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Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction (Review)

Craciunas L, Tsampras N, Raine-Fenning N, Coomarasamy A

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[Intervention Review]

Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction

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ABSTRACT

Background

Most women undergoing assisted reproduction treatment will reach the stage of embryo transfer (ET), but the proportion of embryos that can be successfully implanted after ET has remained small since the mid-1990s. Human chorionic gonadotropin (hCG) is a hormone that is synthesised and released by the syncytiotrophoblast and has a fundamental role in embryo implantation and the early stages of pregnancy. Intrauterine administration of hCG via ET catheter during a mock procedure around the time of ET is a novel approach that has been suggested to improve the outcomes of assisted reproduction.

Objectives

To investigate whether intrauterine (intracavity) administration of hCG (IC-hCG) around the time of ET improves clinical outcomes in subfertile women undergoing assisted reproduction.

Search methods

We performed searches on 9 January 2018 using Cochrane methods.

Selection criteria

We looked for randomised controlled trials (RCTs) evaluating IC-hCG around the time of ET, irrespective of language and country of origin.

Data collection and analysis

Two review authors independently selected studies, assessed risk of bias, extracted data from studies, and attempted to contact study authors when data were missing. We performed statistical analysis using Review Manager 5. We assessed evidence quality using GRADE methods. Primary outcomes were live birth and miscarriage; secondary outcomes were clinical pregnancy rate and complications.

Main results

Seventeen RCTs investigated the effects of IC-hCG administration for 4751 subfertile women undergoing assisted reproduction. IC-hCG was administered in variable doses at different times before the ET. hCG was obtained from the urine of pregnant women or from cell cultures using recombinant DNA technology.

Most studies (12/17) were at high risk of bias in at least one of the seven domains assessed. Common problems were unclear reporting of study methods and lack of blinding. The main limitations for evidence quality were high risk of bias and serious imprecision.

For analyses of live birth and clinical pregnancy, there was considerable heterogeneity (I^2 > 75%) and therefore we present subgroups for dosage and stage of ET. Exploration for sources of heterogeneity revealed two key prespecified variables as important determinants: stage of ET (cleavage vs blastocyst stage) and dose of IC-hCG (< 500 international units (IU) vs ≥ 500 IU). We performed meta-analyses within subgroups defined by stage of embryo and dose of IC-hCG.

Live birth rates among women having cleavage-stage ET with an IC-hCG dose < 500 IU compared to women having cleavage-stage ET without IC-hCG showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude (risk ratio (RR) 0.76, 95% confidence interval (CI) 0.58 to 1.01; one RCT; 280 participants; I^2 = 0%; very low-quality evidence). In a clinic with a live birth rate of 49% per cycle, use of IC-hCG < 500 IU would be associated with a live birth rate ranging from 28% to 50%.

Results show an increase in live birth rate in the subgroup of women undergoing cleavage-stage ET with an IC-hCG dose ≥ 500 IU compared to women having cleavage-stage ET without IC-hCG (RR 1.57, 95% CI 1.32 to 1.87; three RCTs; 914 participants; I^2 = 0%; moderate-quality evidence). At a clinic with a live birth rate of 27% per cycle, use of IC-hCG ≥ 500 IU would be associated with a live birth rate ranging from 36% to 51%.

Results show no substantive differences in live birth among women having blastocyst-stage ET with an IC-hCG dose ≥ 500 IU compared to women having blastocyst-stage ET without IC-hCG (RR 0.92, 95% CI 0.80 to 1.04; two RCTs; 1666 participants; I^2 = 0%; moderate-quality evidence). At a clinic with a live birth rate of 36% per cycle, use of IC-hCG ≥ 500 IU would be associated with a live birth rate ranging from 29% to 38%.

Evidence for clinical pregnancy among women having cleavage-stage ET with an IC-hCG dose < 500 IU showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude (RR 0.88, 95% CI 0.70 to 1.10; one RCT; 280 participants; I^2 = 0%; very low-quality evidence).

Results show an increase in clinical pregnancy rate in the subgroup of women having cleavage-stage ET with an IC-hCG dose ≥ 500 IU compared to women having cleavage-stage ET without IC-hCG (RR 1.49, 95% CI 1.32 to 1.68; 12 RCTs; 2186 participants; I^2 = 18%; moderate-quality evidence).

Results show no substantive differences in clinical pregnancy among women having blastocyst-stage ET with an IC-hCG dose ≥ 500 IU (RR 0.99, 95% CI 0.85 to 1.15; four RCTs; 2091 participants; I^2 = 42%; moderate-quality evidence) compared to women having blastocyst-stage ET with no IC-hCG.

No RCTs investigated blastocyst-stage ET with an IC-hCG dose < 500 IU.

We are uncertain whether miscarriage was influenced by intrauterine hCG administration (RR 1.04, 95% CI 0.81 to 1.35; 11 RCTs; 3927 participants; I^2 = 0%; very low-quality evidence).

Reported complications were ectopic pregnancy (four RCTs; 1073 participants; four events overall), heterotopic pregnancy (one RCT; 495 participants; one event), intrauterine death (three RCTs; 1078 participants; 22 events), and triplets (one RCT; 48 participants; three events). Events were few, and very low-quality evidence was insufficient to permit conclusions to be drawn.

Authors' conclusions

There is moderate quality evidence that women undergoing cleavage-stage transfer using an IC-hCG dose ≥ 500 IU have an improved live birth rate. There is insufficient evidence for IC-hCG treatment for blastocyst transfer. There should be further trials with live birth as the primary outcome to identify the groups of women who would benefit the most from this intervention. There was no evidence that miscarriage was reduced following IC-hCG administration, irrespective of embryo stage at transfer or dose of IC-hCG. Events were too few to allow conclusions to be drawn with regard to other complications.

PLAIN LANGUAGE SUMMARY

The effect of administering pregnancy hormone into the womb of subfertile women undergoing assisted reproduction

Review question

Does administering pregnancy hormone into the womb of subfertile women undergoing assisted reproduction provide any benefit?

Background

Subfertility affects 15% of couples and is defined as the inability to become pregnant naturally following 12 months of regular unprotected sexual intercourse. Assisted reproduction refers to procedures involving handling of both sperm and eggs in the laboratory to create

embryos to be transferred into the womb (embryo transfer (ET)). Administering natural or synthetic pregnancy hormone into the womb of subfertile women undergoing assisted reproduction treatment is a novel approach that might increase the chance of having a baby.

Study characteristics

We evaluated 17 studies (4751 women) comparing administration of pregnancy hormone versus no hormone. The natural or synthetic hormone was administered at variable doses at different times before ET.

Key results

Live birth rates in women having day three ET with human chorionic gonadotropin administered into the uterus (IC-hCG) at a dose < 500 IU compared to women having day three ET without pregnancy hormone showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude (very low-quality evidence: one study; 280 women). In a clinic with a live birth rate of 49% per cycle following day three ET, use of a pregnancy hormone dose < 500 IU would be associated with a live birth rate varying from 28% to 50%.

Live birth rate was increased in a subgroup of women having day three ET with a pregnancy hormone dose of 500 IU or greater compared to women having day three ET without pregnancy hormone (moderate-quality evidence: three studies; 914 women). At a clinic with a live birth rate of 27% per cycle, use of a pregnancy hormone dose of 500 IU or greater would be associated with a live birth rate varying from 36% to 51%.

Trial results show no substantive differences in live birth among women having day five ET with a pregnancy hormone dose of 500 IU or greater compared to women having day five ET without pregnancy hormone (moderate-quality evidence: two studies; 1666 women). At a clinic with a live birth rate of 36% per cycle, use of a pregnancy hormone dose of 500 IU or greater would be associated with a live birth rate varying from 29% to 38%.

We are uncertain whether administration of pregnancy hormone into the womb at any dose or time affected miscarriage (very low-quality evidence: 11 studies; 3927 women).

Evidence for clinical pregnancy among women having day three ET with a pregnancy hormone dose < 500 IU showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude (very low-quality evidence: one study; 280 women).

The clinical pregnancy rate was increased in the subgroup of women having day three ET with a pregnancy hormone dose of 500 IU or greater compared to women having day three ET without pregnancy hormone (moderate-quality evidence: 12 studies; 2186 women).

Trial results show no substantive difference in clinical pregnancy among women having day five ET with a pregnancy hormone dose of 500 IU or greater compared to women having day five ET with no pregnancy hormone (moderate-quality evidence: four studies; 2091 women).

No randomised controlled trials (RCTs) investigated day five ET with a pregnancy hormone dose < 500 IU.

Other complications reported in the included studies were ectopic pregnancy (where the embryo develops outside the womb), heterotopic pregnancy (where embryos develop inside and outside the womb), foetal death, and triplets. Events were few, and insufficient evidence of very low quality does not permit us to determine whether there were differences between groups.

There should be further trials with live birth as the primary outcome to identify the groups of women who would benefit the most from this intervention.

Quality of the evidence

Evidence quality varied from very low to moderate depending on the outcome. The main limitations for the overall quality of the evidence were high risk of bias and serious imprecision.

Summary of findings for the main comparison. Intrauterine administration of hCG for women undergoing assisted reproduction

Intrauterine administration of hCG for women undergoing assisted reproduction

Patient or population: subfertile women undergoing assisted reproduction
Setting: assisted reproduction units
Intervention: intrauterine human chorionic gonadotropin (hCG)
Comparison: no intrauterine hCG

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no hCG	Risk with intrauterine human chorionic gonadotropin (hCG)			
Live birth Cleavage stage: hCG < 500 IU Follow-up: mean 40 weeks	495 per 1000	376 per 1000 (287 to 500)	RR 0.76 (0.58 to 1.01)	280 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b]
Cleavage stage: hCG ≥ 500 IU Follow-up: mean 40 weeks	273 per 1000	428 per 1000 (360 to 510)	RR 1.57 (1.32 to 1.87)	914 (3 RCTs)	⊕⊕⊕⊖ MODERATE[c]
Blastocyst stage: hCG ≥ 500 IU Follow-up: mean 40 weeks	369 per 1000	340 per 1000 (296 to 384)	RR 0.92 (0.80 to 1.04)	1666 (2 RCTs)	⊕⊕⊕⊖ MODERATE[c]
Miscarriage Follow-up: mean 40 weeks	58 per 1000	60 per 1000 (47 to 78)	RR 1.04 (0.81 to 1.35)	3927 (11 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d]
Clinical pregnancy Cleavage stage: hCG < 500 IU Follow-up: mean 12 weeks	579 per 1000	509 per 1000 (405 to 637)	RR 0.88 (0.70 to 1.10)	280 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,d]
Cleavage stage: hCG ≥ 500 IU Follow-up: mean 12 weeks	307 per 1000	458 per 1000 (406 to 517)	RR 1.49 (1.32 to 1.68)	2186 (12 RCTs)	⊕⊕⊕⊖ MODERATE[c]
Blastocyst stage: hCG ≥ 500 IU Follow-up: mean 12 weeks	422 per 1000	418 per 1000 (359 to 485)	RR 0.99 (0.85 to 1.15)	2091 (4 RCTs)	⊕⊕⊕⊖ MODERATE[c]
Complications Follow-up: mean 40 weeks	Other complications reported in the included studies were ectopic pregnancy (4 RCTs; N = 1073; 4 events overall), heterotopic pregnancy (1 RCT; N = 495; 1 event), intrauterine death (3 RCTs; N = 1078; 22 events), and triplets (1 RCT; N = 48;		-	1764 (7 RCTs)	⊕⊖⊖⊖ VERY LOW[c,d]

				3 events). No evidence shows a difference between groups, but events were too few for any conclusions to be drawn.	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; hCG: human chorionic gonadotropin; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded two levels for very serious risk of bias: lack of blinding of participants and personnel, no clear description of allocation concealment, and premature termination of the study following interim analysis.
[b]Downgraded one level for serious imprecision: total events were fewer than 300.
[c]Downgraded one level for serious risk of bias: lack of blinding of participants and personnel, no allocation concealment.
[d]Downgraded two levels for very serious imprecision: total number of events was less than 300, and 95% confidence interval around the pooled effect includes both no effect and appreciable benefit or appreciable harm.

BACKGROUND

Description of the condition

Subfertility is defined as the inability of a couple to conceive spontaneously following 12 months of regular unprotected sexual intercourse. It is estimated that 15% of couples are affected by subfertility of different causes (female factor, male factor, unexplained). Assisted reproduction refers to procedures involving the in vitro (in a laboratory dish) handling of both human gametes (sperm and eggs) with the objective of establishing a pregnancy (Zegers-Hochschild 2009). The most vulnerable step of assisted reproduction is the embryo transfer (ET), as it involves a radical change in the embryo's environment, which makes it prone to demise (Schoolcraft 2001). Most women undergoing assisted reproduction treatment will reach the stage of ET owing to important improvements in ovarian stimulation protocols and laboratory technology, but the proportion of embryos that successfully implant following ET has remained small (less than one-third) since the mid-1990s (Kupka 2014).

The process of implantation involves a reciprocal interaction between the embryo and the endometrium, culminating in a small reception-ready phase of the endometrium, during which implantation can occur. This interaction is dependent on the temporal differentiation of endometrial cells to attain uterine receptivity. Implantation failure is thought to occur as a consequence of impairment of the embryo developmental potential or impairment of uterine receptivity, or both, and the embryo-uterine dialogue (Diedrich 2007).

Many interventions have been attempted with varying degrees of success before ET (endometrial injury (Nastri 2012), dummy ET (Mansour 1990), endometrial preparation (Derks 2009), peri-implantation (heparin (Akhtar 2013), aspirin (Siristatidis 2016)), during ET (ultrasound guidance (Brown 2010), removal of cervical mucus (Craciunas 2014)), and after ET (fibrin sealant, bed rest (Abou-Setta 2014)) to optimise the embryo-endometrial interaction and improve outcomes.

Description of the intervention

Human chorionic gonadotropin (hCG) is a hormone that is synthesised and released by the syncytiotrophoblast. It stimulates ovarian production of progesterone during the first trimester of pregnancy. Intrauterine administration of synthetic or natural hCG around the time of ET is a novel approach that has been suggested to improve the outcomes of assisted reproduction treatment based on the fundamental role of hCG in embryo implantation and the early stages of pregnancy (Cole 2010). The intervention involves intrauterine administration of hCG via an ET catheter during a mock procedure (a trial of the actual ET without using an embryo, performed to assess the difficulty of the ET) using the lowest volume of medium before the conventional ET. The hCG can be released at different points inside the uterine cavity (close to the internal cervical os, mid-cavity, or near the fundus) within minutes, hours, or days before the actual ET. hCG sources for medical treatments include extraction from the urine of pregnant women (natural) or from cell cultures using recombinant DNA technology (rhCG).

How the intervention might work

The hCG may promote peritrophoblastic immune tolerance, which facilitates trophoblast invasion by inducing an increase in endometrial T-cell apoptosis (Kayisli 2003). It also supports trophoblast apposition (the first stage of implantation - loose alignment of the trophoblast to the decidua) and adhesion (second stage of implantation - closer attachment of the trophoblast to the decidua) to the endometrium by regulating proteins involved in implantation (Racicot 2014). Intrauterine injection of urinary hCG alters endometrial secretory parameters (Licht 1998), and cell proliferation and migration are increased in the presence of hCG (Bourdiec 2013).

Why it is important to do this review

Subfertility affects a relatively large proportion of couples, and assisted reproduction treatments remain costly and stressful. All effort should be directed towards increasing the success rate of infertility treatments, and primary research should be translated into clinical practice in an efficient and timely manner. Intrauterine administration of hCG around the time of ET has the potential to improve the outcomes of assisted reproduction treatments; randomised and non-randomised trials have reported varying results (Mansour 2011; Rebolloso 2013).

Previous meta-analyses assessed the efficacy of intrauterine injection of hCG before ET in assisted reproductive cycles, but improvements could be made to the methods of analysis (Dieamant 2016; Osman 2016; Ye 2015). Different studies have evaluated variable circumstances of intrauterine hCG administration in terms of stage of the embryo at transfer (cleavage vs blastocyst), source of hCG (urine vs recombinant), dose of hCG, embryo processing (fresh vs frozen/thawed), and number of embryos transferred, leading to real uncertainties about the role of the intervention. The previous version of this review reported promising outcomes for cleavage-stage ET following intrauterine injection of hCG at a dose of 500 IU or more (Craciunas 2016), but the evidence was weak and newly published randomised controlled trials may have altered our confidence in the results.

OBJECTIVES

To investigate whether intrauterine (intracavity) administration of hCG (IC-hCG) around the time of ET improves clinical outcomes in subfertile women undergoing assisted reproduction.

METHODS

Criteria for considering studies for this review

Types of studies

We included in this review all randomised controlled trials (RCTs) evaluating intrauterine (intracavity) administration of hCG (IC-hCG) around the time of ET, irrespective of language and country of origin. We planned to include only data from the first phase of cross-over RCTs in meta-analyses.

Types of participants

We included subfertile women undergoing in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) followed by ET.

Types of interventions

RCTs comparing intrauterine administration of hCG around the time of ET versus any other active intervention, no intervention, or placebo were eligible for inclusion.

Types of outcome measures

Primary outcomes

- Live birth (delivery of a live foetus after 24 completed weeks of gestation) rate per woman or couple randomised
- Miscarriage (loss of pregnancy before 24 completed weeks of gestation) rate per woman or couple randomised

Secondary outcomes

- Clinical pregnancy (presence of a gestational sac on ultrasound scan) rate per woman or couple randomised
- Complication rate per woman or couple randomised, including ectopic pregnancy, intrauterine growth restriction, foetal or congenital defects, pelvic infection, or other adverse events, reported as an overall complication rate or as individual outcomes, or both (as reported by individual studies)

Search methods for identification of studies

We sought all published and unpublished RCTs of intrauterine hCG administration around the time of ET in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist. Search dates ranged from inception of the databases to 9 January 2018, and we applied no language restrictions.

Electronic searches

We searched the following.

- Cochrane Gynaecology and Fertility Group Specialised Register (searched 9 January 2018) (PROCITE platform) (Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (via the CENTRAL Register of Studies Online (CRSO)) (searched 9 January 2018) (Web platform) (Appendix 2).
- MEDLINE (searched from 1946 to 9 January 2018) (OVID platform) (Appendix 3).
- Embase (searched from 1980 to 9 January 2018) (OVID platform) (Appendix 4).
- PsycINFO (searched from 1806 to 9 January 2018) (OVID platform) (Appendix 5).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (searched from 1961 to 9 January 2018) (EBSCO platform) (Appendix 6).

