnancy (low-quality evidence) is insufficient to guide selection of time-lapse systems and conventional incubation.

Youssef 2015 concluded that evidence was insufficient to support or refute the use of any specific culture medium (very low-quality evidence). Properly designed and executed randomised trials are necessary.

Siristatidis 2018 concluded that evidence was insufficient to show whether metabolomic assessment of embryos before implantation had any meaningful effect on rates of live birth, ongoing pregnancy, or miscarriage. All evidence was of low quality.

9. Embryo transfer

We identified 10 reviews that looked at embryo transfer.

- Glujovsky 2016: "Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology" (DB551).
- Brown 2016: "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).
- Ata 2018: "Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer)" (BA1920).
- 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 2016a: "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).
- Craciunas 2016: "Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction" (LC1966).

9.1. Developmental stage

Glujovsky 2016 reported that fresh blastocyst stage transfer was associated with higher rates of live birth (low-quality evidence) and clinical pregnancy (moderate-quality evidence) than were seen with fresh cleavage stage transfer, but blastocyst transfer was also associated with a reduction in the number of embryos transferred and in the number for embryo freezing. Evidence was insufficient to show whether there was a difference between groups in cumulative pregnancy rates derived from fresh and frozen-thawed cycles following a single oocyte retrieval, but the evidence for this outcome was of very low quality. Thus, although benefit favours blastocyst transfer in fresh cycles, it remains unclear whether the day of transfer impacts cumulative live birth and pregnancy rates.

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 than after double embryo transfer (high-quality evidence). Elective single embryo transfer resulted in fewer multiple pregnancies than double embryo transfer (high-quality evidence). Although pregnancy and live birth rates per fresh IVF cycle were 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 (low-quality evidence).

9.3. Transfer techniques and procedures

Ata 2018 found insufficient evidence to show whether there was a difference between seminal plasma and standard ART groups in rates of live birth (low-quality evidence) or miscarriage (low-quality evidence). Low-quality evidence suggested that seminal plasma application may be associated with more clinical pregnancies than standard ART, and low-quality evidence suggested little or no difference between groups in rates of multiple pregnancy. Evidence was insufficient to permit any conclusions about the risk of ectopic pregnancy, and no data were available on infectious complications or other adverse events. The review authors concluded that seminal plasma application is worth further investigation, with focus on live birth and miscarriage rates.

Bontekoe 2014 reported on the use of adherence compounds in embryo transfer media. They found evidence of improved rates of live birth (moderate-quality evidence) and pregnancy with use of functional concentrations of hyaluronic acid, along with an increase in multiple pregnancy rates (moderate-quality evidence). The review 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. Few studies reported live birth, but moderate-quality evidence showed that cervical dilatation was associated with a lower live birth rate than no intervention. Evidence was insufficient to show whether straightening the endocervical angle, having a full bladder, removing cervical mucus, or flushing the endometrial or endocervical cavity at the time of embryo transfer had an effect on fertility outcomes (low- to moderate-quality evidence). Review authors identified no trials 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, no clear evidence indicated that the use of amoxicillin plus clavulanic acid influenced the clinical pregnancy rate compared with use of no antibiotics (moderate-quality evidence). Live births were not reported.

Brown 2016 reported very low-quality evidence suggesting no difference between day three and day two embryo transfer for live birth, ongoing pregnancy, or clinical pregnancy. Moreover, review authors found no clear evidence of a difference for other outcomes, including multiple pregnancy (moderate-quality evidence) and miscarriage (moderate-quality evidence).

Brown 2016a reported that the evidence suggests that ultrasound guidance improves rates of live birth (low-quality evidence) and clinical pregnancy (moderate-quality evidence) compared with clinical touch, without increasing the chance of multiple pregnancy (moderate-quality evidence), ectopic pregnancy, or miscarriage (low-quality evidence).

Abou-Setta 2014 concluded that evidence was insufficient to support a certain amount of time for women to remain recumbent following ET (moderate-quality evidence), or to support the use of fibrin sealants (low-quality evidence). Review authors found limited evidence to support the use of mechanical closure of the cervical canal following embryo transfer (very low-quality evidence).

Craciunas 2016 concluded that live birth and pregnancy outcomes for cleavage-stage embryo transfer with an intra-cavity human chorionic gonadotropin (IC-hCG) dose of 500 international units or greater were promising (moderate-quality evidence). However this finding was derived from a subgroup analysis. The review authors found no evidence that miscarriage was influenced by intrauterine hCG administration, irrespective of embryo stage at transfer or dose of IC-hCG (very low-quality evidence), and events were too few to allow any conclusions with regard to other complications.

9.4 Interventions for recurrent implantation failure

No reviews have yet been published on this topic. One (Nastri 2013) is at protocol stage.

10. Luteal phase support

We identified three reviews.

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

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

Boomsma 2012 reported no overall differences between peri-implantation glucocorticoids and no glucocorticoids for rates of live birth (low-quality evidence) or clinical pregnancy (moderate-quality evidence). However, a subgroup analysis indicated that for couples undergoing IVF, evidence suggested a higher clinical pregnancy rate for peri-implantation glucocorticoids than for no glucocorticoids. This difference was not observed in couples undergoing ICSI. The review authors urged caution in extrapolating conclusions from this subgroup analysis.

Akhtar 2013 reported that peri-implantation low molecular weight heparin in ART cycles may improve rates of live birth (very low-quality evidence) and clinical pregnancy (low-quality evidence). Side effects were reported with the use of heparin, and no reliable data on long-term effects were available. The review authors concluded that their results do not justify use of heparin outside of well-conducted research trials.

11. Prevention of ovarian hyperstimulation syndrome (OHSS)

We identified four reviews that examined prevention of OHSS.

[See also Al-Inany 2016: "Gonadotrophin-releasing hormone (GnRH) antagonists for ART" in Section 3; and Youssef 2014: "GnRHa

versus hCG for oocyte triggering in antagonist ART cycles" in Section 5.]

- Tang 2016: "Dopamine agonists for preventing ovarian hyperstimulation syndrome" (TH1338).
- D'Angelo 2007: "Embryo freezing for preventing ovarian hyperstimulation syndrome" (ADA561).
- D'Angelo 2017: "Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome" (ADA563).
- Youssef 2016: "Volume expanders for the prevention of ovarian hyperstimulation syndrome" (PMA481).

Tang 2016 reported that dopamine agonists seemed effective for prevention of moderate or severe OHSS in women at high risk of OHSS (low-quality evidence). Review authors found no clear evidence of a difference in rates of live birth (low-quality evidence), clinical pregnancy (moderate-quality evidence), multiple pregnancy (very low-quality evidence), or miscarriage (low-quality evidence). However, dopamine agonists might increase the risk of adverse events, such as gastrointestinal symptoms.

D'Angelo 2007 identified only two randomised trials. The review authors concluded that the evidence was insufficient to support routine cryopreservation and the relative merits of intravenous albumin versus cryopreservation in the reduction of OHSS (very low-quality evidence). Evidence was insufficient to show whether there was a difference in rates of live birth or clinical pregnancy (low-quality evidence).

D'Angelo 2017 found very low-quality evidence to suggest that coasting reduced rates of moderate or severe OHSS more than no coasting. Review authors found no evidence to suggest that coasting was more beneficial than other interventions (early unilateral follicular aspiration, GnRH antagonist, FSH co-trigger, cabergoline), except that very low-quality evidence from a single small study suggested that using FSH co-trigger at the time of hCG administration may be better for reducing the risk of OHSS than coasting. Data were too few to show clearly whether there was a difference between groups for any other outcomes (low-quality evidence).

Youssef 2016 reported that the plasma expanders assessed (human albumin, hydroxyethyl starch (HES), and mannitol) reduced rates of moderate and severe OHSS for women at high risk. Review authors provided no data on live birth but reported evidence that human albumin reduces clinical pregnancy rates (moderate-quality evidence). Although there was no evidence that HES or mannitol had any influence on pregnancy rates, information on effectiveness was based on low- or very low-quality evidence from very few trials, which needs to be confirmed in additional, larger RCTs.

12. Frozen embryo replacement cycles

We identified three reviews that examined frozen cycles.

- Wong 2017: "Fresh versus frozen embryo transfers in assisted reproduction" (KMW1790).
- Ghobara 2017: "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).

Wong 2017 compared a freeze-all strategy for embryo transfer versus a conventional strategy with transfer of fresh and subsequent frozen-thawed embryos, and found that neither strategy was superior to the other in terms of cumulative live birth rates (moderate-quality evidence). Evidence suggested that not performing a fresh transfer lowers risk for women at risk of OHSS.

Ghobara 2017 did not find sufficient evidence to support the use of one cycle regimen in preference to another in preparation for frozen-thawed embryo transfer (FET) in women with regular ovulatory cycles (low- or very low-quality evidence for live birth).

Glujovsky 2010 reported insufficient evidence to show whether one particular intervention for endometrial preparation clearly improves the treatment outcome for women receiving embryo transfers with either frozen embryos or embryos derived from donated oocytes. However, the review authors found evidence of a lower pregnancy rate and a higher cycle cancellation rate when progesterone supplementation was commenced before oocyte retrieval in oocyte donation cycles (moderate-quality evidence). 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.

The choice of category reflected the conclusions of the authors of the individual reviews, in the judgement of the overview authors. There were no disagreements between the overview authors.

1. Indication for assisted reproductive technology (ART)

Promising interventions (more evidence needed)

- In women with unexplained subfertility, evidence suggests that in vitro fertilisation (IVF) may be associated with higher live birth rates than unstimulated intrauterine insemination (IUI) (low-quality evidence), and in women pre-treated with clomiphene +

IUI, IVF appeared to be associated with higher birth rates than IUI + gonadotropins (moderate-quality evidence) (Pandian 2015)

No conclusions possible due to lack of evidence

- In women with unexplained subfertility, there was no conclusive evidence of a difference in live birth rates between IVF and expectant management (very low-quality evidence), and in those who were treatment-naive, there was insufficient evidence to determine whether there was a difference in live birth rates between IVF and IUI + gonadotropins or between IVF and IUI + clomiphene (moderate-quality evidence) (Pandian 2015)
- 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 2009)

2. Pre-ART and adjuvant strategies

Effective interventions

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

Promising interventions (more evidence needed)

- Antioxidants for male subfertility: oral antioxidants given to men in couples with male factor or unexplained subfertility may improve live birth rates (low-quality evidence), but more evidence is needed (low-quality evidence) (Showell 2014)
- Vasodilators for women undergoing fertility treatment: vasodilators may increase clinical pregnancy rates in women undergoing ART (low-quality evidence). Evidence was insufficient to show whether an effect on live birth rates was found, but few studies reported this outcome (moderate-quality evidence) (Gutarra-Vilchez 2014)
- In women undergoing ART who are identified as poor responders, pre-treatment with dehydroepiandrosterone (DHEA) or testosterone may be associated with improved live birth rates (moderate-quality evidence). Evidence is insufficient to permit conclusions about the safety of either androgen (Nagels 2015)
- In women undergoing ART who are identified as poor responders, use of growth hormone appears to increase live birth and clinical pregnancy rates (moderate- to high-quality evidence) (Duffy 2010)

Possibly ineffective interventions (more evidence needed)

- Acupuncture and ART: evidence was insufficient to show whether acupuncture improves live birth or pregnancy rates in assisted conception (low-quality evidence) (Cheong 2013)
- Interventions for women with endometrioma before ART: evidence was insufficient to show whether there was an effect on reproductive outcomes in any of the four included trials. Therapies considered included surgery, medicines, and expectant management (low- to very low-quality evidence) (Benschop 2010)
- Antioxidants for female subfertility: evidence was insufficient to show whether antioxidants were associated with an effect on live birth rates (very low-quality evidence), nor was there a clear difference between groups in clinical pregnancy rates (very low-quality evidence), although more evidence is needed (Showell 2017)
- Ovarian cyst aspiration before in vitro fertilisation treatment for subfertility: evidence is insufficient to show whether cyst aspiration was associated with an effect on clinical pregnancy rates (very low-quality evidence). None of the studies reported live birth (McDonnell 2014)

No conclusions possible due to lack of evidence

- Pre-conception lifestyle advice for people with subfertility: evidence was insufficient to permit a conclusion, with only one RCT (Anderson 2010)
- Aspirin for IVF: evidence from adequately powered RCTs was insufficient to permit a conclusion (Siristatidis 2016)

3. Down-regulation with agonists or antagonists

Effective interventions

- Gonadotrophin-releasing hormone agonist (GnRHa) protocols for pituitary suppression in assisted reproductive technology cycles: the pregnancy rate was higher when GnRHa was used in a long protocol as compared to a short protocol (moderate-quality evidence) (Siristatidis 2015)
- Gonadotrophin-releasing hormone (GnRH) antagonists for ART: use of GnRH antagonists compared with long-course GnRH agonist protocols was associated with a substantial reduction in ovarian hyperstimulation syndrome (OHSS) without reducing the likelihood of achieving live birth (moderate-quality evidence) (Al-Inany 2016)
- Long-term pituitary down-regulation before IVF for women with endometriosis: administration of GnRHa for a period of three to six months before IVF or ICSI in women with endometriosis increased the odds of clinical pregnancy (very low-quality evidence) (Sallam 2006)

Possibly ineffective interventions (more evidence needed)

- Depot versus daily administration of GnRHa protocols for pituitary desensitisation in assisted reproduction cycles: evidence was insufficient to show whether there was a difference in live birth or pregnancy outcomes between depot and daily GnRHa use for pituitary down-regulation in IVF cycles using the long protocol, but substantial differences could not be ruled out (low- to moderate-quality evidence) (Albuquerque 2013)

4. Ovarian stimulation

Effective interventions

- Recombinant versus urinary gonadotrophin for ovarian stimulation in ART cycles: it appears that all available gonadotrophins were equally effective and safe. Review authors stated that the choice of one or the other product would depend upon the availability of the product, the convenience of its use, and the associated costs, and that any specific differences were likely to be too small to justify further research (moderate- to high-quality evidence) (van Wely 2011)
- Long-acting follicle-stimulating hormone (FSH) versus daily FSH for women undergoing assisted reproduction: use of a medium dose (150 to 180 µg) of long-acting follicle-stimulating hormone (FSH) appeared to be a safe treatment option and as effective as daily FSH in women with unexplained subfertility. There was evidence of a reduced live birth rate in women receiving a low dose (60 to 120 µg) of long-acting FSH compared to daily FSH (moderate-quality evidence) (Pouwer 2015)
- Individualised gonadotrophin dose selection using markers of ovarian reserve for women undergoing IVF/ICSI: a decreased dose of FSH in predicted high responders appeared to reduce the likelihood of moderate or severe OHSS (low-quality evidence). Furthermore, ovarian reserve test (ORT) algorithms reduced the incidence of OHSS compared to standard dosing of 150 IU, probably by facilitating dose reductions among women with a predicted high response (moderate-quality evidence) (Lensen 2018)

Promising interventions (more evidence needed)

- Recombinant luteinising hormone (rLH) for controlled ovarian hyperstimulation (COH) in assisted reproductive cycles: there is no clear evidence that co-administration of rLH to recombinant follicle-stimulating hormone (rFSH) in GnRHa down-regulated women resulted in more live births or fewer cases of OHSS than COH with rFSH alone (very low- or low-quality evidence). Nevertheless, pooled clinical and ongoing pregnancy estimates suggested a beneficial effect of co-treatment with rLH (moderate-quality evidence) (Mochtar 2017)
- Use of clomiphene or letrozole for COH (with or without gonadotrophins) reduced the quantity of gonadotrophins required and the incidence of OHSS. Evidence was insufficient to determine whether there was any effect on live birth or pregnancy rates (low- to moderate-quality evidence). However, use of clomiphene citrate or letrozole was possibly associated with an increase in the incidence of cycle cancellations, as well as reductions in the mean number of oocytes retrieved, in both the general IVF population and among poor responders, so the review authors suggested that further evidence is needed before they are adopted into routine clinical practice (low- to moderate-quality evidence) (Kamath 2017)
- FSH replaced by low-dose human chorionic gonadotropin (hCG) in the late follicular phase versus FSH alone for ARTs: the review authors were very uncertain about the effect on live birth, OHSS, and miscarriage, but evidence suggests that this intervention did not reduce the chance of ongoing and clinical pregnancy, and that it was likely to result in an equivalent number of oocytes retrieved while expending less FSH (very low-quality evidence) (Martins 2013)
- Natural cycle IVF for subfertile couples: there was no clear evidence of a difference between natural cycle and standard IVF for outcomes including live birth, OHSS, clinical pregnancy, and multiple pregnancy (very low-quality evidence) (Allersma 2013)

Possibly ineffective interventions (more evidence needed)

- Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI): RCTs provided no evidence to support cycle monitoring by ultrasound plus serum oestradiol was more efficacious than cycle monitoring by ultrasound only on the outcomes of clinical pregnancy and OHSS. A large well-designed RCT is needed (low-quality evidence) (Kwan 2014)
- Combined oral contraceptive pill (COCP), progestogen or oestrogen pre-treatment for ovarian stimulation protocols for women undergoing ARTs: COCP pre-treatment was associated with a lower rate of live birth or ongoing pregnancy than no pre-treatment (moderate-quality evidence). Evidence was insufficient to show whether rates of live birth or ongoing pregnancy were influenced by pre-treatment with progestogens or oestrogens, or by COCP pre-treatment using other stimulation protocols (low- to moderate-quality evidence) (Farquhar 2017)
- The safety and effectiveness of glucocorticoid administration in women undergoing COH for IVF/ICSI cycles were unclear because data were lacking. Glucocorticoids may increase the clinical pregnancy rates but may have little or no impact on live birth rates (low-quality evidence) (Kalampokas 2017)
- Individualised gonadotrophin dose selection using markers of ovarian reserve for women undergoing IVF/ICSI: current evidence did not provide a clear justification for adjusting the standard dose of 150 IU in the case of poor or normal responders (low-quality evidence) (Lensen 2018)

No conclusions possible due to lack of evidence

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

5. Ovulation triggering

Effective interventions

- Recombinant hCG and rLH as the final oocyte maturation triggers did not seem to be better than uhCG for reproductive outcomes of the IVF or ICSI cycle, as there was no clear evidence of a difference between rhCG and uhCG (moderate-quality evidence), or between rhLH and uhCG (very low-quality evidence), with respect to rates of live birth or ongoing pregnancy (Youssef 2016a)

- GnRHa versus hCG for oocyte triggering in antagonist ART cycles: there was evidence of a lower live birth rate (moderate-quality evidence), a reduced ongoing pregnancy rate (low-quality evidence), and a higher miscarriage rate (moderate-quality evidence) among women who received GnRHa. However, OHSS rates were reduced with GnRHa triggering (moderate-quality evidence); therefore there was 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. Simultaneous use of sedation combined with analgesia such as the opiates, further enhanced by paracervical block or acupuncture techniques, resulted in better pain relief than occurred with one modality alone. The review authors proposed that women's preferences and resource availability for choice of pain relief merit consideration in practice.(low- or very low-quality evidence for most comparisons) (Kwan 2018)

Possibly ineffective interventions (more evidence needed)

- hCG priming in in vitro maturation: evidence was insufficient to show whether hCG priming had an effect on live birth or miscarriage rates in oocyte maturation in vivo (IVM) (low-quality evidence). Some evidence suggests that hCG priming may reduce clinical pregnancy rates, but these findings were limited by the small quantity of data included (low-quality evidence) (Reavey 2016)

Ineffective interventions

- Follicular flushing during oocyte retrieval may have little or no effect on live birth rates or clinical pregnancy rates compared with aspiration alone (moderate-quality evidence). Evidence was insufficient to permit any firm conclusions with regard to adverse events or safety (Georgiou 2018)

7. Sperm retrieval

No conclusions possible due to lack of evidence

- Techniques for surgical retrieval of sperm before ICSI for azo-ospermia: evidence was insufficient to support recommendations for any specific sperm retrieval technique for azo-ospermic men undergoing ICSI (only one RCT) (low-quality evidence) (Proctor 2008)
- Advanced sperm selection techniques for assisted reproduction: evidence was insufficient to show whether sperm selected by hyaluronic acid binding improves live birth or pregnancy outcomes in ART, or whether there was a difference in efficacy between the hyaluronic acid binding methods SpermSlow and PICSI. Review authors found no randomised evidence evaluating sperm selection by sperm apoptosis, sperm birefringence, or surface charge (low-quality evidence) (McDowell 2014)

8. Laboratory phase

Effective interventions

- Low oxygen concentrations for embryo culture in ART: review authors found evidence of an increase in live birth rates associated with embryo culture with low oxygen concentrations (moderate-quality evidence) (Bontekoe 2012)

Promising interventions (more evidence needed)

- Assisted hatching on assisted conception (IVF and ICSI): although assisted hatching (AH) appears to offer an increased chance of achieving a clinical pregnancy (moderate-quality evidence), the extent to which it might do so only just reached statistical significance. Review authors found no evidence of an effect on live birth rates (moderate-quality evidence), and multiple pregnancy rates were increased in AH groups (low-quality evidence) (Carney 2012)
- Brief co-incubation of sperm and oocytes for IVF techniques: brief co-incubation of sperm and oocytes may improve ongoing pregnancy and clinical pregnancy rates for women undergoing IVF cycles compared to the standard overnight insemination protocol. More RCTs are required (low-quality evidence) (Huang 2013)
- Vitrification probably increases clinical pregnancy rates compared to slow freezing (moderate-quality evidence). However, the total number of women and of pregnancies was low, and no data on live birth or adverse events.were available (moderate-quality evidence) (Glujovsky 2014)

Possibly ineffective interventions (more evidence needed)

- Regular (ICSI) versus ultra-high magnification sperm selection (IMSI) for assisted reproduction: evidence was insufficient to show whether there was a difference between ICSI and IMSI with respect to rates of live birth (low-quality evidence) or miscarriage (very low-quality evidence), and evidence suggesting that IMSI improved clinical pregnancy was of very low quality (Teixeira 2013)
- Evidence is insufficient to show that metabolomic assessment of embryos before implantation has any meaningful effect on rates of live birth, ongoing pregnancy, or miscarriage (low-quality evidence) (Siristatidis 2018)

Ineffective interventions

- Pre-implantation genetic screening (PGS) for abnormal numbers of chromosomes (aneuploidies) in IVF or ICSI: pre-implantation genetic screening using fluorescent in situ hybridisation decreased live birth rates among women of advanced maternal age and those with repeated IVF failure. RCTs provided no clear evidence of a difference between groups when PGS was offered to women with a good prognosis (moderate-quality evidence) (Twisk 2006)

No conclusions possible due to lack of evidence

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

to permit a conclusion (low- to moderate-quality evidence) (Armstrong 2015)

- Evidence is insufficient to support or refute the use of any specific culture medium (very low-quality evidence). Properly designed and executed randomised trials are necessary (Youssef 2015)

9. Embryo transfer

Effective interventions

- Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women: evidence suggests that ultrasound guidance improves the chance of live birth (low-quality evidence) and clinical pregnancy (moderate-quality evidence) compared with clinical touch, without increasing the chance of multiple pregnancy, ectopic pregnancy, or miscarriage (low- to moderate-quality evidence) (Brown 2016a)
- .Adherence compounds in embryo transfer media for ART: evidence suggested improved live birth and clinical pregnancy rates with the use of hyaluronic acid. Multiple pregnancy rates were also increased in the intervention group, which the review authors suggested might relate to use of an adherence compound together with a policy of transferring more than one embryo (moderate-quality evidence) (Bontekoe 2014)
- Number of embryos for transfer following IVF or ICSI: although in a single ART cycle the live birth rate was lower following single-embryo transfer compared with double-embryo transfer, elective single embryo transfer resulted in fewer multiple pregnancies than double embryo transfer (high-quality evidence). The cumulative live birth rate associated with single-embryo transfer followed by a single frozen and thawed embryo transfer was comparable with that after one cycle of double-embryo transfer (low-quality evidence) (Pandian 2013)
- Evidence suggests that day three and day two embryo transfers following IVF or ICSI are equally effective (very low- to moderate-quality evidence) (Brown 2016)

Promising interventions (more evidence needed)

- Pregnancy outcomes for cleavage-stage embryo transfer using an intra-cavity human chorionic gonadotropin (IC-hCG) dose of 500 international units or greater are promising. However evidence quality was variable, and this finding was derived from a subgroup analysis. No evidence suggests that miscarriage was influenced by intrauterine hCG administration, irrespective of embryo stage at transfer or dose of IC-hCG, and events were too few to allow any conclusions to be drawn with regard to other complications. More research is needed (Craciunas 2016)
- Evidence was insufficient to show whether application of seminal plasma to the genital tract influenced rates of live birth or miscarriage (low-quality evidence). However, low-quality evidence suggests that seminal plasma application may be associated with more clinical pregnancies than standard ART. The review authors concluded that the intervention is worth further investigation, with focus on live birth and miscarriage rates

Possibly ineffective interventions (more evidence needed)

- Techniques for preparation before embryo transfer: evidence was insufficient to show whether benefit was associated with any of the following interventions at the time of embryo transfer: full bladder, removal of cervical mucus, or flushing the endocervical canal or the endometrial cavity (low- to moderate-quality evidence). More and larger studies on embryo transfer preparation techniques are needed (Derks 2009)
- Antibiotics before embryo transfer in ART: administration of amoxicillin and clavulanic acid before embryo transfer reduced upper genital tract microbial contamination but had no clear effect on clinical pregnancy rates (moderate-quality evidence). No data were available 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 were increased with fresh blastocyst transfer, it was also associated with a reduction in the number of embryos transferred and in embryo freezing (low-quality evidence). Researchers provided insufficient evidence to show whether there was a difference between groups in cumulative pregnancy rates derived from fresh and frozen-thawed cycles following a single oocyte retrieval (very low-quality evidence). Future RCTs should report miscarriage and live birth and cumulative live birth rates to facilitate well-informed decisions on the best treatment option available (Glujovsky 2016)
- Post-embryo transfer interventions for patients with IVF and ICSI: evidence was insufficient to support a certain amount of time for women to remain recumbent following embryo transfer, or to support the use of fibrin sealants. Limited evidence was available to support the use of mechanical closure of the cervical canal following embryo transfer. Further well-designed studies are required (Abou-Setta 2014)

10. Luteal phase support

Effective interventions

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

Promising interventions (more evidence needed)

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

Possibly ineffective interventions (more evidence needed)

- Peri-implantation glucocorticoid administration for ART cycles: overall, no clear evidence suggests that administration of

peri-implantation glucocorticoids in ART cycles significantly improved clinical outcomes (moderate-quality evidence) (Boomsma 2012)

11. Prevention of ovarian hyperstimulation syndrome (OHSS)

Effective interventions

- Dopamine agonists for preventing OHSS: dopamine agonists seemed effective for prevention of moderate or severe OHSS in women at high risk of OHSS (low-quality evidence). Review authors found no clear evidence of a difference in rates of live birth, clinical pregnancy, multiple pregnancy, or miscarriage. However, dopamine agonists might increase the risk of adverse events, such as gastrointestinal symptoms (very low- to moderate-quality evidence) (Tang 2016)
- Gonadotrophin-releasing hormone (GnRH) antagonists for ART: as noted in Section 3 above, the use of antagonists compared with long GnRHa protocols was associated with a large reduction in OHSS, and no evidence suggested a difference in live birth rates (moderate-quality evidence) (Al-Inany 2016)
- GnRHa versus hCG for oocyte triggering in antagonist ART cycles: as noted in Section 3 above, researchers provided evidence of a lower live birth rate, a reduced ongoing pregnancy rate, and a higher miscarriage rate among women who received a GnRHa. However, OHSS rates were reduced with GnRHa triggering; therefore there was a tradeoff between benefits and harms (moderate-quality evidence) (Youssef 2014)

Promising interventions (more evidence needed)

- The plasma expanders human albumin, hydroxyethyl starch (HES), and mannitol reduced rates of moderate and severe OHSS in women at high risk. Trials provided no data on live birth but reported evidence that human albumin reduced clinical pregnancy rates. Although no evidence suggests that HES, or mannitol, had any influence on pregnancy rates, evidence of effectiveness was based on very few trials, and this needs to be confirmed in additional, larger RCTs before these plasma expanders should be considered for routine use in clinical practice (low- or very low-quality evidence) (Youssef 2016)

Possibly ineffective interventions (more evidence needed)

- Embryo freezing for preventing OHSS: evidence was insufficient to support routine cryopreservation and the relative merits of intravenous albumin versus cryopreservation (low-quality evidence) (D'Angelo 2007)
- Coasting (withholding gonadotrophins) for preventing OHSS: evidence suggests benefit derived from coasting rather than no coasting to reduce rates of moderate or severe OHSS (low-quality evidence), but evidence does not suggest that coasting was more beneficial than other interventions, such as early unilateral follicular aspiration, gonadotrophin-releasing hormone antagonist, or cabergoline (very low-quality evidence). A single small study suggested that using an FSH co-trigger at the time of hCG administration may be better than coasting for reducing risk of OHSS (very low-quality evidence) (D'Angelo 2017)

12. Frozen embryo replacement cycles

Effective interventions

- A freeze-all strategy for embryo transfer versus a conventional strategy with transfer of fresh and subsequently frozen-thawed embryos: one strategy was not superior to the other in terms of cumulative live birth rates (moderate-quality evidence). Evidence suggests that not performing a fresh transfer lowers risk of OHSS for women at risk of OHSS (low-quality evidence) (Wong 2017)

No conclusions possible due to lack of evidence

- Cycle regimens for frozen-thawed embryo transfer: at the present time, evidence is insufficient to support the use of one intervention in preference to another (Ghobara 2017)
- Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes: evidence was insufficient to support recommendations for any one particular protocol for endometrial preparation over another with regard to pregnancy rates after embryo transfers (Glujovsky 2010)

Overall completeness and applicability of evidence

This overview summarises published Cochrane systematic reviews of all randomised controlled trials on the different stages of an ART cycle and the different populations undergoing ART. We consider it to be complete, although we 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 use of low-cost strategies such as modified natural cycle IVF.

Quality of the evidence

We have assessed each of the reviews by using the AMSTAR tool for assessing systematic reviews. We have presented these results in the 'AMSTAR assessment' table (Table 2). Overall, the quality of the reviews was high and almost all criteria were met. The only exception was assessment of publication bias, which we considered inadequate in two of the 67 reviews. The main limitation of the reviews was that only 44% had been updated with a search within the past three years (to May 2018) or had been deemed "stable, with no updating planned".

Potential biases in the overview process

We identified no specific biases 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

No reviews are comparable with this overview.

Several of the reviews included in this overview have been used to help develop World Health Organization fertility guidelines. The National Institute for Health and Care Excellence (NICE) clinical guidelines on assessment and treatment of people with fertility problems also were based on information provided in many of our reviews (NICE 2013).

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

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

ACKNOWLEDGEMENTS

Dr. Julie Brown, Josephine Rishworth and Dr Willianne Nelen were co-authors of the original version of this overview and the 2015 update and helped with all aspects of the review.

We would like to acknowledge the support of the editorial base of the Cochrane Gynaecology and Fertility Group (formerly the Menstrual Disorders and Subfertility Group)

REFERENCES

References to included reviews

Abou-Setta 2014

Abou-Setta AM, Peters LR, D'Angelo A, Sallam HN, Hart RJ, Al-Inany HG. Post-embryo transfer interventions for assisted reproduction technology cycles. *Cochrane Database of Systematic Reviews* 2014, Issue 8. [DOI: 10.1002/14651858.CD006567.pub3]

Akhtar 2013

Akhtar M, Sur S, Raine-Fenning N, Jayaprakasan K, Thornton JG, Quenby S. Heparin for assisted reproduction. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD009452.pub2]

Al-Inany 2016

Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD001750.pub4]

Albuquerque 2013

Albuquerque LET, Tso LO, Saconato H, Albuquerque MCRM, Macedo CR. Depot versus daily administration of gonadotrophin-releasing hormone agonist protocols for pituitary down regulation in assisted reproduction cycles. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD002808.pub3]

Allersma 2013

Allersma T, Farquhar C, Cantineau AEP. Natural cycle in vitro fertilisation (IVF) for subfertile couples. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD010550.pub2]

Anderson 2010

Anderson K, Norman RJ, Middleton P. Preconception lifestyle advice for people with subfertility. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008189.pub2]

Armstrong 2015

Armstrong S, Arroll N, Cree LM, Jordan V, Farquhar C. Time-lapse systems for embryo incubation and assessment in assisted reproduction. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD011320.pub2]

Ata 2018

Ata B, Abou-Setta AM, Seyhan A, Buckett W. Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer). *Cochrane Database of Systematic Reviews* 2018, Issue 2. [DOI: 10.1002/14651858.CD011809.pub2]

Benschop 2010

Benschop L, Farquhar C, van der Poel N, Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD008571.pub2]

Bontekoe 2012

Bontekoe S, Mantikou E, van Wely M, Seshadri S, Repping S, Mastenbroek S. Low oxygen concentrations for embryo culture in assisted reproductive technologies. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD008950.pub2]

Bontekoe 2014

Bontekoe S, Heineman MJ, Johnson N, Blake D. Adherence compounds in embryo transfer media for assisted reproductive technologies. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: 10.1002/14651858.CD007421.pub3]

Boomsma 2012

Boomsma CM, Keay SD, Macklon NS. Peri-implantation glucocorticoid administration for assisted reproductive technology cycles. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD005996.pub3]

Brown 2016

Brown J, Daya S, Matson P. Day three versus day two embryo transfer following in vitro fertilization or intracytoplasmic sperm injection. *Cochrane Database of Systematic Reviews* 2016, Issue 12. [DOI: 10.1002/14651858.CD004378.pub3]

Brown 2016a

Brown J, Buckingham K, Buckett W, Abou-Setta AM. Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women. *Cochrane Database of Systematic Reviews* 2016, Issue 3. [DOI: 10.1002/14651858.CD006107.pub4]

Carney 2012

Carney SK, Das S, Blake D, Farquhar C, Seif MM, Nelson L. Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)). *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD001894.pub5]

Cheong 2013

Cheong YC, Dix S, Hung Yu Ng E, Ledger WL, Farquhar C. Acupuncture and assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD006920.pub3]

Craciunas 2016

Craciunas L, Tsampras N, Coomarasamy A, Raine-Fenning N. Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD011537.pub2]

D'Angelo 2007

D'Angelo A, Amso NN. Embryo freezing for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD002806.pub2]

D'Angelo 2017

D'Angelo A, Amso NN, Hassan R. Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2017, Issue 5. [DOI: 10.1002/14651858.CD002811.pub4]

Derks 2009

Derks RS, Farquhar C, Mol BWJ, Buckingham K, Heineman MJ. Techniques for preparation prior to embryo transfer. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007682.pub2]

Duffy 2010

Duffy JMN, Ahmad G, Mohiyiddeen L, Nardo LG, Watson A. Growth hormone for in vitro fertilization. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD000099.pub3]

Farquhar 2017

Farquhar C, Rombauts L, Kremer JAM, Lethaby A, Ayeleke RO. Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2017, Issue 5. [DOI: 10.1002/14651858.CD006109.pub3]

Georgiou 2018

Georgiou EX, Melo P, Bronw J, Granne IE. Follicular flushing during oocyte retrieval in assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2018, Issue 4. [DOI: 10.1002/14651858.CD004634.pub3]

Ghobara 2017

Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for frozen-thawed embryo transfer. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD003414.pub3]

Glujovsky 2010

Glujovsky D, Pesce R, Fiszbajn G, Sueldo C, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD006359.pub2]

Glujovsky 2014

Glujovsky D, Riestra B, Sueldo C, Fiszbajn G, Repping S, Nodar F, et al. Vitrification versus slow freezing for women undergoing oocyte cryopreservation. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD010047.pub2]

Glujovsky 2016

Glujovsky D, Farquhar C, Quinteiro Retamar AM, Alvarez Sedo CR, Blake D. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2016, Issue 6. [DOI: 10.1002/14651858.CD002118.pub5]

Gutarra-Vilchez 2014

Gutarra-Vilchez RB, Urrútia G, Glujovsky D, Coscia A, Bonfill Cosp X. Vasodilators for women undergoing fertility treatment. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD010001.pub2]

Huang 2013

Huang Z, Li J, Wang L, Yan J, Shi Y, Li S. Brief co-incubation of sperm and oocytes for in vitro fertilization techniques. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD009391.pub2]

Johnson 2010

Johnson N, van Voorst S, Sowter MC, Strandell A, Mol BWJ. Surgical treatment for tubal disease in women due to undergo in vitro fertilisation. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD002125.pub3]

Kalampokas 2017

Kalampokas T, Pandian Z, Keay SD, Bhattacharya S. Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI. *Cochrane Database of Systematic Reviews* 2017, Issue 3. [DOI: 10.1002/14651858.CD004752.pub2]

Kamath 2017

Kamath MS, Maheshwari A, Bhattacharya S, Lor KY, Gibreel A. Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation. *Cochrane Database of Systematic Reviews* 2017, Issue 11. [DOI: 10.1002/14651858.CD008528.pub3]

Kroon 2012

Kroon B, Hart RJ, Wong BMS, Ford E, Yazdani A. Antibiotics prior to embryo transfer in ART. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD008995.pub2]

Kwan 2014

Kwan I, Bhattacharya S, Kang A, Woolner A. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). *Cochrane Database of Systematic Reviews* 2014, Issue 8. [DOI: 10.1002/14651858.CD005289.pub3]

Kwan 2018

Kwan I, Wang R, Pearce E, Bhattacharya S. Pain relief for women undergoing oocyte retrieval for assisted reproduction. *Cochrane Database of Systematic Reviews* 2018, Issue 5. [DOI: 10.1002/14651858.CD004829.pub4]

Lensen 2018

Lensen SF, Wilkinson J, Leijdekkers JA, La Marca A, Mol BWJ, Marjoribanks J, et al. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). *Cochrane Database of Systematic Reviews* 2018, Issue 2. [DOI: 10.1002/14651858.CD012693.pub2]

Martins 2013

Martins WP, Vieira ADD, Figueiredo JBP, Nastri CO. FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: 10.1002/14651858.CD010042.pub2]

McDonnell 2014

McDonnell R, Marjoribanks J, Hart RJ. Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility. *Cochrane Database of Systematic Reviews* 2014, Issue 12. [DOI: 10.1002/14651858.CD005999.pub2]

McDowell 2014

McDowell S, Kroon B, Ford E, Hook Y, Glujovsky D, Yazdani A. Advanced sperm selection techniques for assisted reproduction. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD010461.pub2]

Mochtar 2017

Mochtar MH, Danhof NA, Ayeleke RO, Van der Veen F, van Wely M. Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles. *Cochrane Database of Systematic Reviews* 2017, Issue 5. [DOI: 10.1002/14651858.CD005070.pub3]

Nagels 2015

Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD009749.pub2]

Nastri 2015

Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, et al. Endometrial injury in women undergoing assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: 10.1002/14651858.CD009517]

Pandian 2010

Pandian Z, McTavish AR, Aucott L, Hamilton MPR, Bhattacharya S. Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF). *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD004379.pub3]

Pandian 2013

Pandian Z, Marjoribanks J, Ozturk O, Serour G, Bhattacharya S. Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD003416.pub4]

Pandian 2015

Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD003357.pub4]

Pouwer 2015

Pouwer AW, Farquhar C, Kremer JAM. Long-acting FSH versus daily FSH for women undergoing assisted reproduction. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD009577.pub3]

Proctor 2008

Proctor M, Johnson N, van Peperstraten AM, Phillipson G. Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD002807.pub3]

Reavey 2016

Reavey J, Vincent K, Child T, Granne IE. Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation. *Cochrane Database of Systematic Reviews* 2016, Issue 11. [DOI: 10.1002/14651858.CD008720.pub2]

Sallam 2006

Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD004635.pub2]

Showell 2014

Showell MG, Mackenzie-Proctor R, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. *Cochrane Database of Systematic Reviews* 2014, Issue 12. [DOI: 10.1002/14651858.CD007411.pub3]

Showell 2017

Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD007807.pub2]

Siristatidis 2009

Siristatidis CS, Maheshwari A, Bhattacharya S. In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD006606.pub2]

Siristatidis 2015

Siristatidis CS, Gibreel A, Basios G, Maheshwari A, Bhattacharya S. Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD006919.pub4]

Siristatidis 2016

Siristatidis CS, Basios G, Pergialiotis V, Vogiatzi P. Aspirin for in vitro fertilisation. *Cochrane Database of Systematic Reviews* 2016, Issue 11. [DOI: 10.1002/14651858.CD004832.pub4]

Siristatidis 2018

Siristatidis CS, Sertedaki E, Vaidakis D, Varounis C, Trivella M. Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies. *Cochrane Database of Systematic Reviews* 2018, Issue 3. [DOI: 10.1002/14651858.CD011872.pub3]

Tang 2016

Tang H, Mourad S, Zhai S-D, Hart RJ. Dopamine agonists for preventing ovarian hyperstimulation syndrome. *Cochrane*

Database of Systematic Reviews 2016, Issue 11. [DOI: 10.1002/14651858.CD008605.pub3]

Teixeira 2013

Teixeira DM, Barbosa MAP, Ferriani RA, Navarro PA, Raine-Fenning N, Nastri CO, et al. Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD010167.pub2]

Tso 2014

Tso LO, Costello MF, Albuquerque LET, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD006105.pub3]

Twisk 2006

Twisk M, Mastenbroek S, van Wely M, Heineman MJ, Van der Veen F, Repping S. Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD005291.pub2]

van der Linden 2015

van der Linden M, Buckingham K, Farquhar C, Kremer JAM, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD009154.pub3]

Van Rumste 2003

van Rumste MME, Evers JLH, Farquhar C. Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD001301]

van Wely 2011

van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F, Al-Inany HG. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD005354.pub2]

Wong 2017

Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. *Cochrane Database of Systematic Reviews* 2017, Issue 3. [DOI: 10.1002/14651858.CD011184.pub2]

Yossry 2006

Yossry M, Aboulghar M, D'Angelo A, Gillett W. In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD004144.pub2]

Youssef 2014

Youssef MAFM, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD008046.pub4]

Youssef 2015

Youssef MMA, Mantikou E, van Wely M, Van der Veen F, Al-Inany HG, Repping S, et al. Culture media for human pre-implantation embryos in assisted reproductive technology cycles. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD007876.pub2]

Youssef 2016

Youssef M, Mourad S. Volume expanders for the prevention of ovarian hyperstimulation syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 8. [DOI: 10.1002/14651858.CD001302.pub2]

Youssef 2016a

Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD003719.pub4]

Additional references

Abou-Setta 2006

Abou-Setta AM, Al-Inany HG, Hornstein MD, Richard-Davis G, Van der Veen F, van der Poel N. Soft versus firm embryo transfer catheters for assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD005636]

Baak 2016

Baak NA, Cantineau AEP, Farquhar C, Brison D. Temperature of embryo culture for assisted reproduction. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD012192]

Benschop 2012

Benschop L, Seshadri S, Toulis KA, Vincent K, Child T, Granne IE, Goulis DG. Immune therapies for women with history of failed implantation undergoing IVF treatment. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD009602]

Boivin 2007

Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human Reproduction* 2007;**22**(6):1506-12.

Checa 2016

Checa MA, Teixeira DM, González-Comadran M, Nastri CO, Martins WP. Luteal phase support for women trying to conceive by intrauterine insemination or sexual intercourse. *Cochrane Database of Systematic Reviews* 2016, Issue 11. [DOI: 10.1002/14651858.CD012396]

Chua 2012

Chua W, Boothroyd C, Walls M, Hart RJ. Slow freeze versus vitrification for embryo cryopreservation. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD009589]

Craciunas 2016a

Craciunas L, Kollmann M, Tsampras N, Raine-Fenning N, Choudhary M. Oxytocin antagonists for assisted reproduction. *Cochrane Database of Systematic Reviews* 2016, Issue 10. [DOI: 10.1002/14651858.CD012375]

ElDaly 2006

ElDaly AA, Al-Fozan HM, Al-Inany HG, Bedaiwy MA, Saleh WF. Aromatase inhibitors for ovulation induction. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: 10.1002/14651858.CD005635.pub2]

Higgins 2011

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

Jones 2012

Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, et al. Pain management for women in labour: an overview of systematic reviews. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD009234.pub2]

Kamath 2017a

Kamath MS, Bosteels J, D'Hooghe TM, Seshadri S, Weyers S, Mol BWJ, et al. Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. *Cochrane Database of Systematic Reviews* 2017, Issue 11. [DOI: 10.1002/14651858.CD012856]

ADDITIONAL TABLES

Nastri 2013

Nastri CO, Teixeira DM, Moroni RM, Navarro PA, Ferriani RA, Martins WP. Interventions for improving reproductive outcomes in women with recurrent implantation failure undergoing assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2013, Issue 10. [DOI: 10.1002/14651858.CD010795]

NICE 2013

National Institute for Health and Clinical Excellence. Fertility: assessment and treatment for people with fertility problems. London: National Institute for Health and Care Excellence, 2013.

Nyachieo 2009

Nyachieo A, Clarke J, Moridi I, Mahdian M. Nonsteroidal anti-inflammatory drugs for assisted reproductive technology. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD007618]

Shea 2007

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007;**7**:10.

Zegers-Hochschild 2009

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology. *Human Reproduction* 2009;**24**:2683-7.

Zhu 2013

Zhu X, Lim CED, Nagels HE. Acupuncture for female subfertility. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: 10.1002/14651858.CD010462]

Table 1. Review characteristics

Review ID	Date assessed as up-to-date	Number of included trials	Population	Intervention	Comparison intervention/control	Outcomes	Review limitations
1. Indication for ART							
ZP672 Pandian 2015 In vitro fertilisation for unexplained subfertility	4/5/2015	8 RCTs	1774 couples with unexplained subfertility	In vitro fertilisation	Expectant management Intrauterine insemination Intrauterine insemination + ovarian stimulation	Live birth Clinical pregnancy Multiple pregnancy OHSS	Serious imprecision resulting from small study numbers and low event rates
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 reanastomosis	Live birth Clinical pregnancy Multiple pregnancy 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	1/5/2013 Review is considered to be stable, with no update planned	No RCTs	N/A	In vitro maturation	In vitro fertilisation Intracytoplasmic sperm injection	Live birth Cycle cancellation Oocyte fertilisation OHSS Miscarriage Preterm birth Congenital abnormalities	Empty review with no trials. No longer being updated
2. Pre-ART and adjuvant strategies							

Table 1. Review characteristics *(Continued)*

2.1. For unselected populations

KA992 Anderson 2010 Pre-conception 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	Trial did not report on fertility outcomes. Evidence was based on a single trial
WM1504 Nastri 2015 Endometrial injury in women undergoing assisted reproductive techniques	19/1/2015	14 RCTs	1063 women undergoing ART	Endometrial injury	No endometrial injury Mock procedure	Live birth rate Clinical pregnancy Multiple pregnancy Miscarriage Ongoing pregnancy Pain/bleeding Implantation	Serious imprecision for most outcomes..Adverse events such as miscarriage and multiple pregnancy were poorly reported
MGS1510 Showell 2014 Antioxidants for male subfertility	31/1/14	3 RCTs*	111 male partners of couples undergoing ART	Antioxidant	Placebo/no treatment Antioxidant Pentoxifylline	Live birth Pregnancy Adverse events DNA fragmentation Sperm parameters Miscarriage	* A further 45 RCTs in this review included subfertile couples not undergoing ART Lack of a clear description of trial methods and inconsistent, inadequate reporting of live births and clinical pregnancies
MGS1630 Showell 2017 Antioxidants for female subfertility	27/9/2016	27 RCTs	Over 3000 women undergoing ART (not all studies reported sample size)	Antioxidant	Placebo/no treatment Antioxidant	Live birth Pregnancy Multiple pregnancy Miscarriage	A further 23 RCTs in this review included subfertile couples not undergoing ART

Table 1. Review characteristics *(Continued)*

							The overall quality of evidence was limited by serious risk of bias associated with poor reporting of methods, imprecision, and inconsistency
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% of studies failing to describe an adequate method of allocation concealment
KH291 Duffy 2010 Growth hormone for in vitro fertilization	01/07/2009	10 RCTs	440 couples undergoing IVF	Growth hormone	Placebo	Live birth Pregnancy Number of women with ≥ 1 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	Main limitations were imprecision and lack of clarity about study methods
VJP951 Siristatidis 2016	9/05/16	13 RCTs	2653 women undergoing IVF	Aspirin	Placebo	Live birth	Poor reporting of study meth-

Table 1. Review characteristics *(Continued)*

Aspirin for in vitro fertilisation	Review is considered to be stable, with no update planned				No treatment	Clinical pregnancy Multiple pregnancy Complications of IVF Complications of pregnancy Miscarriage Ongoing pregnancy	ods, suspected publication bias
HEN1730 Nagels 2015 Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction	12/03/2015	17 RCTs	1496 women, most (15/17 RCTs) identified as poor responders	Testosterone Dehydroepiandrosterone	Placebo or no treatment Oestradiol	Live birth or ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage	Main limitations were lack of blinding, inadequate reporting of study methods, and low event and sample sizes in some trials
2.2. For selected populations							
SG1241 Benschop 2010 Interventions for women with endometrioma prior to assisted reproductive technology	26/11/2010	4 RCTs	312 women undergoing management of endometrioma before ART	Surgical or medical treatment before ART	Placebo/no treatment Other surgical or medical treatment before ART	Live birth Clinical pregnancy Adverse events Quality of life Pain Recurrence Oestradiol levels Number of mature oocytes	No live birth rates reported Two trials were open-label
LDT1201 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	Half the trials were not blinded and lacked details on allocation concealment and randomisation