We combined the MEDLINE search with the Cochrane highly sensitive search strategy for identifying RCTs, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; Chapter 6, Section 6.4.11). We combined the Embase and CINAHL searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

We also searched the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/Default.aspx) and ClinicalTrials.gov for ongoing and registered trials. We searched OpenGrey (www.opengrey.eu/) and Google Scholar (scholar.google.co.uk/) for grey literature. We handsearched abstracts published following major conferences (e.g. the American Society for Reproductive Medicine (ASRM), European Society of Human Reproduction and Embryology (ESHRE)) held in the last five years to find additional studies not yet published in full.

Searching other resources

We screened the reference lists of all included studies and relevant reviews to identify further articles for possible inclusion.

Data collection and analysis

We used Review Manager 5 for input of data and statistical analysis (RevMan 2014), in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors (LC and NT) independently screened the title, abstract, and keywords for each publication to exclude studies that were irrelevant for the objective of this review. We retrieved the remaining publications in full text, and the same two review authors appraised them independently to identify RCTs that were suitable for inclusion. We encountered no disagreements related to study eligibility and documented the selection process with a PRISMA flow chart.

Data extraction and management

Two review authors (LC and NT) independently extracted data using a pre-designed and pilot-tested data extraction form. For studies with multiple publications, we used the main RCT report as the reference, and we supplemented it with additional data from secondary publications. We attempted to contact study authors when published data were insufficient. We encountered no disagreements. One review author (LC) entered data into Review Manager 5 (RevMan 2014), and a second review author (NT) checked entered data against the data extraction form.

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' assessment tool to assess the included studies for selection, performance, detection, attrition, reporting, and other biases. We encountered no disagreements. We included the 'Risk of bias' table in the Characteristics of included studies table, describing the judgements in detail.

Measures of treatment effect

All outcomes were dichotomous. We calculated Mantel-Haenszel risk ratios (RRs) with 95% confidence intervals (CIs) using the numbers of events in the intervention and control groups of each study. For outcomes with event rates below 1%, we used the Peto one-step odds ratio (OR) method to calculate the combined outcome with 95% CI.

Unit of analysis issues

We performed analysis per randomised woman or couple for live birth, clinical pregnancy, miscarriage, and complication rates. We counted multiple live births (twins, triplets) as a single live birth event. We performed a secondary analysis for miscarriage per clinical pregnancy to broaden our understanding of the treatment effect.

If a study included multiple treatment arms based on hCG dose, we planned to split the control group proportionately with the experimental groups to avoid analysing control participants in duplicate.

Dealing with missing data

We attempted to contact authors of the RCTs to obtain missing data so we could perform analyses on an intention-to-treat basis. In the case of unobtainable data, we planned to undertake imputation of individual values for the live birth rate only. We assumed that live births had not occurred in participants without a reported outcome. For other outcomes, we analysed only available data.

Assessment of heterogeneity

We identified heterogeneity by visually inspecting forest plots and by using a standard Chi^2 test with significance set at $P < 0.1$. We used the I^2 statistic to estimate total variation across RCTs that was due to heterogeneity, when I^2 greater than 50% indicated substantial heterogeneity.

Assessment of reporting biases

We conducted a comprehensive search to minimise the potential impact of publication bias and other reporting biases. We planned to use a funnel plot to explore the possibility of small-study effects when the number of included RCTs exceeded 10.

Data synthesis

We combined the data from similar RCTs comparing similar treatments using a random-effects model. We displayed an increase in the odds of an outcome to the right of the centre line and a decrease in the odds of an outcome to the left of the centre line. For comparisons that showed considerable clinical, methodological, or statistical heterogeneity ($I^2 > 75\%$), we did not combine results of RCTs in a meta-analysis. When data were incomplete and could not be presented in the analyses, we reported available data in narrative form.

Subgroup analysis and investigation of heterogeneity

When data were available, we conducted subgroup analyses to investigate the efficacy of intrauterine hCG administration around the time of ET depending on:

- stage of the embryo at transfer (cleavage vs blastocyst);
- source of intracavity hCG (IC-hCG) (urine vs recombinant);
- embryo processing (fresh vs frozen/thawed); and
- number of embryos transferred.

If we detected substantial heterogeneity, we explored possible explanations in sensitivity analyses. Factors considered included treatment indication, age of the women, ovarian stimulation protocol, response to ovarian stimulation, timing of IC-hCG administration, IC-hCG dose and volume of infused medium, method of IC-hCG administration (i.e. type of catheter), embryo quality, endometrial thickness, source of oocytes (i.e. donated, own), and ET difficulty. We took any statistical heterogeneity into account when interpreting the results, especially if we noted variation in the direction of effect.

Sensitivity analysis

We performed sensitivity analysis to examine the stability and robustness of results for the primary outcomes in relation to the following eligibility and analysis factors.

- Inclusion of RCTs without high risk of bias in one or more domains.
- Inclusion of RCTs published as full text.
- Use of a fixed-effect model.
- Calculation of OR.

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

Two review authors working independently (LC and NT) prepared a 'Summary of findings' table using GRADEpro software and comparing hCG versus no hCG (GRADEpro 2015). We resolved disagreements by discussion. In this table, we evaluated the overall quality of the body of evidence for the main review outcomes (live birth rate, miscarriage, clinical pregnancy rate, and complications) using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, and publication bias) (GRADE 2013). We justified, documented, and incorporated judgements about evidence quality (high, moderate, low, or very low) into reporting of results for each outcome.

RESULTS

Description of studies

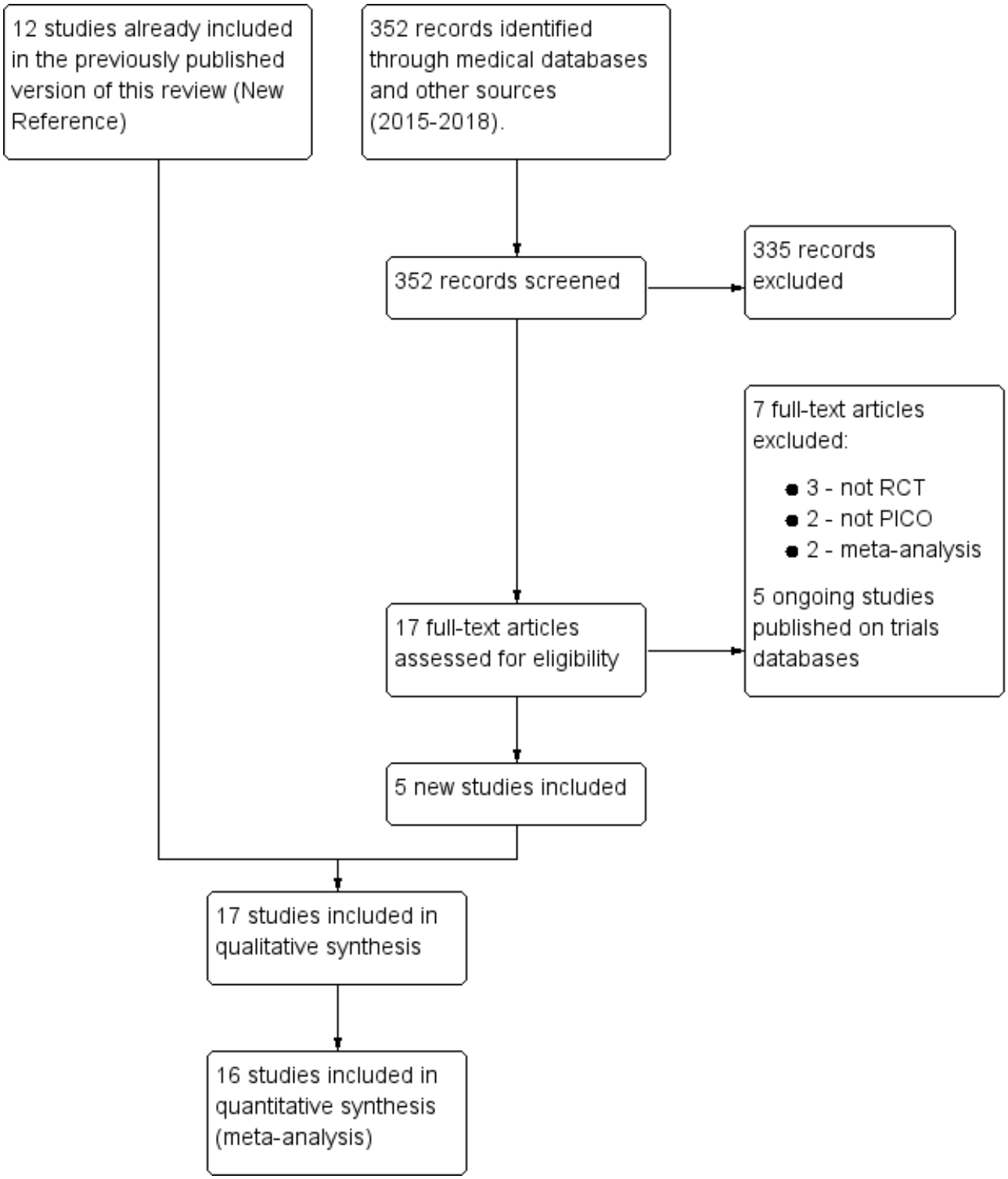
See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

We performed the latest systematic search on 9 January 2018, and we identified 352 publications (14 from CINAHL, 91 from CENTRAL, 133 from EMBASE, 41 from CGFG, 58 from MEDLINE, 2 from PsychINFO, and 13 from other sources).

In this updated review, we have included 17 studies (12 in the previous version), excluded 13 studies (six in the previous version), and identified two studies awaiting classification and five ongoing studies. See Figure 1 for detailed search results.

Figure 1. Study flow diagram.



Included studies

Types of studies

All 17 included studies were parallel-arm RCTs. One study had two experimental arms (IC-hCG 500 IU vs IC-hCG 1000 IU vs control) (Dehghani Firouzabadi 2016), one study had two phases with three experimental arms (phase one: IC-hCG 100 IU vs IC-hCG 200 IU vs control; and phase two: IC-hCG 500 IU vs control) (Mansour 2011), and one study had two experimental arms using two different timings (IC-hCG 500 IU vs control two days before ET; IC-hCG 500 IU vs control on the day of ET) (Wirleitner 2015a).

Researchers performed randomisation at different times during treatment. Five studies randomised participants before the start

of their treatment cycle (Dehghani Firouzabadi 2016; Hong 2014; Mansour 2011; Santibañez 2014; Singh 2014), two studies randomised participants on the day of oocyte retrieval (Navali 2016; Wirleitner 2015a), four studies randomised participants on the day of embryo transfer (Aaleyasin 2015; Cambiaghi 2013; Hosseini 2016; Huang 2016), and the remaining six studies provided insufficient details about the timing of randomisation (Eskandar 2016; Kokkali 2014; Leao 2013; Mostajeran 2017; Wirleitner 2015b; Zarei 2014).

Eleven studies were published as full-text articles (Aaleyasin 2015; Dehghani Firouzabadi 2016; Hong 2014; Hosseini 2016; Huang 2016; Mansour 2011; Mostajeran 2017; Navali 2016; Santibañez 2014; Wirleitner 2015a; Zarei 2014), and six studies were published as abstracts (Cambiaghi 2013; Eskandar 2016; Kokkali 2014; Leao 2013; Singh 2014; Wirleitner 2015b).

Ten studies did not report funding (Aaleyasin 2015; Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hong 2014; Hosseini 2016; Huang 2016; Leao 2013; Mostajeran 2017; Wirleitner 2015a), and seven studies reported internal funding (Kokkali 2014; Mansour 2011; Navali 2016; Santibañez 2014; Singh 2014; Wirleitner 2015b; Zarei 2014). No studies reported external funding.

Participants

Participants were couples/women recruited before undergoing assisted reproductive treatment for different subfertility causes. The number of participants varied between 36 in Leao 2013 and 1186 in Wirleitner 2015a. The studies were conducted in the USA, Austria, Greece, Iran, China, Saudi Arabia, Brazil, Egypt, Mexico, and India.

Interventions

Most studies compared intrauterine administration of urine hCG 500 IU versus controls. One study had two additional arms with lower doses (IC-hCG 100 and 200 IU) (Mansour 2011). One study had an additional arm with a higher dose (IC-hCG 1000 IU) (Dehghani Firouzabadi 2016). One study used 1000 IU (Huang 2016), and another study used 700 IU (Mostajeran 2017). One study used rhCG 250 µg (equivalent of 6500 IU) (Zarei 2014), and another study used intracavity rhCG (IC-rhCG) 40 µL (equivalent to 500 IU) (Singh 2014).

Twelve studies administered IC-hCG within minutes before ET (Aaleyasin 2015; Dehghani Firouzabadi 2016; Eskandar 2016; Hong 2014; Hosseini 2016; Kokkali 2014; Mansour 2011; Mostajeran 2017; Santibañez 2014; Singh 2014; Wirleitner 2015b; Zarei 2014), ranging from less than three minutes in Hong 2014 up to 12 minutes in Zarei 2014. Two studies administered IC-hCG six hours before ET (Cambiaghi 2013; Leao 2013). One study had four groups (two experimental and two controls) at two different timings (two days before ET and three minutes before ET) (Wirleitner 2015a). One study administered IC-hCG three days before ET (Huang 2016). Another study administered IC-hCG at the time of oocyte retrieval (Navali 2016).

For control groups, seven studies administered the same volume of transfer media (Hong 2014), culture media (Aaleyasin 2015; Singh 2014; Wirleitner 2015a; Wirleitner 2015b), or normal saline (Navali 2016; Zarei 2014), all without hCG, and 10 studies did not administer anything before ET (Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hosseini 2016; Huang 2016; Kokkali 2014; Leao 2013; Mansour 2011; Mostajeran 2017; Santibañez 2014).

Outcomes

Eleven studies reported on one of our predefined primary outcomes: Aaleyasin 2015, Mansour 2011, Singh 2014, Wirleitner 2015a, and Wirleitner 2015b reported on live birth; and Aaleyasin 2015, Dehghani Firouzabadi 2016, Hong 2014, Hosseini 2016, Huang 2016, Mansour 2011, Navali 2016, Singh 2014, Wirleitner 2015a, Wirleitner 2015b, and Zarei 2014 reported on miscarriage.

Seventeen studies reported on one of our predefined secondary outcomes: Aaleyasin 2015, Cambiaghi 2013, Dehghani Firouzabadi 2016, Eskandar 2016, Hong 2014, Hosseini 2016, Huang 2016, Kokkali 2014, Leao 2013, Mansour 2011, Mostajeran 2017, Navali 2016, Santibañez 2014, Singh 2014, Wirleitner 2015a, Wirleitner 2015b, and Zarei 2014 reported on clinical pregnancy; and Aaleyasin 2015, Dehghani Firouzabadi 2016, Hosseini 2016, Mansour 2011, Navali 2016, Santibañez 2014, and Zarei 2014 reported on complications.

Studies awaiting classification

Two studies await classification (Badehnoosh 2014; Bhat 2014). These studies reported interim outcomes (implantation rate and fertilisation rate), and it is unclear whether they also collected data on clinical outcomes that might be relevant to our review. We emailed the authors of these studies in February 2016 and January 2018 to ask for more information on the methods and outcome measures of their studies.

Excluded studies

We excluded 13 studies owing to retrospective design (Huang 2017; Jeong 2013; Kanter 2017), non-randomisation (Li 2013; Rebolloso 2013; Riboldi 2013, Volovsky 2016), not meeting the PICO (Giuliani 2015; Strug 2016), and performing a meta-analysis (Dieamant 2016; Osman 2016; Ye 2015). One study was previously published as an abstract (Janati 2013); this has now been replaced by its full manuscript publication (Dehghani Firouzabadi 2016).