Table 1. Review characteristics *(Continued)*

						retrieved Total dose FSH (IU) Number of days gonadotrophin treatment Cycle cancellation Serum E_2 level	
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 procedures	Ovarian cyst aspiration	Conservative treatment	Clinical pregnancy Number of follicles recruited Number of oocytes collected Number of cancelled cycles	Live birth not reported by any of the RCTs; poor reporting of study methods; serious imprecision and inconsistent data in 1 study publication
3. Down-regulation with agonists or antagonists							
LA541 Albuquerque 2013 Depot versus daily administration of gonadotrophin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles	3/7/2012	16 RCTs	1811 women undergoing IVF1811	GnRHa depot	GnRHa daily	Clinical pregnancy Pregnancy per oocyte retrieval procedure Pregnancy per embryo transferred Number of ampoules of gonadotrophin employed Number of days of gonadotrophin treatment Number of oocytes retrieved Abortion Ongoing/delivered pregnancy rates per cycle started Multiple pregnancy rates OHSS	Study quality was unclear owing to poor reporting. Only 4 RCTs reported live births as an outcome, and only 5 described adequate methods for concealment of allocation

Table 1. Review characteristics *(Continued)*

HA412 Al-Inany 2016 Gonadotrophin-releasing hormone antagonists for assisted reproductive technology	28/4/2016	73 RCTs	12,212 women undergoing ART procedures	GnRH antagonist	Long course GnRH agonist	Live birth Ongoing pregnancy Clinical pregnancy Miscarriage OHSS Cycle cancellation	Poor reporting of study methods
HNS881 Sallam 2006 Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis	17/10/2005	3 RCTs	228 women with endometriosis undergoing ART procedures	GnRH agonist	No GnRH agonist	Clinical pregnancy Dose of FSH/HMG (ampoule) Duration of FSH administration (days) Number of oocytes	No blinding, unclear allocation concealment in all trials, and no reporting of live births. Possible unit of analysis error - review being updated
SD265 Siristatidis 2015 Gonadotropin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive technology cycles	23/4/2015	37 RCTs	3872 women undergoing ART procedures	Long protocol (various regimens compared) Short protocol	Short protocol Ultra-short protocol Stop short protocol	Live birth Clinical pregnancy Ongoing pregnancy Number of oocytes Dose of gonadotrophins Cycle cancellation	Poor reporting of methods in primary studies and imprecise findings due to lack of data
4. Ovarian stimulation							
4.1. Medication type							
AM1335 Kamath 2017 Oral medications including clomiphene citrate or aromatase inhibitors with gonadotrophins for controlled ovarian stimulation in women undergoing in vitro fertilisation	10/1/2017	27 RCTs	3599 (22 trials) Subfertile women undergoing ART	Regimens including oral induction medication (e.g. clomiphene citrate, aromatase inhibitors	Gonadotrophin-only regimens for controlled ovarian hyperstimulation	Live birth Miscarriage Ectopic pregnancy Foetal abnormality Ongoing pregnancy Cancellation	Live birth reported in only 5 trials. Most RCTs had suboptimal methods and poor reporting

Table 1. Review characteristics *(Continued)*

				such as letrozole)		OHSS	
AWP1710 Pouwer 2015 Long-acting FSH versus daily FSH for women undergoing assisted reproduction	8/6/15	6 RCTs	3753 women with subfertility	Long-acting FSH	Daily FSH	Live birth Ongoing pregnancy Clinical pregnancy OHSS Multiple pregnancy Miscarriage Adverse events Satisfaction	Some RCTs limited by attrition bias and serious imprecision
MHM931 Mochtar 2017 Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles	9/06/2016	36 RCTs	8125 women with subfertility	Recombinant luteinising hormone plus recombinant follicle-stimulating hormone	Recombinant follicle-stimulating hormone	Live birth Adverse events Ongoing pregnancy Miscarriage Amount of rFSH used Serum oestradiol used Number of oocytes retrieved	Main limitations were risk of bias (associated with poor reporting of methods) and imprecision
IOK973 van Wely 2011 Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproduction 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	Most trials were open-label
WPM1780 Martins 2013	5/2/13	5 RCTs	351 women undergoing COH for ART	Low-dose human chorionic go-	Follicle-stimulating hormone	Live birth OHSS	Only 2 studies reported live births; both were at high

Table 1. Review characteristics *(Continued)*

FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for assisted reproductive techniques				nadotrophin in the late follicular phase	throughout controlled ovarian hyperstimulation	Ongoing pregnancy Clinical pregnancy Miscarriage Total dose of FSH used Oocytes retrieved	risk of attrition bias. Imprecision was due to small overall sample size
DHH752 Farquhar 2017 Oral contraceptive pill, progestogen or oestrogen pre- treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques	16/1/2017	29 RCTs	4701 women with subfertility	COCP Progesterone oestrogen	Placebo or no treatment COCP Progesterone Oestrogen	Live birth Ongoing pregnancy Clinical/ongoing pregnancy Oocytes retrieved Gonadotrophin treatment Pregnancy loss Ovarian cyst formation Multiple pregnancies OHSS	Main limitations were risk of bias and imprecision. Most studies did not describe their methods in adequate detail
BKT841 Kalampokas 2017 Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI	10/10/2016	4 RCTs	416 women with subfertility undergoing IVF or ICSI	Systemic glucocorticoids	Placebo or no treatment	Live birth Clinical pregnancy Miscarrige OHSS Steroidal side effects	Risk of bias and imprecision, with small sample sizes and few events
SL1977 Lensen 2018 Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI)	27/7/17	20 RCTs	6088 women undergoing IVF/ICSI	Higher dose of FSH in women with predicted level of response ORT algorithm for	Lower dose of FSH in women with predicted level of response No ORT algorithm	Live birth or ongoing pregnancy Severe OHSS Moderate or severe OHSS	Clinical heterogeneity, imprecision, and risk of bias associated with lack of blinding

Table 1. Review characteristics *(Continued)*

				FSH dose selection	(use of standard dose)		
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 births, study methods were inadequately described, and serious imprecision was noted
4.3. Interventions for poor responders							
RSS791 Pandian 2010 Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF)	16/03/2009	10 RCTs	625 women considered to be 'poor responders' to COH in IVF treatment	Stop protocol GnRHa protocol GnRHa flare-up protocol GnRH antagonist Low-dose GnRHa flare-up protocol Multiple-dose GnRH antagonist Flare-up protocol Long protocol	Long protocol GnRHa flare-up protocol Spontaneous natural cycle IVF Mini-dose long agonist protocol Modified long protocol	Live birth per woman Clinical pregnancy per woman Ongoing pregnancy per woman Miscarriage Ectopic pregnancy Cancellation Oocytes retrieved Dose of gonadotrophins Total FSH used	Live birth was reported in only 1 trial. Methodological limitations included limited blinding and poor reporting as to how missing data were addressed

Table 1. Review characteristics *(Continued)*

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 Multiple pregnancy Lack of embryos for cryopreservation Cycle cancellation Gestational abnormalities Cancellation of treatment Cost-effectiveness	Few studies, live birth reported in only 1 very small trial. Clinical heterogeneity, as study inclusion criteria differed
5. Ovulation triggering							
MM1690 Youssef 2014 Gonadotropin-releasing hormone agonist versus hCG for oocyte triggering in antagonist assisted reproductive technology cycles	8/9/2014	17 RCTs	1847 women undergoing ART	GnRHa	hCG	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage OHSS	Poor reporting of study methods, serious imprecision
HA413 Youssef 2016a	23/4/2015	18 RCTs	2952 women un-	Recombinant hCG	Urinary hCG	Live birth OHSS	Only 6 of 14 trials reported

Table 1. Review characteristics *(Continued)*

Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF/ICSI cycles			dergoing ART	Recombinant hLH		Clinical pregnancy Miscarriage Oocytes retrieved Tolerance	live birth. Four trials lacked adequate description of allocation concealment, randomisation, and blinding
6. Oocyte retrieval							
IG1250 Reavey 2016 Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation	29/8/2016	4 RCTs	522 women undergoing in vitro maturation for subfertility	Human chorionic gonadotrophin (hCG) priming before immature oocyte retrieval	Placebo or no intervention	Live birth Miscarriage Clinical pregnancy Drug reaction Adverse events Mature oocytes retrieved/fertilised Embryos cleaved/implanted	Lack of blinding, serious imprecision
IOK971 Kwan 2018 Pain relief for women undergoing oocyte retrieval for assisted reproduction	9/11/2017	24 RCTs	3160 women undergoing transvaginal oocyte retrieval during IVF treatment	Conscious sedation and analgesia (CSA) CSA + paracervical block (PCB) Patient-controlled CSA	Placebo CSA + acupuncture CSA + electroacupuncture General anaesthesia Spinal anaesthesia Electroacupuncture + PCB PCB alone	Pain Patient satisfaction Live birth Ongoing pregnancy Clinical pregnancy	Evidence was generally of low quality, mainly because of poor reporting of methods, small sample sizes, and inconsistency between trials. Only 1 study reported live birth

Table 1. Review characteristics *(Continued)*

					Physician-controlled CSA Differing doses of CSA		
SW811 Georgiou 2018 Follicular flushing during oocyte retrieval in assisted reproductive techniques	18/7/2017	10 RCTs	928 women undergoing ART	Follicular flushing	Aspiration alone	Live birth Clinical pregnancy Ongoing pregnancy Oocyte retrieval Adverse events Duration of procedure Pain	Quality of evidence ranged from moderate to very low. Limitations were associated with risk of bias, imprecision, and inconsistency
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 azo-ospermia	Epididymal or testicular techniques for sperm retrieval	Epidydymal or testicular techniques for sperm retrieval	Pregnancy Sperm parameters Fertilisation	No live birth reported. Based on single RCT with poor methods
SMD1810 McDowell 2014 Advanced sperm selection techniques for assisted reproduction	26/5/2014	2 RCTS	581 couples undergoing ART	Sperm selection by hyaluronic acid binding for ICSI	Conventional ICSI Comparison of different hyaluronic acid binding techniques	Live birth Pregnancy Miscarriage	Only 1 study reported live birth. Poor reporting of study methods in 1 study, data discrepancy and serious imprecision in 1 study
8. Laboratory phase							

Table 1. Review characteristics *(Continued)*

DG1352 Glujovsky 2014 Vitrification versus slow freezing for women undergoing oocyte cryopreservation	3/3/14	2 RCTs	106 women undergoing ART and wishing to preserve oocytes	Vitrification	Slow freezing	Clinical pregnancy Ongoing pregnancy	Failure to report live birth, serious imprecision
MWS391 Carney 2012 Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI))	8/8/12	31 RCTs	5728 women undergoing ART	Assisted hatching	No assisted hatching	Live birth Multiple pregnancy Clinical pregnancy Miscarriage Ectopic pregnancy Monozygotic twinning Congenital or chromosomal abnormalities Failure to transfer any embryos Embryo damage In vitro blastocyst development	Few studies described adequate allocation concealment, and 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 3 trials reported on live birth outcomes, and methodological details were unclear in 6 trials

Table 1. Review characteristics *(Continued)*

						Implantation Embryo development Cryopreservation	
SMA991 Twisk 2006 Preimplantation genetic screening for abnormal number 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 pre-implantation genetic screening	IVF/ICSI with no pre-implantation genetic screening	Live birth Clinical pregnancy Multiple pregnancy Miscarriage Ongoing pregnancy Congenital abnormalities	Six of the 9 trials were open-label and provided other methodological details that 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	Only 3 of 8 trials gave information on how randomisation was achieved, and all described unclear methods of allocation concealment. No studies reported live birth
WPM1800 Teixeira 2013 Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	8/5/13	9 RCTs	2014 couples undergoing ART	IMSI	ICSI	Live birth Clinical pregnancy Miscarriage Congenital abnormalities	Only 1 trial reported live birth. Issues such as risk of bias (differences between numbers of oocytes transferred), imprecision, and strong suspicion of publication bias
SCA1950 Armstrong 2015	17/11/14	3 RCTs	994 women undergoing ART	TIme-lapse systems	Conventional embryo incubation	Live birth Miscarriage	Evidence limited by methodological weak-

Table 1. Review characteristics *(Continued)*

Time-lapse systems for embryo incubation and assessment in assisted reproduction						Clinical pregnancy Cumulative clinical pregnancy	nesses, imprecision, and indirectness
MM1610 Youssef 2015 Culture media for human pre-implantation embryos in assisted reproductive technology cycles	27/3/2015	32 RCTs	Over 3666 women undergoing ART	Specific culture medium	Alternative culture medium	Live birth Health of babies born Clinical pregnancy Multiple pregnancy Miscarriage Implantation Cryopreservation Embryo quality Fertilisation	Imprecision and risk of bias, with poor reporting of study methods
CS1968 Siristatidis 2018 Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies	24/11/2016	4 RCTs	802 women undergoing ART	Metabolomic assessment of endometrium, oocytes, or embryos	Other type of assessment (e.g. morphology grading)	Live birth or ongoing pregnancy Miscarriage Clinical pregnancy Other adverse events	Limitations included serious risk of bias (associated with poor reporting of methods, attrition bias, selective reporting, and other biases), imprecision, and inconsistency across trials
9. Embryo transfer							
9.1. Developmental stage							
DB551 Glujovsky 2016 Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology	4/4/2016	27 RCTs	4031 women undergoing ART	Cleavage-stage transfer	Blastocyst-stage transfer	Live birth Clinical pregnancy Multiple pregnancy Miscarriage Embryo freezing	Main limitation was serious risk of bias, associated with failure to describe acceptable methods of ran-

Table 1. Review characteristics *(Continued)*

						Failure to have a transfer Cumulative pregnancy	domisation and unclear or high risk of attrition bias
9.2. Number of embryos							
CO266 Brown 2016 Day three versus day two embryo transfer following in vitro fertilization or intracytoplasmic sperm injection	26/4/2016 Review is considered to be stable, with no update planned	15 RCTs	2894 (14 RCTs) couples undergoing ART	Day 3 embryo transfer	Day 2 embryo transfer	Live birth Ongoing pregnancy Clinical pregnancy Complications Multiple pregnancy Miscarriage Ectopic pregnancy Foetal abnormalities Women's evaluation	Main limitations were poor methodological reporting, selective reporting, inconsistency, and imprecision
ZP661 Pandian 2013 Number of embryos for transfer following in-vitro fertilisation or intracytoplasmic sperm injection	17/07/2012	14 RCTs	2165 couples undergoing ART	Single-embryo transfer Double-embryo transfer	Double-embryo transfer Three-embryo transfer Four-embryo transfer	Live birth Pregnancy Multiple pregnancy Miscarriage	Many of the included studies were small, with half enroling fewer than 60 participants. Clinical heterogeneity between studies was considerable, but evidence of statistical heterogeneity was scant for most analyses. Methodological quality of the studies was mixed

Table 1. Review characteristics *(Continued)*

9.3. Transfer techniques and procedures

BA1920 Ata 2018 Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI, and frozen embryo transfer)	10/10/2017	11 RCTs	3215 women undergoing ART	Seminal plasma to genital tract during the period starting 5 days before embryo transfer and ending 2 days after it	No seminal plasma application	Live birth Miscarriage Live birth or ongoing pregnancy Clinical pregnancy Multiple pregnancy Ectopic pregnancy Infection Adverse events	Quality of the evidence ranged from very low to low. Main limitations were risk of bias (associated with poor reporting of allocation concealment and other methods) and imprecision for the primary outcome of live birth rate
DB552 Bontekoe 2014 Adherence compounds in embryo transfer media for assisted reproductive technologies	13/11/2013	17 RCTs	3898 women undergoing ART	Embryo transfer media enriched with adherence compounds (hyaluronic acid or fibrin sealant)	Embryo transfer media devoid of, or with a low dose of, such adherence compounds	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Implantation Adverse events	Some methodological limitations and serious imprecision were noted
SV602 Derks 2009 Techniques for preparation prior to embryo transfer	18/03/2009	10 RCTs	1693 women (9 RCTs) undergoing IVF	Straightening of the utero-cervical angle Cervical and endometrial preparation Dummy transfer	No intervention or no treatment	Live birth Clinical pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy Adverse events - pain/infection	Only 1 trial reported live birth, and most included trials inadequately explained methodological procedures

Table 1. Review characteristics *(Continued)*

				Embryo afterloading			
EN1382 Kroon 2012 Antibiotics prior to embryo transfer in ART	23/11/2011	1 RCT	350 women undergoing ART	Antibiotics	No treatment	Bacterial contamination of catheter Clinical pregnancy	Analysis of bacterial contamination was not performed for all participants
JB604 Brown 2016a Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women	6/5/2015	21 RCTs	6711 women with any form of infertility undergoing ART	Ultrasound-guided transfer	Clinical touch transfer	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy Foetal abnormalities Complications Ease of transfer	High heterogeneity and poor reporting of methodological detail
AAS605 Abou-Setta 2014 Post-embryo transfer interventions for assisted reproduction technology cycles	19/6/14	4 RCTs	1392 women with subfertility of any cause	Bed rest Bladder emptying Mechanical pressure on cervix Fibrin sealant	Different duration of bed rest No intervention	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy Adverse events – pain Subjective experience	Live birth not reported, lack of blinding
LC1966 Craciunas 2016	10/11/2015	12 RCTs	4038 subfertile women	Intra-cavity hCG before embryo transfer	Placebo or no intervention	Live birth Miscarriage Clinical pregnancy	High risk of bias, serious imprecision

Table 1. Review characteristics *(Continued)*

Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction					Alternative intervention	Complications	
10. Luteal phase support							
MV263 van der Linden 2015 Luteal phase support for ART cycles	25/11/2014	94 RCTs	26,198 women with any cause of subfertility undergoing ART	Progesterone hCG	Placebo or no treatment hCG Progesterone + oestrogen Progesterone + GnRH agonist	Live birth Clinical pregnancy Ongoing pregnancy Miscarriage OHSS Multiple pregnancy	Poor reporting of study methods and imprecision due to small sample sizes
CMB1261 Boomsma 2012 Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	20/09/2011	14 RCTs	1879 couples with subfertility of any cause undergoing ART	Glucocorticoids	No glucocorticoids Placebo	Live birth Ongoing pregnancy Pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy OHSS Implantation	Only 3 trials reported live birth, lack of blinding, and poor reporting
MA1441 Akhtar 2013 Heparin for assisted reproduction	6/5/2013	3 RCTs	386 subfertile women undergoing ART	Heparin	Placebo No treatment	Live birth Adverse effects Clinical pregnancy Multiple pregnancy Maternal complications Foetal complications	Only 3 small RCTs, 1 of which did not adequately describe allocation concealment. High heterogeneity reflecting differing participant

Table 1. Review characteristics *(Continued)*

							inclusion criteria
11. Prevention of ovarian hyperstimulation syndrome (OHSS)							
TH1338 Tang 2016 Dopamine agonists for preventing ovarian hyperstimulation syndrome	15/8/2016	16 RCTs	2091 women at high risk of OHSS undergoing ART	Cabergoline Quinagolide Bromocriptine	Placebo/no treatment Other treatment	OHSS Live birth Miscarriage Clinical pregnancy Multiple miscarriage Adverse events	Poor reporting of study methods (mostly lack of details on randomisation or blinding) and serious imprecision for some comparisons
ADA56 D'Angelo 2017 Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	6/07/2016 Review is considered to be stable, with no update planned	8 RCTs	702 women at high risk of OHSS	Coasting when oestradiol levels were > 2500 pg/mL or > 9000 pmol/L	No coasting Early unilateral follicular aspiration Gonadotrophin-releasing hormone antagonist Follicle-stimulating hormone co-trigger Cabergoline	OHSS Live birth Clinical pregnancy Multiple pregnancy Miscarriage Number of oocytes retrieved	Main limitations were failure to report live birth, risk of bias due to lack of information about study methods, and imprecision due to low event rates and lack of data. Four of the studies were published only as abstracts and provided limited data
ADA561 D'Angelo 2007 Embryo freezing for preventing ovarian hyperstimulation syndrome	26/11/2010 Review is considered to be stable and will not	2 RCTs	151 women down-regulated by GnRHa, undergoing superovulation in	Cryopreservation	Fresh embryo transfer Intravenous albumin	OHSS Clinical pregnancy Live birth Admissions	Evidence based on 2 trials, 1 for each comparison Live birth reported in only 1 trial Seriouis

Table 1. Review characteristics *(Continued)*

	be updated again		IVF and or ICSI cycles				risk of bias in both trials
PMA481 Youssef 2016 Volume expanders for the prevention of ovarian hyperstimulation syndrome	2/11/15	9 RCTs	1867 women with controlled ovarian hyperstimulation and at risk of severe OHSS	Human albumin Hydroxyethyl starch Mannitol	Placebo	OHSS Clinical pregnancy	Imprecision, poor reporting of study methods, and failure to blind outcome assessment
12. Frozen embryo replacement cycles							
KMW1790 Wong 2017 Fresh versus frozen embryo transfers in assisted reproduction	14/11/2016	4 RCTs	1892 women undergoing IVF or ICSI	Freeze-all strategy	Conventional IVF/ICSI strategy with transfer of fresh and subsequently frozen-thawed embryos	Cumulative live birth OHSS Clinical pregnancy Time to pregnancy Multiple pregnancy Miscarriage Pregnancy complications Birth weight Congenital disorders	Serious risk of bias: unclear blinding of investigators for preliminary outcomes of the study, unit of analysis error, and absence of adequate study termination rules Serious imprecision for some outcomes
TG691 Ghobara 2017 Cycle regimens for frozen- thawed embryo transfer (FET)	13/12/2016	18 RCTs	3815 women with a range of causes of subfertility	Natural cycle FET Modified natural cycle FET HT FET Subtypes of ovulation induction FET using	Other regimens	Live birth per woman Clinical pregnancy per woman Ongoing pregnancy per woman Multiple pregnancy Cycle cancellation Miscarriage Endometrial thickness	Failure to report important clinical outcomes, poor reporting of study methods, imprecision due to low event rates. No data were specific to non-ovulatory women

Table 1. Review characteristics *(Continued)*

				clomiphene, hMG, and/or FSH			
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 No detail on causes of infertility was provided	Corticosteroids Low-dose aspirin GnRHa Intramuscular progesterone Day of start of progesterone Artificial cycle hCG before retrieval	No treatment GnRHa Vaginal progesterone Day of start of progesterone Non-artificial cycle Placebo	Live birth Clinical pregnancy Multiple pregnancy Cancelled cycle rates Endometrial thickness Pregnancy loss	Only 8 trials reported adequate details of allocation concealment. Only 1 trial reported on blinding

ART: assisted reproduction technology.
COCP: combined oral contraceptive pill.
COH: controlled ovarian hyperstimulation.
CSA: conscious sedation and analgesia.
E_2: oestrogen.
FET: frozen-thawed embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
hCG: human chorionic gonadotrophin.
hLH: human luteinising hormone.
hMG: human menopausal gonadotrophin.
HT: hormone therapy.
ICSI: intracytoplasmic sperm injection.
IMSI: ultra-high magnification sperm selection.
IVF: in vitro fertilisation.
IU: international units.
N/A: not applicable.
OHHS: ovarian hyperstimulation syndrome.

ORT: ovarian reserve test.
PCB: paracervical block.
PGS: pre-implantation genetic screening.
RCT: randomised controlled trial.
rFSH: recombinant follicle-stimulating hormone.
rLH: recombinant luteinising hormone.

Table 2. AMSTAR assessment

Review no.	First review author	Review title	AMSTAR criteria
			Preu-ontieplsatuide Po- spdplieteofaquali- ten- i- catieni-teri-cmotdal fiedsidydodsbytibofdfor qusesteedticasbypubcon- tidesearof sedpied flict antdon exin- proa- of inand cldudprtiorin- clda- eded atteiaster- sion stsdudietest crieix- ieies odsid-ad- tetrac- de- ered/essed riation scribed
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 2017	Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	# # # # # # # # # #
AM1335	Kamath 2017	Oral medications including clomiphene citrate or aromatase inhibitors with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilisation	# # # # # # # # # #
AMVP611	Proctor 2008	Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia	# # # # # # # # # #
AMY731	Yossry 2006	In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation	# # # # # N/A N/A N/A N/A #
AWP1710	Pouwer 2015	Long-acting FSH versus daily FSH for women undergoing assisted reproduction	# # # # # # # # # #

Table 2. AMSTAR assessment *(Continued)*

BA1920	Ata 2018	Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI, and frozen embryo transfer)	# # # # # # # # # # #
BKT841	Kalampokas 2017	Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI	# # # # # # # # # # #
CMB1261	Boomsma 2012	Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	# # # # # # # # # # #
CO266	Brown 2016	Day three versus day two embryo transfer following in vitro fertilization or intracytoplasmic sperm injection	# # # # # # # # # # #
CS1400	Siristatidis 2009	In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction	# # # # # N/A N/A N/A N/A #
CS1968	Siristatidis 2018	Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies	# # # # # # # # # # #
DB551	Glujovsky 2016	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	# # # # # # # # # # #
DG1352	Glujovsky 2014	Vitrification versus slow freezing for women undergoing oocyte cryopreservation	# # # # # # # # # # #
DHH752	Farquhar 2017	Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques	# # # # # # # # # # #
EN1382	Kroon 2012	Antibiotics prior to embryo transfer in ART	# # # # # # # # # # #
HA412	Al-Inany 2016	Gonadotrophin-releasing hormone antagonists for assisted reproductive technology	# # # # # # # # # # #
HA413	Youssef 2016a	Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF/ICSI cycles	# # # # # # # # # # #
HEN1730	Nagels 2015	Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction	# # # # # # # # # # #
HNS881	Sallam 2006	Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis	# # # # # # # # x #

Table 2. AMSTAR assessment *(Continued)*

IG1250	Reavey 2016	Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation	# # # # # # # # # #
IOK971	Kwan 2018	Pain relief for women undergoing oocyte retrieval for assisted reproduction	# # # # # # # # # #
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	# # # # # # # # # #
IRS911	Cheong 2013	Acupuncture and assisted reproductive technology	# # # # # # # # # #
JB604	Brown 2016a	Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women	# # # # # # # # # #
KA992	Anderson 2010	Pre-conception lifestyle advice for people with subfertility	# # # # # # # # # #
KH291	Duffy 2010	Growth hormone for in vitro fertilization	# # # # # # # # x #
KMW1790	Wong 2017	Fresh versus frozen embryo transfers in assisted reproduction	# # # # # # # # # #
LA541	Albuquerque 2013	Depot versus daily administration of gonadotrophin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles	# # # # # # # # # #
LC1966	Craciunas 2016	Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction	# # # # # # # # # #
LDT1201	Tso 2014	Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome	# # # # # # # # # #
MA1441	Akhtar 2013	Heparin for assisted reproduction	# # # # # # # # # #
MM1610	Youssef 2015	Culture media for human pre-implantation embryos in assisted reproductive technology cycles	# # # # # # # # # #
MGS1510	Showell 2014	Antioxidants for male subfertility	# # # # # # # # # #
MGS1630	Showell 2017	Antioxidants for female subfertility	# # # # # # # # # #
MHM931	Mochtar 2017	Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles	# # # # # # # # # #
MM1690	Youssef 2014	Gonadotropin-releasing hormone agonist versus hCG for oocyte triggering in antagonist assisted reproductive technology cycles	# # # # # # # # # #

Table 2. AMSTAR assessment *(Continued)*

MV263	van der Linden 2015	Luteal phase support in ART cycles	######### #
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	######### #
PMA481	Youssef 2016	Volume expanders for the prevention of ovarian hyperstimulation syndrome	######### #
RBG1760	Gutarra-Vilchez 2014	Vasodilators for women undergoing fertility treatment	######### #
RSS791	Pandian 2010	Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF)	######### #
SB1283	Bontekoe 2012	Low oxygen concentrations for embryo culture in assisted reproductive technologies	######### #
SCA1950	Armstrong 2015	Time-lapse systems for embryo incubation and assessment in assisted reproduction	########x #
SD265	Siristatidis 2015	Gonadotropin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive technology cycles	######### #
SG1241	Benschop 2010	Interventions for women with endometrioma prior to assisted reproductive technology	######### #
SH1141	McDonnell 2014	Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility	######### #
SL1977	Lensen 2018	Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI)	#########
SMA991	Twisk 2006	Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection	######### #
SMD1810	McDowell 2014	Advanced sperm selection techniques for assisted reproduction	######### #

Table 2. AMSTAR assessment *(Continued)*

SV602	Derks 2009	Techniques for preparation prior to embryo transfer	# # # # # # # # # #
SW811	Georgiou 2018	Follicular flushing during oocyte retrieval in assisted reproductive techniques	# # # # # # # # # #
TA1860	Allersma 2013	Natural cycle IVF for subfertile couples	# # # # # # # # # #
TG691	Ghobara 2017	Cycle regimens for frozen-thawed embryo transfer	# # # # # # # # # #
TH1338	Tang 2016	Dopamine agonists for preventing ovarian hyperstimulation syndrome	# # # # # # # # # #
VJP951	Siristatidis 2016	Aspirin for in vitro fertilisation	# # # # # # # # # #
WM1504	Nastri 2015	Endometrial injury in women undergoing assisted reproductive techniques	# # # # # # # # # #
WPM1780	Martins 2013	FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for assisted reproductive techniques	# # # # # # # # # #
WPM1800	Teixeira 2013	Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	# # # # # # # # # #
ZH1093	Huang 2013	Brief co-incubation of sperm and oocytes for in vitro fertilization techniques	# # # # # # # # # #
ZP661	Pandian 2013	Number of embryos for transfer following in-vitro fertilisation or intracytoplasmic sperm injection	# # # # # # # # # #
ZP672	Pandian 2015	In vitro fertilisation for unexplained subfertility	# **x** # # # # # # # #

ART: assisted reproduction techniques.
COH: controlled ovarian hyperstimulation.
FSH: follicle-stimulating hormone.
hCG: human chorionic gonadotrophin.
ICSI: intracytoplasmic sperm injection.
IVF: in vitro fertilisation.
IMSI: ultra-high magnification sperm selection.
N/A: not applicable.
rFSH: recombinant follicle-stimulating hormone.
rLH: recombinant luteinising hormone.

Table 3. Latest search date assessment

Review no.	First review author	Review title	< 3 years since last search (to May 2018) or deemed stable
AAS605	Abou-Setta 2014	Post-embryo transfer interventions for assisted reproduction technology cycles	x
ADA561	D'Angelo 2007	Embryo freezing for preventing ovarian hyperstimulation syndrome	Stable
ADA563	D'Angelo 2017	Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	Stable
AM1335	Kamath 2017	Clomiphene citrate for controlled ovarian stimulation in women undergoing in vitro fertilization	#
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	Stable
AWP1710	Pouwer 2015	Long-acting FSH versus daily FSH for women undergoing assisted reproduction	#
BA1920	Ata 2018	Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI, and frozen embryo transfer)	#
BKT841	Kalampokas 2017	Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI	#
CMB1261	Boomsma 2012	Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	x
CO266	Brown 2016	Day three versus day two embryo transfer following in vitro fertilization or intracytoplasmic sperm injection	Stable
CS1400	Siristatidis 2009	In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction	Stable
CS1968	Siristatidis 2018	Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies	#
DB551	Glujovsky 2016	Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology	#
DB552	Bontekoe 2014	Adherence compounds in embryo transfer media for assisted reproductive technologies	x
DG1351	Glujovsky 2010	Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes	x

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

DG1352	Glujovsky 2014	Vitrification versus slow freezing for women undergoing oocyte cryopreservation	x
DHH752	Farquhar 2017	Oral contraceptive pill, progestogen or oestrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques	#
EN1382	Kroon 2012	Antibiotics prior to embryo transfer in ART	x
HA412	Al-Inany 2016	Gonadotrophin-releasing hormone antagonists for assisted reproductive technology	x
HA413	Youssef 2016a	Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF/ICSI cycles	x
HEN1730	Nagels 2015	Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction	x
HNS881	Sallam 2006	Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis	x
IG1250	Reavey 2016	Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation	#
IOK971	Kwan 2018	Pain relief for women undergoing oocyte retrieval for assisted reproduction	#
IOK972	Kwan 2014	Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)	x
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	x
JB604	Brown 2016a	Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women	#
KA992	Anderson 2010	Pre-conception lifestyle advice for people with subfertility	x
KH291	Duffy 2010	Growth hormone for in vitro fertilization	x
KMW1790	Wong 2017	Fresh versus frozen embryo transfers in assisted reproduction	#
LA541	Albuquerque 2013	Depot versus daily administration of gonadotrophin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles	x
LC1966	Craciunas 2016	Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction	#
LDT1201	Tso 2014	Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome.	x
MA1441	Akhtar 2013	Heparin for assisted reproduction	x
MGS1510	Showell 2014	Antioxidants for male subfertility	x
MGS1630	Showell 2017	Antioxidants for female subfertility	#

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

MHM931	Mochtar 2017	Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles	#
MM1610	Youssef 2015	Culture media for human pre-implantation embryos in assisted reproductive technology cycles	x
MM1690	Youssef 2014	Gonadotropin-releasing hormone agonist versus hCG for oocyte triggering in antagonist assisted reproductive technology cycles	x
MV263	van der Linden 2015	Luteal phase support in ART cycles	#
MVR461	Van Rumste 2003	Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility	Stable
MWS391	Carney 2012	Assisted hatching on assisted conception (IVF and ICSI)	x
NJ472	Johnson 2010	Surgical treatment for tubal disease in women due to undergo in vitro fertilisation	x
PMA481	Youssef 2016	Volume expanders for the prevention of ovarian hyperstimulation syndrome	Stable
RBG1760	Gutarra-Vilchez 2014	Vasodilators for women undergoing fertility treatment	x
RSS791	Pandian 2010	Interventions for 'poor responders' to controlled ovarian hyperstimulation (COH) in in-vitro fertilisation (IVF)	x
SB1283	Bontekoe 2012	Low oxygen concentrations for embryo culture in assisted reproductive technologies	x
SCA1950	Armstrong 2015	Time-lapse systems for embryo incubation and assessment in assisted reproduction	x
SD265	Siristatidis 2015	Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction	x
SG1241	Benschop 2010	Interventions for women with endometrioma prior to assisted reproductive technology	x
SH1141	McDonnell 2014	Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility	x
SL1977	Lensen 2018	Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI)	#
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	x
SV602	Derks 2009	Techniques for preparation prior to embryo transfer	x

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

SW811	Georgiou 2018	Follicular flushing during oocyte retrieval in assisted reproductive techniques	#
TA1860	Allersma 2013	Natural cycle IVF for subfertile couples	x
TG691	Ghobara 2017	Cycle regimens for frozen-thawed embryo transfer	#
TH1338	Tang 2016	Dopamine agonists for preventing ovarian hyperstimulation syndrome	#
VJP951	Siristatidis 2016	Aspirin for in vitro fertilisation	Stable
WM1504	Nastri 2015	Endometrial injury in women undergoing assisted reproductive techniques	#
WPM1780	Martins 2013	FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for assisted reproductive techniques	x
WPM1800	Teixeira 2013	Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	x
ZH1093	Huang 2013	Brief co-incubation of sperm and oocytes for in vitro fertilization techniques	x
ZP661	Pandian 2013	Number of embryos for transfer following in-vitro fertilisation or intracytoplasmic sperm injection	x
ZP672	Pandian 2015	In vitro fertilization for unexplained subfertility	#

ART: assisted reproduction techniques.
COH: controlled ovarian hyperstimulation.
FSH: follicle-stimulating hormone.
hCG: human chorionic gonadotrophin.
ICSI: intracytoplasmic sperm injection.
IVF: in vitro fertilisation.
IMSI: ultra-high magnification sperm selection.
N/A: not applicable.
rFSH: recombinant follicle-stimulating hormone.
rLH: recombinant luteinising hormone.

Table 4. Live birth or live birth/ongoing pregnancy per woman

Outcome Intervention and comparison intervention	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
1. Indication for ART						
Pandian 2015 IVF vs expectant management for unexplained subfertility Live birth	37 per 1000	458 per 1000 (90 to 879)	OR 22 (2.56 to 189.37)	51 (1 RCT)	Very low	Very serious imprecision, questionable applicability, and (for the analysis of clinical pregnancy) serious inconsistency
Pandian 2015 IVF vs unstimulated intra-uterine insemination for unexplained subfertility Live birth	160 per 1000	320 per 1000 (185 to 494)	OR 2.47 (1.19 to 5.12)	156 (2 RCTs)	Low	Very serious imprecision
Pandian 2015 IVF vs intra-uterine insemination + ovarian stimulation with gonadotrophins for unexplained subfertility (treatment naïve women) Live birth	273 per 1000	308 per 1000 (264 to 360)	OR 1.27 (0.94 to 1.73)	745 (4 RCTs)	Moderate	Serious imprecision with wide confidence interval
Pandian 2015 IVF vs intra-uterine insemination + ovarian stimulation with gonadotrophins for unexplained subfertility (pre-treated women) Live birth	219 per 1000	523 per 1000 (374 to 731)	OR 3.90 (2.32 to 6.57)	280 (1 RCT)	Moderate	Serious imprecision (only 9 events)
2. Pre-ART and adjuvant strategies						
2.1. For unselected populations						

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Nastri 2015 *See comment Endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no injury Live birth or ongoing pregnancy	260 per 1000	342 per 1000 (281 to 481)	RR 1.42 (1.08 to 1.85)	1496 (9 RCTs)	Moderate	Serious imprecision
Nastri 2015 *See comment Endometrial injury on the day of oocyte retrieval vs no injury Live birth or ongoing pregnancy	290 per 1000	90 per 1000	RR 0.31 (0.14 to 0.69)	156 (1 RCT)	Low	Very serious imprecision
Showell 2014 Antioxidant vs placebo or no treatment for men Live birth	100 per 1000	286 per 1000 (124 to 533)	Peto OR 3.61 (1.27 to 10.29)	90 (2 RCTs)	Low	Very serious imprecision, with only 90 participants and 25 events
Showell 2017 Antioxidant vs placebo or no treatment for women Live birth	305 per 1000	347 per 1000 (232to 481)	OR 1.21 (0.69 to 2.11)	230 (4 RCTs)	Very low	Very serious risk of bias and very serious imprecision
Cheong 2013 Acupuncture vs no acupuncture on the day of embryo transfer Live birth	281 per 1000	323 per 1000 (254 to 399)	OR 1.22 (0.87 to 1.7)	2505 (8 RCTs)	Low	Imprecision, inadequate explanation of methods, high statistical heterogeneity (I^2 = 69%)
Cheong 2013 Acupuncture vs no acupuncture around the time of oocyte retrieval Live birth	357 per 1000	326 per 1000 (247 to 418)	OR 0.87 (0.59 to 1.29)	464 (2 RCTs)	Low	Imprecision, inadequate explanation of methods, high statistical heterogeneity (I^2 = 69%)
Duffy 2010 Growth hormone vs placebo	146 per 1000	184 per 1000 (64	OR 1.32 (0.4 to 4.43)	80 (2 RCTs)	Moderate	Serious imprecision

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Live birth		to 431)				
Duffy 2010 Growth hormone vs placebo – poor responders Live birth	50 per 1000	221 per 1000 (90 to 447)	OR 5.39 (1.89 to 15.35)	165 (4 RCTs)	Moderate	Some studies did not provide an adequate explanation of randomisation and/or allocation concealment
Gutarra-Vilchez 2014 Vasodilator compared with placebo Live birth	236 per 1000	278 per 1000 (193 to 398)	RR 1.18 (0.82 to 1.69)	350 (3 RCTs)	Moderate	Studies had low or unclear risk of bias but serious imprecision
Siristatidis 2016 Aspirin vs placebo or no treatment Live birth	225 per 1000	204 per 1000 (162 to 258)	RR 0.91 (0.72 to 1.15)	1053 (3 RCTs)	Moderate	Serious imprecision with low event rates
Nagels 2015 DHEA vs placebo or no treatment Live birth or ongoing pregnancy	116 per 1000	192 per 1000 (141 to 256)	OR 1.81 (1.25 to 2.62)	878 (8 RCTs)	Moderate	Serious imprecision with low event rates
Nagels 2015 Testosterone vs placebo or no treatment Live birth or ongoing pregnancy	82 per 1000	188 per 1000 (104 to 317)	OR 2.6 (1.3 to 5.2)	345 (4 RCTs)	Moderate	Serious imprecision with low event rates
2.2. For selected populations						
Tso 2014 Metformin vs placebo or no treatment Live birth	320 per 1000	395 per 1000 (276 to 530)	OR 1.39 (0.81 to 2.40)	551 (5 RCTs)	Low	Serious inconsistency with unexplained heterogeneity (I^2 = 52%). Serious imprecision, as total events are fewer than 300. Data discrepancy in 1 study: sensitivity analysis excluding this RCT yielded an OR of 1.48 (95% CI 0.72 to 3.02) for live birth
3. Down-regulation with agonists or antagonists						

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Albuquerque 2013 GnRHa depot vs daily injection Live birth or ongoing pregnancy	24 per 100	23 per 100 (181 to 292)	OR 0.95 (0.7 to 1.31)	873 (7 RCTs)	Low	Most studies were classified as at unclear risk of bias for all domains. Serious imprecision, as total events were fewer than 300
Al-Inany 2016 GnRH antagonist vs long course GnRH agonist Live birth	286 per 1000	290 per 1000 (254 to 330)	OR 1.02 (0.85 to 1.23)	2303 (12 RCTs)	Moderate	Asymmetrical funnel plot with small study effects in favour of GnRH antagonist
Siristatidis 2015 Long vs short protocol for pituitary suppression Live birth or ongoing pregnancy	138 per 1000	172 per 1000 (131 to 225)	OR 1.3 (0.94 to 1.81)	976 (12 RCTs)	Low	Poor reporting of methods and serious imprecision, with wide confidence intervals
Siristatidis 2015 Long vs ultra-short protocol for pituitary suppression Live birth or ongoing pregnancy	122 per 1000	198 per 1000 (91 to 376)	OR 1.78 (0.72 to 4.36)	150 (1 RCT)	Low	Poor reporting of methods and serious imprecision, with wide confidence intervals
Siristatidis 2015 Long luteal phase protocol vs long follicular phase protocol for pituitary suppression Live birth or ongoing pregnancy	102 per 1000	177 per 1000 (90 to 319)	OR 1.89 (0.87 to 4.1)	223 (1 study)	Low	Poor reporting of methods and serious imprecision, with wide confidence intervals
Siristatidis 2015 Long protocol continued GnRH agonist vs long protocol stop GnRH agonist for pituitary suppression Live birth or ongoing pregnancy	76 per 1000	222 per 1000 (138 to 336)	OR 0.75 (0.42 to 1.33)	290 (3 studies)	Low	Poor reporting of methods and serious imprecision, with wide confidence intervals
Siristatidis 2015 Long protocol (GnRHa until hCG) compared with long protocol (ex-	378 per 1000	351 per 1000 (229 to 499)	OR 0.89 (0.49 to 1.64)	181 (1 study)	Low	Very serious imprecision: small number of events and wide confidence intervals

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

tend GnRHa 12 days after hCG) for pituitary suppression Live birth or ongoing pregnancy						
4. Ovarian stimulation						
4.1. Medication type						
Kamath 2017 Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population Live birth	235 per 1000	216 per 1000 (155 to 299)	RR 0.92 (0.66 to 1.27)	493 (4 RCTs)	Low	Serious imprecision with wide confidence intervals. Method of allocation concealment inadequately reported in some trials
Kamath 2017 Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in poor responders Live birth	49 per 1000	57 per 1000 (24 to 137)	RR 1.16 (0.49 to 2.79)	357 (2 RCTs)	Low	Serious imprecision with wide confidence intervals. Method of allocation concealment inadequately reported in some trials
Pouwer 2015 Long acting FSH (any dose) vs daily FSH Live birth	347 per 1000	330 per 1000 (273 to 348)	RR 0.95 (0.84 to 1.07)	2363 (5 RCTs)	Moderate	Two studies at high risk of attrition bias
Pouwer 2015 Long-acting FSH (low dose) vs daily FSH Live birth	352 per 1000	246 per 1000 (183 to 327)	RR 0.70 (0.52 to 0.93)	645 (4 RCTs)	Moderate	Serious imprecision, with low event rate

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Pouwer 2015 Long-acting FSH (medium dose) vs daily FSH Live birth	255 per 1000	263 per 1000 (229 to 301)	RR 1.03 (0.9 to 1.18)	1685 (3 RCTs)	Moderate	Two studies at high risk of attrition bias
Pouwer 2015 Long-acting FSH (high dose) vs daily FSH Live birth	375 per 1000	161 per 1000 (45 to 570)	RR 0.43 (0.12 to 1.52)	33 (1 RCT)	Very low	Serious imprecision due to very low event rate, plus high risk of attrition bias
Mochtar 2017 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) vs rFSH alone for controlled ovarian hyperstimulation Live birth	173 per 1000	217 per 1000 (151 to 302)	OR 1.32 (0.85 to 2.06)	499 (4 RCTs)	Very low	Imprecision, with wide confidence intervals. Serious risk of bias in certain domains such as random sequence generation and allocation concealment. Serious inconsistency (I^2 > 50%)
van Wely 2011 rFSH vs urinary gonadotrophins Live birth or ongoing pregnancy	237 per 1000	232 per 1000 (213 to 251)	OR 0.97 (0.87 to 1.08)	7339 (28 RCTs)	High	Lack of blinding
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase vs continued FSH for assisted reproductive techniques Live birth	140 per 1000	220 per 1000 (100 to 450)	RR 1.56 (0.75 to 3.25)	130 (2 RCTs)	Very low	Very serious imprecision and high risk of bias
Farquhar 2017 Combined oral contraceptive plus antagonist vs antagonist Live birth or ongoing pregnancy	270 per 1000	215 per 1000 (177 to 260)	OR 0.74 (0.58 to 0.95)	1335 (6 RCTs)	Moderate	Poor reporting of sequence generation and allocation concealment
Farquhar 2017	296 per 1000	273 per 1000 (212 to 345)	OR 0.89	724 (4 RCTs)	Moderate	Serious imprecision with wide confidence intervals

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Combined oral contraceptive plus antagonist vs agonist Live birth or ongoing pregnancy			(0.64 to 1.25)			
Farquhar 2017 Progestogen plus agonist vs agonist Live birth or ongoing pregnancy	170 per 1000	217 per 1000 (124 to 352)	OR 1.35 (0.69 to 2.65)	222 (2 RCTs)	Low	Very serious imprecision with wide confidence intervals
Farquhar 2017 Progestogen plus antagonist vs antagonist Live birth or ongoing pregnancy	292 per 1000	217 per 1000 (69 to 512)	OR 0.67 (0.18 to 2.54)	47 (1 RCT)	Low	Very serious imprecision with wide confidence intervals
Farquhar 2017 Oestrogen plus antagonist vs antagonist Live birth or ongoing pregnancy	299 per 1000	252 per 1000 (184 to 333)	OR 0.79 (0.53 to 1.17)	502 (2 RCTs)	Moderate	Serious imprecision with wide confidence intervals
Farquhar 2017 Oestrogen plus antagonist vs agonist Live birth or ongoing pregnancy	350 per 1000	322 per 1000 (215 to 447)	OR 0.88 (0.51 to 1.5)	242 (2 RCTs)	Very low	Poor reporting of methods; very serious imprecision with wide confidence intervals
Kalampokas 2017 Glucocorticoid supplementation vs placebo Live birth	147 per 1000	157 per 1000 (72 to 308)	OR 1.08 (0.45 to 2.58)	212 (2 RCTs)	Low	Very serious imprecision with few events and wide confidence intervals
Lensen 2018 ORT-based algorithm vs standard dose FSH Live birth or ongoing pregnancy	258 per 1000	266 per 1000 (235 to 300)	OR 1.04 (0.88 to 1.23)	2823 (4 RCTs)	Moderate	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated low responders Live birth or ongoing pregnancy 1. 300/450 IU vs 150 IU 2. 400/450 IU vs 300 IU 3. 600 IU vs 450 IU	1. 109 per 1000	80 per 1000 (38 to 162)	OR 0.71 (0.32 to 1.58)	286 (2 RCTs)	Low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events	
	2. 161 per 1000	129 per 1000 (35 to 380)	OR 0.77 (0.19 to 3.19)	62 (1 RCT)			
	3. 108 per 1000	139 per 1000 (79 to 234)	OR 1.33 (0.71 to 2.52)	356 (1 RCT)			
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated normal responders Live birth or ongoing pregnancy 1. 200 IU vs 100 IU 2. 225/200 IU vs 150 IU 3. 300 IU vs 225 IU	1. 204 per 1000	184 per 1000 (127 to 258)	OR 0.88 (0.57 to 1.36)	522 (2 RCTs)	Low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events	
	2. 193 per 1000	198 per 1000 (120 to 308)	OR 1.03 (0.57 to 1.86)	277 (1 RCT)			
	3. 397 per 1000	300 per 1000 (174 to 465)	OR 0.65 (0.32 to 1.32)	135 (1 RCT)			
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated high responders Live birth or ongoing pregnancy 150 IU vs 100 IU	255 per 1000	251 per 1000 (184 to 333)	OR 0.98 (0.66 to 1.46)	521 (1 RCT)	Low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events	
4.3. Interventions for poor responders							
Pandian 2010 Low-dose GnRHa flare-up vs spontaneous natural cycle IVF Live birth	85 per 1000	86 per 1000 (26 to 245)	OR 1.01 (0.29 to 3.5)	129 (1 RCT)	Low	Serious imprecision, evidence based on a single trial	
4.4. Natural cycle IVF							