Risk of bias in included studies

Figure 2 shows the 'Risk of bias' graph, and Figure 3 shows the 'Risk of bias' summary. See the Characteristics of included studies table for rationales behind each judgement.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

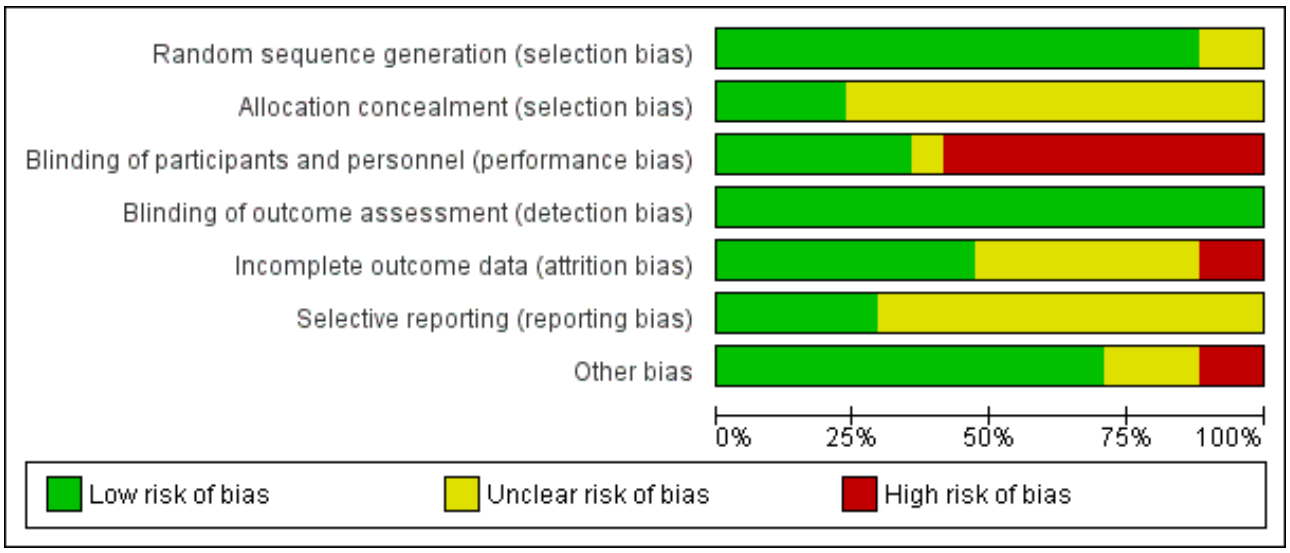
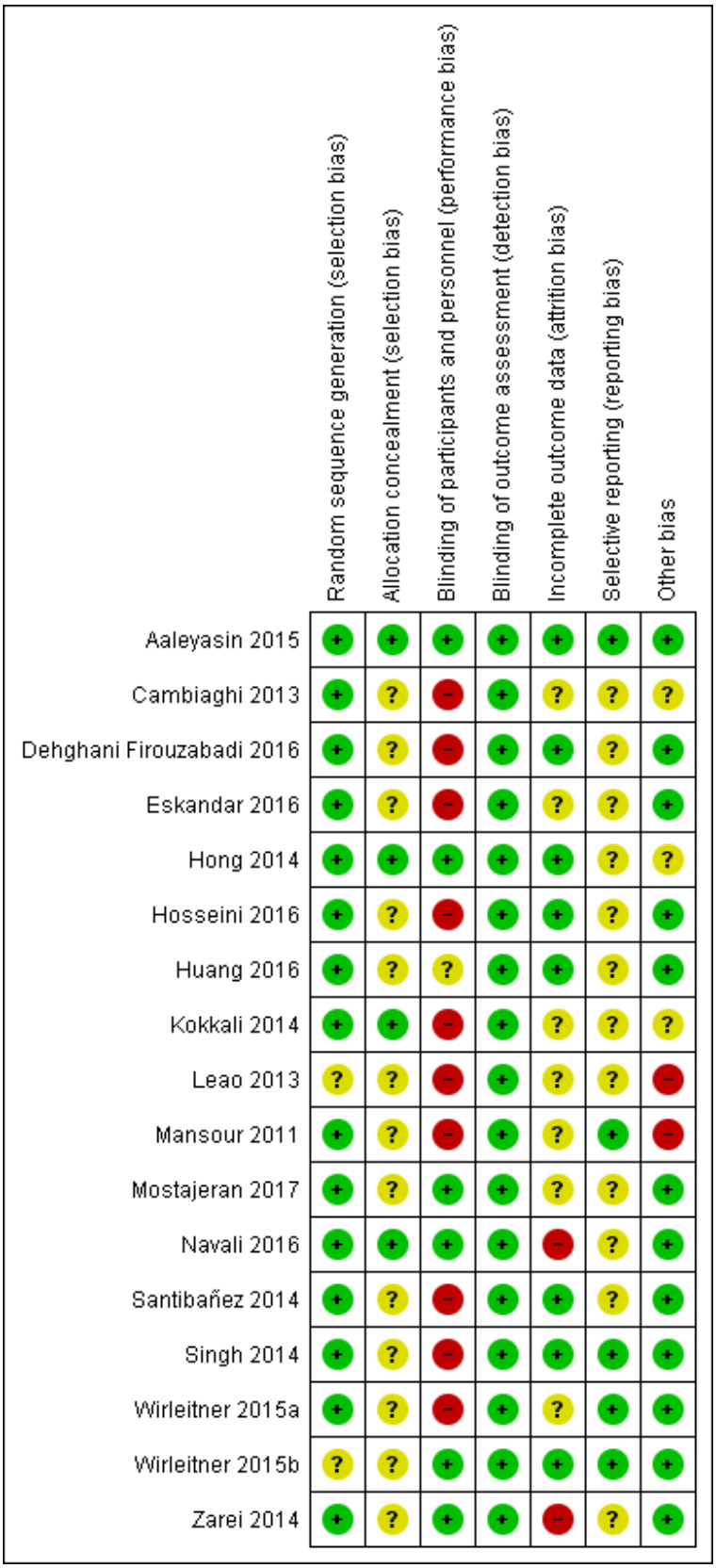


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

All included studies were RCTs. The randomisation technique was adequate in 15 studies (Aaleyasin 2015; Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hong 2014; Hosseini 2016; Huang 2016; Kokkali 2014; Mansour 2011; Mostajeran 2017; Navali 2016; Santibañez 2014; Singh 2014; Wirleitner 2015a; Zarei 2014), which we classified at low risk of bias. Two studies lacked an adequate description of randomisation, and we classified them at unclear risk of bias (Leao 2013; Wirleitner 2015b).

Allocation concealment

Four studies mentioned adequate allocation concealment, and we classified them at low risk of bias (Aaleyasin 2015; Hong 2014; Kokkali 2014; Navali 2016). Thirteen studies lacked a description of methods of allocation concealment, and we classified them at unclear risk of bias (Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hosseini 2016; Huang 2016; Leao 2013; Mansour 2011; Mostajeran 2017; Santibañez 2014; Singh 2014; Wirleitner 2015a; Wirleitner 2015b; Zarei 2014).

Blinding

Six studies documented blinding of participants or personnel (or both), and we classified them at low risk of bias (Aaleyasin 2015; Hong 2014; Mostajeran 2017; Navali 2016; Wirleitner 2015b; Zarei 2014). One study was mentioned to be single-blinded, but it was not clear who was blinded; hence, we classified it as having unclear risk of bias (Huang 2016). We classified the remaining studies at high risk of bias (Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hosseini 2016; Kokkali 2014; Leao 2013; Mansour 2011; Santibañez 2014; Singh 2014; Wirleitner 2015a).

The outcome measurement was not likely to be influenced by lack of blinding; hence, we classified all studies at low risk of bias.

Incomplete outcome data

Eight studies followed up all participants and reported the results adequately (Aaleyasin 2015; Dehghani Firouzabadi 2016; Hong 2014; Hosseini 2016; Huang 2016; Santibañez 2014; Singh 2014; Wirleitner 2015b). We classified these studies at low risk of bias. We classified seven studies at unclear risk of bias (Cambiaghi 2013; Eskandar 2016; Kokkali 2014; Leao 2013; Mansour 2011; Mostajeran 2017; Wirleitner 2015a). Two studies reported large numbers of participants lost to follow-up, and we classified them at high risk of attrition bias (Navali 2016; Zarei 2014).

Selective reporting

Five studies reported on all relevant outcomes, and we classified them at low risk of bias (Aaleyasin 2015; Mansour 2011; Singh 2014; Wirleitner 2015a; Wirleitner 2015b). All studies reported on clinical pregnancy, but if they did not report on live birth, we classified them at unclear risk of bias (Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hong 2014; Hosseini 2016; Huang 2016; Kokkali 2014; Leao 2013; Mostajeran 2017; Navali 2016; Santibañez 2014; Zarei 2014).

Other potential sources of bias

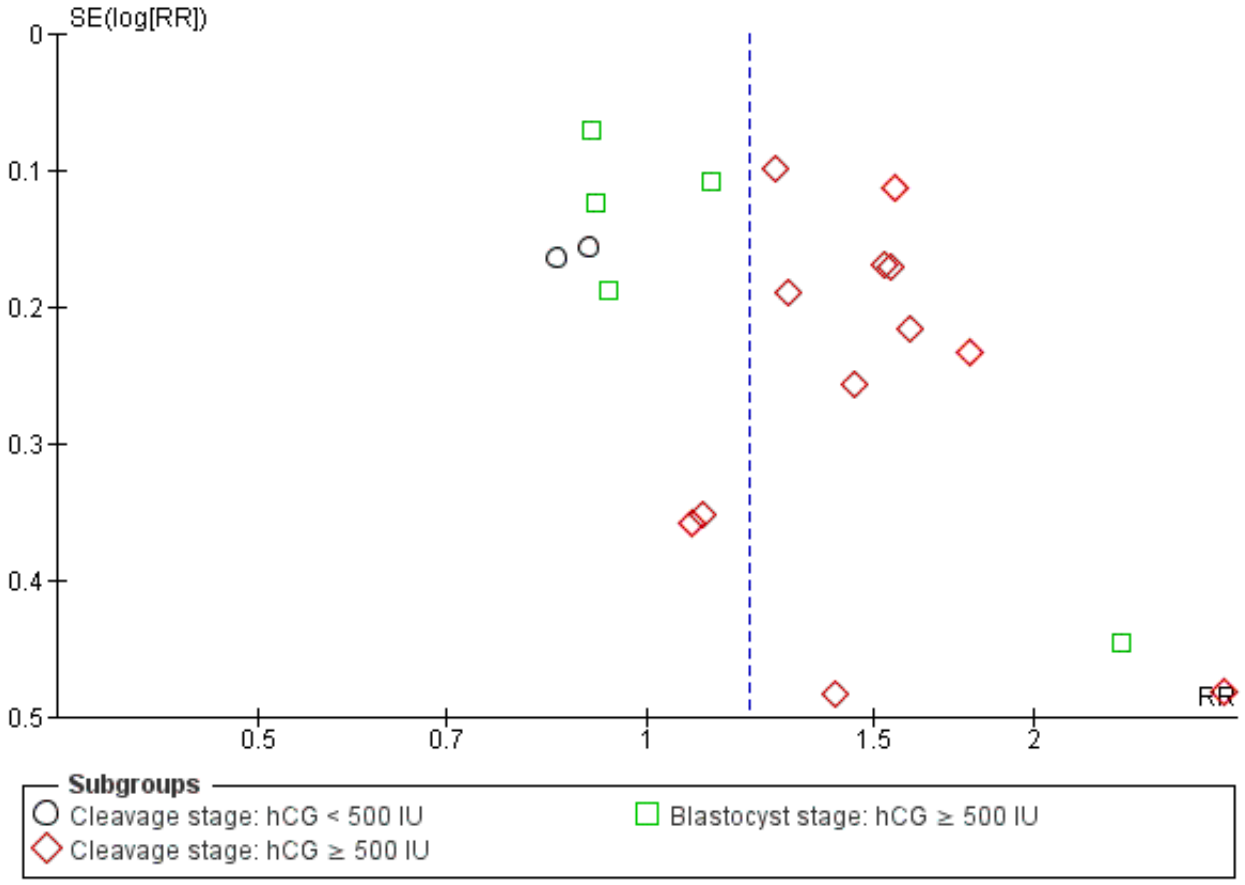
We classified 12 studies at low risk of other potential bias because groups appeared to be comparable at baseline, and we could not identify any other sources of bias (Aaleyasin 2015; Dehghani Firouzabadi 2016; Eskandar 2016; Hosseini 2016; Huang 2016; Mostajeran 2017; Navali 2016; Santibañez 2014; Singh 2014; Wirleitner 2015a; Wirleitner 2015b; Zarei 2014). We classified three studies at unclear risk of bias because they did not report on baseline characteristics between groups (probably because they were available in abstract format only) (Cambiaghi 2013; Kokkali 2014), or they reported a large number of participants who declined to participate after randomisation for various reasons (Hong 2014). We classified two studies at high risk of bias owing to lack of reporting of participant numbers in each study group in Leao 2013, and owing to performance of an interim analysis that changed the study protocol and ended the study prematurely in Mansour 2011.

The overall birth rate in the control groups in Mansour 2011 was 47%, whereas the control group live birth rate ranged from 25% to 39% in the other included studies. The reason for this was unclear. The mean age of women in Mansour 2011 was under 30 years, but this was also the case in Aaleyasin 2015, which reported a control group live birth rate of only 25%. Furthermore, Mansour 2011 randomised women at the beginning of their cycle, and Aaleyasin 2015 randomised women before embryo transfer, which should have led to higher live birth rates (by not including cancelled cycles).

Assessment of publication bias

The funnel plot for clinical pregnancy did not show any evidence of publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, outcome: 1.4 Clinical pregnancy.



Effects of interventions

See: **Summary of findings for the main comparison** Intrauterine administration of hCG for women undergoing assisted reproduction

Note: One study included three experimental arms (Mansour 2011), and another study included two experimental arms based on intrauterine hCG dose (i.e. 100 IU, 200 IU, 500 IU, and 1000 IU, respectively) (Dehghani Firouzabadi 2016). We regarded and analysed them as separate comparisons. We split the control groups proportionately with the experimental groups to avoid analysing control participants in duplicate. One study investigated intrauterine hCG administration at two different timings (day three vs day five administration), and we regarded and analysed them as two separate comparisons (Wirleitner 2015a).

Two of the comparisons showed considerable heterogeneity (I^2 > 75%) (Analysis 1.1; Analysis 1.4), and we did not perform a global meta-analysis as prespecified in the protocol (Craciunas 2015).

Exploration for the sources of heterogeneity in these analyses revealed two key prespecified variables as important determinants: stage of ET (cleavage vs blastocyst stage) and dose of IC-hCG (< 500 IU vs ≥ 500 IU). When we subgrouped the data according to these variables, we found evidence of significant differences between subgroups. We then performed meta-analysis within the subgroups defined by stage of embryo and dose of hCG.

Primary outcomes

Live birth

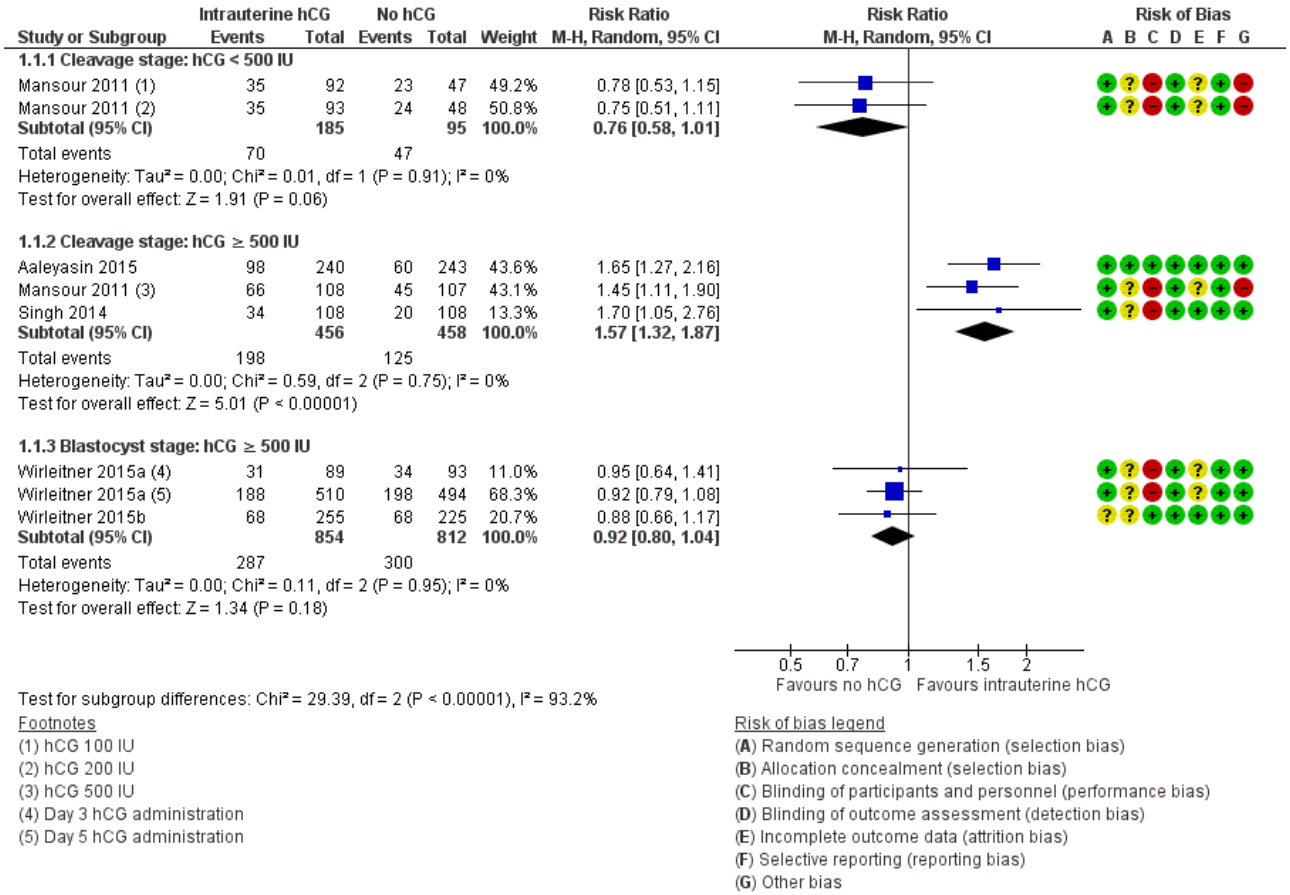
(Analysis 1.1)

Five studies with eight experimental arms reported on live birth (Aaleyasin 2015; Mansour 2011; Singh 2014; Wirleitner 2015a; Wirleitner 2015b) (Analysis 1.1).

Subgroup analysis

The forest plot displayed these studies based on the embryo stage at transfer and the hCG dose (Figure 5). The test for subgroup differences indicated a considerable difference between subgroups (Chi^2 = 29.39, degrees of freedom (df) = 2, P ≤ 0.00001, I^2 = 92.3%).

Figure 5. Forest plot of comparison: 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, outcome: 1.1 Live birth.



- Cleavage stage: IC-hCG less than 500 IU versus no IC-hCG: one RCT with two experimental arms contributed to calculation of the combined outcome (Mansour 2011). The heterogeneity was insignificant (Chi² = 0.01, df = 1, P = 0.91, I² = 0%), and findings showed no benefit of the intervention, which was consistent with no substantive difference or disadvantage of indeterminate magnitude (RR 0.76, 95% CI 0.58 to 1.01; one RCT; N = 280; I² = 0%; very low-quality evidence).
- Cleavage stage: IC-hCG 500 IU or greater versus no IC-hCG: three RCTs contributed to calculation of the combined outcome (Aaleyasin 2015; Mansour 2011; Singh 2014). The heterogeneity was insignificant (Chi² = 0.59, df = 2, P = 0.75, I² = 0%), and the live birth rate was higher in the hCG group (RR 1.57, 95% CI 1.32 to 1.87; three RCTs; N = 914; I² = 0%; moderate-quality evidence). This suggested that in women with a 27% chance of live birth without using IC-hCG, the live birth rate among those using IC-hCG 500 IU or greater will be between 36% and 51%.
- Blastocyst stage: IC-hCG 500 IU or greater versus no IC-hCG: two RCTs with three experimental arms contributed to calculation of the combined outcome (Wirleitner 2015a; Wirleitner 2015b). The heterogeneity was insignificant (Chi² = 0.11, df = 2, P = 0.95, I² = 0%), and results showed no substantive differences between groups in live birth rates (RR 0.92, 95% CI 0.80 to 1.04; two RCTs; N = 1666; I² = 0%; moderate-quality evidence).

Data were insufficient for the prespecified subgroup analyses to be performed based on embryo processing and number of embryos transferred.

Sensitivity analyses

Removing studies with high risk of bias in one or more domains did not alter the results significantly (Mansour 2011; Singh 2014; Wirleitner 2015a), but it meant that no data were available for one of the comparisons.

- Cleavage stage: IC-hCG less than 500 IU versus no IC-hCG (no data).
- Cleavage stage: IC-hCG 500 IU or greater versus no IC-hCG (RR 1.65, 95% CI 1.27 to 2.16; one RCT; N = 483).
- Blastocyst stage: IC-hCG 500 IU or greater versus no IC-hCG (RR 0.88, 95% CI 0.66 to 1.17; one RCT; N = 480).

Removing the studies available in abstract format only did not alter the results significantly (Singh 2014; Wirleitner 2015b).

- Cleavage stage: IC-hCG less than 500 IU versus no IC-hCG (RR 0.76, 95% CI 0.58 to 1.01; one RCT; N = 280; I² = 0%; very low-quality evidence).
- Cleavage stage: IC-hCG 500 IU or greater versus no IC-hCG (RR 1.55, 95% CI 1.28 to 1.87; two RCTs; N = 698; I² = 0%; moderate-quality evidence).

- Blastocyst stage: IC-hCG 500 IU or greater versus no IC-hCG (RR 0.92, 95% CI 0.80 to 1.07; one RCT; N = 1186; I^2 = 0%; moderate-quality evidence).

The calculated combined outcome based on the fixed-effect model was similar to that based on the random-effects model for the following.

- Cleavage stage: IC-hCG less than 500 IU versus no IC-hCG (RR 0.76, 95% CI 0.58 to 1.01; one RCT; N = 280; I^2 = 0%; very low-quality evidence).
- Cleavage stage: IC-hCG 500 IU or greater versus no IC-hCG (RR 1.59, 95% CI 1.33 to 1.90; three RCTs; N = 914; I^2 = 0%; moderate-quality evidence).
- Blastocyst stage: IC-hCG 500 IU or greater versus no IC-hCG (RR 0.91, 95% CI 0.80 to 1.04; two RCTs; N = 1666; I^2 = 0%; moderate-quality evidence).

Results did not differ substantially when odds ratio (OR) was used instead of risk ratio (RR).

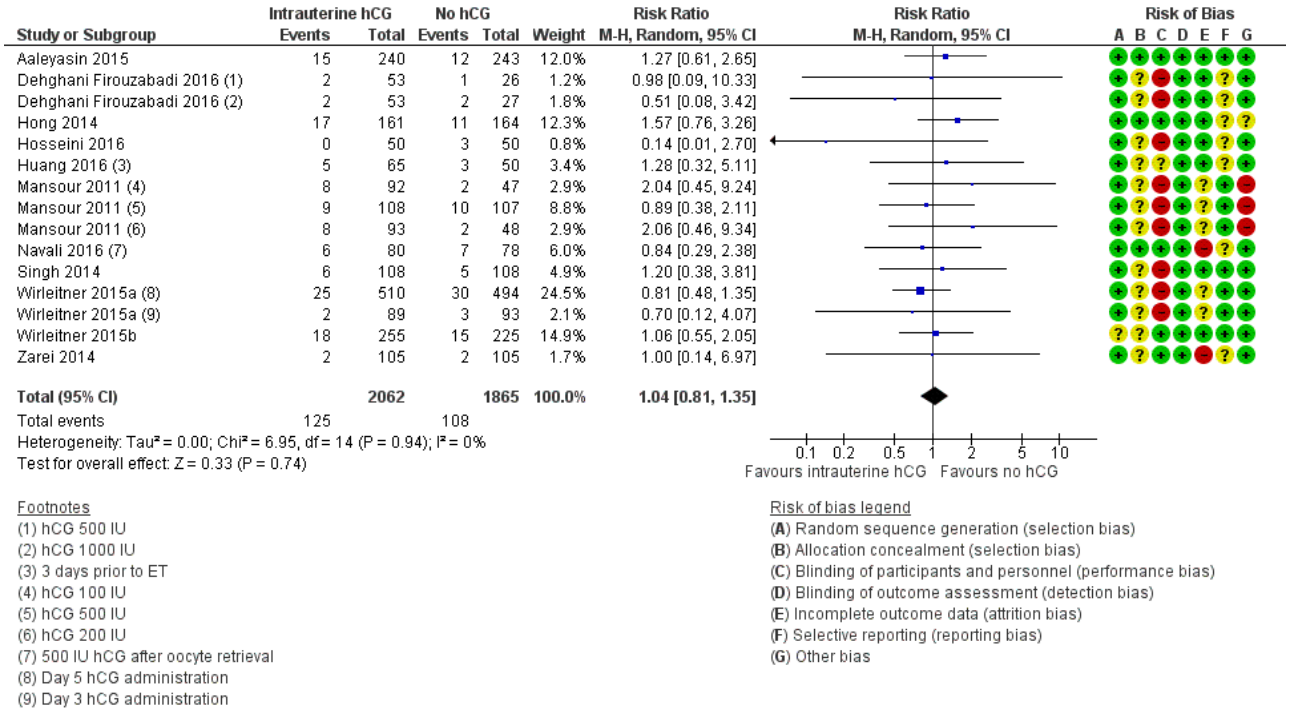
- Cleavage stage: IC-hCG less than 500 IU versus no IC-hCG (OR 0.62, 95% CI 0.38 to 1.03; one RCT; N = 280; I^2 = 0%; very low-quality evidence).
- Cleavage stage: IC-hCG 500 IU or greater versus no IC-hCG (OR 2.10, 95% CI 1.59 to 2.79; three RCTs; N = 914; I^2 = 0%; moderate-quality evidence).
- Blastocyst stage: IC-hCG 500 IU or greater versus no IC-hCG (OR 0.87, 95% CI 0.71 to 1.06; two RCTs; N = 1666; I^2 = 0%; moderate-quality evidence).

Miscarriage

(Analysis 1.2)

Eleven studies with 15 experimental arms reported on miscarriage (Aaleyasin 2015; Dehghani Firouzabadi 2016; Hong 2014; Hosseini 2016; Huang 2016; Mansour 2011; Navali 2016; Singh 2014; Wirleitner 2015a; Wirleitner 2015b; Zarei 2014; Analysis 1.2; Figure 6). Heterogeneity between studies was unsubstantial (Chi^2 = 6.95, df = 14, P = 0.74, I^2 = 0%), and studies provided no evidence of a difference between groups in miscarriage rates (RR 1.04, 95% CI 0.81 to 1.35; 11 RCTs; N = 3927; I^2 = 0%; very low-quality evidence).

Figure 6. Forest plot of comparison: 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, outcome: 1.2 Miscarriage.



Sensitivity analyses

Removing studies with high risk of bias in one or more domains - Dehghani Firouzabadi 2016, Hosseini 2016, Mansour 2011, Navali 2016, Singh 2014, and Wirleitner 2015a - did not alter the results significantly (RR 1.26, 95% CI 0.86 to 1.84; five RCTs; N = 1613; I^2 = 0%; very low-quality evidence).

Removing the two studies available in abstract format only - Singh 2014 and Wirleitner 2015b - did not alter the results significantly (RR 1.03, 95% CI 0.78 to 1.37; nine RCTs; N = 3231; I^2 = 0%; very low-quality evidence).

The calculated combined outcome based on the fixed-effect model was similar to that based on the random-effects model (RR 1.04, 95% CI 0.81 to 1.34; 11 RCTs; N = 3927; I^2 = 0%; very low-quality evidence).

Results did not differ substantially when OR was used instead of RR (OR 1.05, 95% CI 0.80 to 1.37; 11 RCTs; N = 3927; I^2 = 0%; very low-quality evidence).

Secondary analysis per clinical pregnancy

(Analysis 1.3)

Studies provided no evidence of a difference between groups in miscarriage rates calculated per clinical pregnancy (RR 0.84, 95% CI 0.62 to 1.13; 11 RCTs; N = 1620; I^2 = 24%; very low-quality evidence) (Analysis 1.3).

Secondary outcomes

Clinical pregnancy

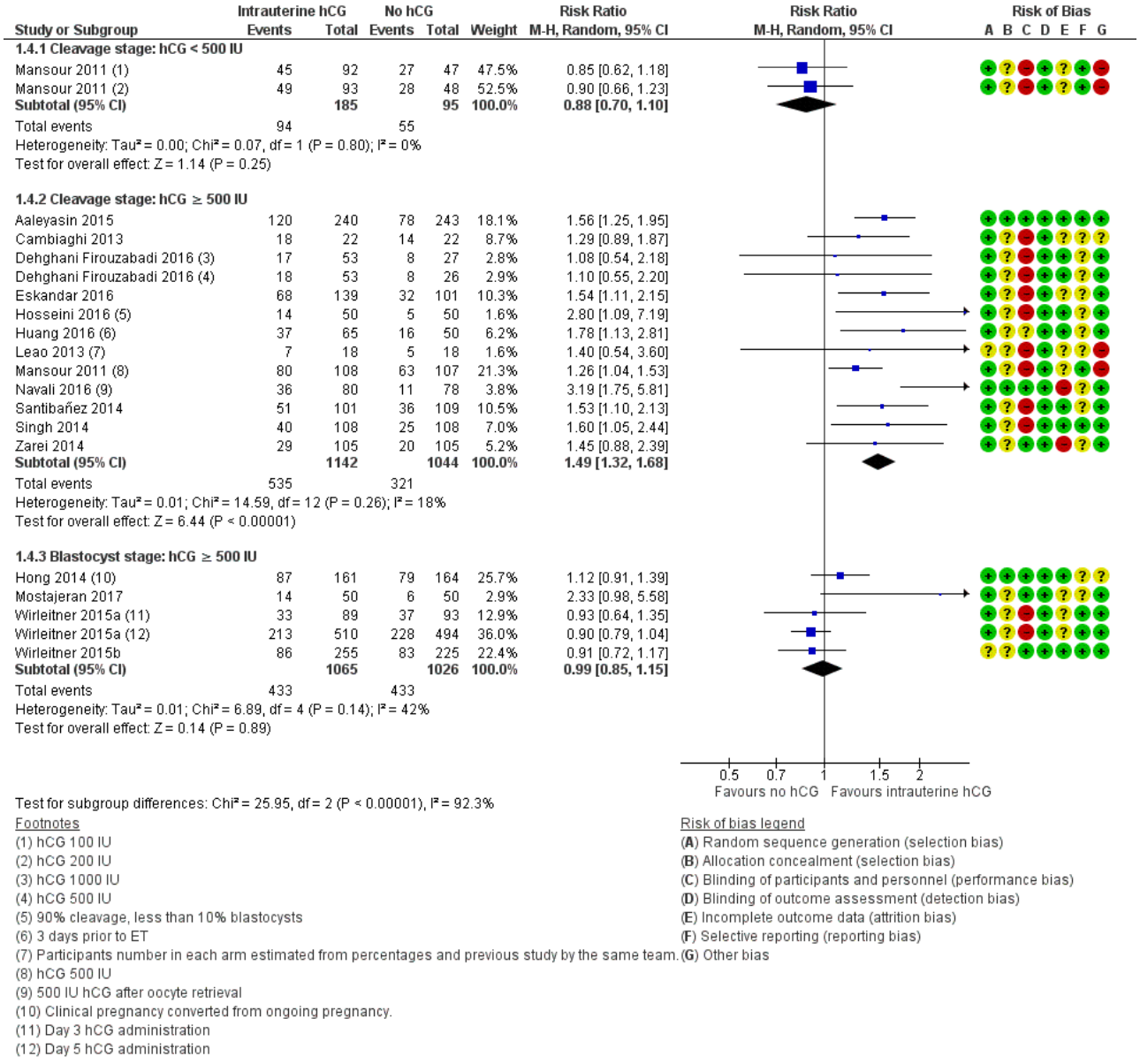
(Analysis 1.4)

All included studies reported clinical pregnancy (Analysis 1.4).

Subgroup analysis

The forest plot displayed the studies based on embryo stage at transfer and hCG dose (Figure 7). The test for subgroup differences indicated a considerable difference between subgroups (Chi^2 = 25.95, df = 2, P ≤ 0.00001, I^2= 92.3%).

Figure 7. Forest plot of comparison: 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, outcome: 1.4 Clinical pregnancy.



- Cleavage stage: IC-hCG less than 500 IU versus no IC-hCG: one RCT with two experimental arms contributed to calculation of the combined outcome (Mansour 2011). Heterogeneity was insignificant (Chi^2 = 0.07, df = 1, P = 0.80, I^2 = 0%), and studies

provided no evidence of a difference between groups in clinical pregnancy rates (RR 0.88, 95% CI 0.70 to 1.10; one RCT; N = 280; I^2 = 0%; very low-quality evidence).

- Cleavage stage: IC-hCG 500 IU or greater versus no IC-hCG: 12 RCTs contributed to calculation of the combined outcome (Aaleyasin 2015; Cambiaghi 2013; Dehghani Firouzabadi 2016; Eskandar 2016; Hosseini 2016; Huang 2016; Leao 2013; Mansour 2011; Navali 2016; Santibañez 2014; Singh 2014; Zarei 2014). Heterogeneity was insignificant (Chi^2 = 14.59, df = 12, P = 0.26, I^2 = 18%), and the clinical pregnancy rate was higher in the hCG group (RR 1.49, 95% CI 1.32 to 1.68; 12 RCTs; N = 2186; I^2 = 18%; moderate-quality evidence).

One study investigated IC-hCG 500 IU and reported no evidence of a difference between groups in clinical pregnancy rates (Kokkali 2014). Data from this study were insufficient to be included in the meta-analysis.

- Blastocyst stage: IC-hCG 500 IU or greater versus no IC-hCG: four RCTs with five experimental arms contributed to calculation of the combined outcome (Hong 2014; Mostajeran 2017; Wirleitner 2015a; Wirleitner 2015b). Heterogeneity was moderate (Chi^2 = 6.89, df = 4, P = 0.14, I^2 = 42%), and studies provided no evidence of a difference between groups in clinical pregnancy rates (RR 0.99, 95% CI 0.85 to 1.15; four RCTs; N = 2091; I^2 = 42%; moderate-quality evidence).

Data were insufficient for the predefined subgroup analyses to be performed based on embryo processing and number of embryos transferred.

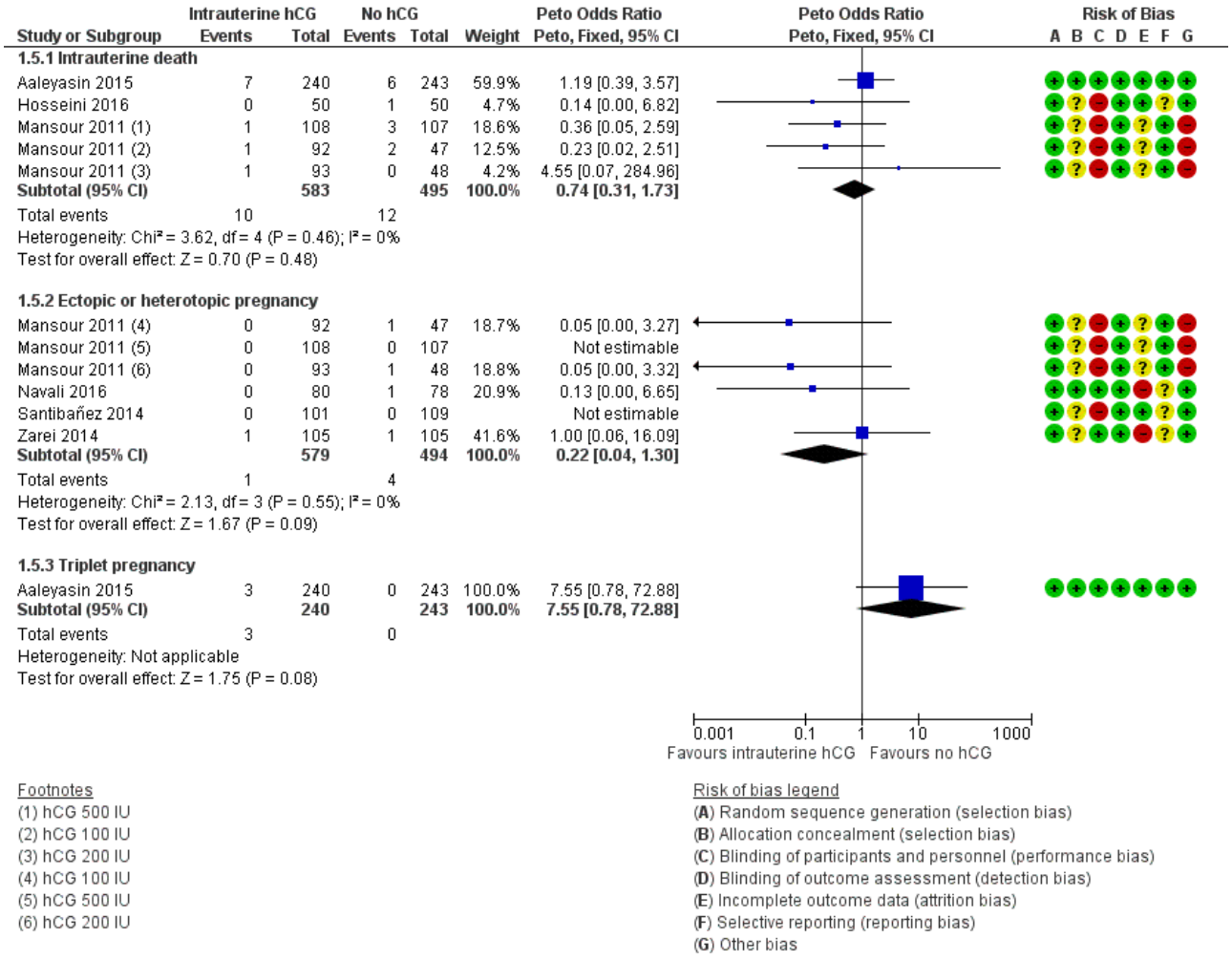
Complications

(Analysis 1.5)

Seven studies with 10 experimental arms reported complications (Aaleyasin 2015; Dehghani Firouzabadi 2016; Hosseini 2016; Mansour 2011; Navali 2016; Santibañez 2014; Zarei 2014; Analysis 1.5).

Evidence was insufficient to show whether there was a difference between groups for any of the mentioned complications: ectopic pregnancy (four studies; N = 1073; four events overall), heterotopic pregnancy (one study; N = 495; one event), intrauterine death (three studies; N = 1078; 22 events), and triplets (one study; N = 48; three events). For intrauterine death, the analysis in Figure 8 displays the Peto OR (which is the default setting for this analysis). Mantel-Haenszel random-effects RRs were almost identical (RR 0.77, 95% CI 0.33 to 1.77; three studies; N = 1078; I^2 = 0%).