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Allersma 2013 Natural cycle vs standard IVF Live birth	125 per 1000	28 per 1000 (1 to 393)	OR 0.20 (0.01 to 4.54)	30 (1 RCT)	Very low	High risk of performance bias and very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist vs hCG Live birth	313 per 1000	176 per 1000 (124 to 242)	OR 0.47 (0.31 to 0.70)	532 (5 RCTs)	Moderate	One study at high risk of bias because of premature termination, substantial heterogeneity, with I^2 = 56%
Youssef 2016a rhCG vs uhCG Live birth or ongoing pregnancy	367 per 1000	396 per 1000 (344 to 454)	OR 1.15 (0.89 to 1.49)	1136 (7 RCTs)	Moderate	Serious imprecision
Youssef 2016a rhLH vs uhCG Live birth or ongoing pregnancy	371 per 1000	359 per 1000 (231 to 512)	OR 0.95 (0.51 to 1.78)	289 (2 studies)	Very low	Poor reporting of study methods, very serious imprecision
6. Oocyte retrieval						
Reavey 2016 hCG priming vs no priming Live birth	310 per 1000	226 per 1000 (97 to 439)	OR 0.65 (0.24 to 1.74)	82 (1 RCT)	Low	Serious risk of bias, serious imprecision
Kwan 2018 Conscious sedation and analgesia plus paracervical block vs electroacupuncture plus paracervical block Live birth	176 per 1000	334 per 1000 (184 to 601)	OR 2.35 (1.09 to 5.05)	149 (1 RCT)	Low	Evidence based on a single trial, serious imprecision
Georgiou 2018 Follicular flushing vs aspiration alone	414 per 1000	401 per 1000 (290 to 524)	OR 0.95 (0.58 to 1.56)	303 (3 RCTs)	Moderate	Serious risk of bias: includes at least 1 open-label study

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Live birth

7. Sperm retrieval						
McDowell 2014 HA culture dish (PICSI) compared with viscous medium containing HA (SpermSlow) for infertility requiring intracytoplasmic sperm injection Live birth	300 per 1000	350 per 1000 (190 to 550)	RR 1.16 (0.65 to 2.05)	99 (1 RCT)	Low	Serious risk of bias, as RCT methods not reported in adequate detail Serious imprecision, as confidence intervals compatible with substantial benefit or harm from the intervention, or with no effect
8. Laboratory phase						
Carney 2012 Assisted hatching vs no assisted hatching Live birth	305 per 1000	311 per 1000 (271 to 356)	OR 1.03 (0.85 to 1.26)	1921 (9 RCTs)	Moderate	Many trials had some methodological limitations or missing information
Bontekoe 2012 Embryo culture with low oxygen concentrations vs atmospheric oxygen concentration Live birth	309 per 1000	383 per 1000 (332 to 440)	OR 1.39 (1.11 to 1.76)	1291 (3 RCTs)	Moderate	One trial reported no allocation concealment, and another trial was unclear about the method of allocation concealment
Twisk 2006 Pre-implantation genetic screening vs no screening in women with advanced age Live birth	259 per 1000	171 per 1000 (133 to 221)	OR 0.59 (0.44 to 0.81)	1062 (5 RCTs)	Moderate	Only 1 study described an adequate method of allocation concealment
Twisk 2006 Pre-implantation genetic screening vs no screening in women with repeated IVF failure Live birth	Not calculated		OR 0.41 (0.20 to 0.88)	139 (1 RCT)	Very low	No allocation concealment, serious imprecision with few events

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Twisk 2006 Pre-implantation genetic screening vs no screening in women with good prognosis Live birth	416 per 1000	263 per 1000 (130 to 461)	OR 0.5 (0.21 to 1.2)	388 (3 RCTs)	Very low	Methodological details unclear or inadequate; high heterogeneity, with I^2 > 60% and serious imprecision
Teixeira 2013 Regular (ICSI) vs ultra-high magnification (IMSI) sperm selection Live birth	380 per 1000	440 per 1000 (300 to 630)	RR 1.14 (0.79 to 1.64)	168 (1 RCT)	Low	Serious imprecision
Armstrong 2015 TLS with or without cell-tracking algorithms vs conventional incubation for embryo incubation in assisted reproduction Live birth	500 per 1000	526 per 1000 (310 to 732)	OR 1.11 (0.45 to 2.73)	76 (1 RCT)	Moderate	Serious imprecision with small sample size and wide confidence intervals
Youssef 2015 Early embryo transfer - GM501 vs ISMI Live birth	264 per 1000	270 per 1000 (160 to 422)	OR 1.03 (0.53 to 2.03)	172 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision
Youssef 2015 Early embryo transfer - GM501 vs Sydney IVF Live birth	188 per 1000	167 per 1000 (81 to 311)	OR 0.87 (0.38 to 1.96)	158 (1 RCT)	Low	Serious risk of bias with poor reporting of study methods, serious imprecision
Youssef 2015 Early embryo transfer - G2 vs Universal IVF Live birth	194 per 1000	269 per 1000 (139 to 457)	OR 1.53 (0.67 to 3.51)	129 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Youssef 2015 Early embryo transfer - Cook (K-SIFM or K-SICM) vs Vitrolife (IVF or G3) Live birth	220 per 1000	216 per 1000 (151 to 302)	OR 0.98 (0.63 to 1.54)	449 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision
Youssef 2015 Early embryo transfer - G2 vs Ham's F10 Live birth	579 per 1000	676 per 1000 (444 to 846)	OR 1.52 (0.58 to 3.99)	72 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision
Youssef 2015 Late embryo transfer - GM501 vs Sydney IVF Live birth	200 per 1000	143 per 1000 (7 to 778)	OR 0.67 (0.03 to 14.03)	12 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision
Youssef 2015 Late embryo transfer - G2 vs Universal IVF Live birth	148 per 1000	250 per 1000 (71 to 591)	OR 1.92 (0.44 to 8.31)	47 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision
Youssef 2015 Late embryo transfer - ECM/Multiblast vs Global Live birth	700 per 1000	538 per 1000 (318 to 746)	OR 0.50 (0.20 to 1.26)	79 (1 RCT)	Very low	Serious risk of bias with poor reporting of study methods, very serious imprecision
Siristatidis 2018 Metabolomic vs non-metabolomic assessment Live birth	296 per 1,000	294 per 1,000 (225 to 377)	OR 0.99 (0.69 to 1.44)	597 (3 RCTs)	Low	Serious risk of bias and serious imprecision
9. Embryo transfer						
9.1. Developmental stage						

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Glujovsky 2016 Blastocyst stage vs cleavage stage embryo transfer in assisted reproductive technology Live birth	286 per 1000	372 per 1000 (324 to 421)	OR 1.48 (1.20 to 1.82)	1630 (13 RCTs)	Low	Several studies did not describe acceptable methods of sequence generation and/or allocation concealment, several were at unclear or high risk of attrition bias, and none clearly reported blinded outcome assessment. Sensitivity analysis restricted to 5 studies with clear description of allocation concealment results in a non-significant effect (OR 1.38, 95% CI 0.96 to 1.99)
Brown 2016 Day 3 vs Day 2 embryo transfer Live birth	315 per 1000	331 per 1000 (280 to 387)	RR 1.05 (0.89 to 1.23)	1200 (3 RCTs)	Very low	All studies lacked details about blinding of participants, researchers, and outcome assessors, serious inconsistency. Only 3 of the 15 included studies reported live birth
9.2. Number of embryos						
Pandian 2013 Single-embryo transfer vs double (1 cycle only) Live birth	450 per 1000	282 per 1000 (242 to 329))	OR 0.48 (0.39 to 0.60)	1564 (9 RCTs)	High	36% of women were non-compliant with treatment allocation in 1 RCT: however no heterogeneity was detected (I^2 = 0%)
Pandian 2013 Repeated single-embryo transfer vs double-embryo transfer Live birth	420 per 1000	373 per 1000 (310 to 441)	OR 0.82 (0.62 to 1.09)	811 (3 RCTs)	Low	No studies described adequate allocation concealment, imprecision
Pandian 2013 Double-embryo transfer vs 3 embryo transfers Live birth	273 per 1000	130 per 1000 (33 to 410)	OR 0.4 (0.09 to 1.85)	45 (1 RCT)	Very low	Methods of randomisation and blinding unclear, evidence based on a single trial with very serious imprecision
Pandian 2013 Double-embryo transfer vs 4 embryo transfers	536 per 1000	288 per 1000 (113 to 548)	OR 0.35 (0.11 to 1.05)	56 (1 RCT)	Very low	Methods of randomisation and blinding unclear, evidence based on a single trial with very serious imprecision

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Live birth						
9.3. Transfer techniques and procedures						
Ata 2018 Seminal plasma to genital tract vs no seminal plasma Live birth	191 per 1000	210 per 1000 (164 to 273)	RR 1.10 (0.86 to 1.43)	948 (3 RCTs)	Low	Serious risk of bias: method of allocation concealment unclear in all included trials, serious imprecision
Bontekoe 2014 Transfer medium enriched with high level of hyaluronic acid vs medium with low level or no hyaluronic acid Live birth	374 per 1000	458 per 1000 (412 to 503)	OR 1.41 (1.17 to 1.69)	1950 (6 RCTs)	Moderate	All studies except 1 at high risk of bias in 1 or more domains
Brown 2016a Ultrasound guidance vs clinical touch for embryo transfer Live birth	210 per 1000	290 per 1000 (256 to 324)	OR 1.53 (1.29 to 1.80)	3117 (4 RCTs)	Low	Poor reporting of study methods, high inconsistency
Derks 2009 Cervical dilatation vs no intervention Live birth	190 per 1000	97 per 1000 (60 to 155)	OR 0.46 (0.27 to 0.78)	288 (1 RCT)	Moderate	Evidence based on a single trial
Craciunas 2016 Intrauterine hCG vs no intrauterine hCG; cleavage stage hCG < 500 IU Live birth	495 per 1000	376 per 1000 (287 to 500)	RR 0.76 (0.58 to 1.01)	280 (1 RCT)	Very low	Very serious risk of bias with poor reporting of methods and premature termination of study, imprecision
Craciunas 2016 Intrauterine hCG vs no intrauterine hCG; cleavage stage hCG ⩾ 500 IU Live birth	247 per 1000	388 per 1000 (326 to 462)	RR 1.57 (1.32 to 1.87)	914 (3 RCTs)	Moderate	Serious risk of bias: poor reporting of methods, lack of blinding

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Craciunas 2016 Intrauterine hCG vs no intrauterine hCG; blastocyst stage hCG ⩾ 500 IU Live birth	366 per 1000	337 per 1000 (293 to 381)	RR 0.92 (0.80 to 1.04)	1666 (2 RCTs)	Moderate	Serious risk of bias: poor reporting of methods, lack of blinding
10. Luteal phase support						
van der Linden 2015 hCG vs placebo/no treatment Live birth or ongoing pregnancy	120 per 1000	194 per 1000 (128 to 281)	OR 1.76 (1.08 to 2.86)	527 (3 RCTs)	Very low	Serious imprecision, inadequate reporting of methods, findings no longer significant when random-effects model used
van der Linden 2015 Progesterone vs placebo/no treatment Live birth or ongoing pregnancy	39 per 1000	66 per 1000 (42 to 103)	OR 1.77 (1.09 to 2.86)	642 (5 RCTs)	Very low	Serious imprecision, inadequate reporting of methods, findings no longer significant when restricted to live births
van der Linden 2015 Progesterone vs hCG regimens Live birth or ongoing pregnancy	198 per 1000	190 per 1000 (138 to 254)	OR 0.95 (0.65 to 1.38)	833 (5 RCTs)	Low	Serious imprecision, inadequate reporting of methods
van der Linden 2015 Progesterone vs progesterone + oestrogen Live birth or ongoing pregnancy	367 per 1000	393 per 1000 (345 to 444)	OR 1.12 (0.91 to 1.38)	1651 (9 RCTs)	Low	Serious imprecision, inadequate reporting of methods
van der Linden 2015 Progesterone vs progesterone + GnRH agonist Live birth or ongoing pregnancy	356 per 1000	255 per 1000 (209 to 309)	OR 0.62 (0.48 to 0.81)	2861 (9 RCTs)	Very low	Inadequate reporting of methods, serious inconsistency (I^2 = 69%). Only 3 studies reported live birth
Boomsma 2012 Peri-implantation glucocorticoids vs no glucocorticoids	115 per 1000	136 per 1000 (80 to 222)	OR 1.21 (0.67 to 2.19)	424 (3 RCTs)	Low	Lacked details around methods, serious imprecision

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Live birth						
Akhtar 2013 Heparin vs control or no heparin Live birth	173 per 1000	271 per 1000 (183 to 378)	OR 1.77 (1.07 to 2.90)	386 (3 RCTs)	Very low	Selection bias found in 1 RCT, high heterogeneity, results sensitive to choice of statistical model
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
D'Angelo 2007 Cryopreservation vs fresh embryo transfer Live birth	373 per 1000	380 per 1000 (229 to 558)	OR 1.03 (0.5 to 2.12)	125 (1 RCT)	Low	Evidence based on a single open-label RCT with insufficient methodological details provided, serious imprecision
D'Angelo 2017 Coasting vs no coasting Live birth	265 per 1000	148 per 1000 (48 to 369)	OR 0.48 (0.14 to 1.62)	68 (1 RCT)	Very low	Evidence based on a single conference abstract, serious imprecision, insufficient methodological details provided
Tang 2016 Dopamine agonist vs placebo or no intervention Live birth	509 per 1000	**512 per 1000** (355 to 665)	**OR 1.01** (0.53 to 1.91)	182 (1 RCT)	Low	Poor reporting of study methods, serious imprecision with wide confidence interval.
12. Frozen embryo replacement cycles						
Wong 2017 Frozen vs fresh and frozen transfer Cumulative live birth rate	579 per 1000	600 per 1000 (556 to 643)	OR 1.09 (0.91 to 1.31)	1892 (4 RCTs)	Moderate	Serious risk of bias associated with lack of power calculation (unclear what determined end of study) and/or use of interim analysis that was calculated per transfer (unit of analysis error) with absence of adequate stopping rules (possible overestimation of treatment effect)
Ghobara 2017 Natural cycle FET vs hormone therapy plus GnRHa suppression FET	316 per 1000	262 per 1000 (153 to 414)	OR 0.77 (0.39 to 1.53)	159 (1 RCT)	Low	Very serious imprecision: single study, few events, wide confidence intervals

Table 4. Live birth or live birth/ongoing pregnancy per woman *(Continued)*

Live birth						
Ghobara 2017 Natural cycle FET vs modified natural cycle FET (hCG trigger) Live birth	267 per 1000	167 per 1000 (55 to 413)	OR 0.55 (0.16 to 1.93)	60 (1 RCT)	Very low	High attrition rate, baseline characteristics unequal, very serious imprecision, with few events and wide confidence intervals
Ghobara 2017 Modified natural cycle FET (hCG trigger) vs hormone therapy FET Live birth	88 per 1000	114 per 1000 (78 to 165)	OR 1.34 (0.88 to 2.05)	959 (1 RCT)	Low	High attrition rate, unclear report of allocation concealment, serious imprecision with wide confidence interval
Ghobara 2017 Modified natural cycle FET (hCG trigger) vs hormone therapy + GnRHa FET Live birth	98 per 1000	423 per 1000 (304 to 553)	OR 1.11 (0.66 to 1.87)	236 (1 RCT)	Low	Unclear risk of bias in most domains, serious imprecision, wide confidence interval
Ghobara 2017 Hormone therapy FET vs hormone therapy + GnRHa FET Live birth	742 per 1000	223 per 1000 (103 to 463)	OR 0.10 (0.04 to 0.30)	75 (1 RCT)	Low	Serious imprecision, serious inconsistency (clinical pregnancy rate in this study higher than in 6 other studies in the same analysis, none of which reported live births)
Ghobara 2017 hMG FET vs clomiphene + hMG FET Live birth	84 per 1000	186 per 1000 (89 to 347)	OR 2.49 (1.07 to 5.80)	209 (1 RCT)	Very low	Unclear risk of bias in all domains, very serious imprecision, few events, confidence interval compatible with benefit in the hMG-only group or with no clinically meaningful effect

ART: assisted reproduction techniques.
CI: confidence interval.
COH: controlled ovarian hyperstimulation.
DHEA: dehydroepiandrosterone.
ET: embryo transfer.
FET: frozen embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.

GnRHa: gonadotrophin-releasing hormone agonist.
HA: hyaluronic acid.
hCG: human chorionic gonadotrophin.
hLH: human luteinising hormone.
hMG: human menopausal gonadotrophin.
HT: hormone therapy.
ICSI: intracytoplasmic sperm injection.
IU: international units.
IV: intravenous.
IVF: in vitro fertilisation.
N/A: not applicable.
OHSS: ovarian hyperstimulation syndrome.
OR: odds ratio.
ORT: ovarian reserve test.
PCB: paracervical block.
PICSI: physiological intracytoplasmic sperm injection.
RCT: randomised controlled trial.
rFSH: recombinant follicle-stimulating hormone.
rhCG: recombinant human chorionic gonadotrophin.
rhLH: recombinant human luteinising hormone.
RR: risk ratio.
TLS: time-lapse imaging.
uhCG: urinary human chorionic gonadotrophin.

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 2015 IVF vs expectant management for unexplained subfertility	127 per 1000	320 per 1000 (135 to 588)	OR 3.24 (1.07 to 9.8)	86 (2 RCTs)	Very low	Very serious imprecision, questionable applicability, and serious inconsistency
Pandian 2015 IVF vs 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 RCTs)	Moderate	Trials lacked adequate methodological details
2. Pre-ART and adjuvant strategies						
2.1. For unselected populations						
Nastri 2015 Endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no injury	211 per 1000	298 per 1000 (386 to 480)	RR 1.34 (1.12 to 1.61)	1972 (13 RCTs)	Moderate	Serious imprecision
Nastri 201 Endometrial injury on the day of oocyte retrieval vs no injury	330 per 1000	120 per 1000	RR 0.36 (0.18 to 0.71)	156 (1 RCT)	Low	Very serious imprecision
Showell 2014 Antioxidant vs placebo or no treatment for men	150 per 1000	318 per 1000 (142 to 567)	2.64 (0.94 to 7.41)	90 (2 RCTs)	Low	Very serious imprecision with only 90 participants and 28 events, confidence intervals cross line of no effect
Showell 2017 Antioxidant vs placebo or no treatment for women	316 per 1000	355 per 1000 (312 to 398)	OR 1.19 (0.98 to 1.43)	2263 (15 RCTs)	Very low	Very serious risk of bias, serious imprecision
Showell 2017 Pentoxifylline vs placebo or no treatment for women	393 per 1000	571 per 1000 (386 to 739)	OR 2.06 (0.97 to 4.38)	112 (1 RCT)	Very low	Questionable applicability: study table refers to male infertility in 51 of 112 participants, very serious imprecision
Duffy 2010 Growth hormone compared with placebo	273 per 1000	401 per 1000	OR 1.78 (0.49 to 6.5)	42 (1 RCT)	Moderate	Evidence based on a single trial, serious imprecision

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

		(155 to 709)				
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 RCTs)	High	Adequate description of methods, no evidence of imprecision or heterogeneity
Gutarra-Vilchez 2014 Vasodilator compared with placebo	274 per 1000	340 per 1000 (274 to 526)	RR 1.38 (1.00 to 1.92)	717 (8 RCTs)	Low	Low or unclear risk of bias but very serious risk of imprecision
Siristatidis 2016 Aspirin vs placebo or no treatment	337 per 1000	347 per 1000 (307 to 395)	RR 1.03 (0.91 to 1.17)	2142 (10 RCTs)	Low	Half of studies failed to report sufficient detail about study methods
Cheong 2013 Acupuncture vs 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 RCTs)	Very low	Only 3/14 studies described adequate allocation concealment, serious heterogeneity (I^2 = 66%), and serious imprecision
Cheong 2013 Acupuncture vs 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 RCTs)	Low	Inadequate description of study methods, serious imprecision
Nagels 2015 DHEA vs placebo or no treatment	208 per 1000	260 per 1000 (210 to 316)	OR 1.34 (1.01 to 1.76)	1246 (12 RCTs)	Moderate	Serious imprecision with low event rates
Nagels 2015 DHEA vs placebo or no treatment	115 per 1000	247 per 1000 (150 to 378)	OR 2.52 (1.36 to 4.68)	345 (4 RCTs)	Moderate	Serious imprecision with low event rates
2.2. For selected populations						
Johnson 2010 Salpingectomy vs no surgical treatment	189 per 1000	359 per 1000 (258 to 441)	OR 2.2 (1.26 to 3.82)	329 (3 RCTs)	Moderate	No evidence of blinding in any trials. Heterogeneity: I^2 = 52%
Johnson 2010 Tubal occlusion vs no surgical treatment	123 per 1000	396 per 1000 (234 to 585)	OR 4.66 (2.17 to 10.01)	209 (2 RCTs)	Moderate	Randomisation methods not fully described

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

Johnson 2010 Aspiration of hydrosalpingeal fluid vs no surgical treatment	188 per 1000	313 per 1000 (125 to 592)	OR 1.97 (0.62 to 6.29)	64 (1 RCT)	Very low	Evidence based on a single trial with serious imprecision
Benschop 2010 Aspiration of endometrioma vs expectant management before ART	200 per 1000	244 per 1000 (101 to 476)	Peto OR 1.29 (0.45 to 3.64)	81 (1 RCT)	Low	Serious imprecision: evidence based on a single trial; wide confidence intervals cross line of no effect
Benschop 2010 Cystectomy of endometrioma vs expectant management before ART	317 per 1000	348 per 1000 (194 to 542)	Peto OR 1.15 (0.52 to 2.55)	109 (1 RCT)	Low	Serious imprecision: evidence based on a single trial; wide confidence intervals cross line of no effect
Benschop 2010 GnRH antagonist vs GnRH before ART	242 per 1000	206 per 1000 (77 to 448)	Peto OR 0.81 (0.26 to 2.54)	67 (1 RCT)	Low	Serious imprecision: evidence based on a single trial; wide confidence intervals cross line of no effect
Benschop 2010 Ablation vs cystectomy before ART	366 per 1000	293 per 1000 (126 to 545)	Peto OR 0.72 (0.25 to 2.08)	65 (1 RCT)	Very low	Unclear risk of bias related to sequence generation Serious imprecision: single small RCT, wide confidence intervals cross line of no effect
Tso 2014 Metformin vs 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 RCTs)	Moderate	Serious imprecision: total events fewer than 300. Data discrepancy in 1 study. However, sensitivity analysis excluding this study did not substantially change findings
McDonnell 2014 Ovarian cyst aspiration before in vitro fertilisation treatment for subfertility	62 per 1000	72 per 1000 (21 to 220)	OR 1.19 (0.33 to 4.29)	159 (2 RCTs)	Very low	Neither of the studies adequately described methods of randomisation and allocation concealment Very serious imprecision, with wide confidence intervals and very low event rates
3. Down-regulation with agonists or antagonists						

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

Albuquerque 2013 GnRHa depot vs daily injection	30 per 1000	29 per 1000 (25 to 35)	OR 0.96 (0.75 to 1.23)	1259 (11 RCTs)	Moderate	Most studies classified as at unclear risk of bias for all domains
Al-Inany 2016 GnRH antagonist vs long course GnRH agonist	303 per 1000	283 per 1000 (267 to 303)	OR 0.91 (0.83 to 1)	9959 (54 RCTs)	Moderate	Serious risk of bias
Sallam 2006 Ultra-long GnRH agonist vs conventional stimulation protocols	Not calculated	Not calculated	OR 4.28 (2.00 to 9.15)	149 (3 RCTs)	Very low	All trials subject to methodological limitations; outcome was an intermediate outcome; evidence of lack of precision Possible unit of analysis error; review being updated
Siristatidis 2015 Long vs short protocol for pituitary suppression	137 per 1000	192 per 1000 (158 to 232)	OR 1.5 (1.18 to 1.9)	1643 (20 studies)	Moderate	Poor reporting of methods
Siristatidis 2015 Long vs ultra-short protocol for pituitary suppression	161 per 1000	230 per 1000 (133 to 370)	OR 1.56 (0.8 to 3.06)	230 (2 RCTs)	Low	Poor reporting of methods, serious imprecision with wide confidence intervals
Siristatidis 2015 Short vs ultra-short protocol for pituitary suppression	195 per 1000	244 per 1000 (102 to 480)	OR 1.33 (0.47 to 3.81)	82 (1 RCT)	Very low	Unclear applicability (participants were poor responders), very serious imprecision with few events and wide confidence intervals
Siristatidis 2015 Long luteal phase vs long follicular phase protocol for pituitary suppression	269 per 1000	281 per 1000 (219 to 351)	OR 1.06 (0.76 to 1.47)	750 (5 studies)	Low	Poor reporting of methods, serious imprecision with wide confidence intervals
Siristatidis 2015 Long protocol continued GnRH agonist vs long protocol stop GnRH agonist for pituitary suppression	235 per 1000	207 per 1000 (135 to 302)	OR 0.85 (0.51 to 1.41)	360 (4 studies)	Low	Poor reporting of methods, serious imprecision with wide confidence intervals
Siristatidis 2015 Long protocol (continued same vs reduced dose GnRHa) for pituitary suppression	377 per 1000	382 per 1000 (292 to 479)	OR 1.02 (0.68 to 1.52)	407 (4 studies)	Low	Poor reporting of methods, imprecision with wide confidence intervals
Siristatidis 2015 Long protocol (GnRHa until hCG) compared with long protocol (extend GnRHa	489 per 1000	494 per 1000 (353 to 636)	OR 1.02 (0.57 to 1.83)	181 (1 study)	Low	Very serious imprecision, few events and wide confidence intervals