Figure 8. Forest plot of comparison: 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, outcome: 1.5 Complications.



DISCUSSION

Summary of main results

This updated systematic review included 17 randomised controlled trials (RCTs) investigating the effect of intrauterine administration of human chorionic gonadotropin (hCG) to 4751 subfertile women undergoing assisted reproduction. Intracavitary hCG (IC-hCG) was administered in variable doses at different times before embryo transfer (ET). hCG was obtained from the urine of pregnant women or from cell cultures using recombinant DNA technology.

For analyses of live birth and clinical pregnancy, there was considerable heterogeneity (I^2 > 75%) and therefore we present subgroups for dosage and stage of ET. Exploration for the sources of heterogeneity revealed two key prespecified variables as important determinants: stage of ET (cleavage vs blastocyst stage) and dose of IC-hCG (< 500 IU vs ≥ 500 IU). We performed meta-analysis within the subgroups defined by stage of embryo and dose of IC-hCG.

Live birth rates among women having cleavage-stage ET with an IC-hCG dose < 500 IU compared to women having cleavage-stage ET without IC-hCG showed no benefit of the intervention and would be consistent with no substantive difference or disadvantage of indeterminate magnitude. In a clinic with a live birth rate of 49% per cycle, use of IC-hCG < 500 IU would be associated with a live birth rate ranging from 28% to 50%.

Results show an increase in live birth rate in the subgroup of women undergoing cleavage-stage ET with an IC-hCG dose ≥ 500 IU compared to women having cleavage-stage ET without IC-hCG (RR 1.57, 95% CI 1.32 to 1.87; three RCTs; 914 participants; I^2 = 0%; moderate-quality evidence). At a clinic with a live birth rate of 27% per cycle, use of IC-hCG ≥ 500 IU would be associated with a live birth rate ranging from 36% to 51%.

Results show no substantive differences in live birth among women having blastocyst-stage ET with an IC-hCG dose ≥ 500 IU compared to women having blastocyst-stage ET without IC-hCG (moderate-quality evidence). At a clinic with a live birth rate of 36% per cycle, use of IC-hCG ≥ 500 IU would be associated with a live birth rate ranging from 29% to 38%.

Evidence for clinical pregnancy among women having cleavage-stage ET with an IC-hCG dose < 500 IU showed no benefit of the intervention and would be consistent with no substantive

difference or disadvantage of indeterminate magnitude (very low-quality evidence).

Results show an increase in clinical pregnancy rate in the subgroup of women having cleavage-stage ET with an IC-hCG dose of 500 IU or greater compared to women having cleavage-stage ET with no IC-hCG (moderate-quality evidence).

Results show no substantive differences in clinical pregnancy in the subgroup of women having blastocyst-stage ET with an IC-hCG dose of 500 IU or greater (moderate-quality evidence).

No RCTs investigated blastocyst-stage ET with an IC-hCG dose < 500 IU.

We are uncertain whether miscarriage and complication rates were influenced by IC-hCG administration, irrespective of embryo stage at transfer or dose of IC-hCG (very low-quality evidence). Reported complications were few, and very low-quality evidence was insufficient to permit conclusions to be drawn.

Overall completeness and applicability of evidence

All RCTs reported on clinical pregnancy, which is an important secondary outcome, but only a few RCTs continued follow-up until live birth, which is the most important primary outcome.

Most RCTs reported miscarriage rates. RCTs rarely reported complications and adverse events, or their absence.

Data were insufficient for all planned subgroup analyses to be performed.

The inclusion criteria for participants ensured a broad range of subfertility causes and women's characteristics similar to those expected in a regular assisted reproduction unit.

Quality of the evidence

We rated most of the studies (12/17) at high risk of bias in at least one of the seven domains assessed. Common problems were unclear reporting of study methods and lack of blinding. Brief reporting of results in studies published as abstracts represents an additional potential source of bias. Ten studies did not report funding, and seven studies reported internal funding. No studies reported external funding.

The quality of the evidence as assessed via GRADE varied from very low to moderate for live birth and clinical pregnancy, which means that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate for some subgroups. The quality of the evidence for miscarriage was very low, meaning that we are very uncertain about the estimate. The main limitations in the overall quality of the evidence were high risk of bias and serious imprecision.

Potential biases in the review process

We performed a systematic search in consultation with the Cochrane Gynaecology and Fertility Group Trials Search Co-ordinator, but we cannot be sure all relevant trials were identified for inclusion. The protocol was pre-published and was followed accordingly (Craciunas 2015). We attempted to contact study authors when data were missing, but only one study author replied, providing clarification and additional data (Mansour 2011). We performed analyses on an intention-to-treat basis. Potential bias in the review process was unlikely. Data from two studies awaiting classification and from five ongoing studies may inform future updates of this review.

Agreements and disagreements with other studies or reviews

One previously published meta-analysis concluded that women undergoing in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) may benefit from IC-hCG injection before ET (Ye 2015). One meta-analysis found no effect of IC-hCG in terms of live birth and miscarriage but reported increased clinical pregnancy following IC-hCG injection (Osman 2016). A third meta-analysis published as an abstract reported increased clinical pregnancy rates and similar implantation, miscarriage, and ongoing pregnancy rates following IC-hCG (Dieamant 2016). These previous meta-analyses included significantly fewer RCTs compared to the present review (five, eight, and six, respectively) and have not explored the sources of heterogeneity based on IC-hCG dose and embryo stage at transfer.

The reported effect of intrauterine hCG administration was consistent within the subgroups of our review, with an apparent different effect based on stage of the embryo at transfer and dose of IC-hCG.

AUTHORS' CONCLUSIONS

Implications for practice

The finding of probably improved clinical pregnancy and live birth for cleavage-stage transfers using an intracavity human chorionic gonadotropin (IC-hCG) dose of 500 IU or greater is clinically important. Given the strength of the evidence, we believe that patients will benefit from this intervention, and it could be incorporated into clinical practice. However, current evidence for IC-hCG treatment does not support its use for blastocyst transfers. Review authors found no evidence that miscarriage was influenced by intrauterine human chorionic gonadotropin (hCG) administration, irrespective of embryo stage at transfer or dose of IC-hCG. Events were too few to allow any conclusions to be drawn with regard to other complications.

Implications for research

The findings of this review should provide a strong foundation for funding and conducting further high-quality randomised controlled trials of intrauterine hCG administration for women undergoing assisted reproduction according to CONSORT (Consolidated Standards of Reporting Trials) guidelines. These trials should be powered adequately and should focus on subgroups (cleavage vs blastocyst, fresh vs frozen/thawed, single vs two or more embryo transfers, cause of subfertility, dose and timing of IC-hCG) to identify the groups of women who would benefit the most from this intervention, and they should report on potential adverse events. Live birth rate must be the primary outcome. Blinding throughout the treatment cycle and during embryo transfer may reduce potential performance bias (adjusting ovarian stimulation doses; deciding the timing of maturation triggering, oocyte retrieval, and technique during embryo transfer, respectively).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aaleyasin 2015

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 483 **Women's age (mean years; experimental vs control):** 29.1 vs 28.7 **Inclusion criteria:** all infertile women who were candidates for the first IVF/ICSI **Exclusion criteria:** aged > 40 years; history of percutaneous epididymal sperm aspiration; testicular sperm extraction; myomectomy; hydrosalpinx; presence of uterine fibroma with the pressure effect on endometrium; endometriosis; azoospermia **Ovarian controlled hyperstimulation:** long GnRH agonist protocol

Aaleyasin 2015 *(Continued)*

	Fertilisation: ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** fresh **Number of embryos transferred (mean; experimental vs control):** 2.8 vs 2.9
Interventions	**Experimental (n = 240):** hCG 500 IU in a volume of 50 µL tissue culture media (Vitrolife, Göteborg, Sweden) was injected into the uterus 5 to 7 minutes before ET **Control (n = 243):** 50 µL tissue culture media (Vitrolife, Göteborg, Sweden) instead of hCG
Outcomes	Clinical pregnancy, miscarriage, live birth, intrauterine death
Notes	**Location:** Shariati Teaching Hospital, Tehran, Iran **Period:** January 2011 to July 2012 **Power calculation:** yes **Funding:** not mentioned **Trial registration:** not mentioned and not found **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	A technician, not belonging to the study personnel, prepared and coded drugs according to the list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants and clinical care providers were blinded to the list until the end of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All participants and clinical care providers were blinded to the list until the end of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Zero women were lost to follow-up.
Selective reporting (reporting bias)	Low risk	Reported on all important outcomes
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Cambiaghi 2013

Methods	**Design:** 2-arm parallel RCT

Cambiaghi 2013 *(Continued)*

Participants	**Number:** 44 **Women's age (mean years; experimental vs control):** not mentioned **Inclusion criteria:** endometrial thickness > 7 mm on the day the donor received hCG and at least 2 blastocysts on the day of ET **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** donor oocytes, protocol not mentioned **Fertilisation:** not mentioned **Stage of the embryo at transfer:** blastocyst **Embryo processing:** fresh **Number of embryos transferred:** not mentioned (likely 2, from inclusion criteria)
Interventions	**Experimental (n = 22):** intrauterine injection of hCG 500 IU 6 hours before ET **Control (n = 22):** ET without any pre-intrauterine injection
Outcomes	Clinical pregnancy
Notes	**Location:** Instituto Paulista de Ginecologia, Obstetricia e Medicina Reproducao, Sao Paulo, Brazil **Period:** January to December 2012 **Power calculation:** no **Funding:** not mentioned **Trial registration:** not mentioned and not found **Publication type:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very brief reporting on results

Cambiaghi 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No reporting on adverse events, miscarriage, or live birth
Other bias	Unclear risk	No reporting on baseline characteristics between groups

Dehghani Firouzabadi 2016

Methods	**Design:** 3-arm parallel RCT
Participants	**Number:** 159 **Women's age:** 20 to 40 years **Inclusion criteria:** women aged 20 to 40 years with a male factor or unexplained infertility and basal FSH < 12 who had undergone assisted reproduction **Exclusion criteria:** azoospermia; presence of uterine myoma; endometriosis; hydrosalpinges; previous IVF/ICSI trials (successful or unsuccessful); history of endocrine disease such as diabetes and thyroid dysfunction; previous history of hysteroscopic operation due to submucosal myoma; intrauterine synechia **Ovarian controlled hyperstimulation:** antagonist protocol **Fertilisation:** ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** fresh **Number of embryos transferred:** 1 to 3
Interventions	**Experimental (n = 53):** hCG 500 IU (40 µL) intrauterine injection 7 minutes before ET **Experimental (n = 53):** hCG 1000 IU (40 µL) intrauterine injection 7 minutes before ET **Control (n = 53):** nothing before ET
Outcomes	Clinical pregnancy, miscarriage
Notes	**Location:** Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran **Period:** April 2012 to March 2013 **Power calculation:** not mentioned **Funding:** not mentioned **Trial registration:** IRCT2012091310328N3 **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Liable women were randomly assigned to 2 test groups in the ratio of 1:1 or to a control group according to computer-generated random numbers (n = 53).

Dehghani Firouzabadi 2016 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported on all randomised participants
Selective reporting (reporting bias)	Unclear risk	No live birth data
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Eskandar 2016

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 240 **Women's age (mean years; experimental vs control):** 32.3 vs 31.5 **Inclusion criteria:** women undergoing embryo transfer **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** IVF and ICSI **Stage of the embryo at transfer:** not mentioned, assumed cleavage (day 3) based on other publications from the same IVF unit **Embryo processing:** not mentioned **Number of embryos transferred:** 2 to 3
Interventions	**Experimental (n = 139):** 500 IU of hCG intrauterine 10 minutes before ET **Control (n = 101):** ET without any pre-intrauterine injection
Outcomes	Clinical pregnancy
Notes	**Location:** Saudi Center for Assisted Reproduction, Abha, Saudi Arabia **Period:** not mentioned **Power calculation:** not mentioned **Funding:** not mentioned **Trial registration:** not mentioned and not found

Eskandar 2016 *(Continued)*

Publication type: abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were divided randomly into 2 groups by a computer-based programme.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very brief reporting on results
Selective reporting (reporting bias)	Unclear risk	No reporting on adverse events, live birth, or miscarriage
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Hong 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 300 **Women's age (mean years; experimental vs control):** 35.0 vs 35.1 **Inclusion criteria:** all participants undergoing fresh or frozen ET within the ART programme when the female partner was younger than 43 years of age **Exclusion criteria:** women could not be simultaneously participating in another prospective clinical trial at the centre, but no other inclusion/exclusion criteria were applied **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** not mentioned **Stage of the embryo at transfer:** blastocyst **Embryo processing:** fresh and frozen/thawed **Number of embryos transferred:** 1 or 2
Interventions	**Experimental (n = 148):** endometrial infusion of 20 µL ET media (synthetic serum substitute and MediCult BlastAssist, Origio) laden with 500 IU of purified urinary placental hCG (Novarel, Ferring Pharmaceuticals) < 3 minutes before ET **Control (152):** endometrial infusion of 20 µL ET media only

Hong 2014 *(Continued)*

Outcomes	Miscarriage and clinical pregnancy (converted from ongoing pregnancy)
Notes	**Location:** Reproductive Medicine Associates of New Jersey, Princeton, New Jersey, USA **Period:** August 2012 to December 2013 **Power calculation:** yes, but not met (778 embryos required, 473 embryos transferred) **Funding:** not mentioned **Trial registration:** NCT01643993 **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random number function was used to create variable blocks of 4 to 8, with participants assigned to the 2 groups in a 1:1 allocation.
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved with sequentially numbered, opaque, sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the physician performing the transfer and the participants were blinded to the assigned treatment group throughout the entirety of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No reports on live births and adverse events
Other bias	Unclear risk	25 participants declined to participate for various reasons after randomisation.

Hosseini 2016

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 100 **Women's age (mean years; experimental vs control):** 30.5 vs 31.3 **Inclusion criteria:** women undergoing assisted reproduction **Exclusion criteria:** history of uterine surgery such as myomectomy; history of recurrent miscarriage; known hydrosalpinx, endometrioma, or endometriosis

Hosseini 2016 *(Continued)*

	Ovarian controlled hyperstimulation: frozen/thawed cycles; preparation of endometrium initiated with hormone replacement protocol, which involved administration of oestrogen, followed by progesterone without ovarian downregulation **Fertilisation:** not mentioned **Stage of the embryo at transfer:** 90%+ cleavage, < 10% blastocysts **Embryo processing:** frozen/thawed **Number of embryos transferred:** 2 to 3
Interventions	**Experimental (n = 50):** case group received intrauterine injection of 40 µL of a 5000-unit hCG vial (Choriomon, IBSA, Lugano) mixed with 0.4 mL of IMSI-type media (equivalent to 500 hCG units) through Labotect catheter (Labotect, Labor-Technik-Gottingen GmbH, Germany). Seven minutes later, embryo transfer was performed with a sterile Labotect catheter, guided by abdominal ultrasound at 1 to 1.5 cm from uterine fundus. **Control (n = 50):** in the control group, embryo transfer was carried out with no intervention
Outcomes	Clinical pregnancy, miscarriage, still birth
Notes	**Location:** Al-Zahra Hospital Fertility Center, Tabriz, Iran **Period:** May 2014 to April 2015 **Power calculation:** no **Funding:** not mentioned **Trial registration:** not mentioned **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	During embryo transfer, participants were randomly divided (according to table of random numbers) into control and case groups (50 patients each).
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible owing to the nature of the intervention (control group received no placebo).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for by outcome measures.
Selective reporting (reporting bias)	Unclear risk	No live birth data
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Huang 2016

Methods	**Design:** 3-arm parallel RCT, only data from control group (not placebo) used
Participants	**Number:** 161 total, 115 used for comparison **Women's age (mean years; experimental vs control):** 33.95 vs 33.08 **Inclusion criteria:** 2 instances of failed transfer of good-quality embryos; undergoing FET cycles; aged 38 years; body mass index (BMI) of 18 to 24; normal endometrial thickness (8 to 16 mm); frozen preservation of ≥ 2 embryos, with at least 1 good-quality embryo **Exclusion criteria:** diseases such as endometrial polyps, intrauterine adhesion, or uterine submucosal myomas, which might cause endometrial abnormalities; adenomyosis; hydropic fallopian tubes, PCOS, or endometriosis ≥ stage III **Ovarian controlled hyperstimulation:** frozen/thawed cycles; preparation of endometrium was conducted with letrozole and progesterone **Fertilisation:** not mentioned **Stage of the embryo at transfer:** cleavage **Embryo processing:** frozen/thawed **Number of embryos transferred:** 2
Interventions	**Experimental (n = 65):** the perfusion group received 1000 IU of hCG (Lizhu, Zhuhai, China) mixed with 1 mL of normal saline via intrauterine injection 3 days before ET **Control (n = 50):** no intrauterine injection
Outcomes	Clinical pregnancy, miscarriage
Notes	**Location:** Center of Reproductive Medicine of Liuzhou Maternity and Child Healthcare Hospital, Guangxi Province, China **Period:** January 2015 and December 2015 **Power calculation:** no **Funding:** not mentioned **Trial registration:** not mentioned **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation via a computerised random digit generator based on patient registration number in order of referral
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blinded mentioned, but not clear who was blinded

Huang 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported on all randomised participants
Selective reporting (reporting bias)	Unclear risk	No live birth data
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Kokkali 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 194 **Women's age (years):** > 40 **Inclusion criteria:** women aged > 40 years receiving donor eggs **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** not mentioned **Stage of the embryo at transfer:** not mentioned **Embryo processing:** not mentioned **Number of embryos transferred:** not mentioned
Interventions	**Experimental (n = 97):** intrauterine hCG 500 IU injection 7 minutes before ET **Control (n = 97):** no intrauterine injection
Outcomes	Clinical pregnancy
Notes	**Location:** Genesis Athens Hospital, Centre for Human Reproduction, Athens, Greece **Period:** July 2012 to September 2013 **Power calculation:** no **Funding:** Genesis Athens Clinic **Trial registration:** not registered **Publication type:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed in a 1:1 fashion to 1 of 2 groups [...] prepared from a computer-generated list.

Kokkali 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	Adequate allocation concealment was ensured by sequentially numbered, opaque, sealed envelopes prepared from a computer-generated list.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very brief reporting on results
Selective reporting (reporting bias)	Unclear risk	No reporting on live birth and adverse events
Other bias	Unclear risk	No reporting on baseline characteristics between groups

Leao 2013

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 36 **Women's age:** not mentioned **Inclusion criteria:** women with 2 previous failures in IVF cycles with ET **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** not mentioned **Stage of the embryo at transfer:** not mentioned **Embryo processing:** not mentioned **Number of embryos transferred:** not mentioned
Interventions	**Experimental (n = 18):** intrauterine injection of hCG 500 IU 6 hours before ET **Control (n = 18):** women were forwarded straight to ET
Outcomes	Clinical pregnancy
Notes	**Location:** IPGO, Sao Paulo, Brazil **Period:** January to December 2012 **Power calculation:** no **Funding:** not mentioned **Trial registration:** not mentioned and not found

Leao 2013 *(Continued)*

Publication type: abstract presented as poster at 5th IVI International Congress, Seville, Spain, 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned with no details
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Very brief reporting on results
Selective reporting (reporting bias)	Unclear risk	No reporting on adverse events, miscarriage, or live birth
Other bias	High risk	Number of participants in each arm was not reported, but was deduced based on percentages and previous study by the same team

Mansour 2011

Methods	**Design:** 2 RCTs within the same study analysed as 4-armed parallel RCT
Participants	**Number:** 280 + 215 = 495 **Women's age (mean years; experimental 100, 200 vs control; 500 vs control):** 29 vs 28.5 vs 29.1; 28.3 vs 28.4 **Inclusion criteria:** women aged < 40 years old with infertility due to male factor **Exclusion criteria:** previous IVF/ICSI trials, including a successful trial; azoospermia; uterine myoma or previous myomectomy; endometriosis; presence of hydrosalpinges **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** fresh **Number of embryos transferred (mean; experimental 100, 200 vs control; 500 vs control):** 2.9 vs 2.8 vs 2.9; 2.9 vs 2.8

Mansour 2011 *(Continued)*

Interventions	**Experimental 100 (n = 92):** 40 µL of tissue culture medium (G-2 plus ref. 10132, Vitrolife, Göteborg, Sweden) containing hCG 100 IU injected intrauterine approximately 7 minutes before ET **Experimental 200 (n = 93):** 40 µL of tissue culture medium (G-2 plus ref. 10132, Vitrolife, Göteborg, Sweden) containing hCG 200 IU injected intrauterine approximately 7 minutes before ET **Experimental 500 (n = 108):** 40 µL of tissue culture medium (G-2 plus ref. 10132, Vitrolife, Göteborg, Sweden) containing hCG 500 IU injected intrauterine approximately 7 minutes before ET **Control (n = 95 + 107):** no intrauterine hCG injection before ET
Outcomes	Live birth, miscarriage, clinical pregnancy, ectopic pregnancy
Notes	**Location:** The Egyptian IVF-ET Center, Cairo, Egypt **Period:** January 2010 to January 2011 **Power calculation:** yes, but not met **Funding:** The Egyptian IVF-ET Center **Trial registration:** NCT01030393 **Publication type:** full text Live birth rate was established by personal communication with study authors, June 2015. Study publication reported number of deliveries, which included 6 women who had stillbirths (3 in each group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised to 2 groups with the use of sealed dark envelopes.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not mentioned. Could explain different withdrawal rates between groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Women lost to follow-up live birth (similar numbers between groups)
Selective reporting (reporting bias)	Low risk	Reported on all important outcomes
Other bias	High risk	Interim analysis with change of protocol and premature ending of study. Relatively high live birth rate in control group, reasons unclear

Mostajeran 2017

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 100 **Women's age:** mean 31.3 ± 5.2 years **Inclusion criteria:** women 20 to 40 years old with body mass index 18 to 30 kg/m² were eligible if they were infertile owing to male factor, had a regular menstrual cycle of 24 to 35 days, and were presumed to be ovulatory **Exclusion criteria:** presence of polycystic ovary syndrome, with uterine pathologies, endometriosis, or presence of hydrosalpinges and any endocrine disease or chronic systemic illness; azoospermia; history of successful IVF or ICSI **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** IVF and ICSI **Stage of the embryo at transfer:** blastocyst **Embryo processing:** frozen/thawed **Number of embryos transferred:** 1 to 3
Interventions	**Experimental (n = 50):** injection of 700 IU of intrauterine hCG (chorionic gonadotropin human, Darou Pakhsh Company, Iran) 10 minutes before embryo transfer **Control (n = 50):** did not receive hCG before embryo transfer
Outcomes	Clinical pregnancy
Notes	**Location:** Fertility and Infertility Center of Isfahan in Iran **Period:** September 2013 to April 2014 **Power calculation:** yes, but inadequate **Funding:** not mentioned **Trial registration:** not mentioned **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly divided into two `50-member` groups by random allocation software. Saghaei, 2004
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Embryo transfer in both groups was done by the attending gynaecologist, who was blinded to the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias

Mostajeran 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No data on miscarriage or live birth
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Navali 2016

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 158 **Women's age (mean years; experimental vs control):** 30.6 vs 32 **Inclusion criteria:** normal ovarian reserve (anti-Müllerian hormone ≥ 0.7 ng/mL); age ≤ 41 years; undergoing ICSI and fresh ET; normal levels of thyroid-stimulating hormone and prolactin **Exclusion criteria:** uncontrolled chronic maternal disease such as endocrinopathy and autoimmune disease, severe endometriosis, severe hydrosalpinx, or non-obstructive azoospermia; high risk for severe ovarian hyperstimulation syndrome (development of > 20 follicles > 10 mm at ovarian stimulation or retrieval of > 16 oocytes on the day of oocyte retrieval); morphological embryo deficiencies **Ovarian controlled hyperstimulation:** flexible antagonist protocol **Fertilisation:** ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** fresh **Number of embryos transferred:** 2 to 3
Interventions	**Experimental (n = 80):** 0.1 mL (500 IU hCG) and 0.4 mL normal saline were pulled into an insulin syringe and injected into the uterus immediately after oocyte retrieval under general anaesthesia **Control (n = 78):** 0.5 mL normal saline injected into the uterus at the same time as experimental group
Outcomes	Clinical pregnancy, miscarriage, ectopic pregnancy
Notes	**Location:** Reproductive Medical Center, Al-Zahra University Hospital, Tabriz University of Medical Sciences, Tabriz, Iran **Period:** September 2015 to February 2016 **Power calculation:** yes, but not met **Funding:** Women's Health Research Center, Tabriz University of Medical Sciences, Iran. No external funds were used. **Trial registration:** IRCT201206165485N4 **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement

Navali 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list with a block size of 4 with 1:1 allocation was used to randomise participants.
Allocation concealment (selection bias)	Low risk	Treatment allocation was placed in a sealed, opaque envelope that was picked up consecutively by an operating room technician during the oocyte retrieval procedure.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Only the technician was aware of the participant's allocation; she prepared and handed the intervention drug to the physician.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only the technician was aware of the participant's allocation; she prepared and handed the intervention drug to the physician.
Incomplete outcome data (attrition bias) All outcomes	High risk	20 (12%) participants were lost to follow-up or were excluded following randomisation.
Selective reporting (reporting bias)	Unclear risk	No data on live birth
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Santibañez 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 210 **Women's age (mean years; experimental vs control):** 36.4 vs 37.3 **Inclusion criteria:** infertile women aged < 40 years who had an indication for an IVF/ICSI **Exclusion criteria:** azoospermia **Ovarian controlled hyperstimulation:** indicated based on individual participant characteristics **Fertilisation:** IVF or ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** fresh and frozen/thawed **Number of embryos transferred (mean):** 2.1
Interventions	**Experimental (n = 101):** 20 µL of embryo culture medium (G-2, Vitrolife, Göteborg, Sweden) that contained hCG 500 IU was administered intrauterine before ET **Control (n = 109):** no intrauterine hCG was administered
Outcomes	Clinical pregnancy, ectopic pregnancy
Notes	Study authors mention "prospective observational study", but the design was in fact RCT. **Location:** Reproductive Medicine Centre, PROCREA, Mexico City **Period:** August 2011 to November 2012

Santibañez 2014 *(Continued)*

Power calculation: yes

Funding: PROCREA

Trial registration: not mentioned and not found

Publication type: full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A simple randomisation sample and assignment were generated in a computer-based programme.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women followed up until pregnancy test/ultrasound scan
Selective reporting (reporting bias)	Unclear risk	No reporting on live birth and miscarriage despite mention of follow-up
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Singh 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 216 **Women's age (mean years; experimental vs control):** 35 vs 34.5 (from ESHRE 2014 oral presentation) **Inclusion criteria:** infertile women aged < 42 years; recurrent implantation failure **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** based on individual participant characteristics (from ESHRE 2014 oral presentation) **Fertilisation:** ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** not mentioned **Number of embryos transferred (mean; experimental vs control):** 2.7 vs 2.5 (from ESHRE 2014 oral presentation)

Singh 2014 *(Continued)*

Interventions	**Experimental (n = 108):** intrauterine administration of rhCG 500 IU in 40 µL 5 minutes before ET **Control (n = 108):** culture medium administered only before ET (from ESHRE 2014 oral presentation)
Outcomes	Clinical pregnancy, miscarriage, live birth (from ESHRE 2014 oral presentation)
Notes	**Location:** Bhopal Test Tube Baby Centre, Infertility, Bhopal, India **Period:** 2006 to 2013 **Power calculation:** not mentioned **Funding:** Bhopal Test Tube Baby Centre **Trial registration:** BTTB/2006/19 (?) **Publication type:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly divided into 2 groups via a computer-generated list.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not mentioned, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Zero women lost to follow-up
Selective reporting (reporting bias)	Low risk	Reported on all important outcomes
Other bias	Low risk	Similar baseline characteristics between groups after randomisation

Wirleitner 2015a

Methods	**Design:** 4-arm parallel RCT (same intervention on day 3 or 5)
Participants	**Number:** 182 + 1004 = 1186 **Women's age (mean years; experimental vs control):** 36.1 vs 35.5; 37.1 vs 36.7 **Inclusion criteria:** fresh autologous blastocyst transfer on day 5; woman aged ≤ 43 years **Exclusion criteria:** oocyte donation cycles; women with reported recurrent implantation failure (≥ 3 negative IVF cycles)

Wirleitner 2015a *(Continued)*

	Ovarian controlled hyperstimulation: GnRH agonist long protocol **Fertilisation:** IVF or IMSI **Stage of the embryo at transfer:** blastocyst **Embryo processing:** fresh **Number of embryos transferred:** 1 or 2
Interventions	**Experimental (day 3) (n = 89):** intrauterine hCG 500 IU (Pregnyl, Organon, Netherlands) dissolved in 40 µL embryo culture medium G-2 PLUS (Vitrolife, Göteborg, Sweden) administered on day 3 (2 days before ET) **Control (day 3) (n = 93):** administration of 40 µL culture medium without hCG on day 3 (2 days before ET) **Experimental (day 5) (n = 510):** intrauterine hCG 500 IU (Pregnyl, Organon, Netherlands) dissolved in 40 µL embryo culture medium G-2 PLUS (Vitrolife, Göteborg, Sweden) administered on day 5 (3 minutes before ET) **Control (day 5) (n = 494):** administration of 40 µL culture medium without hCG on day 3 (3 minutes before ET)
Outcomes	Clinical pregnancy, miscarriage, live birth
Notes	**Location:** IVF Centers Prof. Zech, Bregenz, Austria **Period:** February 2013 to February 2014 **Power calculation:** met only for day 5 administration **Funding:** not mentioned **Trial registration:** not mentioned and not found **Publication type:** full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done electronically with a random number generator.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants blinded, but not personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	19 participants lost to follow-up

Wirleitner 2015a *(Continued)*

Selective reporting (reporting bias)	Low risk	Reports on all relevant outcomes
Other bias	Low risk	Baseline characteristics of participants were comparable between 2 study groups.

Wirleitner 2015b

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 480 **Women's age (mean years; experimental vs control):** 40.3 vs 40.4 **Inclusion criteria:** women aged 38 to 43 years **Exclusion criteria:** recurrent implantation failure **Ovarian controlled hyperstimulation:** GnRH agonist long protocol **Fertilisation:** IMSI **Stage of the embryo at transfer:** blastocyst **Embryo processing:** fresh **Number of embryos transferred:** 1 or 2
Interventions	**Experimental (n = 255):** intrauterine hCG 500 IU dissolved in 40 µL embryo culture medium administered 3 minutes before ET **Control (n = 225):** administration of 40 µL culture medium without hCG 3 minutes before ET
Outcomes	Clinical pregnancy, miscarriage, live birth
Notes	**Location:** IVF-Centers Prof. Zech, Bregenz, Austria **Period:** not mentioned **Power calculation:** yes **Funding:** funded by hospital/clinic(s) - this study was not externally funded **Trial registration:** CRT 355 **Publication type:** abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was mentioned without further details.
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Wirleitner 2015b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were followed up.
Selective reporting (reporting bias)	Low risk	Reports on all relevant outcomes
Other bias	Low risk	Baseline characteristics of participants were comparable between 2 study groups.

Zarei 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 210 **Women's age (mean years; experimental vs control):** 29.9 vs 31.2 **Inclusion criteria:** 18- to 40-year-old women with infertility **Exclusion criteria:** women with autoimmune disorders, endocrinopathies, who had previous successful IVF/ICSI trials; endometriosis; azoospermia; hydrosalpinges **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** not mentioned (likely fresh) **Number of embryos transferred (mean; experimental vs control):** 6.1 vs 5.7
Interventions	**Experimental (n = 105):** rhCG 250 µg (0.5 mL, 6500 IU) (Ovitrelle, Merck Serono, France) through intrauterine injection 12 minutes before ET **Control (n = 105):** intrauterine injection of normal saline (0.5 mL) 12 minutes before ET
Outcomes	Clinical pregnancy, miscarriage, ectopic pregnancy, stillbirth
Notes	**Location:** Reproductive Medicine Center of Mother and Child Hospital, Shiraz, Iran **Period:** December 2011 to November 2012 **Power calculation:** yes **Funding:** Shiraz University of Medical Sciences **Trial registration:** IRCT2012121711790N1

Zarei 2014 *(Continued)*

Publication type: full text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to 2 study groups via a computerised random digit generator based on their registration number in order of referral.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The syringes with volume of 0.5 mL from each group were prepared by the fellowship student and injected blinded by the attending gynaecologist.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinding mentioned (? women ? outcome assessors - in addition to gynaecologists performing the transfer), unlikely to induce bias
Incomplete outcome data (attrition bias) All outcomes	High risk	23/105 participants in intrauterine rhCG group and 7/105 participants in placebo group were lost to follow-up after receiving the allocated treatment (unclear why).
Selective reporting (reporting bias)	Unclear risk	No report on live births
Other bias	Low risk	Baseline characteristics of participants were comparable between 2 study groups.

ART: assisted reproductive technology; BMI: body mass index; ET: embryo transfer; ESHRE: European Society of Human Reproduction and Embryology; FET: frozen embryo transfer; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; ICSI: intracytoplasmic sperm injection; IMSI: intracytoplasmic morphologically selected sperm injection; IU: international unit; IVF: in vitro fertilisation; PCOS: polycystic ovary syndrome; RCT: randomised controlled trial; rhCG: recombinant human chorionic gonadotropin.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dieamant 2016	Meta-analysis
Giuliani 2015	Participants were oocyte donors who did not undergo embryo transfer
Huang 2017	Retrospective
Janati 2013	Included in the first review; replaced now by more recent full publication (Dehghani Firouzabadi 2016)
Jeong 2013	Retrospective
Kanter 2017	Retrospective
Li 2013	Not randomised

Study	Reason for exclusion
Osman 2016	Meta-analysis
Rebolloso 2013	Not randomised
Riboldi 2013	Not randomised
Strug 2016	Participants were oocyte donors who did not undergo embryo transfer.
Volovsky 2016	Case control
Ye 2015	Meta-analysis

Characteristics of studies awaiting assessment *[ordered by study ID]*

Badehnoosh 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 80 **Women's age (mean years; experimental vs control):** 29.5 vs 29.3 **Inclusion criteria:** women undergoing ICSI **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** ICSI **Stage of the embryo at transfer:** not mentioned **Embryo processing:** not mentioned **Number of embryos transferred (mean; experimental vs control):** 2.9 vs 2.8
Interventions	**Experimental:** intrauterine injection of hCG 500 IU dissolved in 40 µL of ET media 10 minutes before ET **Control:** 40 µL of ET media 10 minutes before ET
Outcomes	Implantation rate defined as positive pregnancy test at 2 weeks after ET (biochemical pregnancy)
Notes	We emailed the study authors in February 2016 and January 2018 for more information on study design and outcomes. No reply has yet been received. **Location:** Avicenna Infertility Clinic, Tehran, Iran **Period:** not mentioned **Power calculation:** not mentioned **Funding:** not mentioned **Trial registration:** not mentioned and not found **Publication type:** abstract

Bhat 2014

Methods	**Design:** 2-arm parallel RCT
Participants	**Number:** 32 **Women's age (mean years; experimental vs control):** 29.6 vs 29.6 **Inclusion criteria:** women undergoing IVF **Exclusion criteria:** not mentioned **Ovarian controlled hyperstimulation:** not mentioned **Fertilisation:** IVF or ICSI **Stage of the embryo at transfer:** cleavage **Embryo processing:** fresh and frozen/thawed **Number of embryos transferred (mean; experimental vs control):** 2.9 vs 2.9
Interventions	**Experimental:** intrauterine administration of hCG 500 IU 7 minutes before ET **Control:** ET without hCG
Outcomes	Fertilisation rate
Notes	We emailed the study authors in February 2016 and January 2018 for more information on study design and outcomes. No reply has yet been received. **Location:** Radhakrishna Multispeciality Hospital and IVF Centre in Bengaluru in Southern India **Period:** April 2013 to March 2014 **Power calculation:** not mentioned **Funding:** none **Trial registration:** not mentioned and not found **Publication type:** full text

ET: embryo transfer; hCG: human chorionic gonadotropin; ICSI: intracytoplasmic sperm injection; IU: international unit; IVF: in vitro fertilisation; RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

IRCT2017041733486N1

Trial name or title	Evaluation effect of intrauterine injection of human chorionic gonadotropin before embryo transfer on implantation rate and pregnancy rate in frozen cycles on IVF/ICSI
Methods	Randomised controlled trial
Participants	Women undergoing embryo transfer
Interventions	**Experimental:** interventional group (n 130) was injected with 500 IU of intrauterine hCG before embryo transfer **Control:** the second group (n = 130) did not receive administration of 500 IU hCG

IRCT2017041733486N1 *(Continued)*

Outcomes	Chemical and clinical pregnancy, implantation, miscarriage, ectopic pregnancy
Starting date	October 2017
Contact information	Ziaee Zohreh; 00982188896692; ziaee-z@razi.tums.ac.ir
Notes	

NCT02668965

Trial name or title	The effects of intrauterine infusion of hCG at the time of embryo transfer
Methods	Randomised controlled trial
Participants	Women undergoing embryo transfer
Interventions	**Experimental:** intrauterine infusion with hCG (500 IU) 10 microliters before embryo transfer **Control:** intrauterine infusion with standard embryo culture media 10 microliters before embryo transfer
Outcomes	Implantation, chemical and clinical pregnancy
Starting date	December 2015
Contact information	Savinee Boonsuk, MD; +66818706643; noomnim_mu@hotmail.com
Notes	

NCT02825108

Trial name or title	Intrauterine injection of human chorionic gonadotropin injection (hCG) before embryo transfer on pregnancy outcomes in frozen embryo transfer cycles
Methods	Randomised double-blind clinical trial to evaluate the effect of intrauterine injection of human chorionic gonadotropin (hCG) before frozen embryo transfer (ET)
Participants	All patients with primary infertility who have only 1 fresh implantation failure and are undergoing frozen embryo transfer cycles were enrolled.
Interventions	**Experimental:** participants receive 40 µL of tissue culture medium (G.2plus ref. 10132, Vitrolife, Göteborg, Sweden) containing 500 IU of hCG (Choriomon, IBSA SA, Switzerland), which is injected intrauterine, approximately 7 minutes before embryo transfer **Control:** patients receive only 40 µL of tissue culture medium (G.2plus ref. 10132, Vitrolife, Göteborg, Sweden), which is injected intrauterine, approximately 7 minutes before embryo transfer
Outcomes	Implantation, pregnancy loss/miscarriage
Starting date	January 2015
Contact information	Nasser Aghdami, MD, PhD; (+98)23562000 ext 516; nasser.aghdami@royaninstitute.org Leila Arab, MD; (+98)23562000 ext 414; leara91@gmail.com

NCT02825108 *(Continued)*

Notes	**Contact:** Leila Arab, MD

NCT02870855

Trial name or title	Effect of intrauterine injection of hCG on pregnancy outcome in repeated implantation failure patients
Methods	Randomised controlled trial
Participants	Women who undergo frozen ET
Interventions	**Experimental:** intrauterine injection of hCG before blastocyst transfer **Control:** no hCG injection
Outcomes	Clinical pregnancy, miscarriage, ectopic pregnancy
Starting date	July 2017
Contact information	Yuan Li, doctor; +86-731-82355100; 1002251255@qq.com
Notes	

NCT03238807

Trial name or title	Effect of intrauterine injection of hCG before ET on clinical outcomes in IVF/ICSI cycles
Methods	Randomised controlled trial (RCT) to detect whether intrauterine injection of hCG before ET improves clinical outcomes in IVF/ICSI cycles
Participants	Women undergoing IVF/ICSI
Interventions	**Experimental:** 0.1 mL of the tissue culture medium with 500 IU hCG will be injected inside the uterus before ET **Control:** 0.1 mL of the tissue culture medium without hCG will be injected inside the uterus before ET
Outcomes	Implantation, clinical pregnancy, miscarriage, live birth
Starting date	October 2017
Contact information	KArim S Abdallah, MSc; +201000024188; karimsayed88@hotmail.com
Notes	

ET: embryo transfer; hCG: human chorionic gonadotropin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation; RCT: randomised controlled trial.

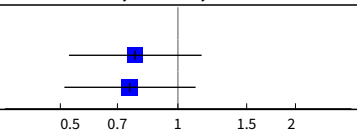
DATA AND ANALYSES

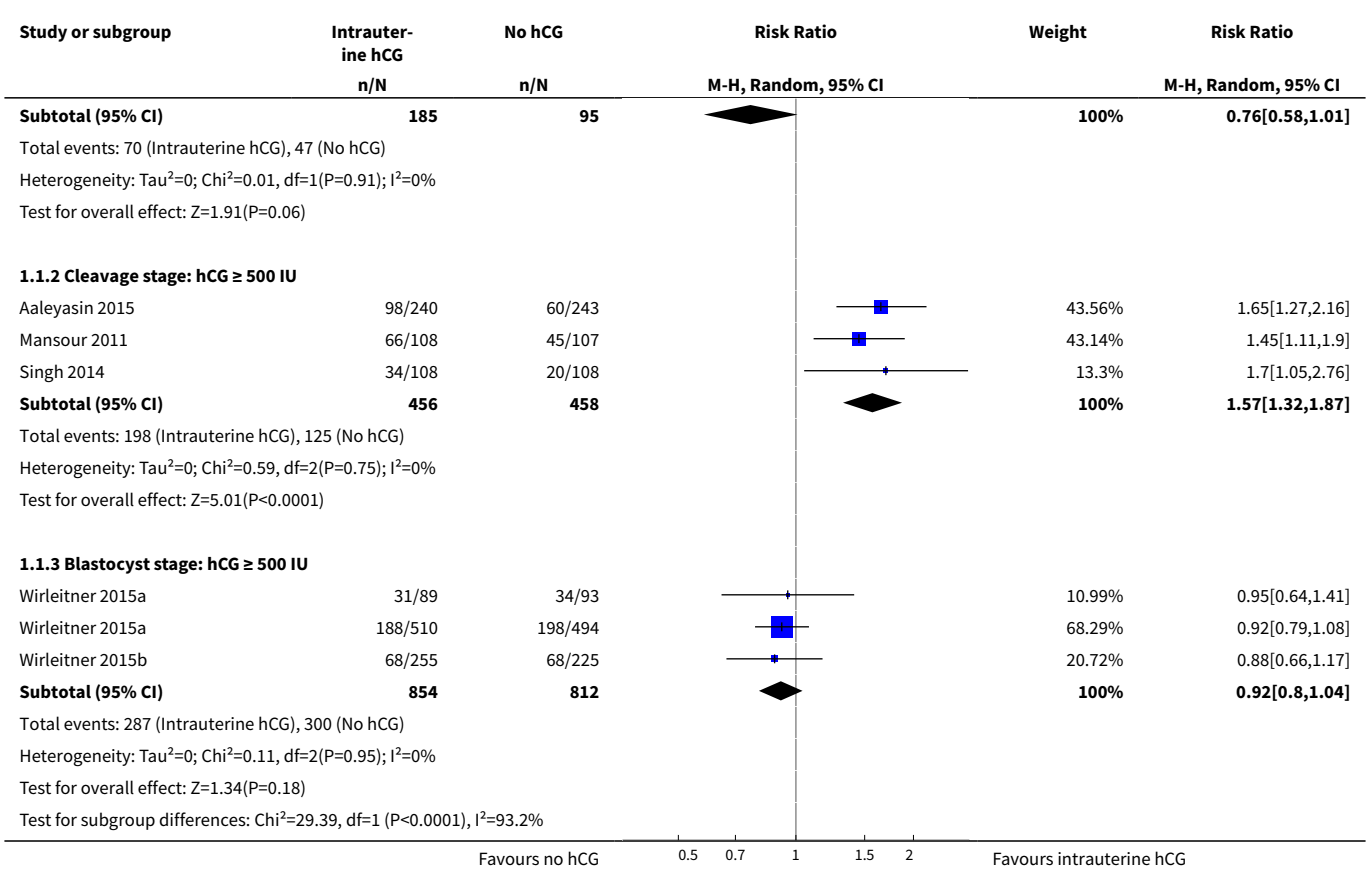
Comparison 1. Intrauterine human chorionic gonadotropin (hCG) versus no hCG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Cleavage stage: hCG < 500 IU	1	280	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.01]
1.2 Cleavage stage: hCG ≥ 500 IU	3	914	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.32, 1.87]
1.3 Blastocyst stage: hCG ≥ 500 IU	2	1666	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.04]
2 Miscarriage	11	3927	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.81, 1.35]
3 Miscarriage per clinical pregnancy	11	1620	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.62, 1.13]
4 Clinical pregnancy	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Cleavage stage: hCG < 500 IU	1	280	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.70, 1.10]
4.2 Cleavage stage: hCG ≥ 500 IU	12	2186	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.32, 1.68]
4.3 Blastocyst stage: hCG ≥ 500 IU	4	2091	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.85, 1.15]
5 Complications	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Intrauterine death	3	1078	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.31, 1.73]
5.2 Ectopic or heterotopic pregnancy	4	1073	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.04, 1.30]
5.3 Triplet pregnancy	1	483	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.55 [0.78, 72.88]

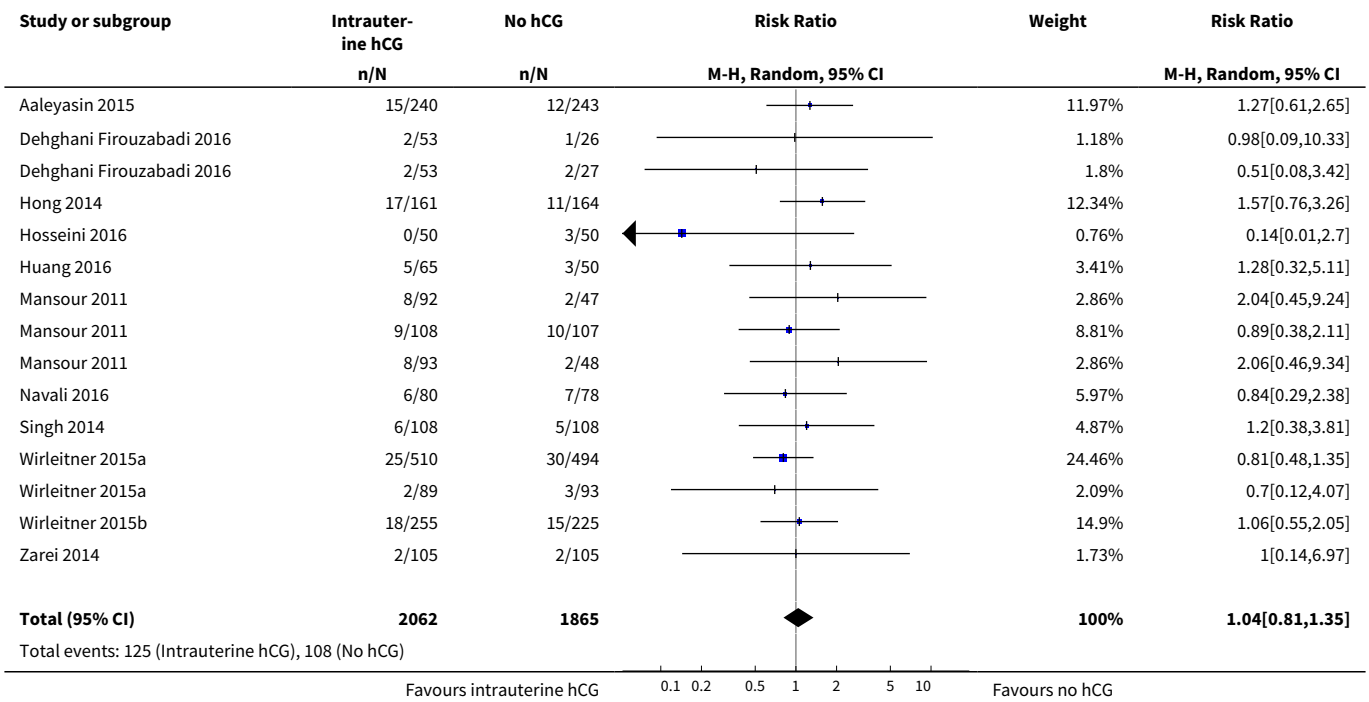
Analysis 1.1. Comparison 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, Outcome 1 Live birth.

Study or subgroup	Intrauterine hCG n/N	No hCG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Cleavage stage: hCG < 500 IU					
Mansour 2011	35/92	23/47		49.2%	0.78[0.53,1.15]
Mansour 2011	35/93	24/48		50.8%	0.75[0.51,1.11]

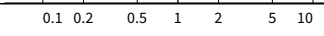




Analysis 1.2. Comparison 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, Outcome 2 Miscarriage.



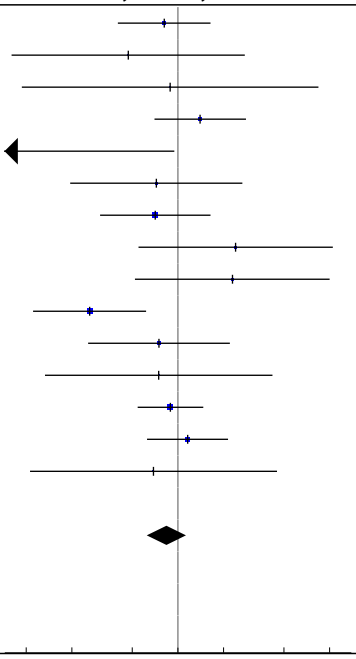
Study or subgroup	Intrauterine hCG n/N	No hCG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=6.95, df=14(P=0.94); I²=0%					
Test for overall effect: Z=0.33(P=0.74)					



Favours intrauterine hCG — Favours no hCG

Analysis 1.3. Comparison 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, Outcome 3 Miscarriage per clinical pregnancy.

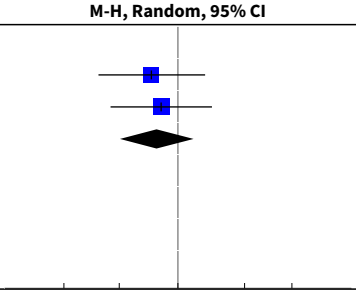
Study or subgroup	Intrauterine hCG n/N	No hCG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aaleyasin 2015	15/120	12/78		11.5%	0.81[0.4,1.64]
Dehghani Firouzabadi 2016	2/17	2/8		2.63%	0.47[0.08,2.76]
Dehghani Firouzabadi 2016	2/18	1/8		1.68%	0.89[0.09,8.44]
Hong 2014	17/87	11/79		11.69%	1.4[0.7,2.81]
Hosseini 2016	0/14	3/5		1.1%	0.06[0,0.95]
Huang 2016	5/37	3/16		4.52%	0.72[0.2,2.66]
Mansour 2011	9/80	10/63		9.09%	0.71[0.31,1.64]
Mansour 2011	8/45	2/27		3.66%	2.4[0.55,10.48]
Mansour 2011	8/49	2/28		3.64%	2.29[0.52,10.02]
Navali 2016	6/36	7/11		8.82%	0.26[0.11,0.62]
Singh 2014	6/40	5/25		6.22%	0.75[0.26,2.2]
Wirleitner 2015a	2/33	3/37		2.75%	0.75[0.13,4.2]
Wirleitner 2015a	25/213	30/228		16.84%	0.89[0.54,1.47]
Wirleitner 2015b	18/86	15/83		13.51%	1.16[0.63,2.14]
Zarei 2014	2/29	2/20		2.36%	0.69[0.11,4.5]
Total (95% CI)	**904**	**716**		**100%**	**0.84[0.62,1.13]**
Total events: 125 (Intrauterine hCG), 108 (No hCG)					
Heterogeneity: Tau²=0.07; Chi²=18.32, df=14(P=0.19); I²=23.56%					
Test for overall effect: Z=1.14(P=0.26)					



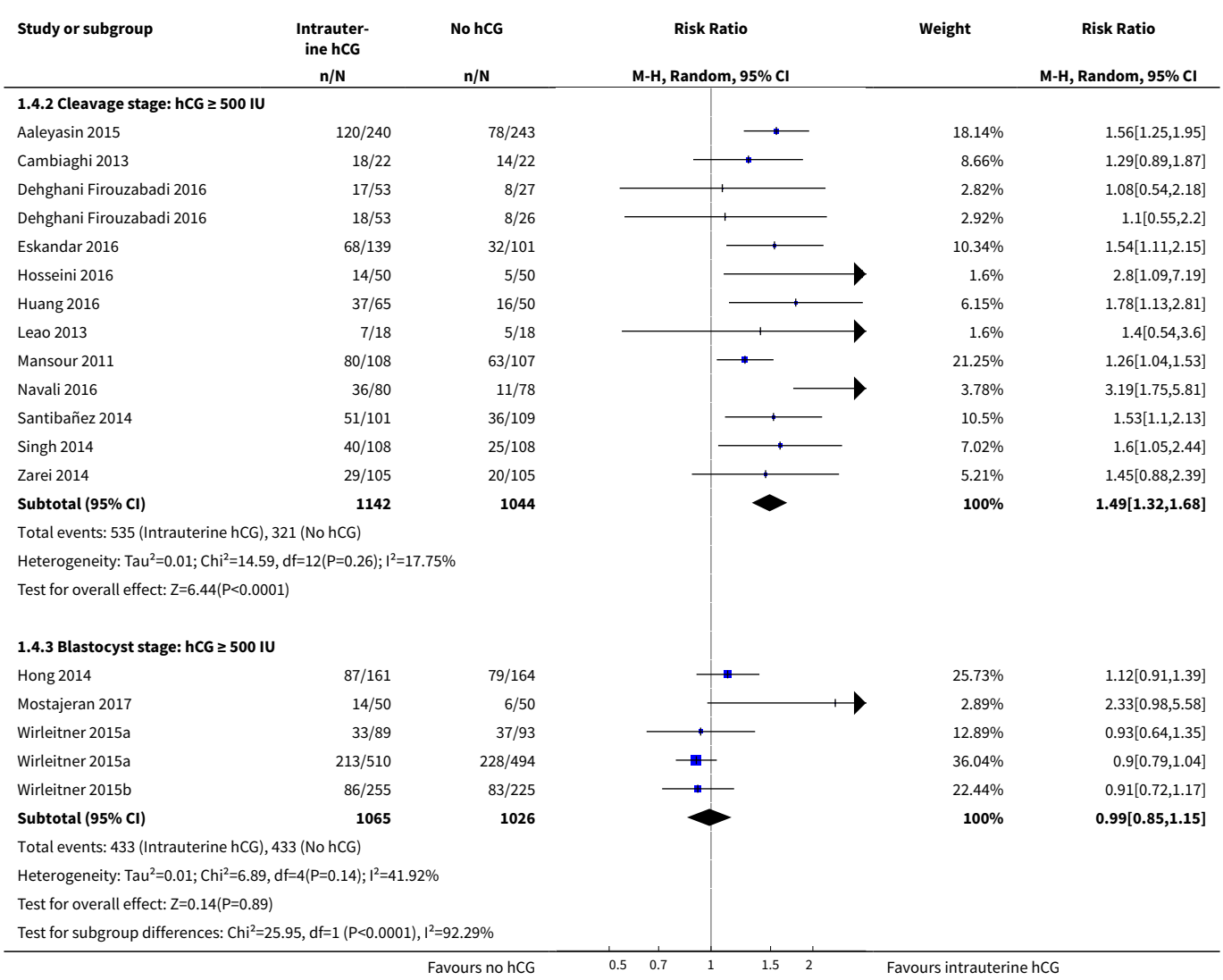
Favours intrauterine hCG — Favours no hCG

Analysis 1.4. Comparison 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, Outcome 4 Clinical pregnancy.

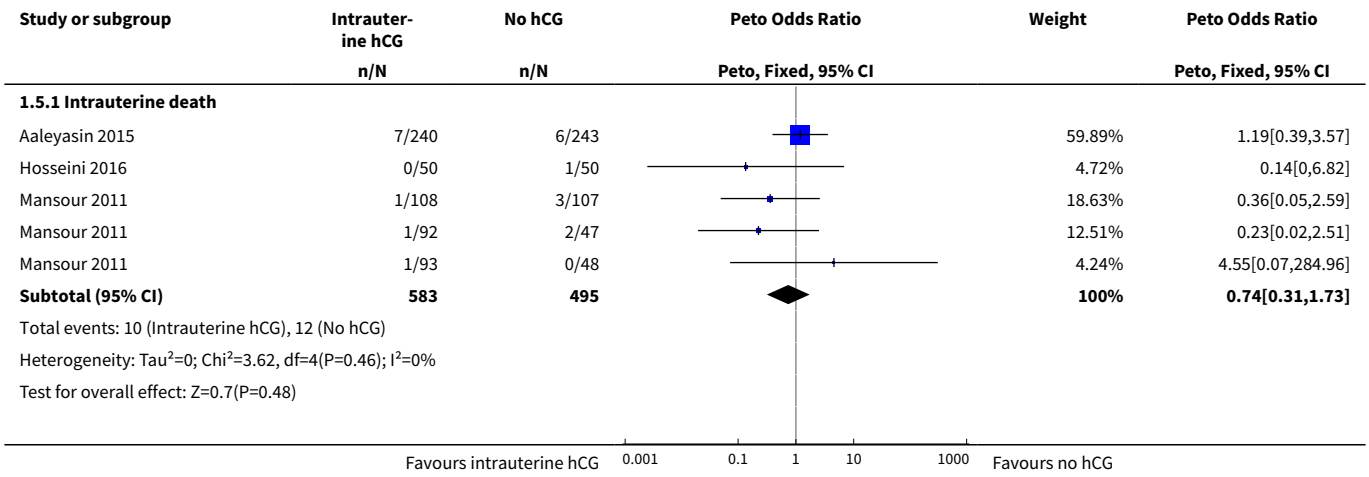
Study or subgroup	Intrauterine hCG n/N	No hCG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Cleavage stage: hCG < 500 IU					
Mansour 2011	45/92	27/47		47.51%	0.85[0.62,1.18]
Mansour 2011	49/93	28/48		52.49%	0.9[0.66,1.23]
Subtotal (95% CI)	**185**	**95**		**100%**	**0.88[0.7,1.1]**
Total events: 94 (Intrauterine hCG), 55 (No hCG)					
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.8); I²=0%					
Test for overall effect: Z=1.14(P=0.25)					

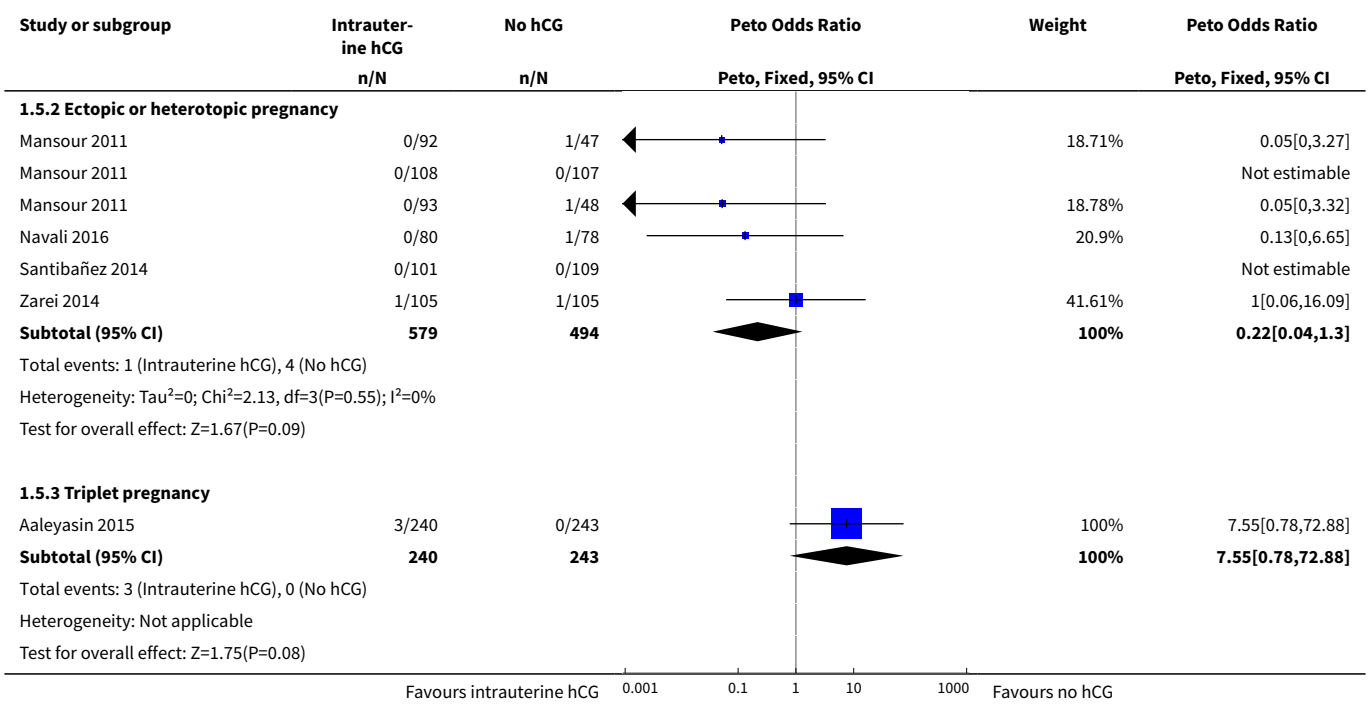


Favours no hCG — Favours intrauterine hCG



Analysis 1.5. Comparison 1 Intrauterine human chorionic gonadotropin (hCG) versus no hCG, Outcome 5 Complications.





APPENDICES

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

PROCITE Platform

Searched 9 January 2018

Keywords CONTAINS "IVF" or "in vitro fertilization" or "in-vitro fertilisation" or "ICSI" or "intracytoplasmic sperm injection" or "ET" or "Embryo" or "in-vitro fertilization" or "Embryo Transfer" or "Embryo Transfer-uterine" or "blastocyst transfer" or Title CONTAINS "IVF" or "in vitro fertilization" or "in-vitro fertilisation" or "ICSI" or "intracytoplasmic sperm injection" or "Embryo" or "in-vitro fertilization" or "ET" or "Embryo" or "in-vitro fertilization" or "Embryo Transfer" or "Embryo Transfer-uterine" or "blastocyst transfer"

AND

Keywords CONTAINS "HCG " or "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "recombinant HCG" or "rhCG" or Title CONTAINS "HCG " or "human chorionic gonadotrophin" or "human chorionic gonadotropin" or "recombinant HCG" or "rhCG"

AND

Keywords CONTAINS "intrauterine human chorionic gonadotrophin" or "intrauterine" or "Intrauterine injection" or "intrauterine instillation "or "uterine cavity injection" or "endometrial" or "Endometrium" or "uterine" or Title CONTAINS "intrauterine human chorionic gonadotrophin" or "intrauterine" or "Intrauterine injection" or "intrauterine instillation "or "uterine cavity injection" or "Endometrium" or "uterine" (113)

Appendix 2. CENTRAL search strategy

Web Platform via CENTRAL Register of Studies online (CRSO)

Searched 9 January 2018

#1 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 2881

#2 (embryo* adj2 transfer*):TI,AB,KY 2522

#3 (blastocyst* adj2 transfer*):TI,AB,KY 264

#4 (assisted reproduct*):TI,AB,KY 851

#5 (ivf or icsi):TI,AB,KY 4126

#6 (in vitro fertili?ation):TI,AB,KY 2200

#7 (intracytoplasmic sperm injection*):TI,AB,KY 1350

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 6556

#9 MESH DESCRIPTOR Chorionic Gonadotropin EXPLODE ALL TREES 697

#10 (Human Chorionic Gonadotrop?in adj7 intrauter*):TI,AB,KY 21

#11 (Human Chorionic Gonadotrop?in adj7 uter*):TI,AB,KY 6

#12 ((endometri* adj2 infusion*) and chorionic):TI,AB,KY 3

#13 ((intra?uter* adj2 infusion*) and chorionic):TI,AB,KY 6

#14 ((intra?uter* adj2 instillation) and chorionic):TI,AB,KY 3

#15 ((endometri* adj2 injection*) and chorionic):TI,AB,KY 3

#16 ((intra?uter* adj2 injection*) and chorionic):TI,AB,KY 36

#17 ((intra?uter* adj2 administration) and chorionic):TI,AB,KY 28

#18 (intrauter* adj7 ?hcg):TI,AB,KY 50

#19 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 767

#20 #8 AND #19 493

Appendix 3. MEDLINE search strategy

OVID Platform

Searched from 1946 to 9 January 2018

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (40939)
2 embryo transfer$.tw. (11209)
3 in vitro fertili?ation.tw. (22663)
4 assisted reproduct*.tw. (13334)
5 (ivf or et).tw. (260179)
6 icsi.tw. (7528)
7 intracytoplasmic sperm injection$.tw. (6590)
8 (blastocyst adj2 transfer$).tw. (843)
9 or/1-8 (297500)
10 exp Chorionic Gonadotropin/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (5410)
11 (Human Chorionic Gonadotrop?in adj7 intrauter$).tw. (87)
12 (Human Chorionic Gonadotrop?in adj7 uter$).tw. (159)
13 (Human Chorionic Gonadotrop?in adj7 intra-uter$).tw. (0)
14 ((endometri$ adj2 infusion$) and chorionic).tw. (1)
15 ((endometri$ adj2 ?instillation) and chorionic).tw. (0)
16 ((intra?uter$ adj2 infusion$) and chorionic).tw. (6)
17 ((intra?uter$ adj2 ?instillation) and chorionic).tw. (6)
18 ((endometri$ adj2 injection$) and chorionic).tw. (5)
19 ((intra?uter$ adj2 injection$) and chorionic).tw. (16)
20 ((intra?uter$ adj2 administration) and chorionic).tw. (14)
21 ((endometri$ adj2 administration) and chorionic).tw. (7)
22 (intrauter$ adj7 ?hcg).tw. (198)
23 (intra-uter$ adj7 ?hcg).tw. (15)
24 (uter$ adj7 ?hcg).tw. (342)
25 or/10-24 (6018)
26 9 and 25 (1776)

27 randomized controlled trial.pt. (515870)
28 controlled clinical trial.pt. (101741)
29 randomized.ab. (452787)
30 randomised.ab. (91845)
31 placebo.tw. (215895)
32 clinical trials as topic.sh. (202549)
33 randomly.ab. (311971)
34 trial.ti. (203432)
35 (crossover or cross-over or cross over).tw. (83358)
36 or/27-35 (1322190)
37 exp animals/ not humans.sh. (4813914)
38 36 not 37 (1219196)
39 26 and 38 (369)

Appendix 4. Embase search strategy

OVID Platform

Searched from 1980 to 9 January 2018

1 exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ (58311)
2 embryo$ transfer$.tw. (17900)
3 in vitro fertili?ation.tw. (26272)
4 assisted reproduct*.tw. (18775)
5 icsi.tw. (13770)
6 intracytoplasmic sperm injection$.tw. (8240)
7 (blastocyst adj2 transfer$).tw. (1906)
8 (ivf or et).tw. (606759)
9 or/1-8 (659662)
10 (Human Chorionic Gonadotrop?in adj7 intrauter$).tw. (122)
11 (Human Chorionic Gonadotrop?in adj7 uter$).tw. (149)
12 (intrauter$ adj7 ?hcg).tw. (286)
13 chorionic gonadotropin/dt, ut [Drug Therapy, Intrauterine Drug Administration] (4766)
14 (uter$ adj3 ?hcg).tw. (127)
15 ((endometri$ adj2 infusion$) and chorionic).tw. (2)
16 ((endometri$ adj2 ?instillation) and chorionic).tw. (0)
17 ((intra?uter$ adj2 infusion$) and chorionic).tw. (8)
18 ((intra?uter$ adj2 ?instillation) and chorionic).tw. (7)
19 ((endometri$ adj2 injection$) and chorionic).tw. (5)
20 ((intra?uter$ adj2 injection$) and chorionic).tw. (44)
21 ((intra?uter$ adj2 administration) and chorionic).tw. (30)
22 ((endometri$ adj2 administration) and chorionic).tw. (14)
23 or/10-22 (5333)
24 9 and 23 (2692)
25 Clinical Trial/ (962568)
26 Randomized Controlled Trial/ (479015)
27 exp randomization/ (76661)
28 Single Blind Procedure/ (30048)
29 Double Blind Procedure/ (142111)
30 Crossover Procedure/ (53667)
31 Placebo/ (302487)
32 Randomi?ed controlled trial$.tw. (169852)
33 Rct.tw. (26427)
34 random allocation.tw. (1709)
35 randomly allocated.tw. (28558)
36 allocated randomly.tw. (2271)
37 (allocated adj2 random).tw. (788)
38 Single blind$.tw. (20051)
39 Double blind$.tw. (177385)
40 ((treble or triple) adj blind$).tw. (725)
41 placebo$.tw. (258956)
42 prospective study/ (414841)
43 or/25-42 (1837099)

44 case study/ (51204)
45 case report.tw. (342456)
46 abstract report/ or letter/ (1012507)
47 or/44-46 (1397981)
48 43 not 47 (1790343)
49 24 and 48 (861)

Appendix 5. PsycINFO search strategy

OVID Platform

Searched from 1806 to 9 January 2018

1 exp reproductive technology/ (1682)
2 in vitro fertili?ation.tw. (684)
3 icsi.tw. (68)
4 intracytoplasmic sperm injection$.tw. (52)
5 (blastocyst adj2 transfer$).tw. (4)
6 (embryo$ adj2 transfer$).tw. (140)
7 or/1-6 (1957)
8 exp Gonadotropic Hormones/ (4096)
9 (Human Chorionic Gonadotrop?in adj7 intrauter$).tw. (0)
10 (Human Chorionic Gonadotrop?in adj7 uter$).tw. (0)
11 (intrauter$ adj7 ?hcg).tw. (0)
12 (uter$ adj7 ?hcg).tw. (0)
13 or/8-12 (4096)
14 7 and 13 (8)

Appendix 6. CINAHL search strategy

EBSCO Platform

Searched from 1961 to 9 January 2018

#	Query	Results
S15	S8 AND S14	59
S14	S9 OR S10 OR S11 OR S12 OR S13	697
S13	TX(Chorionic Gonadotrop?in N7 intrauter*)	1
S12	TX(Chorionic Gonadotrop?in N7 uter*)	3
S11	TX(Human Chorionic Gonadotrop?in N7 intrauter*)	0
S10	TX(Human Chorionic Gonadotrop?in N7 intrauter*)	1
S9	(MM "Gonadotropins, Chorionic")	588
S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	5290
S7	TX embryo* N3 transfer*	1159
S6	TX ovar* N3 hyperstimulat*	456
S5	TX ovari* N3 stimulat*	419
S4	TX IVF or TX ICSI	2204

(Continued)

S3	(MM "Fertilization in Vitro")	1803
S2	TX vitro fertilization	3895
S1	TX vitro fertilisation	3895

WHAT'S NEW

Date	Event	Description
23 October 2018	Amended	Correction of text in Declarations of interest section

HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 5, 2016

Date	Event	Description
15 June 2018	New search has been performed	New study data were added, leading to a change to the conclusions of this review.
15 June 2018	New citation required and conclusions have changed	New searches were performed for this major update, and additional RCTs have contributed data (Dehghani Firouzabadi 2016; Eskandar 2016; Hosseini 2016; Huang 2016; Mostajeran 2017; Navali 2016).
22 June 2016	Amended	Links to an analysis and to a figure were inserted.

CONTRIBUTIONS OF AUTHORS

LC and NT performed the literature search, assessed studies for eligibility, and extracted the data.

LC performed the analyses and drafted the review.

NT, NRF, and AC provided feedback and edited the review.

All review authors agree with the final version of the review.

DECLARATIONS OF INTEREST

LC, NT and AC do not have any conflicts of interest to disclose. NRF has received travel costs or advisory board honoraria from GE Healthcare, Merck Serono and Ferring and provides medico-legal reports for court proceedings. He has shares in two fertility clinics.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We slightly narrowed the Cochrane Gynaecology and Fertility Group Specialised Register search strategy.

We performed a subgroup analysis based on IC-hCG dose to address the heterogeneity.

For outcomes with event rates below 1%, we used the Peto one-step odds ratio (OR) method to calculate the combined outcome with 95% confidence interval.

If a study included multiple treatment arms receiving different doses of hCG, we split the control group proportionately with the experimental groups to avoid analysing control participants in duplicate.

INDEX TERMS

Medical Subject Headings (MeSH)

*Embryo Transfer [adverse effects] [statistics & numerical data]; Abortion, Spontaneous [epidemiology] [etiology]; Chorionic Gonadotropin [*administration & dosage]; Embryo Implantation [drug effects]; Infertility, Female [*drug therapy]; Live Birth [epidemiology]; Pregnancy Rate; Reproductive Control Agents [*administration & dosage]; Uterus

MeSH check words

Adult; Female; Humans; Pregnancy