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

12 days after hCG) for pituitary suppression						
Siristatidis 2015 Long protocol: administration of GnRHa for 2 vs 3 weeks before stimulation for pituitary suppression	585 per 1000	568 per 1000 (355 to 757)	OR 0.93 (0.39 to 2.21)	85 (1 study)	Low	Poor reporting of methods, serious imprecision with wide confidence intervals
Siristatidis 2015 Short protocol compared with stop short protocol for pituitary suppression	226 per 1000	147 per 1000 (81 to 255)	OR 0.59 (0.3 to 1.17)	230 (1 study)	Low	Poor reporting of methods, serious imprecision with wide confidence intervals
4. Ovarian stimulation						
4.1. Medication type						
Kamath 2017 Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population	248 per 1000	248 per 1000 (213 to 288)	RR 1.00 (0.86 to 1.16)	1998 (12 RCTs)	Moderate	In some included trials, method of allocation concealment not adequately described or not mentioned at all
Kamath 2017 Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in poor responders	128 per 1000	109 per 1000 (82 to 143)	RR 0.85 (0.64 to 1.12)	1462 (8 RCTs)	Low	In some included trials, method of allocation concealment not adequately described or not mentioned at all; serious imprecision
Mochtar 2017 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) vs rFSH alone for controlled ovarian hyperstimulation	274 per 1000	282 to 367 per 1000	OR 1.18 (1.03 to 1.34	5071 (23 RCTs)	Moderate	Some trials lacked sufficient methodological details
van Wely 2011 rFSH vs urinary gonadotrophins	282 per 1000	280 per 1000 (263 to 299)	OR 0.99 (0.91 to 1.09)	9482 (41 RCTs)	Moderate	No evidence that blinding was conducted in most studies
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase vs continued FSH for assisted reproductive techniques	350 per 1000	410 per 1000 (320 to 540)	RR 1.19 (0.92 to 1.55	351 (5 RCTs)	Low	Serious imprecision and high risk of bias
Farquhar 2017 Combined oral contraceptive plus agonist vs agonist	333 per 1000	373 per 1000 (209 to 571)	OR 1.19 (0.53 to 2.66)	102 (1 RCT)	Very low	Serious imprecision: single RCT with wide confidence intervals that crossed the line of no effect

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

Farquhar 2017 Combined oral contraceptive plus antagonist vs antagonist	255 per 1000	191 per 1000 (146 to 248)	OR 0.69 (0.5 to 0.96)	847 (4 RCTs)	Low	Serious imprecision and serious risk of bias
Farquhar 2017 Combined oral contraceptive plus antagonist vs agonist	245 per 1000	210 per 1000 (147 to 290)	OR 0.82 (0.53 to 1.26)	472 (3 RCTs)	Low	Serious imprecision; 1 study did not describe satisfactory method of sequence generation, 2 did not describe satisfactory method of allocation concealment, and 1 was at high risk of attrition bias
Kalampokas 2017 Glucocorticoid supplementation vs placebo	236 per 1000	343 per 1000 (233 to 473)	OR 1.69 (0.98 to 2.90)	310 (2 RCTs)	Low	Very serious imprecision (few events, wide confidence interval)
Lensen 2018 ORT-based algorithm vs standard dose FSH	321 per 1000	313 per 1000 (280 to 349)	OR 0.96 (0.82 to 1.13)	2823 (4 RCTs)	Moderate	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated low responders 1. 300/450 IU vs 150 IU 2. 400/450 IU vs 300 IU 3. 600 IU vs 450 IU	1. 184 per 1000	101 per 1000 (53 to 184)	OR 0.50 (0.25 to 1.00)	286 (2 RCTs)	Low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events
	2. 127 per 1000	109 per 1000 (37 to 282)	OR 0.84 (0.26 to 2.69)	110 (2 RCTs)		
	3. 159 per 1000	177 per 1000 (111 to 274)	OR 1.14 (0.66 to 1.99)	356 (1 RCT)		
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated normal responders 1. 200 IU vs 100 IU 2. 225/200 IU vs 150 IU 3. 300 IU vs 225 IU	1. 202 per 1000	179 per 1000 (113 to 274)	OR 0.86 (0.73 to 1.31)	330 (1 RCT)	Low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events
	2. 236 per 1000	232 per 1000 (184 to 288)	OR 0.98 (0.75 to 1.33)	1037 (5 RCTs)		
	3. 441 per 1000	418 per 1000 (266 to 587)	OR 0.91 (0.46 to 1.80)	135 (1 RCT)		
Lensen 2018	275 per 1000	301 per 1000	OR 1.14 (0.78 to 1.66)	521 (1 RCT)	Low	Serious risk of bias associated mainly with performance

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

Higher-dose FSH vs lower-dose FSH in anticipated high responders 150 IU vs 100 IU		(228 to 386)				bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events
4.2. Monitoring						
Kwan 2014 Ultrasound + oestradiol vs ultrasound only	337 per 1000	361 per 1000 (287 to 439)	OR 1.05 (0.79 to 1.54)	617 (4 RCTs)	Low	Methods of allocation concealment inadequately described in the 4 trials. None of these trials adequately described blinding. Serious imprecision with wide confidence intervals
4.3. Interventions for poor responders						
Pandian 2010 Cessation of GnRHa on stop protocol vs conventional GnRHa long protocol	176 per 1000	138 per 1000 (43 to 370)	OR 0.75 (0.21 to 2.74)	70 (1 RCT)	Low	Evidence based on a single trial with no blinding
Pandian 2010 GnRH antagonist vs conventional GnRHa long protocol	67 per 1000	167 per 1000 (34 to 529)	OR 2.8 (0.5 to 15.73)	60 (1 RCT)	Very low	Evidence based on a single trial with lack of methodological detail and serious imprecision
Pandian 2010 GnRHa flare-up vs GnRHa long protocol	286 per 1000	77 per 1000 (16 to 304)	OR 0.21 (0.04 to 1.09)	54 (1 RCT)	Very low	Evidence based on a single trial with lack of methodological detail and serious imprecision
Pandian 2010 GnRH antagonist vs GnRHa flare-up protocol	163 per 1000	163 per 1000 (62 to 363)	OR 1 (0.34 to 2.92)	98 (2 RCTs)	Low	Lack of methodological details and serious imprecision
Pandian 2010 Low-dose GnRHa flare-up protocol vs spontaneous natural cycle IVF	119 per 1000	101 per 1000 (35 to 252)	OR 0.83 (0.27 to 2.5)	129 (1 RCT)	Low	Evidence based on a single trial with lack of methodological detail and serious imprecision
Pandian 2010 Multiple-dose GnRH agonist vs mini-dose long agonist protocol	244 per 1000	227 per 1000 (99 to 439)	OR 0.91 (0.34 to 2.42)	89 (1 RCT)	Low	No allocation concealment or blinding, evidence based on a single trial with serious imprecision

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

Pandian 2010 Flare-up protocol vs modified long protocol	381 per 1000	142 per 1000 (36 to 429)	OR 0.27 (0.06 to 1.22)	42 (1 RCT)	Low	Evidence based on a single trial with serious imprecision
Pandian 2010 Long protocol vs modified long protocol	381 per 1000	105 per 1000 (18 to 398)	OR 0.19 (0.03 to 1.06)	40 (1 RCT)	Low	Evidence based on a single trial with serious imprecision
4.4. Natural cycle IVF						
Allersma 2013 Natural cycle vs standard IVF	112 per 1000	86 per 1000 (36 to 194)	OR 0.75 (0.3 to 1.91)	219 (3 RCTs)	Low	1/3 studies did not report adequate allocation concealment, risk of performance bias; serious imprecision with wide confidence intervals
5. Ovulation triggering						
Youssef 2014 GnRH agonist vs hCG Outcome = ongoing pregnancy rather than clinical pregnancy	256 per 1000	194 per 1000 (157 to 238)	OR 0.7 (0.54 to 0.91)	1198 (11 RCTs)	Low	Substantial heterogeneity: I^2 = 59% to 66%. 5/11 studies at high risk of bias because of early termination and/or inadequate allocation concealment. No studies clearly reported blinded outcome assessment
Youssef 2016a rhCG vs uhCG	330 per 1000	343 per 1000 (300 to 388)	OR 1.06 (0.87 to 1.29)	1806 (13 studies)	Moderate	Serious imprecision
Youssef 2016a rhLH vs uhCG	407 per 1000	392 per 1000 (270 to 530)	OR 0.94 (0.54 to 1.64)	289 (2 studies)	Very low	Poor reporting of study methods, very serious imprecision
6. Oocyte retrieval						
Reavey 2016 hCG priming vs no priming	225 per 1000	131 per 1000 (70 to 230)	OR 0.52 (0.26 to 1.03)	282 (2 RCTs	Low	Serious risk of bias, serious imprecision
Kwan 2018 Conscious sedation and analgesia (CSA) vs CSA + electro-acupuncture	594 per 1000	243 per 1000 (95 to 491)	OR 0.22 (0.07 to 0.66)	61 (1 RCT)	Very low	Serious risk of bias and very serious imprecision with only 1 small RCT
Kwan 2018	344 per 1000	242 per 1000	OR 0.61	61 (1 RCT)	Very low	Serious risk of bias and very serious im-

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

Conscious sedation and analgesia (CSA) vs CSA + acupuncture		(95 to 493)	(0.20 to 1.86)			precision with only 1 small RCT
Kwan 2018 Conscious sedation and analgesia vs general anaesthesia	278 per 1000	278 per 1000 (142 to 475)	OR 1.00 (0.43 to 2.35)	108 (2 RCTs)	Very low	Serious risk of bias and very serious imprecision
Kwan 2018 Conscious sedation and analgesia (CSA) + paracervical block vs general anaesthesia	375 per 1000	296 per 1000	OR 0.70 (0.22 to 1.26	50 (1 RCT)	Very low	Serious risk of bias and very serious imprecision with only 1 small RCT
Kwan 2018 Conscious sedation and analgesia + paracervical block vs spinal anaesthesia	375 per 1000	358 per 1000	OR 0.93 (0.24 to 3.65)	38 (1 RCT)	Very low	Serious risk of bias and very serious imprecision with only 1 small RCT
Kwan 2018 Conscious sedation and analgesia (CSA) + paracervical block vs paracervical block only	253 per 1000	240 per 1000	OR 0.93 (0.44 to 1.96)	150 (1 RCT)	Very low	Very serious imprecision with only 1 RCT
Kwan 2018 Conscious sedation and analgesia (CSA) + paracervical block vs electro-acupuncture + paracervical block	367 per 1000	358 per 1000	OR 0.96 (0.72 to 1.29)	783 (4 RCTs)	Low	Serious risk of bias with serious inconsistency
Kwan 2018 Conscious sedation and analgesia (CSA) + paracervical block vs paracervical block	253 per 1000	240 per 1000 (130 to 399)	OR 0.93 (0.44 to 1.96)	150 (1 RCT)	Low	Very serious imprecision
Kwan 2018 Conscious sedation and analgesia: patient-controlled vs physician-controlled	182 per 1000	168 per 1000	OR 0.91 (0.45 to 1.83)	218 (2 RCTs)	Moderate	Adequate methods, low heterogeneity, suboptimal sample size
Georgiou 2018 Follicular flushing vs aspiration alone	362 per 1000	378 per 1000 (307to 453)	OR 1.07 (0.78 to 1.46)	704 (5 RCTs)	Moderate	Seroius risk of bias: includes at least 1 open-label study
7. Sperm retrieval						
Proctor 2008 Microsurgical epididymal sperm aspiration vs 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 RCT)	Low	Evidence based on a single trial with insufficient methodological detail
McDowell 2014 Conventional sperm selection vs hyaluronan sperm selection (HA-ICSI)	470 per 1000	480 per 1000	RR 0.99 (0.82 to 1.20)	482 (1 RCT)	Low	Serious risk of bias with discrepancy in reporting of pregnancy losses. Serious

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

		(390 to 570)				imprecision as confidence intervals compatible with substantial benefit or harm from the intervention, or with no effect
McDowell 2014 HA culture dish (PICSI) compared with viscous medium containing HA (SpermSlow) for infertility requiring intracytoplasmic sperm injection	400 per 1000	430 per 1000 (250 to 620)	RR 1.07 (0.67 to 1.71)	99 (1 RCT)	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 vs no assisted hatching	332 per 1000	360 per 1000 (334 to 387)	OR 1.13 (1.01 to 1.27)	5728 (31 RCTs)	Moderate	Methodological limitations or missing information in most trials
Glujovsky 2014 Vitrification vs slow freezing for women undergoing oocyte cryopreservation	116 per 1000	449 per 1000	RR 3.86 (1.63 to 9.11)	106 (2 RCTs)	Moderate	Live birth not reported, wide CIs
Van Rumste 2003 Intracytoplasmic sperm injection vs in vitro fertilisation	252 per 1000	329 per 1000 (242 to 428)	OR 1.45 (0.95 to 2.22)	415 (1 RCT)	Low	Details of blinding unclear, evidence based on a single trial
Bontekoe 2012 Embryo culture with low oxygen concentrations vs atmospheric oxygen concentration	369 per 1000	442 per 1000 (387 to 494)	OR 1.35 (1.08 to 1.67	1382 (4 RCTs)	Moderate	In 1 trial, no allocation concealment; in another trial, method of allocation concealment unclear
Twisk 2006 Pre-implantation genetic screening vs no screening in women with advanced age	291 per 1000	187 per 1000 (144 to 235)	OR 0.59 (0.44 to 0.81)	1062 (5 RCTs)	Moderate	Only 1 study described an adequate method of allocation concealment
Twisk 2006 Pre-implantation genetic screening vs no screening in women with repeated IVF failure	Not calculated		OR 0.49 (0.24 to 1.02	139 (1 RCT)	Very low	No allocation concealment and serious imprecision with few events
Huang 2013 Brief co-incubation vs standard insemination	177 per 1000	337 per 1000 (238 to 453)	OR 2.36 (1.45 to 3.85)	372 (3 RCTs)	Low	One trial lacked adequate explanation of methods of sequence generation. Allocation conceal-

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

						ment was not mentioned in any trial
Teixeira 2013 Regular (ICSI) vs ultra-high magnification (IMSI) sperm selection for assisted reproduction	330 per 1000	430 per 1000 (360 to 520)	RR 1.29 (1.06 to 1.55)	2014 (9 RCTs)	Very low	High risk of bias (differences within studies between number of oocytes transferred), inconsistency across studies, publication bias strongly suspected
Armstrong 2015 TLS with or without cell-tracking algorithms vs conventional incubation for embryo incubation in assisted reproduction	558 per 1000	609 per 1000 (548 to 668)	OR 1.23 (0.96 to 1.59)	994 (3 RCTs)	Low	Overall high risk of selection, performance, attrition, and reporting bias. Largest study used donor and autologous oocytes, whereas the remaining 2 studies used autologous oocytes only. Donor oocytes were generally from young women, which may behave differently from the usual population of oocytes and embryos of couples undergoing ART
Siristatidis 2018 Metabolomic vs non-metabolomic assessment	421 per 1000	446 per 1000 (446 to 586)	OR 1.11 (0.85 to 1.45)	924 (4 RCTs)	Low	Serious risk of bias and serious imprecision
9. Embryo transfer						
9.1. Developmental stage						
Glujovsky 2016 Blastocyst stage transfer vs cleavage stage transfer	362 per 1000	425 per 1000 (393 to 455)	OR 1.30 (1.14 to 1.47)	4031 (27 RCTs)	Moderate	Several studies did not describe acceptable methods of sequence generation and/or allocation concealment, several were at unclear or high risk of attrition bias, and none clearly had blinded outcome assessment
9.3. Transfer techniques and procedures						
Ata 2018 Seminal plasma to genital tract vs no seminal plasma	220 per 1000	252 per 1000 (222 to 288)	RR 1.15 (1.01 to 1.31)	2768 (10 RCTs)	Very low	Very serious risk of bias and serious imprecision. Post hoc sensitivity analysis excluding studies at overall high risk of

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

						bias negated the statistical significance of the finding (RR 1.06, 95% CI 0.81 to 1.39; participants = 547; studies = 3; I^2 = 0%)
Brown 2016 Day 2 vs day 3 embryo transfer	386 per 1000	417 per 1000 (378 to 459)	OR 1.08 (0.98 to 1.19)	2461 (12 RCTs)	Very low	Serious inconsistency, poor reporting of allocation concealment and blinding, high risk of selective reporting
Bontekoe 2014 Transfer medium enriched with high level of hyaluronic acid vs medium with low level or no hyaluronic acid	350 per 1000	428 per 1000 (394 to 462)	OR 1.39 (1.21 to 1.6)	3542 (14 RCTs)	Moderate	All studies except 1 were at high risk of bias in at least 1 domain, moderate heterogeneity (I^2 = 46%)
Brown 2016a Ultrasound guidance vs clinical touch for embryo transfer	267 per 1000	323 per 1000 (299 to 346)	OR 1.31 (1.17 to 1.45)	6711 (20 RCTs)	Moderate	Poor reporting of study methods
Kroon 2012 Antibiotics before embryo transfer vs no antibiotics	355 per 1000	359 per 1000 (266 to 465)	1.02 (0.66 to 1.58)	350 (1 RCT)	Moderate	Serious imprecision with single RCT
Derks 2009 Cervical dilatation vs no intervention	232 per 1000	124 per 1000 (78 to 189)	OR 0.47 (0.28 to 0.77)	288 (1 RCT)	Moderate	Evidence based on a single RCT
Derks 2009 Straightening the endocervical angle vs no intervention	271 per 1000	267 per 1000 (175 to 384)	OR 0.98 (0.57 to 1.68)	273 (2 RCTs)	Moderate	Serious imprecision
Derks 2009 Removal of cervical mucus vs no intervention	327 per 1000	320 per 1000 (169 to 522)	OR 0.97 (0.42 to 2.25)	97 (1 RCT)	Low	Lack of methodological details, serious imprecision: evidence based on a single trial
Derks 2009 Flushing the endocervical canal vs no intervention	413 per 1000	445 per 1000 9360 to 533)	OR 1.14 (0.8 to 1.62)	537 (3 RCTs)	Low	Lack of methodological details; heterogeneity (I^2 > 50%)
Derks 2009 Flushing the endometrial cavity vs no intervention	519 per 1000	584 per 1000 (437 to 718)	OR 1.3 (0.72 to 2.36)	181 (1 RCT)	Low	Lack of methodological details, serious imprecision with ev-

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

						idence based on a single trial
Abou-Setta 2014 Mechanical pressure vs no intervention	478 per 1000	637 per 1000 (561 to 706)	OR 1.92 (1.4 to 2.63)	639 (1 RCT)	Very low	Evidence based on a single trial; method of randomisation unclear and trial open-label
Abou-Setta 2014 Fibrin sealant vs no intervention	291 per 1000	287 per 1000 (181 to 422)	OR 0.98 (0.54 to 1.78)	211 (1 RCT)	Low	Evidence based on a single trial with inadequate allocation concealment
Abou-Setta 2014 More bed rest vs less bed rest	302 per 1000	276 per 1000 (206 to 362)	OR 0.88 (0.6 to 1.31	542 (2 RCTs)	Moderate	One trial was open-label
Craciunas 2016 Intrauterine hCG vs no intrauterine hCG; cleavage stage hCG < 500 IU	579 per 1000	509 per 1000 (405 to 637)	RR 0.88 (0.70 to 1.10)	280 (1 RCT)	Very low	Very serious risk of bias, with poor reporting of methods and premature termination of study; serious imprecision
Craciunas 2016 Intrauterine hCG vs no intrauterine hCG; cleavage stage hCG⩾ 500 IU	321 per 1000	453 per 1000 (401 to 507)	RR 1.41 (1.25 to 1.58)	1414 (7 RCTs)	Moderate	Serious risk of bias: poor reporting of methods, lack of blinding
Craciunas 2016 Intrauterine hCG vs no intrauterine hCG; blastocyst stage hCG ⩾ 500 IU	430 per 1000	408 per 1000 (370 to 455)	RR 0.95 (0.86 to 1.06)	1991 (3 RCTs)	Moderate	Serious risk of bias: poor reporting of methods, lack of blinding
10. Luteal phase support						
van der Linden 2015 hCG vs placebo/no treatment	155 per 1000	192 per 1000 (141 to 256)	OR 1.3 (0.9 to 1.88)	746 (5 RCTs)	Very low	Poor reporting of study methods, very serious imprecision
van der Linden 2015 Progesterone vs placebo/no treatment	100 per 1000	174 per 1000 (126 to 234)	OR 1.89 (1.3 to 2.75)	841 (7 RCTs)	Low	Poor reporting of study methods, very serious imprecision
van der Linden 2015 Progesterone vs hCG regimens	284 per 1000	300 per 1000 (263 to 340)	OR 1.08 (0.9 to 1.3)	2355 (16 RCTs)	Moderate	Poor reporting of study methods
van der Linden 2015	433 per 1000	391 per 1000	OR 0.86 (0.72 to 1.04)	2169 (14 RCTs)	Low	Poor reporting of study methods, serious inconsistency

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

Progesterone vs progesterone + oestrogen		(355 to 443)				
van der Linden 2015 Progesterone vs progesterone + GnRH agonist	405 per 1000	310 per 1000 (258 to 367)	OR 0.66 (0.51 to 0.85)	2435 (8 RCTs)	Low	Poor reporting of study methods, serious inconsistency
Boomsma 2012 Peri-implantation glucocorticoids vs no glucocorticoids	290 per 1000	320 per 1000 (275 to 369)	OR 1.15 (0.93 to 1.43)	1759 (13 RCTs)	Moderate	Most studies lacked adequate blinding
Akhtar 2013 Heparin vs placebo or no treatment	250 per 1000	271 per 1000 (256 to 458)	OR 1.61 (1.03 to 2.53)	386 (3 RCTs)	Low	Imprecise, sensitive to choice of statistical model: estimate using random-effects model: OR 1.66, 95% CI 0.94 to 2.90
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
D'Angelo 2007 Cryopreservation vs fresh embryo transfer	463 per 1000	482 per 1000 (318 to 654)	OR 1.08 (0.54 to 2.19)	125 (1 RCT)	Low	Evidence based on a single open-label RCT that provided insufficient methodological details. Serious imprecision
D'Angelo 2007 Cryopreservation vs intravenous albumin	385 per 1000	36 per 1000 (0 to 423)	OR 0.06 (0 to 1.17)	26 (1 RCT)	Low	Evidence based on a single open-label trial with serious imprecision
Youssef 2016 Intravenous human albumin vs no treatment or placebo	396 per 1000	321 per 1000 (265 to 381)	OR 0.72 (0.55 to 0.94)	1069 (7 RCTs)	Moderate	Lack of blinding, inadequate reporting of allocation concealment, unclear risk of attrition bias
Youssef 2016 Intravenous hydroxyethyl starch vs placebo	120 per 1000	141 per 1000 (63 to 286)	OR 1.2 (0.49 to 2.93)	168 (1 RCT)	Very low	Lack of blinding, inadequate reporting of allocation concealment, unclear risk of attrition bias, and serious imprecision, with low event rate
Youssef 2016 Mannitol vs placebo	276 per 1000	245 per 1000 (152 to 371)	OR 0.85 (0.47 to 1.55)	226 (1 RCT)	Low	Inadequate reporting of allocation concealment, serious imprecision, with low event rate
D'Angelo 2017 Coasting vs no coasting	390 per 1000	344 per 1000	OR 0.82 (0.46 to 1.44)	207 (2 RCTs)	Low	Insufficient methodological details pro-

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

		(228 to 480)				vided and serious imprecision
D'Angelo 2017 Coasting vs early unilateral follicular aspiration	317 per 1000	237 per 1000 (104 to 454)	OR 0.67 (0.25 to 1.79)	83 (2 RCTs)	Very low	One study did not clearly describe methods; lack of blinding, very serious imprecision
D'Angelo 2017 Coasting vs gonadotrophin-releasing hormone antagonist	553 per 1000	478 per 1000 (342 to 619)	OR 0.74 (0.42 to 1.31)	190 (1 RCT)	Low	Method of sequence generation not reported; lack of blinding and serious imprecision
D'Angelo 2017 Coasting vs follicle-stimulating hormone administration at time of hCG	510 per 1000	489 per 1000 (309 to 676)	OR 0.92 (0.43 to 2.01)	102 (1 RCT)	Very low	Method of sequence generation not reported; lack of blinding and serious imprecision
D'Angelo 2017 Coasting vs cabergoline	367 per 1000	180 per 1000 (85 to 338)	OR 0.38 (0.16 to 0.88)	120 (2 RCTs)	Very low	One study did not clearly define methods; method of sequence generation not reported; lack of blinding, few events
Tang 2016 Dopamine agonist vs placebo or no intervention	401 per 1000	352 per 1000 (266 to 450)	OR 0.81 (0.54 to 1.22)	432 (4 RCTs)	Moderate	Poor reporting of study methods
12. Frozen embryo replacement cycles						
Ghobara 2017 Oestrogen + progesterone frozen thawed embryo transfer (FET) vs natural cycle FET	205 per 1000	214 per 1000 (93 to 419)	OR 1.06 (0.4 to 2.8)	100 (1 RCT)	Very low	Evidence based on a single trial, insufficient methodological details provided, open-label, and serious imprecision
Ghobara 2017 Oestrogen + progesterone frozen thawed embryo transfer (FET) vs GnRHa, oestrogen, and progesterone preparations FET	215 per 1000	173 per 1000 (125 to 232)	OR 0.76 (0.52 to 1.1)	725 (4 RCTs)	Low	Heterogeneity > 50%, included open-label trials; some trials failed to provide adequate methodological details
Ghobara 201 Oestrogen + progesterone frozen thawed embryo transfer (FET) vs FSH ovulation induction FET	128 per 1000	109 per 1000 (949 to 228)	OR 0.84 (0.35 to 2.02)	194 (1 RCT)	Very low	Evidence based on a single trial with insufficient methodological details provided; trial was open-label. Also serious imprecision
Ghobara 2017	96 per 1000	75 per 1000 (22	OR 0.76	119	Very low	Evidence based on a single trial with in-

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

Clomiphene frozen thawed embryo transfer (FET) vs oestrogen and progesterone FET		to 228)	(0.21 to 2.77)	(1 RCT)		sufficient methodological details provided. Also serious imprecision
Ghobara 2017 Clomiphene frozen thawed embryo transfer (FET) vs GnRHa + oestrogen and progesterone FET	162 per 1000	75 per 1000 (23 to 221)	OR 0.42 (0.12 to 1.47)	104 (1 RCT)	Very low	Evidence based on a single trial with insufficient methodological details provided. Also serious imprecision
Ghobara 2017 Clomiphene + hMG frozen thawed embryo transfer (FET) vs hMG FET	275 per 1000	148 per 1000	OR 0.46 (0.23 to 0.92)	209 (1 RCT)	Low	Evidence based on a single trial with insufficient methodological details provided
Glujovsky 2010 GnRH agonists vs control for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	215 per 1000	246 per 1000 (167 to 347)	OR 1.19 (0.73 to 1.94)	778 (5 RCTs)	Moderate	All trials were open-label; insufficient reporting of methodological details in many studies
Glujovsky 2010 Intramuscular progesterone vs vaginal progesterone for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	282 per 1000	361 per 1000 (278 to 452)	OR 1.44 (0.98 to 2.1)	655 (4 RCTs)	Moderate	All trials were open-label; insufficient reporting of methodological details in many studies. Wide confidence interval crosses the line of no effect
Glujovsky 2010 Starting progesterone on the day of oocyte pickup (OPU) or the day after OPU vs starting progesterone the day before OPU	381 per 1000	533 per 1000 (400 to 712)	OR 1.8 (1.13 to 3.08)	282 (1 RCT)	Moderate	Serious risk of bias with no intention-to-treat analysis

ART: assisted reproduction techniques.
CI: confidence interval.
COH: controlled ovarian hyperstimulation.
CSA: conscious sedation and analgesia.
DHEA: dehydroepiandrosterone.
E_2: oestrogen.
ET: embryo transfer.
FET: frozen embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
HA: hyaluronic acid.
HA-ICSI: conventional sperm selection vs hyaluronan sperm selection.
hCG: human chorionic gonadotrophin.
hLH: human luteinising hormone.
hMG: human menopausal gonadotrophin.
HT: hormone therapy.
ICSI: intracytoplasmic sperm injection.
IU: international units.

IV: intravenous.
IVF: in vitro fertilisation.
N/A: not applicable.
OHSS: ovarian hyperstimulation syndrome.
OPU: oocyte pickup.
OR: odds ratio.
ORT: ovarian reserve test.
PCB: paracervical block.
PICSI: physiological intracytoplasmic sperm injection.
RCT: randomised controlled trial.
rFSH: recombinant follicle-stimulating hormone.
rhCG: recombinant human chorionic gonadotrophin.
rhLH: recombinant human luteinising hormone.
RR: risk ratio.
TLS: time-lapse imaging.
uhCG: urinary human chorionic gonadotrophin.
VAS: visual analogue scale.

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 2015 IVF vs intrauterine insemination + ovarian stimulation for unexplained subfertility (treatment naïve women)	58 per 1000	66 per 1000 (26 to 158)	OR 1.15 (0.43 to 3.06)	324 (2 RCTs)	Low	Serious risk of bias and serious imprecision
2. Pre-ART and adjuvant strategies						
For selected populations						
Tso 2014 Metformin vs placebo or no treatment	270 per 1000	97 per 1000 (62 to 153)	OR 0.29 (0.18 to 0.49)	798 (8 RCTs	Moderate	Serious imprecision, as total events were fewer than 300
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot vs daily injection	3 per 100	2 per 100 (1 to 6)	OR 0.84 (0.29 to 2.42)	570 (5 RCTs)	Low	Most studies classified as at unclear risk of bias for all domains. Serious imprecision as total events were fewer than 300
Al-Inany 2016 GnRH antagonist vs long course GnRH agonist	114 per 1000	73 per 1000 (62 to 85)	OR 0.61 (0.51 to 0.72)	7944 (36 studies)	Moderate	Serious risk of bias
4. Ovarian stimulation						

Table 6. OHSS per woman *(Continued)*

4.1. Medication type

Kamath 2017 Clomiphene citrate or letrozole with or without gonadotropins (with or without midcycle antagonist) compared to gonadotropins (with GnRH agonists or midcycle antagonist) in IVF and ICSI cycles in general population	63 per 1000	14 per 1000 (7 to 27)	Peto OR 0.21 (0.11 to 0.41)	1067 (5 RCTs)	Low	Serious risk of bias associated with unclear reporting of methods of allocation concealment. Imprecision as there were few participants and few events
Pouwer 2015 Long-acting FSH (low dose) vs daily FSH	47 per 1000	57 per 1000 (26 to 125)	RR 1.22 (0.56 to 2.66)	645 (3 RCTs)	Moderate	Serious imprecision with few events
Pouwer 2015 Long-acting FSH (medium dose) vs daily FSH	63 per 1000	60 per 1000 (45 to 85)	RR 0.96 (0.68 to 1.35)	3075 (5 RCTs)	Low	Serious imprecision as wide confidence intervals compatible with clinically meaningful benefit in either arm or with no effect. High risk of attrition bias in 2 studies
Pouwer 2015 Long-acting FSH (high dose) vs daily FSH	0 per 1000	0 per 1000 (0 to 0)	RR 1.73 (0.09 to 32.75)	33 (1 RCT)	Very low	Very serious imprecision as very wide confidence intervals compatible with clinically meaningful benefit in either arm or with no effect. High risk of attrition bias
Mochtar 2017 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) vs rFSH alone for controlled ovarian hyperstimulation	13 per 1000	5 per 1000 (2 to 13)	OR 0.38 (0.14 to 1.01)	2178 (6 RCTs)	Low	Very serious imprecision with wide confidence intervals and low event rates
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase vs continued FSH for assisted reproductive techniques	3 per 100	1 per 100 (0 to 4)	OR 0.30 (0.06 to1.59)	351 (5 RCTs)	Very low	Very serious imprecision, inconsistency, and high risk of bias
Farquhar 2017 Combined oral contraceptive pill plus antagonist vs antagonist	17 per 1000	25 per 1000 (5 to 133)	OR 1.5 (0.26 to 8.8)	234 (1 RCT)	Very low	Serious imprecision as wide confidence intervals compatible with clinically meaningful benefit in either arm or with no effect. High risk of attrition bias
Farquhar 2017 Combined oral contraceptive pill plus antagonist vs agonist	55 per 1000	35 per 1000 (12 to 100)	OR 0.63 (0.21 to 1.92)	290 (2 RCTs)	Very low	Serious imprecision with wide confidence intervals that cross the line of no ef-

Table 6. OHSS per woman *(Continued)*

						fect. One RCT has high risk of attrition bias
Lensen 2018 ORT-based algorithm vs standard dose FSH Moderate or severe OHSS	8 per 1000	14 per 1000 (8 to 25)	OR 0.58 (0.34 to 1.00)	2823 (4 RCTs)	Low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Serious imprecision associated with small number of events
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated low responders Moderate or severe OHSS 1. 300/450 IU vs 150 IU 2. 400/450 IU vs 300 IU 3. 600 IU vs 450 IU	1. 0 per 1000	0 per 1000 (0 to 0)	Not estimable	286 (2 RCTs)	Very low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Very serious imprecision associated with very small number of events
	2. 0 per 1000	0 per 1000 (0 to 0)	Not estimable	62 (1 RCT)		
	3. 0 per 1000	0 per 1000 (0 to 0)	OR 7.23 (0.14 to 364)	356 (1 study)		
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated normal responders Moderate or severe OHSS 1. 200 IU vs 100 IU 2. 225/200 IU vs 150 IU 3. 300 IU vs 225 IU	1. 31 per 1000	19 per 1000 (7 to 56)	OR 0.62 (0.21 to 1.87)	522 (2 RCTs)	Very low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Very serious imprecision associated with very small number of events
	2. 27 per 1000	32 per 1000 (14 to 73)	OR 1.21 (0.51 to 2.85)	740 (4 RCTs)		
	3. 44 per 1000	30 per 1000 (5 to 156)	OR 0.67 (0.11 to 3.99)	135 (1 study)		
Lensen 2018 Higher-dose FSH vs lower-dose FSH in anticipated high responders Moderate or severe OHSS 150 IU vs 100 IU	16 per 1000	36 per 1000 (13 to 96)	OR 2.31 (0.80 to 6.67)	521 (1 RCT)	Very low	Serious risk of bias associated mainly with performance bias due to lack of blinding and/or selective reporting. Very serious imprecision associated with very small number of events
4.2. Monitoring						
Kwan 2014 Ultrasound + oestradiol vs ultrasound only	36 per 1000	36 per 1000 (18 to 75)	OR 1.03 (0.48 to 2.20)	781 (6 RCTs)	Low	Methods of randomisation inadequately described in 3 of the 6 trials, allocation concealment inadequately described in all 6 trials, and blinding inadequately described in 5 of the 6 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 Natural cycle vs standard IVF	67 per 1000	13 per 1000 (1 to 393)	OR 0.10 (0.01 to 4.06)	60 (1 RCT)	Very low	Allocation concealment method not reported, very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist vs hCG	5 per 1000	1 per 1000 (0 to 2)	OR 0.15 (0.05 to 0.47)	989 (8 RCTs)	Moderate	All studies at high risk of bias in 1 or more domains. None clearly reported blinded outcome assessment
Georgiou 2018 rFSH vs urinary gonadotrophins	19 per 1000	22 per 1000 (16 to 30)	OR 1.18 (0.86 to 1.61)	7740 (32 RCTs)	High	Lack of blinding
Youssef 2016a rhCG vs uhCG	10 per 1000	17 per 1000 (11 to 84)	OR 1.76 (0.37 to 8.45)	417 (3 RCTs)	Low	Very serious imprecision
Youssef 2016a rhLH vs uhCG	126 per 1000	107 per 1000 (55 to 197)	OR 0.83 (0.40 to 1.70)	289 (2 RCTs)	Very low	One trial lacked adequate methodological details; serious imprecision
10. Luteal phase support						
van der Linden 2015 hCG vs placebo/no treatment	41 per 1000	155 per 1000 (76 to 292)	OR 4.28 (1.91 to 9.6)	387 (1 RCT)	Low	Poor reporting of study methods, serious imprecision with low event rate
van der Linden 2015 Progesterone vs hCG regimens	118 per 1000	58 per 1000 (39 to 87)	OR 0.46 (0.30 to 0.71)	1293 (5 studies)	Low	Poor reporting of study methods with serious imprecision
van der Linden 2015 Progesterone compared with progesterone + oestrogen	51 per 1000	30 per 1000 (11 to 82)	OR 0.58 (0.2 to 1.68)	461 (2 RCTs)	Low	Poor reporting of study methods with serious imprecision
van der Linden 2015 Progesterone compared with progesterone + GnRH agonist	50 per 1000	50 per 1000 (17 to 137)	OR 1.00 (0.33 to 3.01)	300 (1 RCT)	Very low	Poor reporting of study methods with very serious imprecision
Akhtar 2013 Heparin vs placebo or no treatment	250 per 1000	349 per 1000 (256 to 458)	OR 1.61 (1.03 to 2.53)	386 (3 RCTs)	Very low	Selection bias found in 1 study. High heterogeneity. Results sensitive to choice of statistical model
Boomsma 2012	194 per 1000	159 per 1000	OR 0.82 (0.33 to	151 (2 RCTs)	Low	Methodological limitations and serious imprecision

Table 6. OHSS per woman *(Continued)*

Peri-implantation glucocorticoids vs no glucocorticoids		(64 to 392)	2.02)			
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
Tang 2016 Dopamine agonist vs placebo/no treatment	286 per 1000	97 per 1000 (71 to 135)	OR 0.27 (0.19 to 0.39)	1022 (8 RCTs)	Moderate	Poor reporting of study methods
D'Angelo 2007 Cryopreservation vs fresh embryo transfer	60 per 1000	8 per 1000 (1 to 128)	OR 1.12 (0.01 to 2.29)	125 (1 RCT)	Low	Evidence based on a single open-label study with insufficient methodological details provided. Serious imprecision
D'Angelo 2007 Cryopreservation vs intravenous albumin	77 per 1000	308 per 1000 (41 to 824)	OR 5.33 (0.51 to 56.24)	26 (1 RCT)	Very low	Evidence based on a single open-label trial with serious imprecision
Youssef 2016 Intravenous human albumin vs no treatment or placebo	122 per 1000	85 per 1000 (61 to 117)	OR 0.67 (0.47 to 0.95)	1452 (7 RCTs)	Very low	Lack of blinding, inadequate reporting of allocation concealment, unclear risk of attrition bias, serious imprecision with low event rate, and serious inconsistency (I^2 = 69%)
Youssef 2016 Intravenous hydroxyethyl starch vs placebo	164 per 1000	50 per 1000 (23 to 104)	OR 0.27 (0.12 to 0.59)	272 (2 RCTs)	Very low	Inadequate reporting of allocation concealment and blinding with unclear risk of attrition bias
Youssef 2016 Mannitol vs placebo or no treatment	517 per 1000	289 per 1000 (191 to 407)	OR 0.38 (0.22 to 0.64)	226 (1 RCT)	Low	Inadequate reporting of allocation concealment and serious imprecision with low event rate
D'Angelo 2017 Coasting vs no coasting	457 per 1000	85 per 1000 (40 to 168)	OR 0.11 (0.05 to 0.24)	207 (2 RCTs)	Low	Serious risk of bias as 1 study did not clearly describe the methods used and studies were not blinded. Serious imprecision
D'Angelo 2017 Coasting vs early unilateral follicular aspiration	244 per 1000	240 per 1000 (99 to 479)	OR 0.98 (0.34 to 2.85)	83 (2 RCTs)	Very low	One study did not clearly describe methods; lack of blinding and serious imprecision
D'Angelo 2017 Coasting vs gonadotrophin-releasing hormone antagonist	No events occurred	No events occurred	Not estimable	190 (1 RCT)	Very low	Method of sequence generation not reported; lack of blinding and very serious imprecision
D'Angelo 2017	No events occurred	15 events all in the coasting arm	OR 43.74 (2.54 to 754.58)	102 (1 RCT)	Very low	Method of sequence generation not reported; lack of blinding and very serious imprecision

Table 6. OHSS per woman *(Continued)*

Coasting vs follicle-stimulating hormone administration at time of hCG						
D'Angelo 2017 Coasting vs cabergoline	100 per 1000	180 per 1000 (71 to 387)	OR 1.98 (0.69 to 5.68)	120 (2 RCTs)	Very low	One study did not clearly define methods; method of sequence generation not reported, lack of blinding, very serious imprecision
12. Frozen embryo replacement cycles						
Wong 2017 Frozen vs fresh and frozen embryo transfer Per cycle with ovarian stimulation	70 per 1000	18 per 1000 (11 to 28)	OR 0.24 (0.15 to 0.38)	1633 (2 RCTs)	Low	Serious risk of bias and serious imprecision with low event rate

ART: assisted reproduction techniques.
CI: confidence interval.
FET: frozen embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
HA: hyaluronic acid.
hCG: human chorionic gonadotrophin.
hLH: human luteinising hormone.
hMG: human menopausal gonadotrophin.
ICSI: intracytoplasmic sperm injection.
IU: international units.
IVF: in vitro fertilisation.
OHSS: ovarian hyperstimulation syndrome.
OR: odds ratio.
ORT: ovarian reserve test.
RCT: randomised controlled trial.
rFSH: recombinant follicle-stimulating hormone.
rhCG: recombinant human chorionic gonadotrophin.
rhLH: recombinant human luteinising hormone.
RR: risk ratio.
uhCG: urinary human chorionic gonadotrophin.

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 (RCTs)	Quality of the evidence (GRADE)	Comments
1. Indication for ART						
Pandian 2015 IVF vs unstimulated intrauterine insemination for unexplained subfertility	30 per 1000	31 per 1000 (1 to 460)	OR 1.03 (0.04 to 27.29)	43 (1 RCT)	Very low	Very serious imprecision

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

Pandian 2015 IVF vs intrauterine insemination + ovarian stimulation for unexplained subfertility (treatment naïve women)	58 per 1000	47 per 1000 (28 to 78)	OR 0.81 (0.47 to 1.39)	848 (4 RCTs)	Moderate	Serious imprecision with wide confidence interval
2. Pre-ART and adjuvant strategies						
Siristatidis 2016 Aspirin vs placebo or no treatment	84 per 1000	56 per 1000 (31 to 105)	RR 0.67 (0.37 to 1.25)	656 (2 RCTs)	Low	Very serious imprecision with very low event rate and wide confidence interval
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 RCTs)	Moderate	Serious imprecision
Cheong 2013 Acupuncture vs no acupuncture on or around the day of embryo transfer	56 per 1000	72 per 1000 (42 to 122)	OR 1.32 (0.74 to 2.35)	795 (2 RCTs)	Low	Only 1/2 studies described adequate allocation concealment; wide confidence intervals crossed the line of no effect
Nastri 2015 Endometrial injury before ovulation induction (pipelle induced) vs no endometrial injury	278 per 1000	251 per 1000 (81 to 559)	OR 0.87 (0.23 to 3.3)	46 (1 RCT)	Very low	Evidence based on a single trial with serious 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 RCTs)	Moderate	Studies had low or unclear risk of bias but serious imprecision
Nagels 2015 DHEA vs placebo or no treatment	Not calculable	Not calculable	OR 3.23 (0.13 to 81.01)	267 (5 RCTs)	Very low	Very serious imprecision
Nagels 2015 Testosterone vs placebo or no treatment	Not calculable	Not calculable	OR 3.09 (0.48 to 19.98)	292 (3 RCTs)	Very low	Very serious imprecision
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot vs daily injection	24 per 100	25 per 100 (13 to 43)	OR 1.1 (0.49 to 2.46)	132 (4 RCTs)	Low	Most studies classified as at unclear risk of bias for all domains. Serious imprecision as total events were fewer than 300
Boomsma 2012	38 per 1000	74 per 1000 (31 to 168)	OR 2.02	372 (4 RCTs)	Moderate	Poor reporting of methodological details

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

Peri-implantation glucocorticoids vs no glucocorticoids			(0.8 to 5.11)			
4. Ovarian stimulation						
4.1. Medication type						
Kamath 2017 Clomiphene citrate (± urinary or recombinant gonadotrophin) vs urinary or recombinant gonadotrophin in either long or short protocols	233 per 1000	211 per 1000 (109 to 372)	OR 0.88 (0.4 to 1.95)	160 (4 RCTs)	Moderate	Poor reporting of methodological details
Farquhar 2017 Combined oral contraceptive pill plus antagonist vs antagonist	47 per 1000	98 per 1000 (25 to 313)	OR 2.21 (0.53 to 9.26)	125 (2 RCTs)	Low	Very serious imprecision with wide confidence intervals
Farquhar 2017 Combined oral contraceptive pill plus antagonist vs agonist	147 per 1000	189 per 1000 (127 to 273)	OR 1.36 (0.85 to 2.19)	546 (4 RCTs)	Moderate	Serious imprecision with wide confidence intervals
Farquhar 2017 Progesterone plus antagonist vs antagonist	42 per 1000	44 per 1000 (3 to 438)	OR 1.05 (0.06 to 17.76)	47 (1 RCT)	Low	Very serious imprecision with wide confidence intervals
Farquhar 2017 Oestrogen plus antagonist vs agonist	No events in this group	Only two events (both in this group)	OR 2.24 (0.09 to 53.59)	22 (1 RCT)	Very low	Poor reporting of methods and very serious imprecision
Kalampokas 2017 Glucocorticoid supplementation vs placebo	Not calculable	Not calculable	OR 3.32 (0.12 to 91.60)	20 (1 study)	Very low	Risk of bias and very serious imprecision with only 1 event (in glucocorticoid group)
4.4. Natural cycle IVF						
Allersma 2013 Natural cycle vs standard IVF	29 per 1000	6 per 1000 (0 to 117)	OR 0.21 (0.01 to 4.38)	132 (1 RCT)	Very low	Methods of sequence generation and allocation concealment not stated, high risk of attrition bias, very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist vs hCG	82 per 1000	134 per 1000 (71 to 238)	OR 1.74 (0.86 to 3.5)	342 (3 RCTs)	Moderate	No evidence of blinding in many trials
van Wely 2011 rFSH vs urinary gonadotrophins	85 per 1000	78 per 1000 (66 to 92)	OR 0.91 (0.76 to	6329 (25 RCTs)	Moderate	No evidence of blinding in many trials

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

			1.09)			
8. Laboratory phase						
Twisk 2006 Pre-implantation genetic screening vs no screening in women with advanced age	200 per 1000	206 per 1000 (113 to 347)	OR 1.04 (0.51 to 2.13)	199 (4 RCTs)	Low	Poor reporting of methods and serious imprecision
Carney 2012 Assisted hatching vs no assisted hatching	102 per 1000	136 per 1000 (112 to 162)	OR 1.38 (1.11 to 1.7)	3447 (14 RCTs)	Low	Methodological limitations or missing information in most trials. Inconsistency between trials (I^2 = 57%)
Bontekoe 2012 Embryo culture with low oxygen concentration vs atmospheric oxygen concentration	88 per 1000	113 per 1000 (80 to 158)	OR 1.33 (0.91 to 1.95)	1382 (4 RCTs)	Low	Poor reporting of methods and serious imprecision
Siristatidis 2018 Metabolomic vs non-metabolomic assessment	189 per 1000	255 per 1000 (139 to 421)	OR 1.52 (0.71 to 3.23)	181 (2 RCTs)	Low	Serious risk of bias and serious imprecision
9. Embryo transfer						
9.1. Developmental stage						
Glujovsky 2016 Cleavage stage transfer vs blastocyst stage transfer	122 per 1000	127 per 1000 (103 to 156)	OR 1.05 (0.83 to 1.33)	3019 (19 RCTs)	Low	Several studies did not describe acceptable methods of sequence generation and/or allocation concealment, several were at unclear or high risk of attrition bias, and none clearly had blinded outcome assessment.
9.2. Number of embryos						
Pandian 2013 Single- vs double-embryo transfer (one cycle only)	144 per 1000	20 per 1000 (12 to 32)	OR 0.12 (0.07 to 0.20)	1612 (10 RCTs)	High	Moderate heterogeneity attributable to 36% of women non-compliant with treatment allocation in 1 study (I^2 = 45%)
Pandian 2013 Repeated single-embryo transfer vs double-embryo transfer	133 per 1000	5 per 1000 (2 to 19)	OR 0.03 (0.01 to 0.13)	811 (3 RCTs)	Moderate	Methods poorly described
Pandian 2013	91 per 1000	17 per 1000	OR 0.17	45	Very low	Randomisation and blinding unclear; ev-

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

Double-embryo transfer vs three embryo transfers		(1 to 278)	(0.01 to 3.85)	(1 RCT)		idence based on a single trial with very serious imprecision
Pandian 2013 Double-embryo transfer vs four embryo transfers	214 per 1000	107 per 1000 (27 to 349)	OR 0.44 (0.1 to 1.97)	56 (1 RCT)	Very low	Randomisation, allocation concealment, and blinding unclear; evidence based on a single trial with very serious imprecision
9.3. Transfer techniques						
Ata 2018 Seminal plasma to genital tract vs no seminal plasma	70 per 1000	77 per 1000 (53 to 114)	RR 1.11 (0.76 to 1.64)	1642 (5 RCTs)	Low	Serious imprecision, serious risk of bias: allocation concealment poorly reported or not utliised
Brown 2016 Day 3 vs day 2 embryo transfer	106 per 1000	118 per 1000 (91 to 152)	OR 1.12 (0.86 to 1.44)	1837 (8 RCTs)	Moderate	Poor reporting of allocation concealment and blinding
Bontekoe 2014 Transfer medium enriched with high level of hyaluronic acid vs medium with low level or no hyaluronic acid	20 per 1000	37 per 1000 (240 to 328)	OR 1.86 (1.49 to 2.31)	1951 (5 RCTs)	Moderate	All studies except 1 at high risk of bias in 1 or more domains
Brown 2016a Ultrasound guidance vs clinical touch for embryo transfer	60 per 1000	67 per 1000 (53 to 85)	OR 1.13 (0.87 to 1.45)	3379 (8 RCTs)	Moderate	Poor reporting of study methods
Abou-Setta 2014 Less bed rest vs more bed rest	73 per 1000	113 per 1000 (25 to 383)	OR 1.62 (0.33 to 7.9)	542 (2 RCTs)	Very low	Heterogeneity (I^2 > 70%) and serious imprecision with wide confidence intervals; 1 trial open
Abou-Setta 2014 Mechanical pressure on cervix vs no intervention	121 per 1000	243 per 1000 (174 to 329)	OR 2.33 (1.53 to 3.56)	639 (1 RCT)	Very low	Evidence based on a single trial; open-label trial with unclear method of randomisation
11. Prevention of OHSS						
D'Angelo 2017 Coasting vs no coasting	268 per 1000	102 per 1000 (42 to 228)	OR 0.31 (0.12 to 0.81)	139 (1 RCT)	Low	Poor reporting of methods
D'Angelo 2017 Coasting vs gonadotrophin-releasing hormone antagonist	181 per 1000	156 per 1000 (79 to 284)	OR 0.84 (0.39 to 1.80)	98 (1 RCT)	Very low	Method of sequence generation not reported, lack of blinding, serious imprecision

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

Tang 2016 Dopamine agonist vs placebo/no intervention	50 per 1000	17 per 1000 (1 to 303)	OR 0.32 (0.01 to 8.26)	40 (1 RCT)	Very low	Poor reporting of study methods and very serious imprecision
12. Frozen embryo replacement cycles						
Wong 2017 Frozen vs fresh and frozen embryo transfer	161 per 1000	176 per 1000 (141 to 217)	OR 1.11 (0.85 to 1.44)	1630 (2 RCTs)	Low	Serious risk of bias and serious imprecision
Ghobara 2017 Natural cycle FET vs hormone therapy FET	Not estimable	Not estimable	OR 2.48 (0.09 to 68.14)	21 (1 RCT)	Very low	Unclear risk of bias, very serious imprecision: no events in control group
Ghobara 2017 Natural cycle FET vs hormone therapy plus GnRHa suppression FET	63 per 1000	38 per 1000 (9 to 144)	OR 0.58 (0.13 to 2.50)	159 (1 RCT)	Low	Very serious imprecision: single study, few events, wide confidence intervals
Ghobara 2017 hMG FET vs clomiphene + hMG FET	28 per 1000	39 per 1000 (9 to 157)	OR 1.41 (0.31 to 6.48)	209 (1 RCT)	Very low	Unclear risk of bias in all domains, very serious imprecision with very few events and wide confidence intervals

ART: assisted reproduction techniques.
CI: confidence interval.
DHEA: dehydroepiandrosterone.
FET: frozen embryo transfer.
GnRH: gonadotrophin-releasing hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
hCG: human chorionic gonadotrophin.
hMG: human menopausal gonadotrophin.
IVF: in vitro fertilisation.
OHSS: ovarian hyperstimulation syndrome.
OR: odds ratio.
RCT: randomised controlled trial.
rFSH: recombinant follicle-stimulating hormone.
rhCG: recombinant human chorionic gonadotrophin.
RR: risk ratio.
uhCG: urinary human chorionic gonadotrophin.

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	207 per 1000	233 per 1000	OR 1.1	616	Low	Only 2/6 studies described adequate allo-

Table 8. Miscarriage per woman *(Continued)*

Acupuncture vs no acupuncture on or around the day of embryo transfer		(160 to 303)	(0.73 to 1.67)	(6 RCTs)		cation concealment, serious imprecision
Cheong 2013 Acupuncture vs 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 RCTs)	Low	Only 1/4 studies described adequate allocation concealment, serious imprecision
Siristatidis 2016 Aspirin vs placebo or no treatment	43 per 1000	47 per 1000 (29 to 76)	RR 1.10 (0.68 to 1.77)	1497 (5 RCTs)	Low	Serious imprecision with low event rate
Tso 2014 Metformin vs placebo or no treatment	139 per 1000	110 per 1000 (65 to 182)	OR 0.76 (0.43 to 1.37)	521 (6 RCTs)	Moderate	Serious imprecision with low event rate
Nastri 2015 Endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no control	158 per 1000	147 per 1000 (100 to 242)	RR 0.99 (0.63 to 1.53)	500 (8 RCTs)	Low	Serious imprecision and high risk of bias in included studies
Benschop 2010 Aspiration of endometrioma vs expectant management	100 per 1000	97 per 1000 (25 to 316)	Peto OR 0.97 (0.23 to 4.15)	81 (1 RCT)	Very low	Very serious imprecision as evidence based on a single trial with wide confidence intervals that crossed the line of no effect
Benschop 2010 GnRH antagonist vs GnRH agonist	30 per 1000	29 per 1000 (2 to 331)	Peto OR 0.97 (0.06 to 15.85)	67 (1 RCT)	Very low	Very serious imprecision as evidence based on a single trial with wide confidence intervals that crossed the line of no effect
Johnson 2010 Salpingectomy vs no surgical treatment	53 per 1000	46 per 1000 (17 to 117)	OR 0.86 (0.31 to 2.38)	329 (3 RCTs)	Moderate	Randomisation methods not fully described. Serioius imprecision with wide confidence intervals that crossed the line of no effect
Johnson 2010 Tubal occlusion vs no surgical treatment	67 per 1000	60 per 1000 (6 to 399)	OR 0.89 (0.09 to 9.28)	65 (1 RCT)	Very low	Evidence based on a single trial. Evidence of imprecision: wide confidence intervals that crossed the line of no effect
Johnson 2010 Aspiration of hydrosalpingeal fluid vs no surgical treatment	31 per 1000	63 per 1000 (6 to 436)	OR 2.07 (0.18 to 24.01)	64 (1 RCT)	Very low	Evidence based on a single trial. Serious imprecision: wide confidence intervals that crossed the line of no effect

Table 8. Miscarriage per woman *(Continued)*

Gutarra-Vilchez 2014 Vasodilator compared with placebo	69 per 1000	58 per 1000 (26 to 132)	RR 0.84 (0.37 to 1.91)	350 (3 RCTs)	Moderate	Studies had low or unclear risk of bias but serious imprecision
Nagels 2015 DHEA vs placebo	64 per 1000	38 per 1000 (19 to 74)	OR 0.58 (0.29 to 1.17)	950 (8 RCTs)	Moderate	Serious imprecision
Nagels 2015 Testosterone vs placebo	25 per 1000	50 per 1000 (15 to 155)	OR 2.04 (0.58 to 7.13)	345 (4 RCTs)	Low	Very serious imprecision
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot vs daily injection	13 per 100	14 per 100 (9 to 22)	OR 1.16 (0.7 to 1.94)	512 (9 RCTs)	Low	Most studies classified as at unclear risk of bias for all domains. Serious imprecision as total events were fewer than 300
Al-Inany 2016 GnRH antagonist vs long course GnRH agonist	48 per 1000	49 per 1000 (40 to 61)	OR 1.03 (0.82 to 1.29)	7082 (34 RCTs)	Moderate	Serious risk of bias
Boomsma 2012 Peri-implantation glucocorticoids vs no glucocorticoids	57 per 1000	80 per 1000 (47 to 132)	OR 1.44 (0.82 to 2.51)	832 (7 RCTs)	Low	Methodological limitations including lack of blinding and serious imprecision
4. Ovarian stimulation						
4.1. Type of medication						
Pandian 2010 Multiple-dose GnRH agonist vs mini-dose long agonist protocol	22 per 1000	46 per 1000 (4 to 353)	OR 2.1 (0.18 to 23.98)	89 (1 RCT)	Very low	Single trial with no allocation concealment or blinding and very serious imprecision
Kamath 2017 Clomiphene citrate (+/- urinary or recombinant gonadotrophin) vs 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 RCTs)	Moderate	Poor reporting of methods in most trials
Kamath 2017 Clomiphene citrate (+/- urinary or recombinant gonadotrophin) and mid cycle antagonists vs 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 RCTs)	Moderate	Poor reporting of methods in most trials

Table 8. Miscarriage per woman *(Continued)*

Mochtar 2017 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) vs rFSH alone for controlled ovarian hyperstimulation	70 per 1000	65 per 1000 (45 to 93)	OR 0.93 (0.63 to 1.36)	1711 (13 RCTs)	Moderate	Serious imprecision with wide confidence intervals
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase vs continued FSH for assisted reproductive techniques	160 per 1000	170 per 1000 (80 to 360)	RR 1.08 (0.50 to 2.31)	127 (4 RCTs)	Very low	Very serious imprecision and high risk of bias
Farquhar 2017 Combined oral contraceptive pill plus antagonist vs antagonist	270 per 1000	215 per 1000 (177 to 260)	OR 0.74 (0.58 to 0.95)	1335 (6 RCTs)	Moderate	Serious risk of bias due to poor reporting of sequence generation and allocation concealment
Farquhar 2017 Combined oral contraceptive pill plus antagonist vs agonist	296 per 1000	273 per 1000 (212 to 345)	OR 0.89 (0.64 to 1.25)	724 (4 RCTs)	Moderate	Serious imprecision with wide confidence intervals
Farquhar 2017 Progestagen plus agonist vs agonist	36 per 1000	78 per 1000 (24 to 220)	OR 2.26 (0.67 to 7.55)	222 (2 RCTs)	Low	Very serious imprecision with wide confidence intervals
Farquhar 2017 Progestagen plus antagonist vs antagonist	208 per 1000	86 per 1000 (16 to 354)	OR 0.36 (0.06 to 2.09)	47 (1 RCT)	Low	Very serious imprecision with wide confidence intervals
Farquhar 2017 Oestrogen plus antagonist vs antagonist	208 per 1000	40 per 1000 (5 to 279)	OR 0.16 (0.02 to 1.47)	49 (1 RCT)	Very low	Serious risk of bias due to poor reporting; very serious imprecision with wide confidence intervals
Farquhar 2017 Oestrogen plus antagonist vs agonist	72 per 1000	110 per 1000 (46 to 240)	OR 1.59 (0.62 to 4.06)	220 (1 RCT)	Very low	Serious risk of bias due to poor reporting; very serious imprecision with wide confidence intervals
Kalampokas 2017 Glucocorticoid supplementation vs placebo	Not calculable	Not calculable	OR 1.00 (0.05 to 18.57)	20 (1 RCT)	Very low	Serious risk of bias and very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist vs hCG	67 per 1000	111 per 1000 (73 to 165)	OR 1.74 (1.10 to 2.75)	1198 (11 RCTs)	Moderate	5/11 studies at high risk of bias because of early termination and/or inadequate allocation concealment. None clearly reported blinded outcome assessment

Table 8. Miscarriage per woman *(Continued)*

van Wely 2011 rFSH vs urinary gonadotrophins	50 per 1000	57 per 1000 (46 to 70)	OR 1.16 (0.93 to 1.44)	6663 (30 RCTs)	Moderate	No evidence of blinding in many trials
Youssef 2016a rhCG vs uhCG	51 per 1000	37 per 1000 (21 to 63)	OR 0.72 (0.41 to 1.25)	1347 (9 RCTs)	Low	Very serious imprecision
Youssef 2016a rhLH vs uhCG	66 per 1000	62 per 1000 (25 to 144)	OR 0.94 (0.37 to 2.38)	280 (2 RCTs)	Low	One trial lacked adequate methodological details and had serious imprecision
6. Oocyte retrieval						
Reavey 2016 hCG priming vs no priming	70 per 1000	43 per 1000 (16 to 115)	OR 0.60 (0.21 to 1.72)	282 (2 RCTs)	Low	Serious risk of bias and serious 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 RCT)	Low	Serious risk of bias as study methods not reported in adequate detail. Serious imprecision as 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 vs atmospheric oxygen concentration	75 per 1000	94 per 1000 (65 to 133)	OR 1.28 (0.86 to 1.9)	1291 (3 RCTs)	Low	Methodological limitations and serious imprecision
Carney 2012 Assisted hatching vs no assisted hatching	45 per 1000	46 per 1000 (32 to 68)	OR 1.03 (0.69 to 1.54)	2131 (14 RCTs)	Moderate	Methodological limitations or missing information in most trials
Twisk 2006 Pre-implantation genetic screening vs 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 RCTs)	Moderate	Most included trials lacked adequate methodological details
Twisk 2006 Pre-implantation genetic screening vs 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 RCTs)	Very low	Open-label studies with evidence of imprecision; heterogeneity > 60%

Table 8. Miscarriage per woman *(Continued)*

Huang 2013 Brief co-incubation vs standard insemination	24 per 1000	47 per 1000 (9 to 217)	OR 1.98 (0.35 to 11.09)	167 (1 RCT)	Low	One trial only; method of randomisation or allocation concealment not stated
Teixeira 2013 Regular (ICSI) vs ultra-high magnification (IMSI) sperm selection for assisted reproduction	220 per 1000	180 per 1000 (130 to 250)	RR 0.82 (0.59 to 1.14)	552 (6 RCTs)	Very low	High risk of bias and very serious imprecision
Armstrong 2015 TLS with or without cell-tracking algorithms vs conventional incubation	143 per 1000	105 per 1000 (73 to 143)	OR 0.7 (0.47 to 1.04)	994 (3 RCTs)	Low	Overall high risk of selection, performance, attrition, and reporting bias. Largest study used donor and autologous oocytes, whereas the remaining 2 studies used autologous oocytes only. Donor oocytes were generally from young women, which may behave differently from the usual population of oocytes and embryos from couples undergoing ART
Siristatidis 2018 Metabolomic vs non-metabolomic assessment	114 per 1000	109 per 1000 (61 to 184)	OR 0.96 (0.52 to 1.78)	434 (2 RCTs)	Low	Serious risk of bias and serious imprecision
9. Embryo transfer						
Ata 2018 Seminal plasma to genital tract vs no seminal plasma	38 per 1000	38 per 1000 (21 to 67)	RR 1.01 (0.57 to 1.79)	1209 (4 RCTs)	Low	Serious risk of bias associated with poor reporting; serious imprecision
Glujovsky 2016 Cleavage stage transfer vs blastocyst stage transfer	68 per 1000	78 per 1000 (68 to 119)	OR 1.15 (0.88 to 1.50)	2917 (18 RCTs)	Low	Several studies did not describe acceptable methods of sequence generation and/or allocation concealment, several were at unclear or high risk of attrition bias, and none clearly reported blinded outcome assessment. Serious imprecision as findings were compatible with benefit in either group or with no effect
Brown 2016 Day 3 vs day 2 embryo transfer	59 per 1000	69 per 1000 (50 to 95)	OR 1.16 (0.84 to	2153 (9 RCTs)	Moderate	Poor reporting of allocation concealment and blinding

Table 8. Miscarriage per woman *(Continued)*

			1.60)			
Brown 2016a Ultrasound guidance vs clinical touch for embryo transfer	44 per 1000	44 per 1000 (33 to 57)	OR 0.99 (0.74 to 1.31)	4053 (11 RCTs)	Low	Poor reporting of study methods
Derks 2009 Cervical dilatation vs no intervention	35 per 1000	23 per 1000	OR 0.64 (0.21 to 1.93)	288 (1 RCT)	Moderate	Serious imprecision and evidence based on a single trial
Abou-Setta 2014 Less bed rest vs more bed rest	47 per 1000	75 per 1000 (38 to 143)	OR 1.63 (0.79 to 3.35)	542 (2 RCTs)	Moderate	Open-label trial
Craciunas 2016 Intrauterine hCG vs no intrauterine hCG	48 per 1000	52 per 1000 (40 to 68)	RR 1.09 (0.83 to 1.43)	3395 (7 RCTs)	Very low	Serious risk of bias and very serious imprecision
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
Tang 2016 Dopamine agonists vs placebo or no treatment	72 per 1000	49 per 1000 (15 to 151)	OR 0.66 (0.19 to 2.28)	168 (2 RCTs)	Low	Poor reporting of study methods and serious imprecision
D'Angelo 2017 Coasting vs no coasting	57 per 1000	49 per 1000 (15 to 148)	OR 0.85 (0.25 to 2.86)	207 (2 RCTs)	Very low	One study did not clearly describe the methods used; studies not blinded; serious imprecision
12. Frozen embryo transfer cycles						
Wong 2017 Fresh vs fresh and frozen embryo transfer	184 per 1000	131 per 1000 (105 to 162)	OR 0.67 (0.52 to 0.86)	1892 (4 RCTs)	Low	Serious risk of bias and serious imprecision
Ghobara 2017 Natural cycle FET vs modified natural cycle FET (hCG trigger)	24 per 1000	5 per 1000 (0 to 92)	OR 0.20 (0.01 to 4.13)	168 (1 RCT)	Very low	Serious risk of bias as there was no allocation concealment. Very serious imprecision associated with single study, few events, and wide confidence intervals
Ghobara 2017 Modified natural cycle FET (hCG trigger) vs hormone therapy + GnRHa FET	68 per 1000	51 per 1000 (18 to 138)	OR 0.74 (0.25 to 2.19)	236 (1 RCT)	Low	Unclear risk of bias in most domains, serious imprecision with wide confidence intervals
Ghobara 2017	48 per 1000	31 per 1000 (18 to 53)	OR 0.64 (0.37 to 1.12)	991 (6 RCTs)	Low	Unclear reporting of methods, serious im-

Table 8. Miscarriage per woman *(Continued)*

Hormone therapy FET vs hormone therapy + GnRHa FET						precision with wide confidence intervals
Ghobara 2017 hMG FET vs clomiphene + hMG FET	37 per 1000	49 per 1000 (13 to 164)	OR 1.33 (0.35 to 5.09)	209 (1 RCT)	Very low	Unclear risk of bias in all domains, very serious imprecision with very few events and wide confidence intervals

ART: assisted reproduction techniques.
CI: confidence interval.
DHEA: dehydroepiandrosterone.
ET: embryo transfer.
FET: frozen embryo transfer.
FSH: follicle-stimulating hormone.
GnRH: gonadotrophin-releasing hormone.
GnRHa: gonadotrophin-releasing hormone agonist.
HA: hyaluronic acid.
hCG: human chorionic gonadotrophin.
hMG: human menopausal gonadotrophin.
IMSI: ultra-high magnification sperm selection.
IVF: in vitro fertilisation.
OHSS: ovarian hyperstimulation syndrome.
OR: odds ratio.
PICSI: physiological intracytoplasmic sperm injection.
RCT: randomised controlled trial.
rFSH: recombinant follicle-stimulating hormone.
rhCG: recombinant human chorionic gonadotrophin.
RR: risk ratio.
TLS: time-lapse imaging.
uhCG: urinary human chorionic gonadotrophin.

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

- Benschop 2012: "Immune therapies for women with history of failed implantation undergoing IVF treatment"- KH1670
- Nyachieo 2009: "Nonsteroidal anti-inflammatory drugs for assisted reproductive technology" - LMW1121
- Zhu 2013: "Acupuncture for female subfertility" - XZ1550
- Kamath 2017a:"Screening hysteroscopy in subfertile women undergoing assisted reproduction" - JK1940
- Siristatidis 2018: "Endometrial injection of embryo culture supernatant for subfertile women in assisted reproduction" - CS1985

Embryo transfer

- Baak 2016: "Temperature of embryo culture for assisted reproduction" - NAB1977
- Craciunas 2016a: "Oxytocin antagonists for assisted reproduction" - LC1971
- Nastri 2013:"Interventions for improving reproductive outcomes in women with recurrent implantation failure undergoing assisted reproductive techniques" - WPM1850

Frozen cycles

- Chua 2012: "Slow freeze versus vitrification for embryo cryopreservation" - CB994

Luteal phase support

- Abou-Setta 2006: "Soft versus firm embryo transfer catheters for assisted reproductive technology" - GG603
- Checa 2016: "Luteal phase support for women trying to conceive by intrauterine insemination or sexual intercourse" - MAC1967

Titles

Three active titles were identified.

- AYW1983 - "Day 3 versus day 5 embryo biopsy for preimplantation genetic diagnosis"
- JML1979 - "GM-CSF (granulocyte macrophage colony stimulating factor) supplementation in culture media for subfertile women undergoing ART"
- SHJ881 - "Long-term GnRH agonist therapy before in vitro fertilization (IVF) for improving fertility outcomes in women with endometriosis"

WHAT'S NEW

Date	Event	Description
19 June 2018	New citation required and conclusions have changed	The addition of 9 new reviews has led to a change in the conclusions of this overview
19 June 2018	New search has been performed	In the 2018 update, we added 9 new reviews (Ata 2018; Craciunas 2016; Kalampokas 2017; Lensen 2018; Nagels 2015; Reavey 2016; Siristatidis 2018; Wong 2017; Youssef 2015) and updated the findings of 18 reviews (Al-Inany 2016; Brown 2016; Brown 2016a; D'Angelo 2017; Farquhar 2017; Georgiou 2018; Ghobara 2017; Glujovsky 2016; Kamath 2017; Kwan 2018; Mochtar 2017; Pandian 2015; Showell 2017; Siristatidis 2015; Siristatidis 2016; Tang 2016; Youssef 2016; Youssef 2016a)

HISTORY

Protocol first published: Issue 5, 2013
Review first published: Issue 8, 2013

Date	Event	Description
19 April 2016	Amended	Updated declaration of interest
23 September 2015	Amended	Corrected minor typos in text
11 September 2015	Amended	Made minor corrections to text and data tables
13 August 2015	Amended	Made minor correction to data in additional tables
8 July 2015	New citation required but conclusions have not changed	Additional information has not led to a change in the conclusions of this review
1 July 2015	New search has been performed	Added one new review: SCA1950 (Armstrong 2015) Updated three reviews: MV263 (van der Linden 2015), AWP1710 (Pouwer 2015), and WM 1504 (Nastri 2015)
22 December 2014	New citation required but conclusions have not changed	Added evidence from four new and six updated reviews

Date	Event	Description
31 October 2014	New search has been performed	Updated six reviews: AAS605 (Abou-Setta 2014); DB552 (Bontekoe 2014); IOK972 (Kwan 2014); MGS1510 (Showell 2014); MM1690 (Youssef 2014); LDT 1201(Tso 2014) Added four new reviews: DG1352 (Glujovsky 2014); RBG1760 (Gutarra-Vilchez 2014); SMD1810 (McDowell 2014); SH1141 (McDonnell 2014)
13 November 2013	Amended	Made minor correction to data in one included review - no effect on findings of this overview
14 October 2013	Amended	Made minor amendment to abstract and results

CONTRIBUTIONS OF AUTHORS

For the 2018 update, JM and CF extracted and checked the data, drafted the text and interpreted the evidence.

DECLARATIONS OF INTEREST

Professor Farquhar, and Jane Marjoribanks are authors on some of the included reviews. They have no conflicts of interest related to commercial funding.

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

SOURCES OF SUPPORT

Internal sources

- University of Auckland research grant, New Zealand.

External sources

- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans