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Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection (Review)

Kamath MS, Mascarenhas M, Kirubakaran R, Bhattacharya S

Kamath MS, Mascarenhas M, Kirubakaran R, Bhattacharya S.
Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection.
Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD003416.
DOI: 10.1002/14651858.CD003416.pub5.

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[Intervention Review]

Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection

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Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2020.

Citation: Kamath MS, Mascarenhas M, Kirubakaran R, Bhattacharya S. Number of embryos for transfer following in vitro fertilisation or intra-cytoplasmic sperm injection. *Cochrane Database of Systematic Reviews* 2020, Issue 8. Art. No.: CD003416. DOI: 10.1002/14651858.CD003416.pub5.

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ABSTRACT

Background

Transfer of more than one embryo during in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) increases multiple pregnancy rates resulting in an increased risk of maternal and perinatal morbidity. Elective single embryo transfer offers a means of minimising this risk, but this potential gain needs to be balanced against the possibility of jeopardising the overall live birth rate (LBR).

Objectives

To evaluate the effectiveness and safety of different policies for the number of embryos transferred in infertile couples undergoing assisted reproductive technology cycles.

Search methods

We searched the Cochrane Gynaecology and Fertility Group specialised register of controlled trials, CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform from inception to March 2020. We handsearched reference lists of articles and relevant conference proceedings. We also communicated with experts in the field regarding any additional studies.

Selection criteria

We included randomised controlled trials (RCTs) comparing different policies for the number of embryos transferred following IVF or ICSI in infertile women. Studies of fresh or frozen and thawed transfer of one to four embryos at cleavage or blastocyst stage were eligible.

Data collection and analysis

Two review authors independently extracted data and assessed trial eligibility and risk of bias. The primary outcomes were LBR and multiple pregnancy rate. The secondary outcomes were clinical pregnancy and miscarriage rates. We analysed data using risk ratios (RR), Peto odds ratio (Peto OR) and a fixed effect model.

Main results

We included 17 RCTs in the review (2505 women). The main limitation was inadequate reporting of study methods and moderate to high risk of performance bias due to lack of blinding. A majority of the studies had low numbers of participants.

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None of the trials compared repeated single embryo transfer (SET) with multiple embryo transfer. Reported results of multiple embryo transfer below refer to double embryo transfer.

Repeated single embryo transfer versus multiple embryo transfer in a single cycle

Repeated SET was compared with double embryo transfer (DET) in four studies of cleavage-stage transfer. In these studies the SET group received either two cycles of fresh SET (one study) or one cycle of fresh SET followed by one frozen SET (three studies). The cumulative live birth rate after repeated SET may be little or no different from the rate after one cycle of DET (RR 0.95, 95% CI (confidence interval) 0.82 to 1.10; I^2 = 0%; 4 studies, 985 participants; low-quality evidence). This suggests that for a woman with a 42% chance of live birth following a single cycle of DET, the repeated SET would yield pregnancy rates between 34% and 46%. The multiple pregnancy rate associated with repeated SET is probably reduced compared to a single cycle of DET (Peto OR 0.13, 95% CI 0.08 to 0.21; I^2 = 0%; 4 studies, 985 participants; moderate-quality evidence). This suggests that for a woman with a 13% risk of multiple pregnancy following a single cycle of DET, the risk following repeated SET would be between 0% and 3%. The clinical pregnancy rate (RR 0.99, 95% CI 0.87 to 1.12; I^2 = 47%; 3 studies, 943 participants; low-quality evidence) after repeated SET may be little or no different from the rate after one cycle of DET. There may be little or no difference in the miscarriage rate between the two groups.

Single versus multiple embryo transfer in a single cycle

A single cycle of SET was compared with a single cycle of DET in 13 studies, 11 comparing cleavage-stage transfers and three comparing blastocyst-stage transfers.One study reported both cleavage and blastocyst stage transfers.

Low-quality evidence suggests that the live birth rate per woman may be reduced in women who have SET in comparison with those who have DET (RR 0.67, 95% CI 0.59 to 0.75; I^2 = 0%; 12 studies, 1904 participants; low-quality evidence). Thus, for a woman with a 46% chance of live birth following a single cycle of DET, the chance following a single cycle of SET would be between 27% and 35%. The multiple pregnancy rate per woman is probably lower in those who have SET than those who have DET (Peto OR 0.16, 95% CI 0.12 to 0.22; I^2 = 0%; 13 studies, 1952 participants; moderate-quality evidence). This suggests that for a woman with a 15% risk of multiple pregnancy following a single cycle of DET, the risk following a single cycle of SET would be between 2% and 4%. Low-quality evidence suggests that the clinical pregnancy rate may be lower in women who have SET than in those who have DET (RR 0.70, 95% CI 0.64 to 0.77; I^2 = 0%; 10 studies, 1860 participants; low-quality evidence). There may be little or no difference in the miscarriage rate between the two groups.

Authors' conclusions

Although DET achieves higher live birth and clinical pregnancy rates per fresh cycle, the evidence suggests that the difference in effectiveness may be substantially offset when elective SET is followed by a further transfer of a single embryo in fresh or frozen cycle, while simultaneously reducing multiple pregnancies, at least among women with a good prognosis.

The quality of evidence was low to moderate primarily due to inadequate reporting of study methods and absence of masking those delivering, as well as receiving the interventions.

PLAIN LANGUAGE SUMMARY

Number of embryos for transfer in women undergoing assisted reproductive technology (ART)

Review question

How many embryos should be transferred in couples undergoing ART?

Background

Multiple pregnancy causes serious health risks for mothers and babies. Single embryo transfer (SET) can reduce the chance of having twins, triplets or higher order multiples but this needs to be balanced against the risk of lowering the chance of pregnancy or live birth. We reviewed the evidence about the number of embryos transferred in women undergoing ART. The evidence is current to March 2020.

Study characteristics

We found 17 randomised controlled trials with a total of 2505 participants. Most were not commercially funded. None of the trials compared repeated single embryo transfer (SET) with multiple embryo transfer. A majority of the studies had low numbers of participants. Reported results of multiple embryo transfer below refer to double embryo transfer.

Key findings

Repeated single embryo transfer versus multiple embryo transfer in a single cycle

Based on low-quality evidence, there was no indication that overall live birth and clinical pregnancy rates differed substantially when repeated SET (either two cycles of single embryo transfer or one cycle of single embryo transfer followed by transfer of a single frozen embryo) was compared with double embryo transfer (DET). For a woman with a 42% chance of live birth following a single cycle of DET,

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the chance following repeated single embryo transfer would be between 34% and 46%. Moderate-quality evidence suggests that the risk of multiple birth is much lower in the SET group (between 0% and 3%) compared to a 13% chance of multiple pregnancy following a single cycle of DET. The chance of miscarriage rate is similar between the two groups.

Single versus multiple embryo transfer in a single cycle

We found low-quality evidence that the rates of live birth and clinical pregnancy (CPR) were lower after one cycle of fresh SET compared with the outcome of one cycle of fresh DET. For a woman with a 46% chance of live birth following one cycle of DET, the chance following one cycle of SET was between 27% and 35%. However, the risk of multiple pregnancy was higher after DET. There was no difference in the chance of miscarriage between the two groups.

Conclusion

While live birth and clinical pregnancy was lower following SET compared to DET after single fresh cycle, there was no difference between overall live birth rate and CPR following consecutive SET versus a single cycle of DET. However, the multiple pregnancy rate is much lower following SET compared to DET. Most of the evidence currently available concerns younger women with a good prognosis.

Quality of evidence

The quality of evidence was low to moderate primarily due to inadequate reporting of study methods and absence of masking those delivering, as well as receiving the interventions.

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Summary of findings 1. Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle of IVF or ICSI

Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle of IVF or ICSI

Patient or population: transfer following in vitro fertilisation or intracytoplasmic sperm injection
Setting: clinic
Intervention: repeated single (mixed policies)
Comparison: multiple embryo transfer

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
		Risk with multiple embryo transfer	Risk with repeated single (mixed policies)				
Cumulative live birth	pooled	420 per 1000	399 per 1000 (344 to 462)	RR 0.95 (0.82 to 1.10)	985 (4 RCTs)	⊕⊕⊖⊖ LOW [1]	
Cumulative live birth	SET + 1 FET versus DET (×1) (cleavage stage)	421 per 1000	392 per 1000 (333 to 459)	RR 0.93 (0.79 to 1.09)	878 (3 RCTs)	⊕⊕⊖⊖ LOW [1]	
	SET (×2) versus DET (×1) (cleavage stage)	407 per 1000	464 per 1000 (285 to 755)	RR 1.14 (0.70 to 1.84)	107 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2]	
Multiple pregnancy	pooled	127 per 1000	18 per 1000 (11 to 30)	Peto odds ratio 0.13 (0.08 to 0.21)	985 (4 RCTs)	⊕⊕⊕⊖ MODERATE [3]	
Multiple pregnancy	SET + 1 FET versus DET (×1) (cleavage stage)	128 per 1000	19 per 1000 (12 to 31)	Peto odds ratio 0.13 (0.08 to 0.22)	878 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3]	
	SET (×2) versus DET (×1) (cleavage stage)	111 per 1000	15 per 1000 (4 to 63)	Peto odds ratio 0.12 (0.03 to 0.54)	107 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2 3 4]	
Clinical pregnancy rate	pooled	515 per 1000	489 per 1000	RR 0.95	943	⊕⊕⊖⊖ LOW [1]	

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			(432 to 556)	(0.84 to 1.08)	(3 RCTs)	
Miscarriage rate	pooled	76 per 1000	149 per 1000 (71 to 289)	Peto odds ratio 2.14 (0.93 to 4.95)	282 (2 RCTs)	⊕⊕⊝⊝ LOW [3 4]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds 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

[1] Very serious risk of bias, downgraded by 2 levels: high risk or unclear risk of bias for allocation concealment, high risk of bias for performance bias due to lack of blinding.
[2] Serious risk of indirectness, downgraded by 1 level: single centre study.
[3] Serious risk of bias, downgraded by 1 level: high risk or unclear risk of bias for allocation concealment. We did not downgrade for performance bias as it is unlikely, that any change in clinician's behaviour due to knowledge of group allotment will influence outcomes such as multiple pregnancy or miscarriage rates.
[4] Serious risk of imprecision, downgraded by 1 level: wide confidence interval.

Summary of findings 2. Single compared to multiple embryo transfer in a single cycle following IVF or ICSI

Single compared to multiple embryo transfer in a single cycle following in vitro fertilisation or intracytoplasmic sperm injection

Patient or population: transfer following in vitro fertilisation or intracytoplasmic sperm injection
Setting: clinic
Intervention: single embryo transfer
Comparison: multiple embryo transfer (in a single cycle)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Com-ments
	Risk with multiple (in a single cycle)	Risk with Single				
Live birth	463 per 1000	310 per 1000 (273 to 347)	RR 0.67 (0.59 to 0.75)	1904 (12 RCTs)	⊕⊕⊝⊝ LOW [1]	

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Multiple pregnancy	151 per 1000	28 per 1000 (21 to 38)	Peto odds ratio 0.16 (0.12 to 0.22)	1952 (13 RCTs)	⊕⊕⊕⊖ MODERATE [2]
Clinical pregnancy	547 per 1000	383 per 1000 (350 to 421)	RR 0.70 (0.64 to 0.77)	1860 (10 RCTs)	⊕⊕⊖⊖ LOW [1]
Miscarriage rate	72 per 1000	69 per 1000 (46 to 99)	Peto odds ratio 0.96 (0.66 to 1.42)	1560 (7 RCTs)	⊕⊕⊖⊖ LOW [2,3]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds 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

[1] Very serious risk of bias, downgraded by 2 levels: unclear or high risk for allocation concealment, high risk for performance bias due to lack of blinding in majority of the included studies.
[2] Serious risk of bias, downgraded by 1 level: high risk or unclear risk of bias for allocation concealment. We did not downgrade for performance bias as it is unlikely, that any change in clinician's behaviour due to knowledge of group allotment will influence outcomes such as multiple pregnancy or miscarriage rates.
[3] Serious risk of imprecision, downgraded by 1 level: wide confidence interval.

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BACKGROUND

Description of the condition

Historically, in an effort to achieve 'acceptable' pregnancy rates, most women undergoing in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) have received transfer of multiple embryos. This practice results in high rates of multiple pregnancy, however, leading to poor clinical outcomes for the mother, her children or both (ASRM 2012).

In the 1990s it was calculated that women undergoing assisted reproductive technology (ART) had an approximately 20-fold increased risk of twins and 400-fold increased risk of higher order pregnancies (Martin 1998). In 2014, twins accounted for nearly 17% of all live births resulting from ART in Europe (De Geyter 2018). Widespread concern about the medical, social and economic consequences of multiple pregnancy has prompted the development of strategies aimed at promoting birth of a single healthy baby following ART (ESHRE 2000).

Compared with singleton births, twins have a four-fold increased risk of perinatal mortality, and for triplets the risk is increased six-fold (ESHRE 2000). An earlier study of 50,258 births following IVF and ICSI pregnancies reported that twins accounted for half the total neonatal deaths and one-third of the perinatal deaths (Sullivan 2012). Twins had a significantly higher perinatal mortality rate compared to singletons (27.8 per 1000 births and 12.4 per 1000 births, respectively). The relatively high congenital malformation rates observed in babies born after IVF and ICSI are attributed to the high proportion of multiple births in this population (Sebire 2000 [pers comm]; Wennerholm 2000). In babies with very low birth weight, twin gestation is an independent risk factor for neurodevelopmental impairment including cerebral palsy, severe bilateral hearing loss and bilateral blindness (Wadhawan 2009).

Twin pregnancy also increases the risk of obstetric complications, with a high incidence of miscarriage, pregnancy-induced hypertension, gestational diabetes, premature labour and abnormal delivery (FIVNAT 1995; ESHRE 2000). After the initial sense of achievement of parenthood, the care of children from a multiple gestation is often associated with practical difficulties and high stress levels (Garel 1992; Doyle 1996; Garel 1997). More hours per week are required to care for six-month-old triplets and to carry out the necessary household tasks. Even in families with material resources and plenty of help, emotional stress is not uncommon and may necessitate psychiatric help (Garel 1997).

The economic impact of multiple pregnancies on health services is another consideration. In an Australian study, the average cost of ART twin delivery was almost three times as high as for an ART singleton, while for higher order multiple births the cost was up to 11 times greater (Chambers 2007). It has been suggested that redeployment of money saved by reduction of multiple pregnancies could allow for increased provision of ART treatment in the UK at no extra cost (Ledger 2006).

Description of the intervention

IVF or ICSI is followed by the transfer of one or multiple (usually between two to four) fresh or frozen and thawed embryos within the uterine cavity. Surplus embryos can be frozen and transferred in a subsequent natural or hormone-stimulated transfer cycle.

There is a worldwide trend for an increase in the rates of elective single embryo transfer, defined as the transfer of a single embryo, chosen from a larger number of available embryos, at cleavage or blastocyst stage. In Europe in 2014, about 35% of all embryo transfers were of single embryos but much higher rates are reported in some countries (80% in Sweden in 2014, and 89% in Australia and New Zealand in 2017) (Australia New Zealand ART data 2017; De Geyter 2018).

Embryos are often transferred after culture for two or three days, when they contain two to eight cells (cleavage stage). The rationale for cleavage-stage transfer is that the uterus is the best environment for the survival of the embryo (Laverge 2001). Over the past decade there has been a shift in practice to the transfer of embryos on day five or six, when they have developed into blastocysts. Blastocyst transfer has been shown to be successful (Papanikolaou 2006; Khalaf 2008); it requires laboratory expertise and experience in extended embryo culture. An advantage of blastocyst transfer is that embryos surviving five days are more likely to be viable than embryos at two or three days, and so the likelihood of implantation is higher. Disadvantages of blastocyst transfer include a higher risk of cycles being cancelled (Marek 1999); and fewer embryos being available for cryopreservation due to arrested embryo progression.

A Cochrane Review comparing cleavage-stage versus blastocyst transfer reported that blastocyst transfer was associated with a small but significant increase in the live birth rate per couple (Glujovsky 2016). There was no significant difference between the cleavage versus blastocyst stage in rates per couple of cumulative pregnancy following fresh and frozen-thawed transfer after one oocyte retrieval. Multiple birth rates did not differ between the two groups.

How the intervention might work

A strategy of reducing the risk of multiple pregnancy by limiting the number of embryos transferred needs to be balanced against the risk of jeopardising the overall pregnancy rate. An obvious solution is to consider an individualised embryo transfer policy based on identification of key clinical and laboratory parameters associated with a higher implantation rate.

A study from Germany found no significant difference in pregnancy rates following elective transfer of two and three embryos (22% vs. 22.5%) (Ludwig 2000). The multiple pregnancy rates were 16.1% and 24% following two and three embryos transfer, respectively. In a study which used a donor oocyte recipient model, the pregnancy rates (57.8% vs. 55.8%) were comparable following transfer of two and three embryos (Licciardi 2001). The multiple pregnancy rates were 40.5% and 51% following two and three embryos, respectively.

Use of elective single embryo transfer at the cleavage stage (day two or three) has been limited in clinical practice for fear that the overall success rates of ART would decline. This assumption has been supported by the published results of single embryo transfer where only one embryo was available. Because no opportunity for selection of more suitable embryos exists, the implantation potential of the only available embryo is usually poor, with clinical pregnancy rates of around 10% (FIVNAT 1995; Giorgetti 1995; Preutthipan 1996; Yaron 1997; Lieberman 1998; Westergaard 2000). In a situation where the transferred embryos are the only available

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embryos, pregnancy rates are unfavourable even for multiple embryo transfer (Ludwig 2000).

A study from Finland reported a 20.2% pregnancy rate in 94 women who had only one embryo available for transfer compared with a rate of 29.7% in women who had multiple embryos available and from which a single high-quality embryo was selected for transfer. The cumulative pregnancy rate after frozen and thawed embryo transfers in the elective single embryo transfer group was 47.3% per oocyte retrieval. By comparison, the pregnancy rate for double embryo transfers was 29.4% per transfer, of which 23.9% were twin pregnancies (Vilska 1999).

Another strategy for reducing multiple pregnancy is multifetal pregnancy reduction. However, this procedure is invasive; can have long term adverse psychological consequences for the potential parents (Berkowits 1996; McKinney 1996); and may be unacceptable to some couples given the attendant ethical and legal issues.

Why it is important to do this review

The National Institute for Health and Care Excellence (NICE) guidelines recommend single embryo transfer (SET) for women aged less than 37 years and no more than two embryos for women aged 37 and beyond (NICE 2013). The American Society of Reproductive Medicine (ASRM) recommends single embryo transfer for women aged less than 38 years and not more than three embryos for women aged 38 to 40 years (ASRM 2017).

In an individual patient data meta-analysis, authors reported significantly lower live birth rate following fresh elective SET (eSET) compared to double embryo transfer (DET), but the cumulative live births were comparable (McLernon 2010). Similar findings were reported by another systematic review which compared SET versus DET at cleavage stage (Gelbaya 2010). However, success of eSET policy depends on good and reliable cryopreservation programme. Clinicians in Europe have generally accepted the desirability of reducing multiple births by limiting the number of embryos transferred, especially if this can be achieved without unduly reducing live birth rates (Roberts 2011). It is important to find ways to limit the risk of multiple pregnancy without reducing the chance of achieving live birth in couples undergoing ART cycles. This updated systematic review evaluates the effectiveness and safety of different policies for the number of embryos transferred in couples who undergo ART.

OBJECTIVES

To evaluate the effectiveness and safety of different policies for the number of embryos transferred in infertile couples undergoing assisted reproductive technology cycles.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (for example studies with evidence of inadequate sequence generation such as alternate days, chart numbers) as they are associated with a high risk of bias. Cross-over trials were eligible but we planned that only data from the first phase would be included in the meta-analysis as the cross-over design is not valid in this context.

Types of participants

Women who underwent embryo transfer following IVF or ICSI treatment for female or male infertility with their own gametes or as oocyte or embryo donation recipients were eligible for inclusion.

Types of interventions

We compared the following interventions.

1. Repeated single embryo transfer versus repeated multiple embryo transfer
2. Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle
3. Single versus multiple embryo transfer in a single cycle
4. Double embryo transfer versus more than two embryos transferred
5. Other fresh or frozen cycle comparisons

Mixed policies covered different SET strategies such as two fresh cycles of SET or a single fresh SET followed by transfer of a single frozen embryo in a natural or hormone-stimulated cycle.

It was required that elective transfer of embryos followed an initial fresh IVF or ICSI treatment using standard protocols for controlled ovarian stimulation, oocyte retrieval under ultrasound guidance, insemination, embryo culture, and transcervical replacement of embryos (cleavage stage or blastocyst) using standard culture medium and catheters for the culture and transfer of embryos respectively.

Studies could (in addition) transfer one or more frozen-thawed embryos in one or both arms using standard procedures in a natural or hormone-stimulated cycle.

We excluded studies comparing cleavage-stage transfer versus blastocyst-stage transfer.

Types of outcome measures

Primary outcome

(1) Effectiveness: live birth rate per woman or couple, or cumulative live birth rate per woman or couple (in trials with multiple transfers or multiple cycles).

We defined live birth as delivery of a live foetus after 20 completed weeks of gestational age (duration of pregnancy). We counted the delivery of single, twin, or multiple pregnancies as one live birth. Cumulative live birth rate reflects the number of live births following fresh and frozen embryo transfers after a single ART treatment leading to oocyte collection, or (where stated) after multiple ART cycles. It is calculated by dividing the total number of live births in each group by the total number of women randomised in each group. One ART cycle is defined as a single treatment leading to oocyte collection and a fresh embryo transfer or a frozen embryo transfer (where fresh embryo transfer was not performed).

(2) Safety: multiple pregnancy rate per woman or couple. The demonstration of more than one sac with a fetal pole on ultrasound scan defines a multiple pregnancy.

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Secondary outcomes

(1) Effectiveness: clinical pregnancy rate per woman or couple.

We defined clinical pregnancy as the presence of a gestational sac on ultrasound scan or confirmation of products of conception by pathological examination in the event of spontaneous miscarriage or ectopic pregnancy.

(2) Safety: miscarriage rate per woman. Miscarriage rate per randomised woman, defined as the spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestation.

Search methods for identification of studies

We searched for all relevant published and unpublished RCTs without language restriction and in consultation with the Cochrane Gynaecology and Fertility Group (CGFG) Information Specialist.

Electronic searches

We searched the following electronic databases:

- The CGFG's specialised register of controlled trials; searched 16 March 2020, PROCITE platform (Appendix 1);
- Cochrane Central Register of Studies Online (CENTRAL CRSO); searched 16 March 2020, Web platform (Appendix 2);
- MEDLINE; searched from 1946 to 16 March 2020, OVID platform (Appendix 3);
- Embase; searched from 1980 to 16 March 2020, OVID platform (Appendix 4);
- PsycINFO; searched from 1806 to 16 March 2020, OVID platform (Appendix 5);
- CINAHL; searched from 1961 to 16 March 2020, EBSCO platform (Appendix 6).

The MEDLINE search was limited by the Cochrane Highly Sensitive Search Strategy filter for identifying randomised trials, which appears in the *Cochrane Handbook of Systematic Reviews of Interventions* (Version 5.1.0, Chapter 6, 6.4.11) (Higgins 2011). We combined the Embase (OVID platform only) searches with a trial filter developed by the Scottish Intercollegiate Guidelines Network (SIGN) (https://www.sign.ac.uk/what-we-do/methodology/search-filters/).

Other electronic sources of trials included the following.

- Trials registers for ongoing and registered trials.
  * www.ClinicalTrials.gov;
  * www.who.int/trialsearch/Default.aspx
- OpenGrey for unpublished literature from Europe at www.opengrey.eu.
- Citation index: Web of Science.

Searching other resources

We handsearched other resources as follows.

- Conference proceedings: International Federation of Fertility Societies (IFFS), American Society for Reproductive Medicine (ASRM), British Fertility Society (BFS), European Society of Human Reproduction and Embryology (ESHRE) between 1997 and 2020
- Bibliographies of the identified studies

We personally communicated with experts and investigators in the field to get information on newly planned studies and information on existing embryo transfer policies.

Data collection and analysis

Selection of studies

At least two review authors (including MM and MSK) independently selected trials for inclusion in the review from those identified by the search strategy. They resolved disagreements about study eligibility by discussion with a third author (SB).

Data extraction and management

Three review authors (MM, MSK and RK) independently performed quality assessment and data extraction. They invited the senior review author (SB) to resolve any disagreements by discussion. They sought additional information on trial methodology or trial data from the principal authors of trials which appeared to meet the eligibility criteria but were unclear in aspects of methodology, or where the data were in a form unsuitable for meta-analysis.

Assessment of risk of bias in included studies

We assessed the included studies for risk of bias using the Cochrane 'Risk of bias' tool to evaluate the following: random sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias. At least three authors (MM, MSK and RK) assessed these six domains. They resolved any disagreements by consensus or by discussion with another author (SB). The assessments are presented in the 'Risk of bias' tables (see Characteristics of included studies).

Measures of treatment effect

All data were dichotomous. We used the numbers of events in the control and intervention groups of each study to calculate the Mantel-Haenszel risk ratios (RRs) with 95% confidence intervals (CIs). We used Peto odds ratios for outcomes with low event rates. Where outcome data were reported as a percentage of the total number of participants, we included them in the analyses by multiplying the percentage by the total number of participants (n) in that group and dividing by 100.

Unit of analysis issues

The primary analysis was per woman randomised; we included per pregnancy data for the outcome 'miscarriage'. We counted multiple live births (for example twins or triplets) as one live birth event. We planned to include only first-phase data from cross-over trials. We did not include 'per cycle' data in tables of comparison but reported them descriptively.

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible and made attempts to obtain missing data from the original investigators by contacting them by email. We sent reminder emails when we did not get any response to the initial email. We assumed live births or clinical pregnancies would not have occurred in women without a reported outcome.

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Assessment of heterogeneity

The authors considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. Clinical heterogeneity in subfertility (such as variations in entry criteria and subtle differences in the treatment used that are important from a clinical aspect) cannot be avoided because most centres use their own protocols which can vary in some aspects. When trials met the inclusion criteria and had performed the same intervention we considered it appropriate to pool their results. Statistical heterogeneity was assessed by inspecting the scatter in the data points and the overlap in their CIs and, more formally, by checking the results of the I^2 statistic. We took an I^2 measurement greater than 50% to indicate substantial heterogeneity (Higgins 2011). If we detected substantial heterogeneity, we explored possible explanations in sensitivity analyses. Even when included trials in a comparison group were statistically homogeneous, there were potentially considerable differences in clinical features (clinical heterogeneity). We took these differences into account when analysing and interpreting the pooled results.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there were sufficient studies (preferably more than 10) for the primary outcomes, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We combined the data from primary studies using Review Manager 5 (RevMan 5) software to calculate pooled Mantel-Haenszel RRs and 95% CIs, using a fixed-effect model, with the following comparisons.

1. Repeated single embryo transfer versus repeated multiple embryo transfer
2. Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle
3. Single versus multiple embryo transfer in a single cycle
4. Double embryo transfer versus more than two embryos transferred
5. Other fresh or frozen cycle comparisons

We stratified data by the stage of embryo transfer (cleavage or blastocyst).

We reformatted the comparisons of interest, as above. The choice of repeated single versus repeated multiple embryo transfer as the first comparison of interest reflects the view that a policy of repeated SET may optimise the chance of live birth while minimising the risk of multiple pregnancy (Roberts 2011).

An increase in the odds of a particular outcome, which may be beneficial (for example live birth) or detrimental (for example multiple pregnancy) is displayed graphically in the meta-analyses to the right of the centre line and a decrease in the odds of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

If data were available, we planned to conduct subgroup analyses to determine the separate evidence within groups for different prognostic characteristics.

We planned subgroup analysis for the following prognostic factor.

- Cleavage stage versus blastocyst stage transfer

If we detected substantial heterogeneity, we planned to explore possible explanations in sensitivity analyses. We planned to take any statistical heterogeneity into account when interpreting the results.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding study eligibility and statistical methods. We considered whether the review conclusions would have differed if:

1. eligibility had been restricted to studies without high or unclear risk of bias in any domain;
2. a random-effects model had been adopted;
3. the summary effect measure had been odds risk rather than relative risk ratio.

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

We generated 'Summary of findings' tables using GRADEPro software and Cochrane methods (GRADEpro GDT; Higgins 2011). These tables evaluated the overall quality of the body of evidence for the primary review outcomes for selected comparisons: these were 'Repeated single compared to mixed policies for transfer following in vitro fertilisation or intracytoplasmic sperm injection' and 'Single compared to multiple (in a single cycle) for transfer following in vitro fertilisation or intracytoplasmic sperm injection'.

Items assessed were study limitations (that is risk of bias), consistency of effect, imprecision, indirectness and publication bias. We incorporated judgements about evidence certainty (high, moderate or low) into the reporting of results.

We have used the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT). We have justified all decisions to down- or upgrade the certainty of evidence using footnotes and have made comments to aid reader's understanding of the review where necessary. Two review authors have independently made decisions about evidence quality, and have resolved any disagreements by discussion.

We included the following outcomes in the 'Summary of findings' tables.

1. Live birth rate per woman randomised
2. Multiple pregnancy rate per woman randomised
3. Clinical pregnancy per woman randomised
4. Miscarriage rate per woman randomised

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RESULTS

Description of studies

Results of the search

The search for the previous 2013 update identified 640 articles (including duplicates). Five new studies were included in the previous 2013 update (ASSETT 2003; Gardner 2004; Thurin 2005; ECOSSE 2006; Prados 2015); these were added to the seven studies in the earlier 2009 update (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; Thurin 2004; Lukassen 2005; Heijnen 2006; van Montfoort 2006). Six studies were excluded (Motta 1998 A & B; Livingstone 2001; Bowman 2004; Elgindy 2011; Guerif 2011; Forman 2012). In addition, two studies excluded from the previous 2009 version of the review were included (Komori 2004; Mostajeran 2006). Finally, 14 trials were included in the previous 2013 update (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; ASSETT 2003; Gardner 2004; Komori 2004; Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006; Heijnen 2006; Mostajeran 2006; van Montfoort 2006; Prados 2015). One of the included studies was unpublished data; this is now published in a peer-reviewed journal (Prados 2015). One study which was awaiting classification in the earlier update was published and is now among included studies for the current update (Clua 2015). Of the two ongoing studies in the previous update, one is completed and we have included it in the current update (Abuzeid 2017); and we have excluded the other completed study (Forman 2012).

2020: the targeted update search resulted in 2230 records. After removing 973 duplicates, we screened a total of 1257 records. Two reviewers independently examined the titles and abstracts and identified 30 records as potentially eligible, and obtained the full text for examination. Among these 30 records, we found two records from a previously excluded study—Forman 2012—and therefore excluded them. We excluded two records arising from Thurin 2009 which had earlier appeared as a companion paper along with one of the included studies—Thurin 2004—in the previous version. We excluded 18 records from 16 studies (Eijkemans 2006; Harrild 2009; Forman 2013; Schoolcraft 2013; Forman 2014; López-Regalado 2014a; Bensdorp 2015; Zhang 2015; Brabers 2016; Hatırnaz 2016; Rodriguez 2016; Yang 2016; Lao 2017; van Loendersloot 2017; IRCT20141217020351N10; NCT03758833). Two of these excluded studies had a main paper and a companion paper (Bensdorp 2015; Zhang 2015). One of the records was from an included study in the earlier update (Mostajeran 2006). One of the records was the main paper of a study which was already included in the previous update (published as a conference abstract) (Prados 2015). Finally, we included three new studies (six records; one study had a main paper, abstract paper and clinical trial registry record; one more study had a main paper and clinical trial registry record) (López-Regalado 2014b; Clua 2015; Abuzeid 2017).

For details, see Figure 1.

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Figure 1. Study flow diagram.

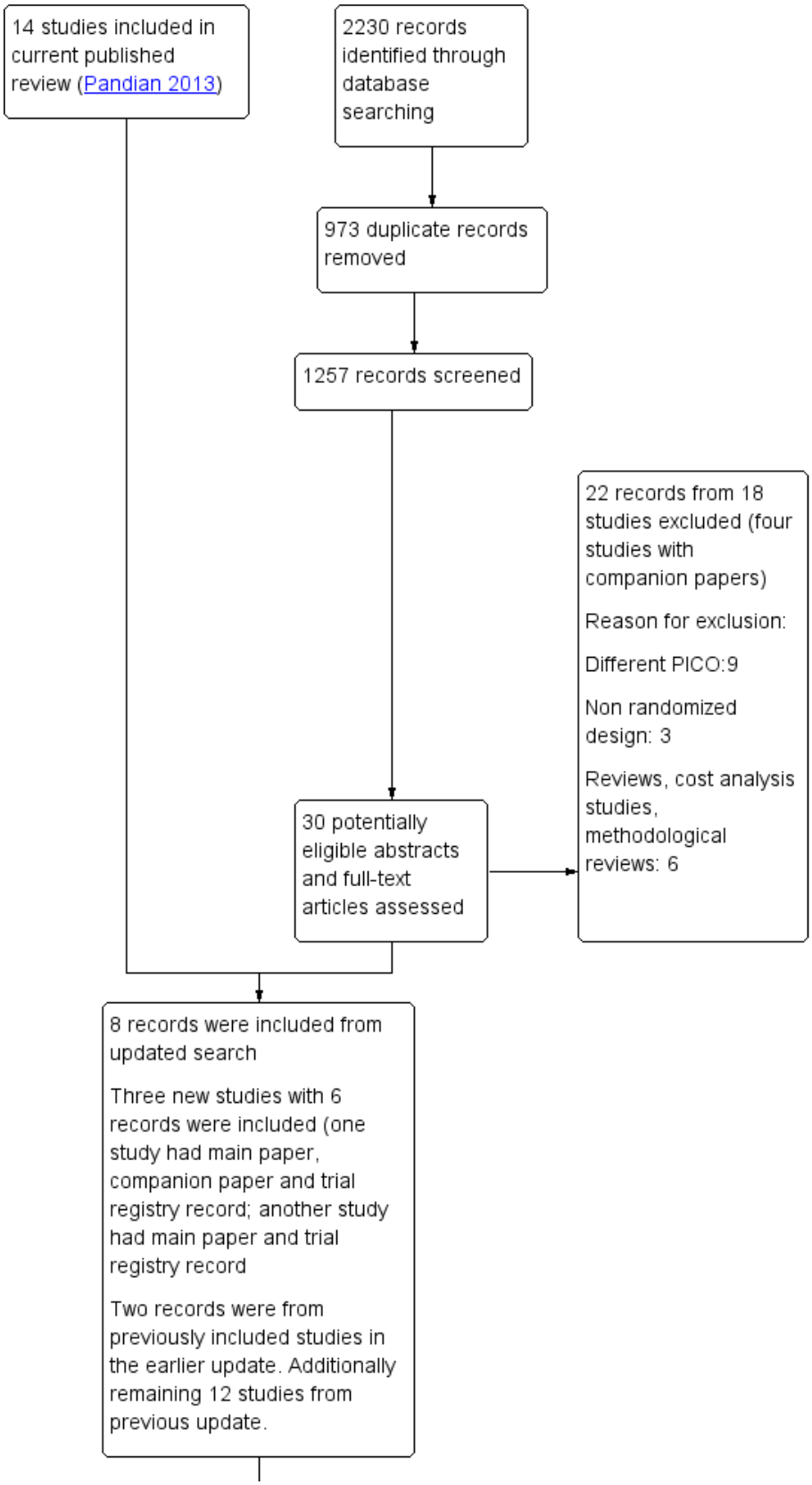

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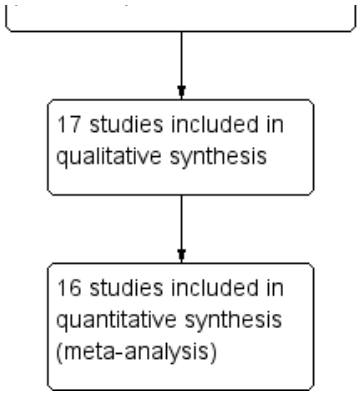
Figure 1. (Continued)



Included studies

For this update, we added three studies to the 14 included in the earlier update, making a total of 17 included studies. We sought additional information from authors of all the new trials and replies were received from three (López-Regalado 2014b; Clua 2015; Abuzeid 2017).

See the 'Characteristics of included studies' table.

Study design and setting

We included 17 studies with a total of 2505 participants in the review (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; ASSETT 2003; Gardner 2004; Komori 2004; Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006; Heijnen 2006; Mostajeran 2006; van Montfoort 2006; López-Regalado 2014b; Clua 2015; Prados 2015; Abuzeid 2017). All were randomised parallel-group trials. Six were multicentre (Martikainen 2001; ASSETT 2003; Thurin 2004; Thurin 2005; ECOSSE 2006; Heijnen 2006). Sample sizes ranged from 23 to 661 women.

Of the four unpublished studies that we have added to the previous update, one was a pilot trial published as part of a PhD dissertation (Thurin 2005). Another, the 'Australian study of single embryo transfer', was stopped early because its implementation immediately and substantially altered consumer decision making: this had the effect of more than tripling rates of elective single embryo transfer during the study period and reducing study participation rates (M Davies, University of Adelaide, personal communication) (ASSETT 2003). A UK trial, known as the 'Efficacy and cost effectiveness of selective single embryo transfer' (ECOSSE) study, was also stopped early due to poor recruitment (ECOSSE 2006). The fourth unpublished study was finally published and we have included it in the current update (Prados 2015).

Eleven studies reported their funding sources. Seven reported non-commercial funding (Gerris 1999; ASSETT 2003; ECOSSE 2006; Mostajeran 2006; van Montfoort 2006; López-Regalado 2014b; Prados 2015); and four reported pharmaceutical company funding (Gardner 2004; Thurin 2004; Thurin 2005; Abuzeid 2017).

Participants

Study inclusion criteria differed with regard to participant age. Most studies had a maximum age threshold. This varied across studies and included 34 years (Gerris 1999), 35 years (Vauthier-Brouzes 1994; Lukassen 2005; Abuzeid 2017), 36 years (Thurin 2004), 38 years (ECOSSE 2006; López-Regalado 2014b; Prados 2015), and 40 years (ASSETT 2003). One study included women aged between 38 and 45 years (Heijnen 2006); while another required them to be at least 36 years old (Thurin 2005). Other studies used a variety of age limits (Martikainen 2001; van Montfoort 2006). One of the studies included oocyte donation cycles only and recipients' ages were between 18 and 50 years (Clua 2015).

Two studies only included women in their first treatment cycle (Gerris 1999; van Montfoort 2006); while four included women with an indication for IVF or ICSI either for the first time or after a previous successful treatment (Vauthier-Brouzes 1994; Lukassen 2005; Heijnen 2006; López-Regalado 2014b). Five studies included women in their first or second IVF or ICSI treatment cycle (ASSETT 2003; Thurin 2004; Thurin 2005; Clua 2015; Abuzeid 2017). In a multicentre study, one centre included women in their first treatment cycle only and another centre included women in their first or second cycle (Martikainen 2001). One study included all women undergoing IVF and embryo transfer who agreed to participate (Gardner 2004).

The duration of infertility was mentioned in eight studies (Gerris 1999; Thurin 2004; Lukassen 2005; Thurin 2005; Heijnen 2006; van Montfoort 2006; López-Regalado 2014b; Abuzeid 2017); and nine mentioned the indication(s) for treatment (Martikainen 2001; Thurin 2004; Lukassen 2005; Thurin 2005; Heijnen 2006; Mostajeran 2006; van Montfoort 2006; López-Regalado 2014b; Abuzeid 2017). See 'Prognostic factors' in Table 1.

Two studies did not provide details of participant characteristics (Komori 2004; Mostajeran 2006).

Interventions

All the studies included embryo transfer after fresh IVF or ICSI cycles; and three studies included frozen cycles administered to one or both groups (Thurin 2004; Thurin 2005; López-Regalado 2014b). Several other studies also administered frozen cycles during follow-up but not as part of the randomised comparison (Vauthier-Brouzes 1994; Martikainen 2001; ECOSSE 2006; Prados 2015; Clua 2015; Abuzeid 2017).

Interventions in the included studies were as follows.

- One fresh single embryo transfer (SET) plus one frozen embryo transfer (1FET) in a natural or hormone-stimulated cycle

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compared with one fresh cycle of double embryo transfer (DET) (Thurin 2004; Thurin 2005; López-Regalado 2014b)
- Two fresh cycles of SET compared with one fresh cycle of DET (Lukassen 2005)
- One fresh cycle of SET plus multiple cycles of frozen DET compared with one cycle of fresh DET plus multiple cycles of frozen DET (ECOSSE 2006)
- One fresh cycle of SET compared with one fresh cycle of DET (Gerris 1999; Martikainen 2001; ASSETT 2003; Gardner 2004; van Montfoort 2006; Clua 2015; Prados 2015; Abuzeid 2017)
- One fresh cycle of DET compared with one fresh cycle of triple embryo transfer (TET) (Heijnen 2006);
- Fresh or frozen DET compared with fresh or frozen TET, multiple cycles (Komori 2004)
- Two fresh cycles of DET compared to two fresh cycles of TET (Heijnen 2006)
- Three fresh cycles of DET compared to three fresh cycles of TET (Heijnen 2006)
- Fresh DET compared with fresh TET where the number of cycles used was unclear (Mostajeran 2006)
- One fresh cycle of DET compared with one fresh cycle of four embryo transfer (FET) (Vauthier-Brouzes 1994)

One study reported only 'per cycle' data (Komori 2004). There was a large disparity between the number of women (169) and the number of cycles (212), and it was unclear how many women were included in each group. The data from this study were therefore unusable.

Four studies that randomised women to more than one embryo transfer cycle reported interim data after the first fresh cycle of SET versus DET (Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006). In the case of ECOSSE 2006, these were the only data available, as the trial was stopped due to poor recruitment and data were only available for the first cycle (i.e. fresh DET versus fresh SET).

Protocols for ovarian stimulation, oocyte recovery and embryo transfer were clearly described in 12 studies (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; Thurin 2004; Lukassen 2005; Thurin 2005; Heijnen 2006; van Montfoort 2006; López-Regalado 2014b; Clua 2015; Prados 2015; Abuzeid 2017). Good-quality embryos were transferred in all studies, usually at cleavage stage. However, in four studies all or some women had embryos transferred at blastocyst rather than cleavage stage; this applied to a small number of women in two studies (Thurin 2004; Thurin 2005), half the women in one study (Prados 2015), and all women in another study (Gardner 2004). The stage of embryo transfer was not mentioned in one study (Mostajeran 2006).

Natural progesterone was used for luteal phase support in most cases (Gerris 1999; Martikainen 2001; Gardner 2004; Thurin 2004; Lukassen 2005; Thurin 2005; Heijnen 2006; van Montfoort 2006; Clua 2015; Prados 2015; Abuzeid 2017). One study used both human chorionic gonadotropin (HCG) and natural progesterone for luteal phase support (Vauthier-Brouzes 1994).

Outcomes

Primary outcomes

1. Live birth rate and cumulative live birth rate

Fourteen studies reported live birth rate per couple (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; ASSETT 2003; Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006; Heijnen 2006; van Montfoort 2006; López-Regalado 2014b; Clua 2015; Prados 2015; Abuzeid 2017). One reported 'take home baby' per cycle only (Komori 2004).

Six studies reported cumulative live birth rates (ASSETT 2003; Thurin 2004; Lukassen 2005; Thurin 2005; Heijnen 2006; López-Regalado 2014b).

2. Multiple pregnancy rate per woman or couple

All but one study reported multiple pregnancy rate per couple. One reported multiple pregnancy per cycle only (Komori 2004).

Secondary outcomes

1. Clinical pregnancy rate

Thirteen studies reported pregnancy rate per couple (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; Gardner 2004; Thurin 2004; Lukassen 2005; Heijnen 2006; Mostajeran 2006; van Montfoort 2006; López-Regalado 2014b; Prados 2015; Clua 2015; Abuzeid 2017).

2. Miscarriage rate per woman

Six studies reported miscarriage rate (Martikainen 2001; Lukassen 2005; van Montfoort 2006; López-Regalado 2014b; Clua 2015; Abuzeid 2017).

Excluded studies

See Characteristics of excluded studies.

We excluded 31 studies from the review for the following reasons.

- Seven studies were not randomised (Bowman 2004; van Montfoort 2005; Moustafa 2008; Guerif 2011; López-Regalado 2014a; Hatırnaz 2016; Lao 2017).
- Eighteen studies did not report a comparison of interest (Staessen 1993; Gardner 1998; Motta 1998 A & B; Livingstone 2001; Frattarelli 2003; Levitas 2004; Pantos 2004; Heijnen 2007; Thurin 2009; Elgindy 2011; Forman 2012; Forman 2013; Forman 2014; Bensdorp 2015; Zhang 2015; Yang 2016; IRCT20141217020351N10; NCT03758833).
- Six studies were reviews, costs analysis and methodological studies (Eijkemans 2006; Harrild 2009; Schoolcraft 2013; Brabers 2016; Rodriguez 2016; van Loendersloot 2017).

Risk of bias in included studies

See Characteristics of included studies; Figure 2; Figure 3.

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Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

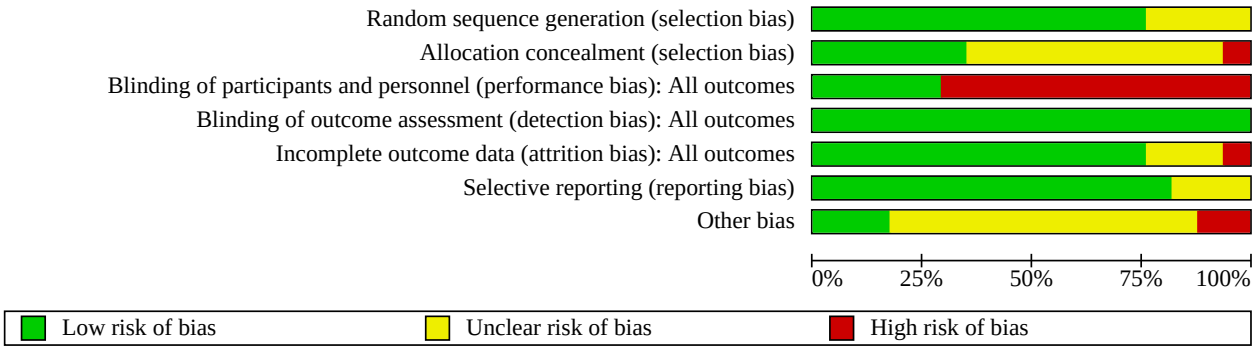

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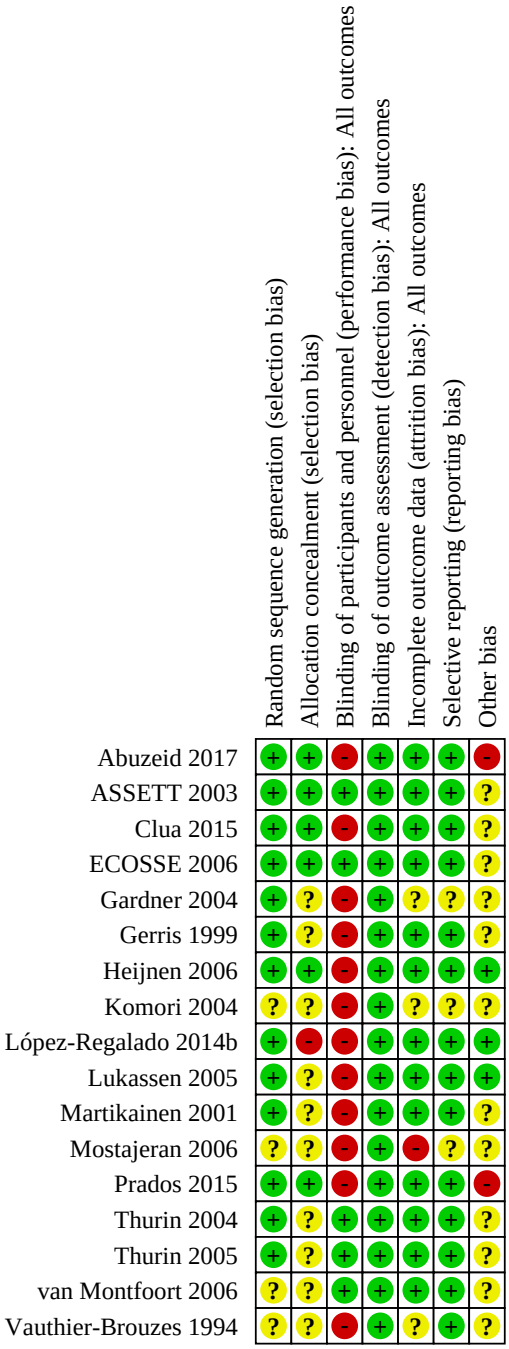
Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Generation of random sequence

Thirteen studies were at low risk of bias related to random sequence generation (Gerris 1999; Martikainen 2001; ASSETT 2003; Gardner 2004; Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006; Heijnen 2006; Lopez 2014a; Clua 2015; Prados 2015; Abuzeid 2017). Four studies did not describe their randomisation methods and were therefore at unclear risk of this bias (Vauthier-Brouzes 1994; Komori 2004; Mostajeran 2006; van Montfoort 2006).

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Allocation concealment

Six studies were at low risk of bias related to allocation concealment. They used sealed opaque envelopes (ASSETT 2003; Abuzeid 2017),remote allocation (ECOSSE 2006; Heijnen 2006; Prados 2015) or used concealed allocation created by statistical unit (Clua 2015). In the other 10 studies a satisfactory method of allocation concealment was not described clearly enough or no information was given, and we therefore rated the risk of this bias as unclear (Gerris 1999; Martikainen 2001; ASSETT 2003; Gardner 2004; Thurin 2004; Lukassen 2005; Thurin 2005; Lopez 2014a; Clua 2015; Abuzeid 2017). One study was considered to be at high risk for selection bias since the embryologist had access to randomisation numbers (Lopez 2014a).

Blinding

We rated five trials at low risk of performance and detection bias related to blinding, as neither the patient nor physician knew whether one embryo or two embryos had been transferred (ASSETT 2003; Thurin 2004; Thurin 2005; ECOSSE 2006; van Montfoort 2006). Four studies were unblinded (Lukassen 2005; Prados 2015; Clua 2015; Abuzeid 2017); and the others did not mention blinding. We rated these 12 studies at high risk of performance bias as lack of blinding could potentially influence clinicians behaviour and affect outcomes such as live birth and clinical pregnancy rates (Vauthier-Brouzes 1994; Gerris 1999; Martikainen 2001; Gardner 2004; Komori 2004; Lukassen 2005; Heijnen 2006; Mostajeran 2006; López-Regalado 2014b; Prados 2015; Clua 2015; Abuzeid 2017). However, we categorised these 12 studies as low risk of detection bias since all the outcomes were objective in nature.

Incomplete outcome data

We rated 12 studies as at low risk of this bias as they included all randomised women in the analysis (Gerris 1999; Martikainen 2001; ASSETT 2003; Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006; Heijnen 2006; van Montfoort 2006; Lopez 2014a; Clua 2015; Prados 2015). We also categorised another study at low risk for attrition bias as authors reported withdrawal of only one randomised women among 50 randomised in the intervention group (n = 49 in intervention group versus n = 50 in control group) (Abuzeid 2017). We rated three studies as at unclear risk of this bias because it was unclear how many women were included in the analysis (Vauthier-Brouzes 1994; Gardner 2004; Komori 2004). We rated one study at high risk of this bias because it was unclear how many women were randomised: women non-compliant with the drug regimen or who had ovarian hyperstimulation syndrome (numbers not stated) were excluded and three women with ectopic pregnancy were also excluded from the analysis (Mostajeran 2006) .

Selective reporting

We judged 14 studies to be at low risk of this bias. We deemed three studies to be at unclear risk of this bias: two studies that did not report live birth (Gardner 2004; Mostajeran 2006); and one study which only reported 'per cycle' data (Komori 2004).

Other potential sources of bias

We judged three studies to be at low risk of other potential biases (Heijnen 2006; López-Regalado 2014b; Lukassen 2005); and 12 at unclear risk. We deemed two studies to be at high risk for other sources of bias (Prados 2015; Abuzeid 2017). One study gave women the option of changing the number of embryos transferred or the day of transfer if they were unhappy with the group to which they were randomised (Prados 2015). A large number of participants (21%) chose to change, including 36% of women in the SET groups who changed to DET. Although the study was analysed by 'intention to treat', the results were deemed to be at high risk of bias due to the high level of non-compliance and the fact that nearly all the changes were in the same direction. In another study, the proportion of top-quality blastocysts were significantly higher in one group (Abuzeid 2017). This could potentially influence the outcomes and we categorised the study to be at high risk for other potential source of bias. Further, the planned sample size was 200 (according to trial registry information), but only 100 women were randomised.

Effects of interventions

See: **Summary of findings 1** Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle of IVF or ICSI; **Summary of findings 2** Single compared to multiple embryo transfer in a single cycle following IVF or ICSI

The results below are formatted by type of comparison, as follows.

1. Repeated single embryo transfer versus repeated multiple embryo transfer
2. Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle
3. Single versus multiple embryos transfer in a single cycle
4. Double embryo transfer versus more than two embryos transferred
5. Other fresh or frozen cycle comparisons

1. Repeated single embryo transfer versus repeated multiple embryo transfer.

No studies compared repeated single embryo transfer versus repeated multiple transfer.

2. Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in single cycle

Four studies, all of cleavage-stage transfer, made this comparison (Thurin 2004; Thurin 2005; Lukassen 2005; Lopez 2014a).

Specific interventions were as follows (with the number of cycles in brackets).

- Single embryo transfer (×2) versus double embryo transfer (×1) (SET (×2) versus DET (×1)) (Lukassen 2005).
- Single embryo transfer (×1) plus transfer of one frozen-thawed embryo in a natural or hormone-stimulated cycle versus double embryo transfer (×1) (SET + 1 FET versus DET (×1)) (Thurin 2004; Thurin 2005; Lopez 2014a).

Primary outcomes

2.1 Cumulative live birth rate

When we pooled the four studies, the cumulative live birth rate after repeated single embryo transfer may be little or no different from the rate after one cycle of DET (RR 0.95, 95% CI 0.82 to 1.10; I^2 = 0%; 4 studies, 985 women; low-quality evidence) (Thurin 2004; Lukassen 2005; Thurin 2005; Lopez 2014a). This suggests that for a woman with a 42% chance of live birth following a single cycle of DET, the chance following repeated SET would be between 34% and 46%.

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Sensitivity analysis

There were no studies which were at low risk of bias for the outcome. The overall findings did not materially change with the use of a random-effects model rather than a fixed-effect model or with use of odds ratio rather than risk ratio.

2.1.1 SET + 1 FET versus DET (×1)

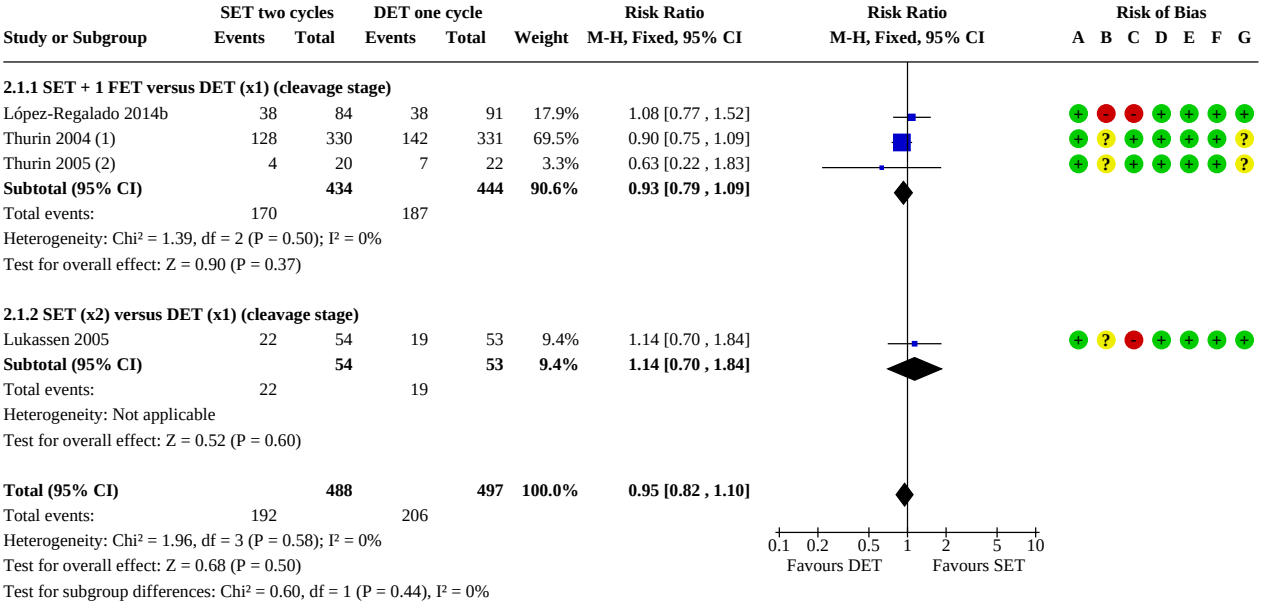
Three studies reported cumulative live birth rates after SET followed by 1 FET versus DET in a single cycle (Thurin 2004; Thurin 2005; Lopez 2014a). There may be little or no difference in cumulative live birth rates following SET + 1 FET versus DET (RR 0.93, 95% CI 0.79 to 1.09; I^2 = 0%; 3 studies, 878 women; low-quality evidence).

2.1.2 SET (×2) versus DET (×1)

A single study compared cumulative live birth rate after two fresh cycles of SET versus a single fresh cycle of DET (Lukassen 2005). We are uncertain whether cumulative live birth rate improves following two fresh cycles of SET compared to single fresh cycle of DET (RR 1.14, 95% CI 0.70 to 1.84; 1 study, 107 women; very low quality evidence).

See Analysis 2.1; Figure 4

Figure 4. Forest plot of comparison: 2 Repeated SET (mixed policies) versus multiple ET in a single cycle, outcome: 2.1 Cumulative live birth.



Footnotes

(1) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5
(2) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5)

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

2.2 Multiple pregnancy rate

When the four studies were pooled, the multiple pregnancy rate after repeated single embryo transfer probably reduces compared to a single cycle of DET (Peto odds ratio (OR) 0.13, 95% CI 0.08 to 0.21; I^2 = 0%; 4 studies, 985 women; moderate-quality evidence) (Thurin 2004; Lukassen 2005; Thurin 2005; Lopez 2014a). This suggests that for a woman with a 13% risk of multiple pregnancy following a single cycle of DET, the risk following repeated SET would be between 0% and 3%.

Sensitivity analysis

There were no studies which were at low risk of bias for the outcome.

2.2.1 SET + 1 FET versus DET (×1)

Three studies reported multiple pregnancy rates after SET plus 1 FET versus DET in a single cycle (Thurin 2004; Thurin 2005; Lopez 2014a). The multiple pregnancy rate probably reduces following SET + 1 FET versus DET (Peto OR 0.13, 95% CI 0.08 to 0.22; I^2 = 0%; 3 studies, 878 women; moderate-quality evidence).

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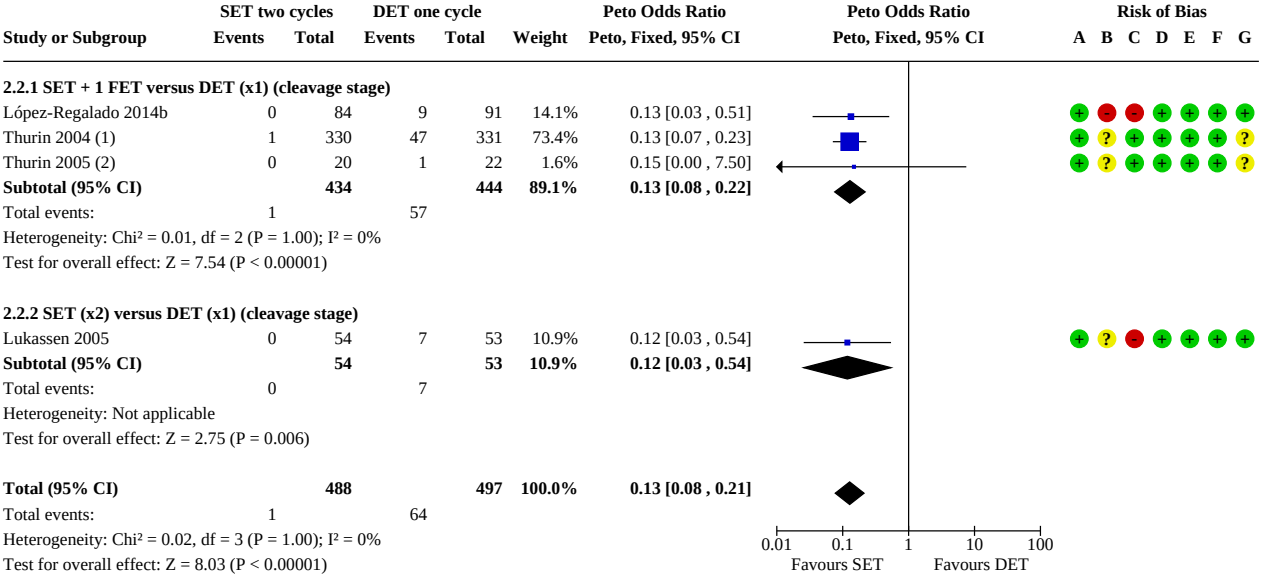
2.2.2 SET (×2) versus DET (×1)

A single study compared the multiple pregnancy rate after two fresh cycles of SET versus a single fresh cycle of DET (Lukassen 2005). We are uncertain whether multiple pregnancy rate reduces following two fresh SET compared to single cycle of DET (Peto OR 0.12, 95% CI 0.03 to 0.54; 1 study, 107 women; very low quality evidence).

See Analysis 2.2; Figure 5

Figure 5. Forest plot of comparison: 2 Repeated SET (mixed policies) versus multiple ET in a single cycle, outcome: 2.2 Multiple pregnancy.



Footnotes

(1) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5
(2) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5)

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Secondary outcomes

2.3 Clinical pregnancy rate

When data from the three studies reporting this outcome were pooled, the clinical pregnancy rate after repeated single embryo transfer appeared to be little or no different from the rate after one cycle of DET (RR 0.99, 95% CI 0.87 to 1.12; I^2 = 47%; 3 studies, 943 women; low-quality evidence) (Thurin 2004; Lukassen 2005; Lopez 2014a). This suggests that for a woman with a 51% chance of clinical pregnancy following a single cycle of DET, the corresponding chance following repeated SET would be between 43% and 56%.

2.3.1 SET + 1 FET versus DET (×1)

Two studies reported the clinical pregnancy rate after SET followed by 1 FET versus DET in a single cycle (Thurin 2004; Lopez 2014a). We found no difference between the groups (RR 0.97 95% CI 0.84 to 1.11; I^2 = 65%; 2 studies, 836 women). Substantial heterogeneity was noted with no obvious explanation.

2.3.2 Fresh SET (×2) versus DET (×1)

A single study compared the clinical pregnancy rate after two fresh cycles of SET versus a single fresh cycle of DET and did not find a difference between the two groups (RR 1.18, 95% CI 0.81 to 1.71; 1 study, 107 women) (Lukassen 2005).

See Analysis 2.3

2.4 Miscarriage rate per woman randomised

Two studies reported the miscarriage rate after two cycles of SET versus a single fresh cycle of DET (Lukassen 2005; Lopez 2014a). The miscarriage rate after repeated episodes of single embryo transfer may be little or no different from the rate after one cycle of DET (Peto OR 2.14, 95% CI 0.93 to 4.95; I^2 = 0%; 2 studies, 282 women; low-quality evidence). This suggests that for a woman with a 8% chance of miscarriage following a single cycle of DET, the chance following repeated SET would be between 7% and 29%.

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There was no difference in miscarriage rate per pregnancy between the two groups (Peto OR 1.87, 95% CI 0.77 to 4.53).

2.4.1 SET + 1 FET versus DET (×1)

No difference in miscarriage rate was found after SET followed by 1 FET versus DET in a single fresh cycle (Lopez 2014a) (Peto OR 2.86, 95% CI 0.85 to 9.67; 1 study, 175 women). There was no difference in miscarriage rate per pregnancy between the two groups (Peto OR 2.46, 95% CI 0.70 to 8.68).

2.4.2 Fresh SET (×2) versus DET (×1)

No difference in miscarriage rate was found following two fresh SET versus DET (Lukassen 2005) (Peto OR 1.65, 95% CI 0.52 to 5.23; 1 study, 107 women). There was no difference in miscarriage rate per pregnancy between the two groups (Peto OR 1.44, 95% CI 0.42 to 4.96).

See Analysis 2.4.

3. Single versus multiple embryo transfer in a single cycle

Eleven studies of cleavage-stage transfer made this comparison (Gerris 1999; Martikainen 2001; ASSETT 2003; Thurin 2004; Lukassen 2005; Thurin 2005; ECOSSE 2006; van Montfoort 2006; Lopez 2014a; Clua 2015; Prados 2015); as did three of blastocyst-stage transfer (Abuzeid 2017; Gardner 2004; Prados 2015). One study reported both cleavage and blastocyst stage transfers (Prados 2015).

All compared one cycle of single versus one cycle of double embryo transfer (SET (×1) versus DET (×1)). As noted above, for five of these studies the data for this comparison derive from an interim analysis, as women in one or both arms were randomised to undergo further transfer cycles if the first cycle did not result in pregnancy (Thurin 2004; Thurin 2005; Lukassen 2005; ECOSSE 2006; Lopez 2014a). However, the two new studies in the update did not randomise women in two groups following an unsuccessful cycle and all women underwent DET in a subsequent cycle, hence we included only the data from first treatment cycle in the pooled analysis (Abuzeid 2017; Clua 2015).

Primary outcomes

3.1 Live birth rate

Eleven studies of cleavage-stage transfer and two of blastocyst transfer reported this outcome. See Analysis 3.1; Figure 6.

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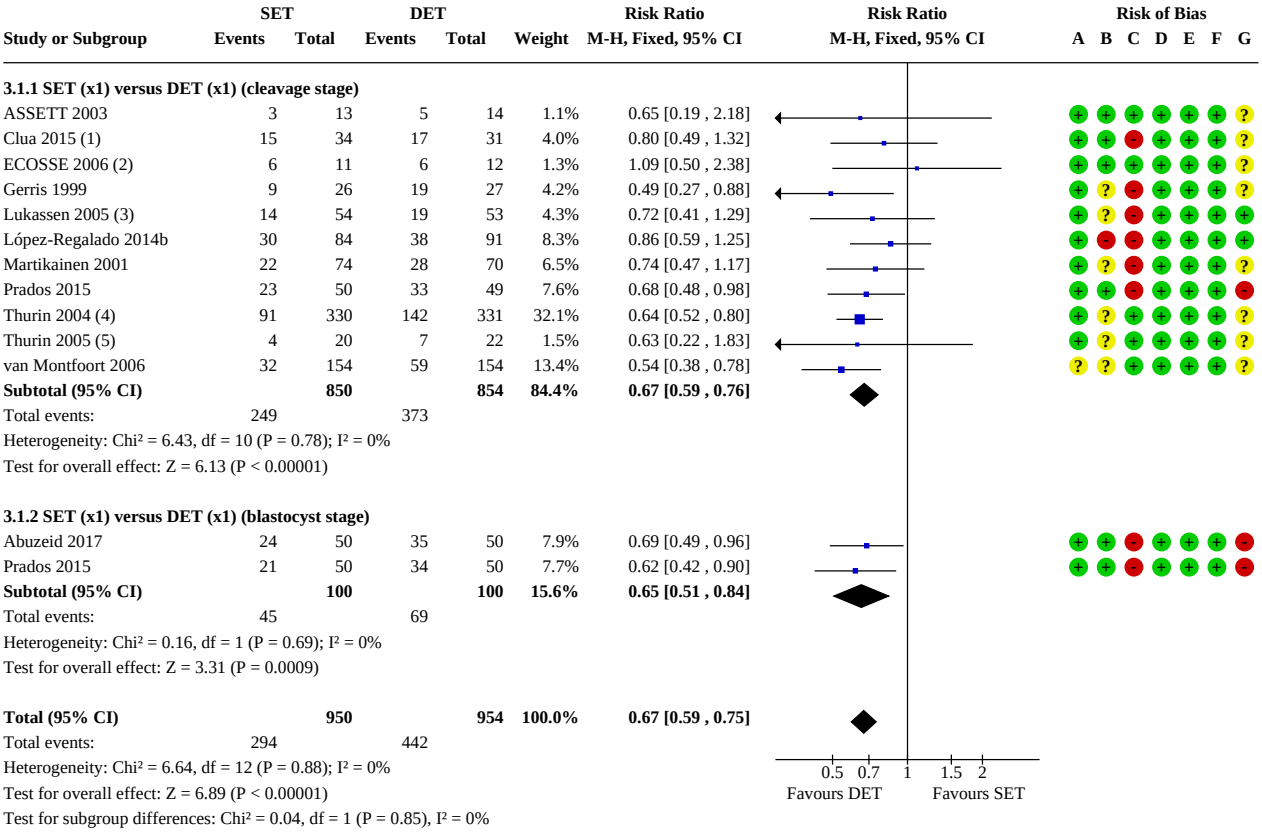
Figure 6. Forest plot of comparison: 2 Single versus multiple (in a single cycle), outcome: 2.1 Live birth.



Footnotes

(1) Study included only oocyte donation cycles
(2) Interim analysis from (planned) multi-cycle study.
(3) Interim analysis from multi-cycle study.
(4) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5. Interim analysis from multi-cycle study.
(5) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5). Interim analysis from multi-cycle study.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

When we pooled all studies, low-quality evidence suggests that the live birth rate per woman may reduce in women who had SET than those who had DET (RR 0.67, 95% CI 0.59 to 0.75; I^2 = 0%; 12 studies, 1904 women; low-quality evidence). This suggests that for a woman with a 46% chance of live birth following a single cycle of DET, the chance following a single cycle of SET would be between 27% and 35%.

Sensitivity analysis

There were no studies which were at low risk of bias for the outcome. The overall findings did not materially change with the use of a random-effects model rather than a fixed-effect model or with use of odds ratio rather than risk ratio.

Subgroup analysis

We performed subgroup analysis according to stage of transfer (cleavage versus blastocyst stage). It showed no evidence between the subgroups – test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.85), I^2 = 0%.

3.1.1 SET (×1) versus DET (×1) cleavage stage

These findings applied in comparisons of cleavage-stage transfer (RR 0.67, 95% CI 0.59 to 0.76; I^2 = 0%; 11 studies, 1704 women).

3.1.2 SET (×1) versus DET (×1) blastocyst stage

These findings also applied in the comparison of blastocyst transfer (RR 0.65, 95% CI 0.51 to 0.84; I^2 = 0%; 2 studies, 200 women).

A funnel plot for this outcome was not suggestive of publication bias. See Figure 7

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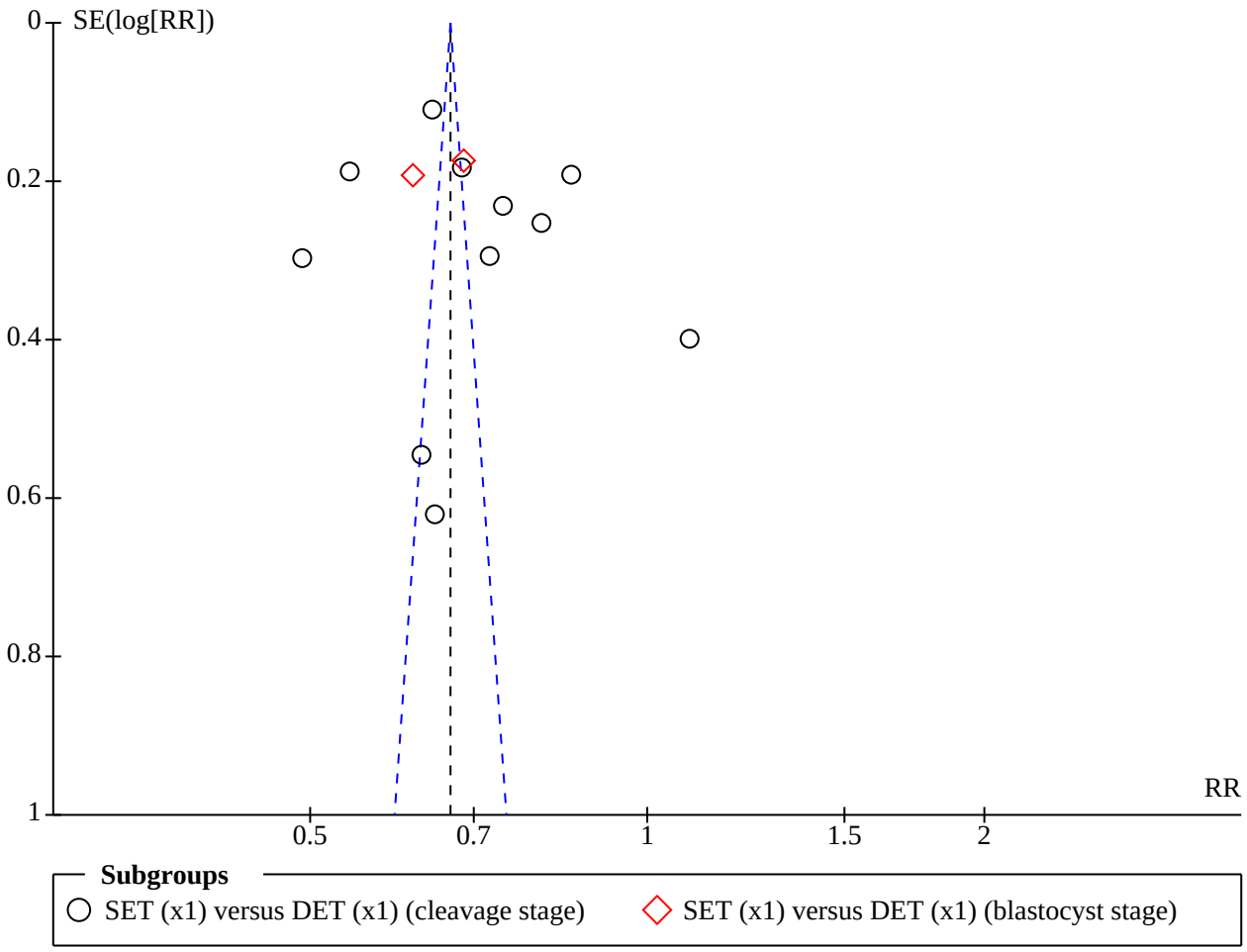
Figure 7. Funnel plot of comparison: 3 Single versus multiple (in a single cycle), outcome: 3.1 Live birth.



3.2 Multiple pregnancy rate

Eleven studies of cleavage-stage transfer and three of blastocyst transfer reported this outcome. See Analysis 3.2; Figure 8.

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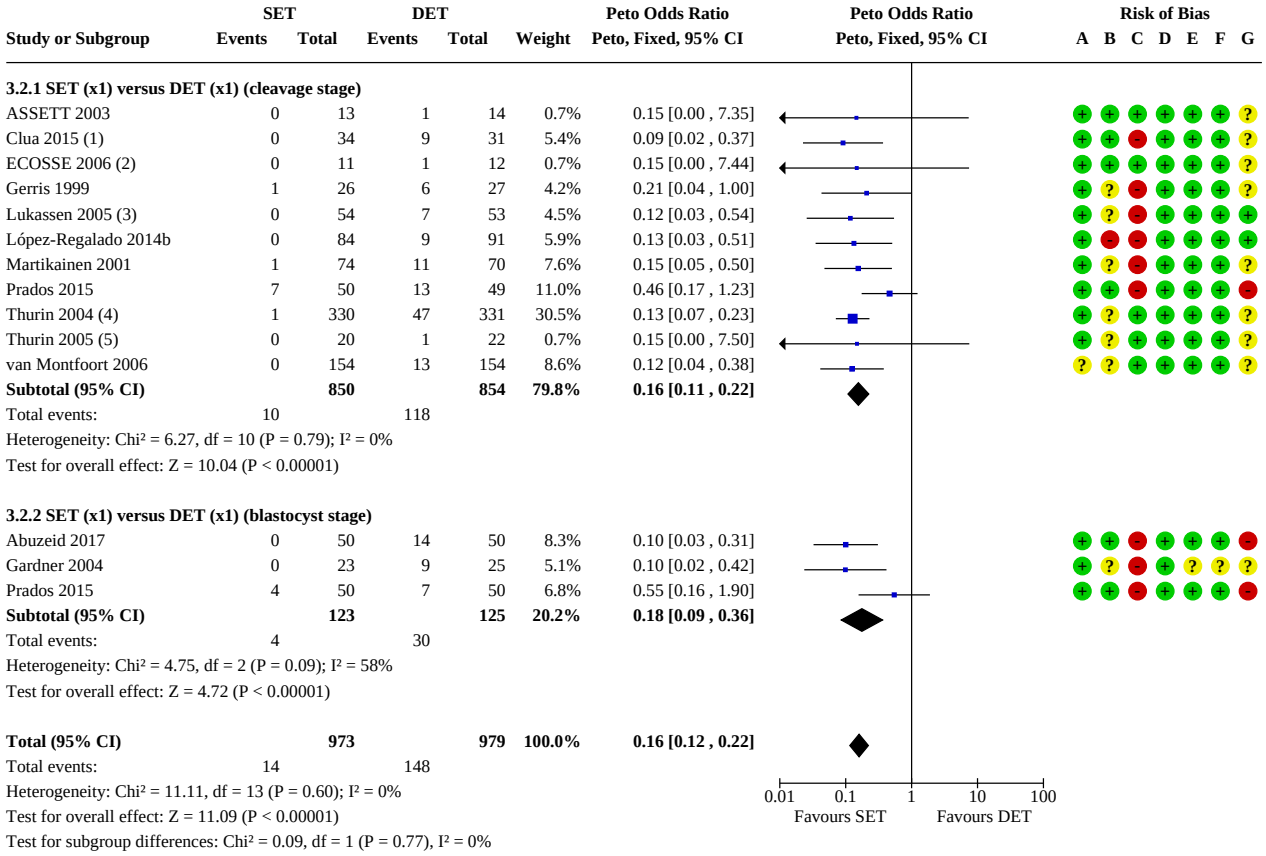
Figure 8. Forest plot of comparison: 2 Single versus multiple (in a single cycle), outcome: 2.2 Multiple pregnancy.



Footnotes

(1) Study included only oocyte donation cycles
(2) Interim analysis from (planned) multi-cycle study.
(3) Interim analysis from multi-cycle study.
(4) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5.Interim analysis from multi-cycle study.
(5) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5).Interim analysis from multi-cycle study.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

When we pooled all studies, moderate-quality evidence suggests the multiple pregnancy rate per woman probably reduces in those who had SET than those who had DET (Peto OR 0.16, 95% CI 0.12 to 0.22; I^2 = 0%; 13 studies, 1952 women; moderate-quality evidence). This suggests that for a woman with a 15% risk of multiple pregnancy following a single cycle of DET, the risk following a single cycle of SET would be between 2% and 4%.

Sensitivity analysis

There were no studies which were at low risk of bias for the outcome.

Subgroup analysis

We performed subgroup analysis according to stage of transfer (cleavage versus blastocyst stage). It showed no evidence between the subgroups – test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.77), I^2 = 0%.

3.2.1 SET (×1) versus DET (×1) cleavage stage

These findings applied in comparisons of cleavage-stage transfer (Peto OR 0.16, 95% CI 0.11 to 0.22; I^2 = 0%; 11 studies, 1704 women).

3.2.2 SET (×1) versus DET (×1) blastocyst stage

These findings also applied in comparisons of blastocyst transfer (Peto OR 0.18, 95% CI 0.09 to 0.36; I^2 = 58%; 3 studies, 248 women). Heterogeneity in this subgroup analysis appeared to derive from a study at high risk of bias (Prados 2015). Treatment contamination

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(also known as 'cross-over') occurred in a high proportion of cases in this study and would be expected to attenuate any treatment difference. I^2 reduced to 0% when this study was excluded from the analyses, without materially affecting the conclusion.

Secondary outcomes

3.3 Clinical pregnancy rate

Eight studies of cleavage-stage transfer and three of blastocyst transfer reported this outcome. See Analysis 3.3

When we pooled 10 studies, low-quality evidence suggests that the clinical pregnancy rate per woman may reduce in women who had SET than those who had DET (RR 0.70, 95% CI 0.64 to 0.77; I^2 = 0%; 10 studies, 1860 women; low-quality evidence). This suggests that for a woman with a 55% chance of clinical pregnancy following a single cycle of DET, the chance following repeated SET would be between 35% and 42%.

Subgroup analysis

We performed subgroup analysis according to stage of transfer (cleavage versus blastocyst stage). It showed no evidence between the subgroups – test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 = 0%.

3.3.1 SET (×1) versus DET (×1) cleavage stage

These findings applied in comparisons of cleavage-stage transfer (RR 0.69, 95% CI 0.62 to 0.78; I^2 = 19%; 8 studies, 1612 women).

3.3.2 SET (×1) versus DET (×1) blastocyst stage

These findings also applied in comparisons of blastocyst transfer (RR 0.74, 95% CI 0.62 to 0.88; I^2 = 0%; 3 studies, 248 women).

3.4. Miscarriage rate per woman randomised

Six studies of cleavage-stage transfer and one of blastocyst transfer reported this outcomes. See Analysis 3.4.

When seven studies were pooled, there may be little or no difference in the miscarriage rate per women between those who had SET and those who had DET (Peto OR 0.96, 95% CI 0.66 to 1.42; I^2 = 27%; 7 studies, 1560 women; low-quality evidence). This suggests that for a woman with a 7% chance of miscarriage following a single cycle of DET, the chance following repeated SET would be between 4% and 10%.

The miscarriage rate per pregnancy was higher in SET group compared to DET group (Peto OR 1.62, 95% CI 1.07 to 2.47).

Subgroup analysis

We performed subgroup analysis according to stage of transfer (cleavage versus blastocyst stage). It showed no evidence between the subgroups – test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.96), I^2 = 0%.

3.4.1 SET (×1) versus DET (×1) cleavage stage

Six studies of cleavage-stage transfer reported this outcome. We found no difference between the two groups (Peto OR 0.96, 95% CI 0.65 to 1.43; I^2 = 40%; 6 studies, 1460 women). The miscarriage rate per pregnancy was lower in DET group compared to SET following cleavage stage transfer (Peto OR 1.65, 95% CI 1.06 to 2.56).

3.4.2 SET (×1) versus DET (×1) blastocyst stage

One study of blastocyst stage transfer reported this outcome and there was no difference between the two groups (Peto OR 1.00, 95% CI 0.24 to 4.21; 1 study, 100 women).There was no difference in miscarriage rate per pregnancy blastocysts stage subgroup (Peto OR 1.38, 95% CI 0.32 to 6.06).

4. Double embryo transfer versus more than two embryos transferred

Three studies tested other fresh cycle comparisons. Two were of cleavage-stage transfer (Vauthier-Brouzes 1994; Heijnen 2006). The day of transfer of the third study was not reported (Mostajeran 2006). Specific interventions were as follows (with the number of cycles in brackets).

- DET (×1) versus triple embryo transfer (TET) (×1) (Heijnen 2006; Mostajeran 2006)
- DET (×1) versus four embryo transfer (×1) (Vauthier-Brouzes 1994)
- DET (×2) versus TET (×2) (Heijnen 2006)
- DET (×3) versus TET (×3) (Heijnen 2006)

Primary outcomes

4.1 Live birth rate or cumulative live birth rate across single or repeated IVF cycles

4.1.1 DET (×1) versus TET (×1)

We found no difference between the groups in the live birth rate (RR 0.48, 95% CI 0.14 to 1.68; 1 study, 45 women) (Heijnen 2006).

4.1.2 DET (×1) versus four embryo transfer (×1)

We found no difference between the groups in the live birth rate (RR 0.53, 95% CI 0.27 to 1.05; 1 study, 56 women) (Vauthier-Brouzes 1994).

4.1.3 DET (×2) versus TET (×2)

We found no difference between the groups in the cumulative live birth rate after two cycles of DET versus two cycles of TET (RR 0.84, 95% CI 0.37 to 1.92; 1 study, 45 women) (Heijnen 2006).

4.1.4 DET (×3) versus TET (×3)

We found no difference between the groups in the cumulative live birth rate after three cycles of DET versus three cycles of TET (RR 0.86, 95% CI 0.43 to 1.71; 1 study, 45 women) (Heijnen 2006).

See Analysis 4.1.

Sensitivity analysis

There were no studies which were at low risk of bias for the outcome. The overall findings did not materially change with the use of a random-effects model rather than a fixed-effect model or with use of odds ratio rather than risk ratio.

4.2 Multiple pregnancy rate

4.2.1 DET (×1) versus TET (×1)

There was lower multiple pregnancy rate in the DET group than in the TET group (Peto OR 0.36, 95% CI 0.14 to 0.93; I^2 = 0%; 2 studies, 343 women) (Heijnen 2006; Mostajeran 2006).

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4.2.2 DET (×1) versus four embryo transfer (×1)

We found no difference between the groups in the multiple pregnancy rate (Peto OR 0.46, 95% CI 0.11 to 1.88; 1 study, 56 women) (Vauthier-Brouzes 1994).

See Analysis 4.2.

Sensitivity analysis

There were no studies which were at low risk of bias for the outcome.

Secondary outcomes

4.3 Clinical pregnancy rate

4.3.1 DET (×1) versus TET (×1)

There was no difference between the groups in the clinical pregnancy rate (RR 0.75, 95% CI 0.53 to 1.06; 2 studies, 343 women) (Heijnen 2006; Mostajeran 2006).

4.3.2 DET (×1) versus four embryo transfer (×1)

We found no difference between the groups in the clinical pregnancy rate (RR 0.76, 95% CI 0.47 to 1.26; 1 study, 56 women) (Vauthier-Brouzes 1994).

See Analysis 4.3

4.4 Miscarriage rate

No studies reported this outcome.

5. Other fresh or frozen cycle comparisons

One study of cleavage-stage transfer compared DET versus TET among 169 participants (Komori 2004). A total of 106 cycles of fresh or frozen embryos were apparently administered in each group, but study reporting was unclear and, moreover, outcomes were reported per cycle rather than per woman. Attempts to contact the authors were unsuccessful. Study findings were reported descriptively below.

Primary outcomes

5.1 Cumulative live birth rate

5.1.1 DET versus TET, apparently using fresh or frozen embryos for multiple cycles

We found no difference between the groups for this outcome using 'per cycle' data (30 versus 26 live births resulting from 106 cycles in each group) (Komori 2004).

5.2 Multiple pregnancy rate

5.2.1 DET versus TET, apparently using fresh or frozen embryos for multiple cycles

There was a lower incidence of multiple births per pregnancy in the DET group (6/40 pregnancies versus 14/29 pregnancies) (Komori 2004).

Secondary outcomes

5.3 Clinical pregnancy rate

5.3.1 DET versus TET, apparently using fresh or frozen embryos for multiple cycles

We found no difference between the groups for this outcome using 'per cycle' data (40 versus 29 pregnancies resulting from 106 cycles in each group) (Komori 2004).

5.4 Miscarriage rate

This outcome was not reported.

DISCUSSION

Summary of main results

The main finding of this updated systematic review is that low-quality evidence indicates that live birth rate (LBR) may be reduced by a strategy of elective single embryo transfer (SET) when compared to double embryo transfer (DET) in a single fresh assisted reproductive technology (ART) cycle. We observed the reduced LBR following SET compared to DET in subgroups of women receiving cleavage stage as well as blastocyst stage transfer. The risk of multiple pregnancy is probably lower following SET compared to DET and the quality of evidence was moderate (Summary of findings 2). The clinical pregnancy rate per woman may be lower in those who had SET in comparison with those who had DET in a single fresh ART cycle. There may be little or no difference in the miscarriage rate per women between those who had SET and those who had DET.

After pooling of four studies of cleavage-stage transfer, low-quality evidence suggests that the cumulative live birth rate after repeated single embryo transfers (either SET followed by transfer of a single frozen embryo in a natural or hormone-stimulated cycle, or two fresh cycles of SET) may be no different from that after a single cycle of DET (Summary of findings 1). For a typical clinic with a 42% chance of live birth following a single cycle of DET, the live birth rate following repeated SET would be between 34% and 46%. Moderate-quality evidence suggests that the multiple pregnancy rate after repeated single embryo transfer is probably lower in comparison with that after a single cycle of DET. This suggests that for a woman with a 13% risk of multiple pregnancy following a single cycle of DET, the risk following repeated SET would be between 0% and 3%. There may be little or no difference in clinical pregnancy and miscarriage rates after consecutive SETs compared to the rates after one cycle of DET.

Three studies of cleavage-stage transfer of fresh embryos compared outcomes following DET versus three or four embryos. There was no difference in live birth rates following a single ART cycle, but the DET group was found to have lower multiple pregnancy rates compared to the three embryo transfer (TET) group. The cumulative live birth rate did not differ between the two groups following two and three ART cycles. The clinical pregnancy rate also did not differ between the two groups.

Most of the evidence currently available is from a cohort of younger women (aged less than 35 years) with a good prognosis.

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Overall completeness and applicability of evidence

No studies compared repeated single versus repeated multiple embryo transfer within the same ART cycle. This comparison was planned in one study but the study was closed due to poor enrolment, with only 23 participants (ECOSSE 2006). This comparison would be a useful way to structure future trials in order to determine the safety and effectiveness of different embryo transfer policies, given that a number of embryos have been produced. Policy in this context means the strategy for using up the available embryos until success is achieved or the supply of embryos is exhausted. A comparison of repeated multiple- versus repeated single-embryo transfer would address the policy question by determining 'cumulative' success rates.

The vast majority of participants in the studies included in the current and previous versions of the review had a good prognosis (aged under 36 years and with sufficient good-quality embryos). Only two small studies focused on older women (Thurin 2005; Heijnen 2006). One of the studies noted a potential for bias, as only a small proportion of older women volunteered for the trial, probably due to a preference for double embryos or twins, or both (Gardner 2004). Future studies should include older women and those with previously failed IVF cycles or lack of good-quality embryos.

Per cycle, DET appears to be more expensive than SET (Tiitinen 2001; Gerris 2004; Thurin 2006; Chambers 2007; Fiddelers 2007). The higher cost is mainly due to the increased rate of multiple births and premature births in the DET group, and fewer pregnancies in the SET group. Long-term costs related to multiple births and prematurity in the DET group have not yet been adequately assessed. A decision tree analysis indicated that the direct health care costs of DET was higher than SET + 1FET across all age groups. In women under 32 years, DET was less effective (a lower live birth rate) and more expensive than SET + 1FET. For women aged 32 and over, DET was more effective (a higher live birth rate) but still more expensive than SET + 1FET (van Loendersloot 2017). Studies have reported an increased risk of 'large for gestational age' (LGA) babies following frozen cycles compared to fresh cycles, hence there is a need to gather long-term safety data on children born following frozen cycles (Maheshwari 2016; Maheshwari 2018). In order to implement a policy of multiple single embryo transfers per woman, providers require either an efficient cryopreservation service or the ability to provide multiple fresh IVF cycles. The former is likely to be a safer and less invasive option for the women concerned.

Only three studies specifically addressed blastocyst transfer (Gardner 2004; Prados 2015; Abuzeid 2017). There were only two studies comparing DET with three embryo transfer (Heijnen 2006; Mostajeran 2006); and one study comparing DET versus four embryo transfer (Vauthier-Brouzes 1994). It is unlikely that such trials involving transfer of more than two embryos will be conducted in the future due to unacceptably high risk of multiple births.

Quality of the evidence

This update had five comparisons.

1. Repeated single embryo transfer versus repeated multiple embryo transfer
2. Repeated single embryo transfer (mixed policies) versus multiple embryo transfer in a single cycle
3. Single versus multiple embryo transfer in a single cycle
4. Double embryo transfer versus more than two embryos transferred
5. Other fresh or frozen cycle comparisons

There were no studies reporting comparisons between repeated SET versus repeated multiple embryo transfer. In the comparison between repeated SET versus single cycle of DET, we reported on cumulative live birth, multiple pregnancy, clinical pregnancy and miscarriage rate for studies comparing repeated SET versus single cycle of DET. The quality of evidence for primary outcomes was low to moderate. We downgraded the level of evidence by one or two levels due to unclear or high risk of selection bias due to inadequate description of allocation concealment and high risk of performance bias due to lack of blinding. We considered that awareness of group allotment is likely to influence clinicians' behaviour and performance for live birth and clinical pregnancy outcomes. Substantial statistical heterogeneity was noted for miscarriage rate but there was no obvious explanation. See Summary of findings 1.

For studies which reported single versus multiple embryo transfer in a single cycle, we reported live birth, multiple pregnancy, clinical pregnancy and miscarriage rate. The overall quality of evidence for main outcomes was low to moderate. We categorised the majority of studies at unclear risk of bias due to inadequate reporting of allocation concealment and at high risk of performance bias due to lack of blinding. We noted substantial statistical heterogeneity for miscarriage rate but there was no obvious explanation. See Summary of findings 2.

Three studies compared DET versus transfer of three or four embryos. Studies were at unclear risk of bias for inadequate reporting of allocation concealment methodology and at high risk of performance bias due to lack of blinding.

Under the 'other fresh or frozen' comparison, we described the results of one study which compared DET versus three embryo transfer, apparently using fresh or frozen embryos for multiple cycles. Only 'per cycle' data were available.

Potential biases in the review process

The search for the updated review was comprehensive, and included a search for ongoing trials through clinical trial registries. We contacted authors of three new studies asking for clarification about their results and got a satisfactory reply from each one of them.

One of the review authors was a primary investigator of one of the included studies (ECOSSE 2006). Our comparison of one cycle of fresh SET versus one cycle of DET includes data from studies for which this was an interim analysis (Analysis 3.1). This may be a potential source of bias. A post hoc sensitivity analysis excluding these studies did not materially influence the live birth rate in this analysis.

We are unaware of any other potential biases in the review process.

Agreements and disagreements with other studies or reviews

Other studies and reviews are broadly in agreement with the current review.

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A project commissioned by the UK National Institutes of Health Research Health Technology Assessment Programme used statistical modelling, analysis of registry and cohort data, and exploration of consumer perspectives to explore options for increasing SET and reducing the incidence of multiple births (Roberts 2011). The analysis concluded that couples have approximately one-third less chance of a live birth if they have one fresh cycle of SET rather than DET, but that use of repeat cycles using cryopreservation might compensate for the lost potential in each individual transfer while reducing the likelihood of multiple births. However, the authors recognised that a policy of repeat SET (with use of cryopreserved eggs) would involve challenges including appropriate patient selection, optimisation of freezing techniques, and the emotional, financial and physical burden associated with additional treatment cycles.

Earlier systematic reviews (Gelbaya 2010; McLernon 2010) and a report from the American Society for Reproductive Medicine (ASRM 2012) have reached similar conclusions.

A large Dutch cohort study is currently in progress, which aims to assess the long-term costs and health outcomes of ART singleton and twin children and the long term cost-effectiveness of SET versus DET strategies. Outcomes were to be reported at 1-year, 5-year and 18-year follow-up (van Heesch 2010). The investigators have reported 5-year follow-up results and found significantly higher hospital costs from birth up to the age of five years following multiple birth compared to singleton birth (van Heesch 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Although DET achieves higher live birth and clinical pregnancy per fresh cycle, the evidence suggests that the difference in effectiveness may be substantially offset when elective SET is followed by a further transfer of a single embryo in fresh or frozen cycle, while simultaneously reducing multiple pregnancies, at least among women with a good prognosis.

The quality of evidence was low to moderate primarily due to inadequate reporting of study methods and absence of masking those delivering, as well as receiving the interventions.

Implications for research

More evidence is needed on policies for repeated embryo transfer, including the most safe and effective way to use available embryos within a single ART cycle until success is achieved or the supply of embryos is exhausted. As studies to date have been conducted largely among women with a good prognosis undergoing ART, future studies should include older women (above 36 years), blastocyst stage transfers, subgroups categorised by cause of infertility and those with previously failed ART cycles or without good-quality embryos. Investigators should also consider blinding of clinicians and embryologists to minimise the risk of performance bias. The tasks of embryo transfer counselling and the embryo transfer procedure may be performed by two different individuals to minimise bias. Longer-term cost-effectiveness analyses are also needed, which should take into account costs related to multiple births and also costs of cryopreservation in the various strategies. There is a need to gather more long-term safety data following frozen cycles. While there are very few studies comparing double embryo transfer versus three/four embryo transfer, it is unlikely that such randomised trials involving transfer of more than two embryos will be possible due to unacceptably high risk of multiple births.

ACKNOWLEDGEMENTS

We would like to thank the following for their contributions to the 2020 update.

All staff at the editorial base of the Cochrane Gynaecology and Fertility Review Group; and in particular, Helen Nagels (Managing Editor) and Information Specialist Marian Showell, for help with the literature searches.

Drs Jeanette MacKenzie, Evi Vogiatzi and Rik van Eekelen who provided peer review comments.

We also thank all the authors who replied to our email queries about their study: Dr Elisabet Clua, Dr Maria Luisa López-Regalado and Dr OM Abuzeid.

We also thank the following.

- Zabeena Pandian, who was the lead author of the original review and two subsequent updates.
- Other co-authors for their contribution in the previous versions: Allan Templeton, Ozkan Ozturk, Gamal Serour, and Jane Marjoribanks.
- Statistician Andy Vail (University of Manchester University, UK) for methodological advice.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

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Abuzeid 2017

Study characteristics	
Methods	Randomised controlled trial Single centre USA
Participants	Inclusion criteria: women undergoing fresh assisted reproductive technology (ART); age < 35 years, day 3 follicle stimulating hormone (FSH) < 10 miu/ml; no history of poor response, no more than 1 previous in vitro fertilisation (IVF) failure, no uterine cavity abnormalities and no contraindication to treatment medications or procedures. Exclusion criteria: patients with uterine abnormalities such as submucous fibroid, endometrial polyps, uterine septum or significant uterine arcuate anomaly were not excluded if they were corrected hysteroscopically and post-procedure sono-infusion-hysterogram (SIH) was normal.
Interventions	Intervention (n = 50): single fresh blastocyst transfer; if unsuccessful, a frozen double blastocyst transfer was done. Control (n = 50): fresh double blastocyst transfer was done. However, since both arms received double blastocyst transfer, we did not take the data from second cycle.
Outcomes	Live birth rate, cumulative live birth rate, clinical pregnancy rate, multiple pregnancy rate, implantation rate, miscarriage rate, ectopic rate
Notes	The study was first published as a conference abstract. Subsequently, the study was published in peer reviewed journal. The authors were contacted for clarification. The authors replied to all study related queries. The trial was registered (ISRCTN69937179).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized at the time of blastocyst transfer by computer generated table".
Allocation concealment (selection bias)	Low risk	Envelopes were prepared by research assistant who was not involved in recruitment, consent, assignment or treatment. Group assignment was placed in sequentially numbered, identical sealed envelopes. The subject group assignment was blinded from the all study staff (nurse coordinator, nurses, embryologists, physicians) by placing the group assignment in sequentially numbered, sealed identical envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Author reply: no blinding for clinician or embryologist. We categorised the study to be at high risk for performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The clinician or embryologist were not blinded. However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes.
Incomplete outcome data (attrition bias)	Low risk	Authors mention all the dropouts and exclusions. All the randomised women are accounted for in the flow chart.

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Abuzeid 2017 *(Continued)*

All outcomes		The attrition after randomisation was minimal (1 in intervention vs none in comparison).
Selective reporting (reporting bias)	Low risk	The trial was registered (ISRCTN69937179) and pre-stated outcomes were reported in the manuscript
Other bias	High risk	Partially funded by Ferring Pharmaceuticals. The authors provided trial registry number, the trial was retrospectively registered. In the baseline characteristics, the proportion of excellent blastocysts transferred were significantly higher in SET group. This can potentially influence the outcomes. Duration of infertility was mentioned. The planned sample size was 200 (as per trial registry information), but just 100 women were randomised.

ASSETT 2003

Study characteristics	
Methods	Multicentre randomised controlled trial
Participants	Female age < 35 yrs if no previous ART pregnancy, < 40 if previous ART pregnancy. At least 4 good-quality embryos or at least 3 if previous ART pregnancy successful 27 women randomised
Interventions	Cleavage-stage transfer: SET (n = 13) versus DET (n = 14) Eligibility into the trial was restricted to a single cycle of treatment. All subsequent cycles of treatment were performed under conditions of routine care.
Outcomes	Cumulative live birth, twin live birth, clinical ongoing pregnancy (fetal heartbeat), complications during pregnancy, delivery and neonatal period, perinatal mortality and morbidity, use of neonatal intensive care
Notes	Unpublished trial. This study was stopped because its implementation immediately and substantially altered patients' decision making, which more than tripled the rates of elective single embryo transfer during the study period, and reduced participation rates (M Davies, University of Adelaide, personal communication). Funded by National Health and Medical Research Council Grant no: 158006) (M Davies, University of Adelaide, personal communication)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Pre-randomised envelopes were used and stored in the laboratory, opened in numerical order

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ASSETT 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were not informed of the number of embryos transferred nor the number of embryos suitable for freezing until immediately after their embryo transfer, doctors were also not informed of the randomisation until after their patients' embryo transfer, database manager and data analyser were also blinded until completion of data analysis by using codes to represent the 2 treatment groups. The code was held by an independent third party We categorised the study at low risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients were not informed of the number of embryos transferred nor the number of embryos suitable for freezing until immediately after their embryo transfer, doctors were also not informed of the randomisation until after their patients' embryo transfer, database manager and data analyser were also blinded until completion of data analysis by using codes to represent the 2 treatment groups. The code was held by an independent third party We categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes described in the protocol were reported
Other bias	Unclear risk	Day of randomisation on day of embryo transfer

Clua 2015

Study characteristics	
Methods	Randomised controlled trial Single centre Spain
Participants	Included women were recipients between 18 and 50 years, undergoing first or second synchronised fresh oocyte donation cycle with minimum of 5 embryos with at least 2 good-quality embryos on day 3 after oocyte retrieval Exclusion: Medical indication for single embryo transfer (Turner syndrome, uterine pathology/surgery, diabetes, hypertension, cardiovascular disease, serious general disease) and severe male factor
Interventions	Intervention (SET, n = 34): Elective single embryo transfer (since at least 2 good quality embryos on day 3 was entry criteria), They were transferred at cleavage stage Control (DET, n = 31): Elective DET, Control had at least 2 good-quality embryos with 5 available embryos on day 3 as entry eligibility. They were transferred at cleavage stage Subsequent frozen cycle did not follow randomised numbers. They were DET in frozen cycle as per unit policy. They were not included in the analysis
Outcomes	Live birth rate, cumulative live birth, clinical pregnancy rate, implantation rates, multiple pregnancy rate, miscarriage rate

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Clua 2015 *(Continued)*

Notes	The authors responded to all the study-related queries The trial was terminated prematurely due to unacceptable high levels of multiple pregnancies in control arm The trial was registered with clinical trial registry (NCT01228474) Funding details were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"based on a computer generated simple randomization list".
Allocation concealment (selection bias)	Low risk	"One or two embryos were transferred based on computer generated simple randomization list with concealed allocation created by statistical and epidemiology unit" Authors reply "We allocated the patients to a hidden random sequence through a computer-generated simple randomization list"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Author reply: no blinding for clinician or embryologist We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Author reply: no blinding for clinician or embryologist However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition reported after randomisation in either group
Selective reporting (reporting bias)	Low risk	The trial was registered (ClinicalTrials.gov Identifier: NCT01228474) and prestated outcomes were reported in the manuscript
Other bias	Unclear risk	Baseline characteristics were comparable in both the groups The trial was prematurely terminated. The trial was terminated (at 65) before reaching the planned sample size (n = 160) due to high number of multiple births in the comparison

ECOSSE 2006

Study characteristics

Methods	Randomised controlled trial, computer-generated random sequence, n = 23 women analysed
Participants	Inclusion criteria: all women receiving IVF or intracytoplasmic sperm injection (ICSI) treatment with an optimal chance of achieving pregnancy, i.e. women aged less than 37 years, first or second cycle of treatment, 4 or more good quality embryos at the time of embryo transfer

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ECOSSE 2006 *(Continued)*

	Exclusion criteria: women undergoing pre-implantation genetic diagnosis, or assisted hatching, or a history of recurrent miscarriage
Interventions	Cleavage-stage transfer: SET fresh + multiple SET frozen (n = 11) versus DET fresh + multiple DET frozen (n = 12) Both groups: if a pregnancy does not result in the fresh cycle, women will be encouraged to return for replacement of frozen-thawed embryos in subsequent cycles over the next 12 months
Outcomes	Cumulative live birth, twin live birth, clinical pregnancy (at least 1 gestational sac with heartbeat), biochemical pregnancy (positive test), miscarriage, ectopic pregnancy preterm delivery, low birth weight, congenital abnormality
Notes	Unpublished trial. This study was stopped because of poor recruitment (planned for 700 women, enrolled only 23) Funded by the Wellcome Trust (UK) (grant ref: 067469) and the Bertarelli Foundation (Switzerland)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Telephone randomisation performed by the embryologist (call to the Aberdeen Fertility Centre)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, couples and clinician or nurse who performed the embryo transfer were blinded to the number of embryos transferred We categorised the study at low risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded, couples and clinician or nurse who performed the embryo transfer were blinded to the number of embryos transferred However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the protocol were reported
Other bias	Unclear risk	Duration of infertility not reported.

Gardner 2004

Study characteristics	
Methods	Randomised controlled trial. 48 women randomised

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Gardner 2004 *(Continued)*

Participants	Women aged up to 43 years, undergoing IVF and embryo transfer with their own oocytes. Day 3 FSH no more than 10 mIU/ml, E2 under 80 pg/ml, hysteroscopically normal endometrial cavity, at least 10 follicles over 12 mm in diameter on day of hCG administration
Interventions	Blastocyst stage transfer: Single versus double blastocyst transfer
Outcomes	Ongoing pregnancy (defined as gestational sac with cardiac activity noted on ultrasound exam at least 4.5 weeks after embryo transfer), multiple gestation
Notes	Supported in part by grants from Organon International and Vitrolife AB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Methods not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding status not stated We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding status not stated However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No dropouts mentioned, but results presented as percentages so it is unclear whether all women were included in analysis
Selective reporting (reporting bias)	Unclear risk	Live birth not reported
Other bias	Unclear risk	Baseline characteristics (indication for IVF, age, baseline ovarian reserve) similar. Duration of infertility not reported

Gerris 1999

Study characteristics

Methods	Randomised controlled trial. States external concealment for concealment of allocation. Good-quality embryos transferred, morphology of good-quality embryos defined. Protocols for ovarian stimulation, oocyte retrieval, insemination and embryo transfer clearly described. Natural progesterone used for luteal phase support. Semen was prepared using mini-percoll gradient prior to insemination. Medi-Cult medium used for embryo culture. Wallace embryo transfer catheter was used for transfer. Embryo transfer was performed on day 3, 64 to 67 hours after insemination, results expressed using 95% confidence intervals analysis 53 women randomised

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Gerris 1999 *(Continued)*

Participants	First IVF/ICSI cycle. Female age < 34 years. Average duration of infertility 3.5 years
Interventions	1 embryo transfer versus 2 embryo transfer
Outcomes	Clinical pregnancy rate, live birth rate, multiple pregnancy rate per woman or couple and implantation rates
Notes	Method of randomisation not mentioned. Blinding not stated. Power calculation not reported. Intention-to-treat analysis not performed. Withdrawals and dropouts not mentioned clearly. Indication for treatment not mentioned. Previous treatment not mentioned Sponsored by the Foundation Marguerite-Marie Delacroix, dedicated to the prevention of cerebral palsy, Belgium

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	States external concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding status not stated We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding status not stated However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women included in analysis
Selective reporting (reporting bias)	Low risk	Reports live birth and multiple pregnancy rates
Other bias	Unclear risk	Duration of infertility reported. Indication for treatment not mentioned. Previous treatment not mentioned

Heijnen 2006

Study characteristics

Methods	2-centre randomised controlled trial. Randomisation performed before embryo quality was known 45 women randomised
Participants	Patients on the waiting list for IVF/ICSI. Women > 38 years and had an indication for IVF/ICSI either for the first time or after a previous IVF/ICSI childbirth

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Heijnen 2006 *(Continued)*

Interventions	Cleavage stage transfer (day 3 or 4): 2 embryo transfer in the first 3 cycles versus 3 embryo transfer in the first 3 treatment cycles
Outcomes	Cumulative live birth rate, live birth rate, multiple pregnancy rate
Notes	Chi^2 test and Mann–Whitney U test used for analysis. Randomisation was performed before information on embryo quality was available. Power calculation not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Remote: "Randomization was carried out using sealed envelopes opened by the study coordinator on the phone"
Allocation concealment (selection bias)	Low risk	Remote: "Randomization was carried out using sealed envelopes opened by the study coordinator on the phone"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned. We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding not mentioned However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 45 women analysed by intention to treat
Selective reporting (reporting bias)	Low risk	Reports cumulative live birth rate, live birth rate, multiple pregnancy rate.
Other bias	Low risk	Duration of infertility reported

Komori 2004

Study characteristics

Methods	Single-centre RCT
Participants	Women attending IVF clinic: 169 analysed (212 cycles)
Interventions	Cleavage-stage transfer (day 2): 2 versus 3 embryo transfer, number of cycles unclear
Outcomes	Clinical pregnancy (gestational sac), ongoing pregnancy, live birth, multiple pregnancy
Notes	'Per cycle' data only

Risk of bias

Bias	Authors' judgement	Support for judgement

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Komori 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not described; "patients were randomly divided into two groups"
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding not mentioned However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts and withdrawals not reported, 'per cycle' data only
Selective reporting (reporting bias)	Unclear risk	Reports expected outcomes, but only as 'per cycle' data
Other bias	Unclear risk	No information reported about baseline characteristics

Lukassen 2005

Study characteristics	
Methods	Randomised controlled trial 107 women randomised
Participants	First IVF/ICSI cycle. Female age < 35 years, FSH < 10IU/L. At least 1 good-quality embryo should be available
Interventions	Cleavage-stage transfer (day 3): SET (2 cycles) versus DET transfer In the second cycle protocol violations occurred in 4 patients (received 2 embryos)
Outcomes	Clinical pregnancy rate, live birth rate, multiple pregnancy rates and miscarriage rates per woman/couple. Cumulative pregnancy rates, Cumulative live birth rates, Cumulative multiple pregnancy rates and miscarriage rates for 1 plus 1 fresh embryo transfer
Notes	Good quality embryos transferred, but morphologic characteristics not defined clearly. Embryo transfer took place on day 3 after insemination. Patients and physicians not blinded to treatment. Power calculation reported. Details of those lost to follow-up given. Duration of infertility and indication for treatment provided. Protocols for IVF/ICSI described. Methods of statistical analysis mentioned Chi^2 test and Student's t-test were used for analysis

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

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Lukassen 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	"Allocation to the randomized group by an opaque, sealed envelope took place just before embryo transfer by the laboratory personnel to maintain concealment to the last moment". Does not specify that envelopes were consecutively numbered.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients and physicians not blinded to treatment We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients and physicians not blinded to treatment However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women analysed
Selective reporting (reporting bias)	Low risk	Reports cumulative live birth rate, live birth rate, multiple pregnancy rate
Other bias	Low risk	Duration of infertility reported

López-Regalado 2014b

Study characteristics	
Methods	Randomised controlled trial Single centre Spain
Participants	Inclusion criteria: women undergoing IVF, < 38 years, BMI 19 to 29 kg/m^2; FSH < 15 mIU/ml on day 3; first or second cycle with previous attempt with positive pregnancy test. Exclusion criteria: patients were excluded if infertility > 5 years; had previous surgery (fibroid, endometriosis, hydrosalphinx); uterine malformations; repeated spontaneous abortions (2 or more).
Interventions	Intervention (n = 84): 2 transfers; first fresh single embryo transfer followed by frozen SET if unsuccessful. In some cases of OHSS with freeze all, single embryo transfer done in frozen cycle. Control (n = 91): fresh double embryo transfer, on day 2 or 3 If freeze all for OHSS, then only 1 cycle of frozen transfer with 2 embryos.
Outcomes	Live birth rate, cumulative live birth rate, clinical pregnancy rate, ongoing pregnancy rate, multiple pregnancy rate, miscarriage rate.
Notes	Authors replied to all the data related queries satisfactorily. The trial was registered under clinical trial registry (NCT01909570).

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López-Regalado 2014b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization numbers..."
Allocation concealment (selection bias)	High risk	The allocation concealment was not described in the manuscript. Author reply: randomisation was carried out through a list of random numbers, a single embryologist had access to this list of random numbers.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No clear mention of blinding in the manuscript. Author reply: Embryologist performed the interview for randomisation. Embryologist had the information about group allotment. The study was double blind until the day of transfer to clinicians, patients, nurses and embryologists. Due to lack of blinding of clinician and embryologist on the day of embryo transfer, we categorised the study at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No clear mention of blinding in the manuscript. However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The attrition was similar in both the arms. Intention-to-treat analysis was done. We categorised as low risk for attrition bias.
Selective reporting (reporting bias)	Low risk	The trial was registered (ClinicalTrials.gov Identifier: NCT01909570). All the prespecified outcomes were reported in the final manuscript.
Other bias	Low risk	Important baseline variables were similar in both the groups. Duration of infertility mentioned. Received institutional grant (Instituto Carlos III, code number: FIS09-1968). No other source of bias detected.

Martikainen 2001

Study characteristics	
Methods	Multicentre randomised controlled trial 144 women randomised
Participants	Fresh IVF/ICSI treatment who had/not had more than 1 previous failed treatment. Frozen embryo transfers were analysed separately. At least 4 good-quality embryos should be available for inclusion in the trial.
Interventions	Cleavage-stage transfer: 1 embryo transfer (n = 74) versus 2 embryo transfer (n = 70).

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Martikainen 2001 *(Continued)*

	Good-quality embryos transferred. Morphology of good-quality embryos described clearly. Protocols for IVF/ICSI clearly defined. Effectiveness of 1 versus 2 embryo transfer in frozen replacement cycles analysed separately. All centres involved used various age limits for inclusion of women. Embryos cultured in Medi-Cult medium. IVF-500 medium or Sydney IVF medium (Cook IVF) catheters were used for embryo transfer. Embryo transfer performed 46 to 50 hours after oocyte recovery. Natural progesterone used for luteal phase support. Chi^2 test and 2-tailed t-tests used for statistical analysis
Outcomes	Reports clinical pregnancy rate, live birth rate, multiple pregnancy rates per woman/couple. Implantation and miscarriage rates
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table, balanced in sets of 10
Allocation concealment (selection bias)	Unclear risk	Not clear: allocation done by laboratory personnel
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not stated However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women included in analysis
Selective reporting (reporting bias)	Low risk	Reports cumulative live birth rate, live birth rate, multiple pregnancy rate
Other bias	Unclear risk	Duration of infertility not mentioned

Mostajeran 2006

Study characteristics	
Methods	Single-centre RCT
Participants	ART candidates referred to university clinic, 298 analysed
Interventions	1 cycle of double embryo transfer (155 analysed) versus triple embryo transfer (143 analysed). Day of transfer not reported
Outcomes	Clinical pregnancy (fetal heart on ultrasound); multiple pregnancy
Notes	

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Mostajeran 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated: "the subjects were randomly divided into two groups"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not mentioned We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding not mentioned However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Women who did not follow the prescribed drug regimen or who had OHSS were excluded (numbers not reported). 3 women with ectopic pregnancy also excluded - not stated which group they were in
Selective reporting (reporting bias)	Unclear risk	Live birth not reported
Other bias	Unclear risk	Duration of infertility not mentioned

Prados 2015

Study characteristics	
Methods	Randomised open-label controlled trial, designed to show equivalence Patients were informed on day 3 of embryo culture of the assigned group by their physician. Randomised women were allowed to change group if they did not feel confident and expressed a desire to modify the day or number of transferred embryos. Both ITT and per protocol analysis reported
Participants	Inclusion criteria Women requesting fertility treatment, aged under 38 years, and first trial of in vitro fertilisation or intracytoplasmic sperm injection. At least 4 good-quality embryos on day 3 of embryo development Exclusion criteria Patients who underwent pre-implantation genetic diagnosis or oocyte donation treatments were excluded. Patients were also excluded if the sperm was not obtained from an ejaculate sample 199 women randomised
Interventions	Day 3 of embryo culture: Cleavage stage SET (n = 50) Cleavage stage DET (n = 49) Day 5 of embryo culture:

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Prados 2015 *(Continued)*

	Blastocyst stage SET (n = 50) Blastocyst stage DET (n = 50) The number of embryos transferred on subsequent thawed embryo cycles was determined independently of the randomised group the patient belonged to. Protocols for IVF, embryo culture, transfer and freezing reported in detail in study publication
Outcomes	Multiple birth, live birth, patient acceptance
Notes	In press December 2012 Study enrolment ceased before planned sample size (n = 412) due to change in embryo cryopreservation programme at IVI Seville. Sponsored by the Instituto Valenciano de Infertilidad, Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of web site Randomization.com to generate randomly permuted blocks of 8 subjects per block
Allocation concealment (selection bias)	Low risk	The randomisation was kept in a locked drawer in the administration office where the clinical staff who enrolled participants had no access. The assigned group was requested by phone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open label However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT outcomes reported for all women randomised
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Groups well-balanced at baseline High proportion of participants changed groups (mostly from SET to DET): Cleavage-stage SET = 30 (50 randomised) Cleavage-stage DET = 71 (49 randomised) Blastocyst-stage SET = 37 (50 randomised) Blastocyst-stage DET = 57 (50 randomised) Study data were analysed by intention to treat (as reported in this review) and also per protocol

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Thurin 2004

Study characteristics	
Methods	Multicentre randomised controlled trial 661 women randomised
Participants	First or second IVF cycle who had at least 2 embryos of good quality available for transfer or freezing. Female age < 36 years. Duration and cause for infertility mentioned
Interventions	Transfer on day 2 (93%), day 3 (5%) (cleavage stage), or day 5 (2% to 3%) (blastocyst stage) a. 1 embryo transfer (n = 330) versus 2 embryo transfer (n = 331) b. 1 fresh plus 1 thawed embryo transfer cycle versus 2 embryo transfer (fresh)
Outcomes	Clinical pregnancy rate, live birth rate, multiple pregnancy rates and miscarriage rates per woman/couple. Cumulative pregnancy rates; cumulative live birth rates; cumulative multiple pregnancy rates and miscarriage rates for 1 embryo transfer plus 1 thawed embryo transfer cycle
Notes	Power calculation performed. Good-quality embryos transferred, morphologic characteristics defined clearly. Embryo transfer took place on day 2, 3 or 5 days after oocyte retrieval. Women lost to follow-up mentioned. Fisher's non-parametric permutation test and Fisher's exact test used for statistical analysis and 95% confidence intervals calculated. 8 women in each group (2.4%) had blastocyst transfer at day 5 Supported by a grant from Serono Nordic

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation at a ratio of 1:1
Allocation concealment (selection bias)	Unclear risk	Method not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study We categorised the study to be at low risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study We categorised the study to be at low risk for detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women analysed
Selective reporting (reporting bias)	Low risk	Cumulative live birth rate, live birth rate, multiple pregnancy rate
Other bias	Unclear risk	No mean duration of infertility given. 8 women in each group (2.4%) had blastocyst transfer at day 5

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Thurin 2005

Study characteristics	
Methods	Multicentre randomised controlled trial. Computer-generated randomisation at a ratio of 1:1 27 women randomised
Participants	Female age ≥ 36 years. First or second IVF/ICSI cycle. At least 2 good-quality embryos available
Interventions	Transfer at cleavage stage (23/27; 85%) or blastocyst stage (4/27; 15%) DET fresh versus SET fresh + SET frozen
Outcomes	Reports live birth rate per woman, multiple live birth per woman
Notes	Unpublished trial, pilot study, part of a thesis Supported by a grant from Serono Nordic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation at a ratio of 1:1
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study We categorised the study to be at low risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study We categorised the study to be at low risk for detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Women lost to follow-up mentioned ITT performed
Selective reporting (reporting bias)	Low risk	Reports cumulative live birth rate, live birth rate, multiple pregnancy rate
Other bias	Unclear risk	No mean duration of infertility given

van Montfoort 2006

Study characteristics	
Methods	Randomised controlled trial 308 women randomised

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van Montfoort 2006 *(Continued)*

Participants	First IVF cycle. Participants had to have at least 2 oocytes (2PN embryos)
Interventions	Cleavage-stage transfer (day 2 or 3): 1 embryo versus 2 embryo transfer
Outcomes	Reports clinical pregnancy rate, multiple pregnancy rate per woman/couple
Notes	Randomisation performed immediately prior to embryo transfer, but method of randomisation not stated. Patient population was stratified with respect to female age (< 38 and > 38 years), fertilisation technique (IVF/ICSI). Power calculation performed. Number lost to follow-up mentioned. Duration and cause for infertility mentioned. Analysis of variance (ANOVA) with Tukey's multiple test procedure and Chi^2 test were used for statistical analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	"by using a nontransparent box containing the sealed opaque envelopes, the randomization procedure was blinded". Does not state that envelopes were consecutively numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study We categorised the study to be at low risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study We categorised the study to be at low risk for detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women included in analysis
Selective reporting (reporting bias)	Low risk	Reports pregnancy rate, multiple pregnancy rate, miscarriage rate
Other bias	Unclear risk	Duration of infertility not provided

Vauthier-Brouzes 1994

Study characteristics

Methods	Randomised controlled trial 56 women included in analysis
Participants	Fresh IVF/ICSI cycle. Frozen embryo transfers analysed separately. Age ≤ 35 years. Cleavage rate ≥ 70% for IVF. Good-quality embryos transferred. Morphological characteristics of good-quality embryos defined. Study and control groups were comparable in terms of age, number of hMG ampoules required for ovarian stimulation, mean number of oocytes obtained and the number of embryos obtained. Indications for IVF was also comparable in both groups. Protocols for IVF/ICSI defined. HCG and natural progesterone used for luteal phase support. IVF using donor sperm was also included and the number

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Vauthier-Brouzes 1994 *(Continued)*

	of patients who used donor sperm for IVF was also comparable in the 2 groups. Patients who had a single, successful previous IVF attempt were also included
Interventions	Cleavage stage transfer: 2 (n = 28) versus 4 (n = 28) embryo transfer
Outcomes	Clinical pregnancy rate, live birth rate and multiple pregnancy rate per woman/couple
Notes	Method of randomisation not mentioned. Blinding not stated. Allocation concealment not clear. Power calculation not reported. Intention-to-treat analysis not performed. Details of withdrawals, dropouts not given. Duration of infertility and indication for treatment not provided. Methods of statistical analysis not clearly mentioned. Embryo culture medium and catheter used for embryo transfer not described. Day of embryo transfer also unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated We categorised the study to be at high risk for performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not stated However, due to objective nature of outcomes, we categorised the study at low risk for detection bias for all outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details of withdrawals, dropouts not given.
Selective reporting (reporting bias)	Low risk	Reports live birth rate and multiple pregnancy rate per woman/couple
Other bias	Unclear risk	Day of embryo transfer also unclear

ART - assisted reproductive technology; SET - single embryo transfer; DET - double embryo transfer; ICSI - intracytoplasmic sperm injection; IVF - in vitro fertilisation; mIU/ml - milli international unit/ millilitre; RCT - randomised controlled trial; ITT - intention to treat; BMI - body mass index; 2 PN - 2 pronuclei; OHSS - ovarian hyperstimulation syndrome; E2 - estradiol; kg/m2 - kilograms/ metre ^{2}; pg/ml - picograms/ millilitre

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

Study	Reason for exclusion
Bensdorp 2015	RCT comparing convention IVF and SET vs modified natural cycle IVF vs 3 cycles of IUI
Bowman 2004	Non-randomised study of double blastocyst transfer versus single blastocyst plus frozen transfers. NB: same publication also includes Livingstone 2001.

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Study	Reason for exclusion
Brabers 2016	Secondary analysis looking at decision-making process.
Eijkemans 2006	Review article on methodological considerations in decision making
Elgindy 2011	Compares cleavage versus blastocyst transfer. On average more embryos were transferred in the cleavage-stage group but this was not prespecified policy.
Forman 2012	Compares quantitative chromosome-screened SET (pre implantation genetic screening) versus morphology-based DET.
Forman 2013	Compares preimplantation genetic screening SET vs morphology based DET along with cost analysis
Forman 2014	Compares obstetric outcomes of pregnancies following preimplantation genetic screening SET vs morphology-based DET
Frattarelli 2003	Compares cleavage versus blastocyst transfer. On average more embryos were transferred in the cleavage-stage group but this was not prespecified policy
Gardner 1998	Compares cleavage versus blastocyst transfer. On average more embryos were transferred in the cleavage-stage group but this was not prespecified policy
Guerif 2011	Not randomised controlled trial
Harrild 2009	Individualised participant data (IPD) meta analysis
Hatırnaz 2016	In vitro maturation (IVM) cycles; retrospective study
Heijnen 2007	The ovarian stimulation regimes used for the 2 randomised groups (SET versus DET) were significantly different
IRCT20141217020351N10	Compared sequential day 3 and day 5 transfer with single-day 5 embryo transfer
Lao 2017	Non randomised design
Levitas 2004	Compares cleavage versus blastocyst transfer. On average more embryos were transferred in the cleavage-stage group but this was not prespecified policy
Livingstone 2001	No comparison of interest - compares double cleavage-stage embryo versus single blastocyst-stage embryo. Mentioned in same paper as Bowman 2004
López-Regalado 2014a	Retrospective cohort study
Motta 1998 A & B	RCT comparing 3 to 5 cleavage-stage versus 1 to 3 blastocyst-stage embryos
Moustafa 2008	Quasi-randomised trial - days of week used
NCT03758833	Comparing morphology based screening (SET) vs pre implantation genetic screening SET
Pantos 2004	Compares cleavage versus blastocyst transfer. On average more embryos were transferred in the cleavage-stage group but this was not prespecified policy
Rodriguez 2016	Pre-implantation genetic screening cost analysis study
Schoolcraft 2013	Review article

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Study	Reason for exclusion
Staessen 1993	Not randomised controlled trial
Thurin 2009	Orginal trial was included which included randomised group evaluating SET vs DET. Current trial looked at cumulative live birth following subsequent frozen transfer of 1 or 2 embryos (not randomised in 1 or 2 embryos) on both arms
van Loendersloot 2017	Cost effectiveness study
van Montfoort 2005	Not randomised controlled trial
Yang 2016	Compared time lapse and preimplantation genetic screening versus only time lapse screening
Zhang 2015	Compared fresh conventional IVF DET vs minimal stimulation frozen SET cycles

DATA AND ANALYSES

Comparison 2. Repeated SET (mixed policies) versus multiple ET in a single cycle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Cumulative live birth	4	985	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
2.1.1 SET + 1 FET versus DET (x1) (cleavage stage)	3	878	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
2.1.2 SET (x2) versus DET (x1) (cleavage stage)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.70, 1.84]
2.2 Multiple pregnancy	4	985	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.08, 0.21]
2.2.1 SET + 1 FET versus DET (x1) (cleavage stage)	3	878	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.08, 0.22]
2.2.2 SET (x2) versus DET (x1) (cleavage stage)	1	107	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.03, 0.54]
2.3 Clinical pregnancy rate	3	943	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.12]
2.3.1 SET + 1 FET versus DET (x1) (cleavage stage)	2	836	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.11]
2.3.2 SET (x2) versus DET (x1) (cleavage stage)	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.81, 1.71]
2.4 Miscarriage	2	282	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.14 [0.93, 4.95]
2.4.1 SET + 1 FET versus DET (x1) (cleavage stage)	1	175	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.86 [0.85, 9.67]

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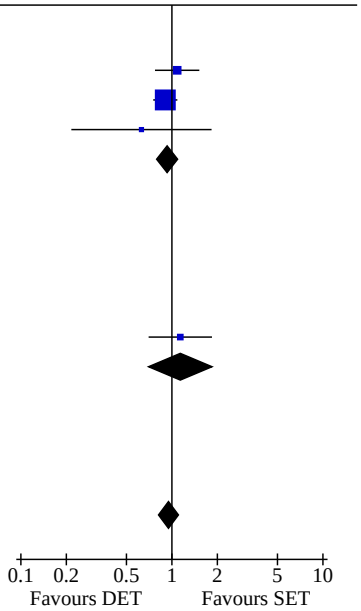
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.2 SET (x2) versus DET (x1) (cleavage stage)	1	107	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.52, 5.23]

Analysis 2.1. Comparison 2: Repeated SET (mixed policies) versus multiple ET in a single cycle, Outcome 1: Cumulative live birth

Study or Subgroup	SET two cycles Events	SET two cycles Total	DET one cycle Events	DET one cycle Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 SET + 1 FET versus DET (x1) (cleavage stage)						
López-Regalado 2014b	38	84	38	91	17.9%	1.08 [0.77 , 1.52]
Thurin 2004 (1)	128	330	142	331	69.5%	0.90 [0.75 , 1.09]
Thurin 2005 (2)	4	20	7	22	3.3%	0.63 [0.22 , 1.83]
Subtotal (95% CI)		**434**		**444**	**90.6%**	**0.93 [0.79 , 1.09]**
Total events:	170		187			
Heterogeneity: Chi² = 1.39, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
2.1.2 SET (x2) versus DET (x1) (cleavage stage)						
Lukassen 2005	22	54	19	53	9.4%	1.14 [0.70 , 1.84]
Subtotal (95% CI)		**54**		**53**	**9.4%**	**1.14 [0.70 , 1.84]**
Total events:	22		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
Total (95% CI)		**488**		**497**	**100.0%**	**0.95 [0.82 , 1.10]**
Total events:	192		206			
Heterogeneity: Chi² = 1.96, df = 3 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%						



Footnotes

(1) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5

(2) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5)

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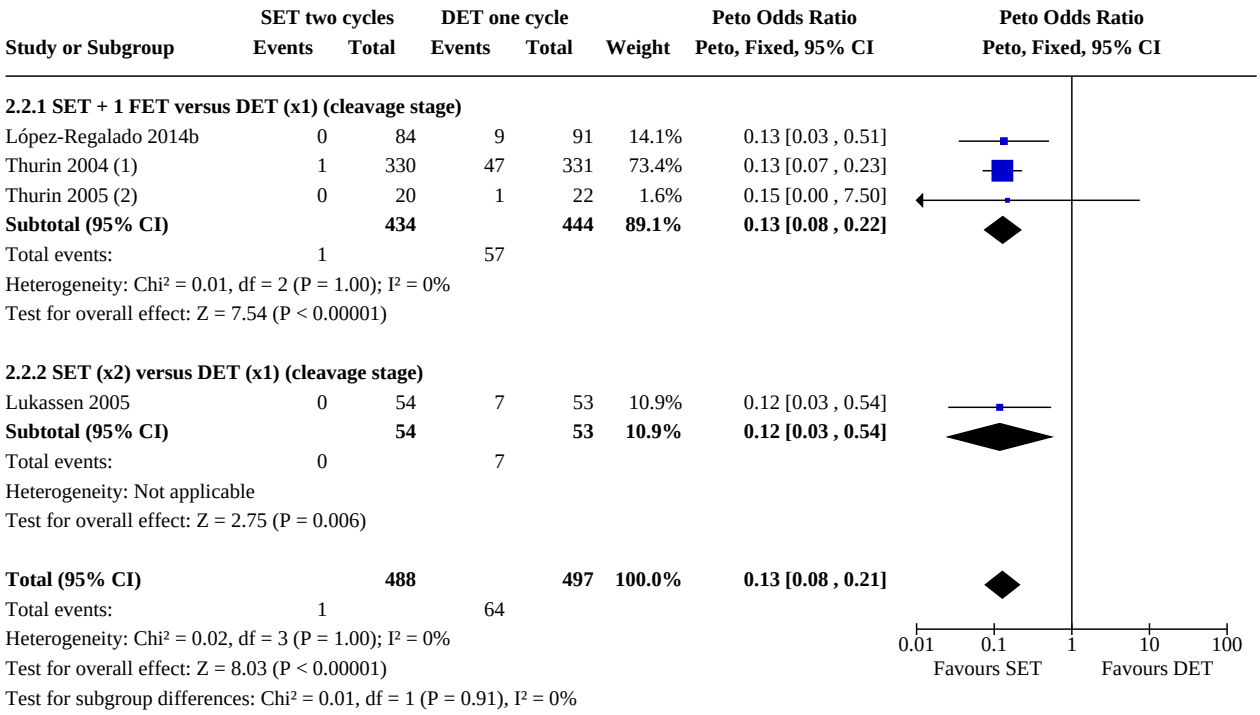
Analysis 2.2. Comparison 2: Repeated SET (mixed policies) versus multiple ET in a single cycle, Outcome 2: Multiple pregnancy



Footnotes

(1) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5

(2) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5)

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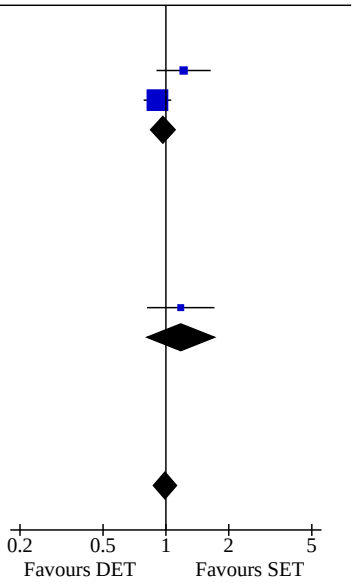
Analysis 2.3. Comparison 2: Repeated SET (mixed policies) versus multiple ET in a single cycle, Outcome 3: Clinical pregnancy rate

Study or Subgroup	SET two cycles Events	SET two cycles Total	DET one cycle Events	DET one cycle Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 SET + 1 FET versus DET (x1) (cleavage stage)						
López-Regalado 2014b	46	84	41	91	16.5%	1.22 [0.90 , 1.64]
Thurin 2004 (1)	158	330	174	331	72.9%	0.91 [0.78 , 1.06]
Subtotal (95% CI)		**414**		**422**	**89.4%**	**0.97 [0.84 , 1.11]**
Total events:	204		215			
Heterogeneity: Chi² = 2.85, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 0.48 (P = 0.63)						
2.3.2 SET (x2) versus DET (x1) (cleavage stage)						
Lukassen 2005	30	54	25	53	10.6%	1.18 [0.81 , 1.71]
Subtotal (95% CI)		**54**		**53**	**10.6%**	**1.18 [0.81 , 1.71]**
Total events:	30		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**468**		**475**	**100.0%**	**0.99 [0.87 , 1.12]**
Total events:	234		240			
Heterogeneity: Chi² = 3.80, df = 2 (P = 0.15); I² = 47%						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Chi² = 0.95, df = 1 (P = 0.33), I² = 0%						

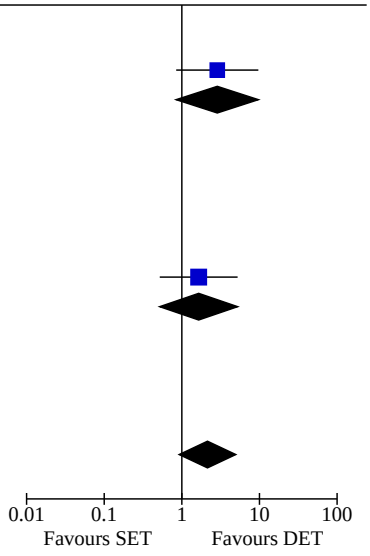


Footnotes

(1) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5

Analysis 2.4. Comparison 2: Repeated SET (mixed policies) versus multiple ET in a single cycle, Outcome 4: Miscarriage

Study or Subgroup	SET two cycles Events	SET two cycles Total	DET one cycle Events	DET one cycle Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.4.1 SET + 1 FET versus DET (x1) (cleavage stage)						
López-Regalado 2014b	8	84	3	91	47.3%	2.86 [0.85 , 9.67]
Subtotal (95% CI)		**84**		**91**	**47.3%**	**2.86 [0.85 , 9.67]**
Total events:	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.69 (P = 0.09)						
2.4.2 SET (x2) versus DET (x1) (cleavage stage)						
Lukassen 2005	8	54	5	53	52.7%	1.65 [0.52 , 5.23]
Subtotal (95% CI)		**54**		**53**	**52.7%**	**1.65 [0.52 , 5.23]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**138**		**144**	**100.0%**	**2.14 [0.93 , 4.95]**
Total events:	16		8			
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.78 (P = 0.08)						
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%						



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Comparison 3. Single versus multiple embryo transfer (in a single cycle)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Live birth	12	1904	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.59, 0.75]
3.1.1 SET (x1) versus DET (x1) (cleavage stage)	11	1704	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.59, 0.76]
3.1.2 SET (x1) versus DET (x1) (blastocyst stage)	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.51, 0.84]
3.2 Multiple pregnancy	13	1952	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.12, 0.22]
3.2.1 SET (x1) versus DET (x1) (cleavage stage)	11	1704	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.11, 0.22]
3.2.2 SET (x1) versus DET (x1) (blastocyst stage)	3	248	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.09, 0.36]
3.3 Clinical pregnancy rate	10	1860	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.64, 0.77]
3.3.1 SET (x1) versus DET (x1) (cleavage stage)	8	1612	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.62, 0.78]
3.3.2 SET (x1) versus DET (x1) (blastocyst stage)	3	248	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.62, 0.88]
3.4 Miscarriage	7	1560	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.66, 1.42]
3.4.1 SET (x1) versus DET (x1) (cleavage stage)	6	1460	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.65, 1.43]
3.4.2 SET (x1) versus DET (x1) (blastocyst stage)	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.24, 4.21]

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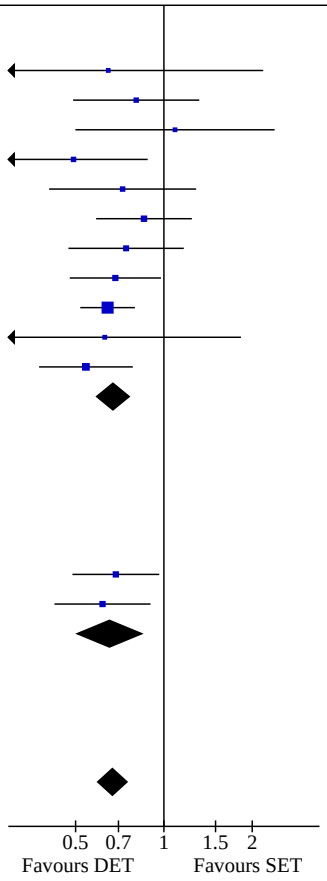
Analysis 3.1. Comparison 3: Single versus multiple embryo transfer (in a single cycle), Outcome 1: Live birth

Study or Subgroup	SET Events	SET Total	DET Events	DET Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 SET (x1) versus DET (x1) (cleavage stage)						
ASSETT 2003	3	13	5	14	1.1%	0.65 [0.19 , 2.18]
Clua 2015 (1)	15	34	17	31	4.0%	0.80 [0.49 , 1.32]
ECOSSE 2006 (2)	6	11	6	12	1.3%	1.09 [0.50 , 2.38]
Gerris 1999	9	26	19	27	4.2%	0.49 [0.27 , 0.88]
Lukassen 2005 (3)	14	54	19	53	4.3%	0.72 [0.41 , 1.29]
López-Regalado 2014b	30	84	38	91	8.3%	0.86 [0.59 , 1.25]
Martikainen 2001	22	74	28	70	6.5%	0.74 [0.47 , 1.17]
Prados 2015	23	50	33	49	7.6%	0.68 [0.48 , 0.98]
Thurin 2004 (4)	91	330	142	331	32.1%	0.64 [0.52 , 0.80]
Thurin 2005 (5)	4	20	7	22	1.5%	0.63 [0.22 , 1.83]
van Montfoort 2006	32	154	59	154	13.4%	0.54 [0.38 , 0.78]
Subtotal (95% CI)		**850**		**854**	**84.4%**	**0.67 [0.59 , 0.76]**
Total events:	249		373			
Heterogeneity: Chi² = 6.43, df = 10 (P = 0.78); I² = 0%						
Test for overall effect: Z = 6.13 (P < 0.00001)						
3.1.2 SET (x1) versus DET (x1) (blastocyst stage)						
Abuzeid 2017	24	50	35	50	7.9%	0.69 [0.49 , 0.96]
Prados 2015	21	50	34	50	7.7%	0.62 [0.42 , 0.90]
Subtotal (95% CI)		**100**		**100**	**15.6%**	**0.65 [0.51 , 0.84]**
Total events:	45		69			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Total (95% CI)		**950**		**954**	**100.0%**	**0.67 [0.59 , 0.75]**
Total events:	294		442			
Heterogeneity: Chi² = 6.64, df = 12 (P = 0.88); I² = 0%						
Test for overall effect: Z = 6.89 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%						



Footnotes

(1) Study included only oocyte donation cycles
(2) Interim analysis from (planned) multi-cycle study.
(3) Interim analysis from multi-cycle study.
(4) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5. Interim analysis from multi-cycle study.
(5) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5). Interim analysis from multi-cycle study.

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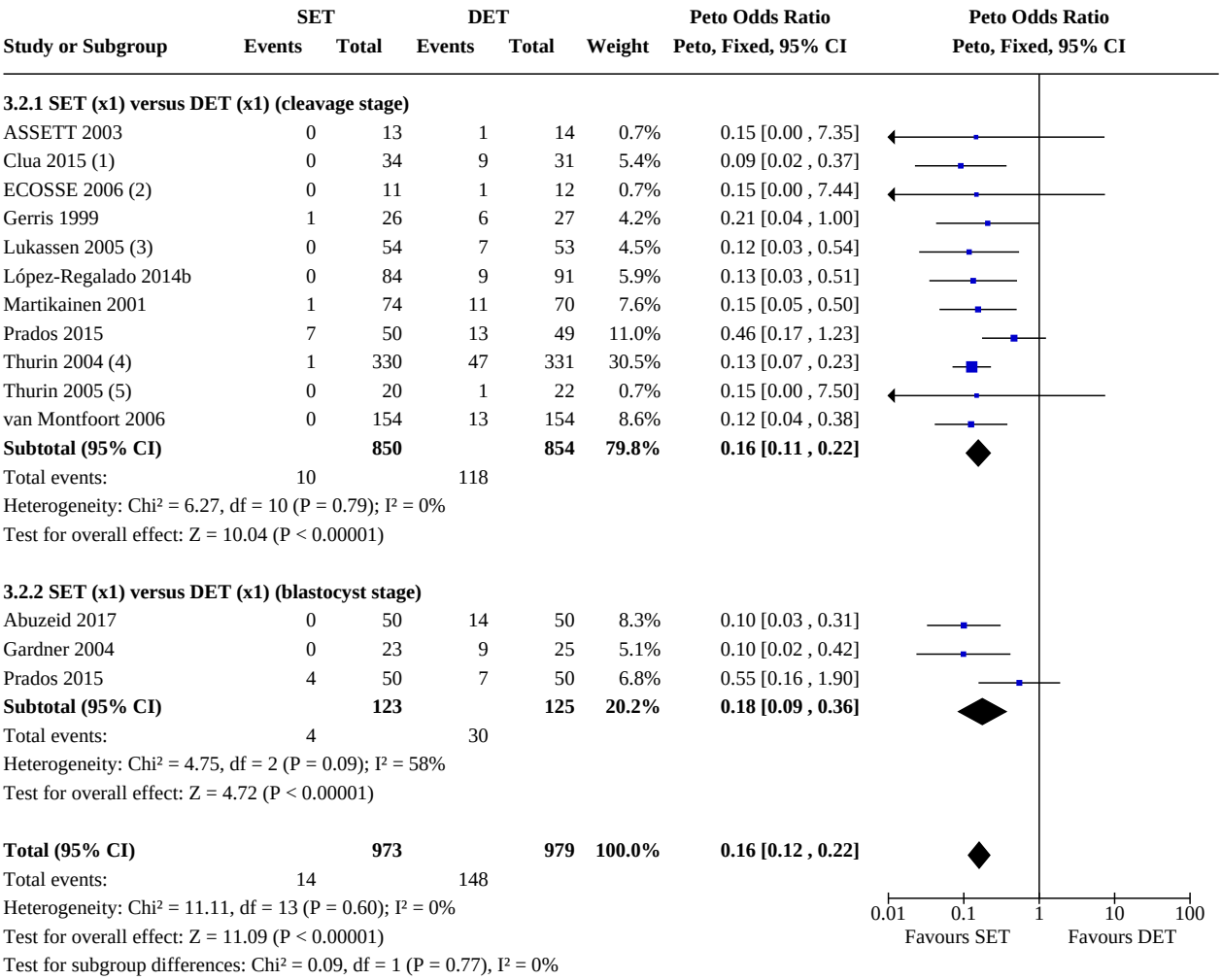
Analysis 3.2. Comparison 3: Single versus multiple embryo transfer (in a single cycle), Outcome 2: Multiple pregnancy



Footnotes

(1) Study included only oocyte donation cycles
(2) Interim analysis from (planned) multi-cycle study.
(3) Interim analysis from multi-cycle study.
(4) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5.Interim analysis from multi-cycle study.
(5) Includes three women in the DET group and one in the SET group who had blastocyst transfer (day 5).Interim analysis from multi-cycle study.

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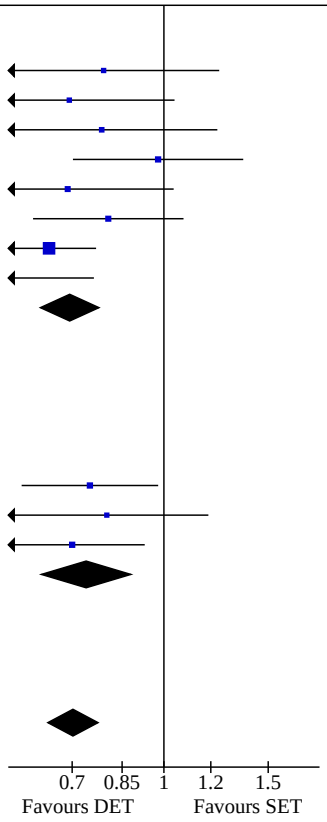
Analysis 3.3. Comparison 3: Single versus multiple embryo transfer (in a single cycle), Outcome 3: Clinical pregnancy rate

Study or Subgroup	SET Events	SET Total	DET Events	DET Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 SET (x1) versus DET (x1) (cleavage stage)						
Clua 2015 (1)	16	33	19	31	3.9%	0.79 [0.50 , 1.24]
Gerris 1999	14	26	21	27	4.1%	0.69 [0.46 , 1.04]
Lukassen 2005 (2)	20	54	25	53	5.0%	0.79 [0.50 , 1.23]
López-Regalado 2014b	37	84	41	91	7.7%	0.98 [0.70 , 1.36]
Martikainen 2001	24	74	33	70	6.7%	0.69 [0.46 , 1.04]
Prados 2015	29	50	36	50	7.1%	0.81 [0.60 , 1.08]
Thurin 2004 (3)	111	330	174	331	34.2%	0.64 [0.53 , 0.77]
van Montfoort 2006	33	154	62	154	12.2%	0.53 [0.37 , 0.76]
Subtotal (95% CI)		**805**		**807**	**80.7%**	**0.69 [0.62 , 0.78]**
Total events:	284		411			
Heterogeneity: Chi² = 8.61, df = 7 (P = 0.28); I² = 19%						
Test for overall effect: Z = 6.31 (P < 0.00001)						
3.3.2 SET (x1) versus DET (x1) (blastocyst stage)						
Abuzeid 2017	30	50	40	50	7.9%	0.75 [0.58 , 0.98]
Gardner 2004	14	23	19	25	3.6%	0.80 [0.54 , 1.19]
Prados 2015	28	50	40	50	7.9%	0.70 [0.53 , 0.93]
Subtotal (95% CI)		**123**		**125**	**19.3%**	**0.74 [0.62 , 0.88]**
Total events:	72		99			
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² = 0%						
Test for overall effect: Z = 3.41 (P = 0.0006)						
Total (95% CI)		**928**		**932**	**100.0%**	**0.70 [0.64 , 0.77]**
Total events:	356		510			
Heterogeneity: Chi² = 9.16, df = 10 (P = 0.52); I² = 0%						
Test for overall effect: Z = 7.11 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%						



Footnotes

(1) Study included only oocyte donation cycles

(2) Interim analysis from multi-cycle study.

(3) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5.Interim analysis from multi-cycle study.

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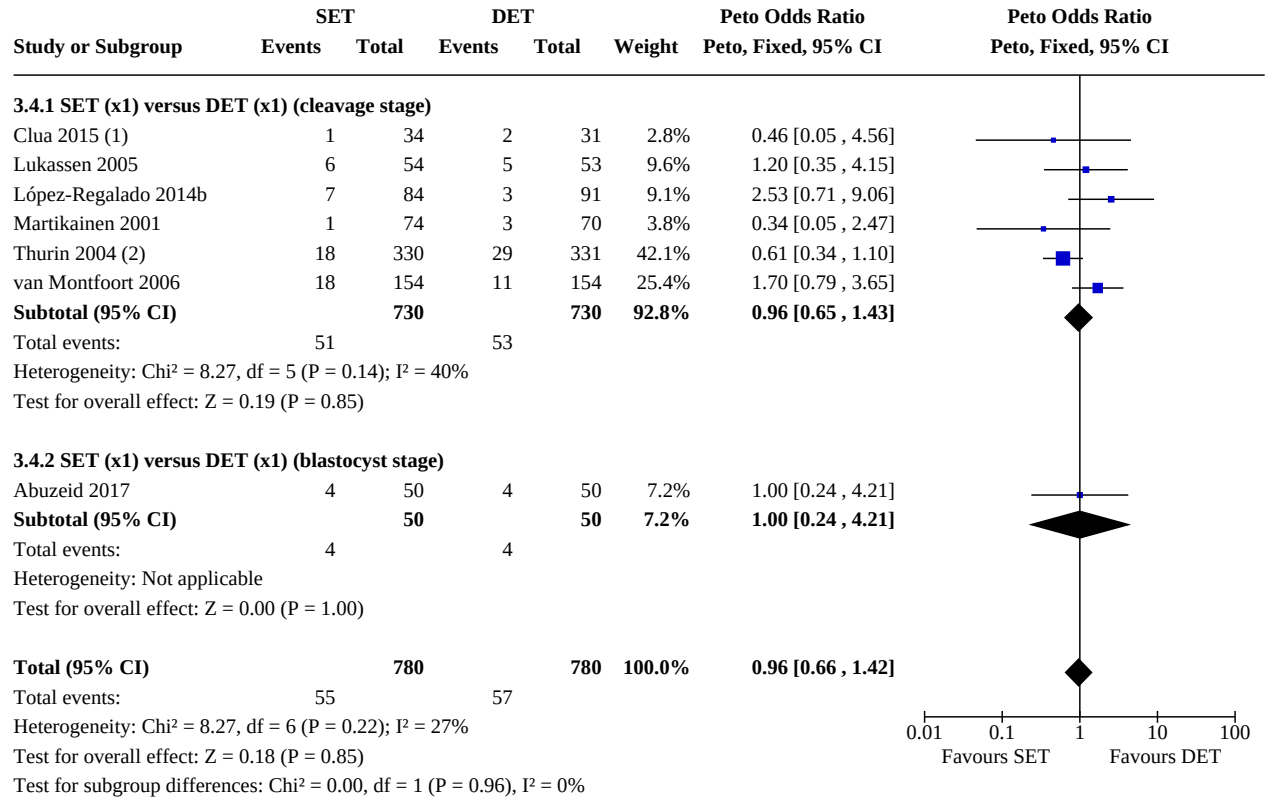
Analysis 3.4. Comparison 3: Single versus multiple embryo transfer (in a single cycle), Outcome 4: Miscarriage



Footnotes

(1) Study included only oocyte donation cycles

(2) Includes 8 women in each group (2.4%) who had blastocyst transfer at day 5. Interim analysis from multi-cycle study.

Comparison 4. Double embryo transfer versus more than two embryos transferred

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Live or cumulative live birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 DET (x1) versus TET (x1)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.14, 1.68]
4.1.2 DET (x1) versus four embryo transfer (x1)	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.27, 1.05]
4.1.3 DET (x2) versus TET (x2)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.37, 1.92]
4.1.4 DET (x3) versus TET (x3)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.43, 1.71]
4.2 Multiple pregnancy	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.2.1 DET versus TET	2	343	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.14, 0.93]

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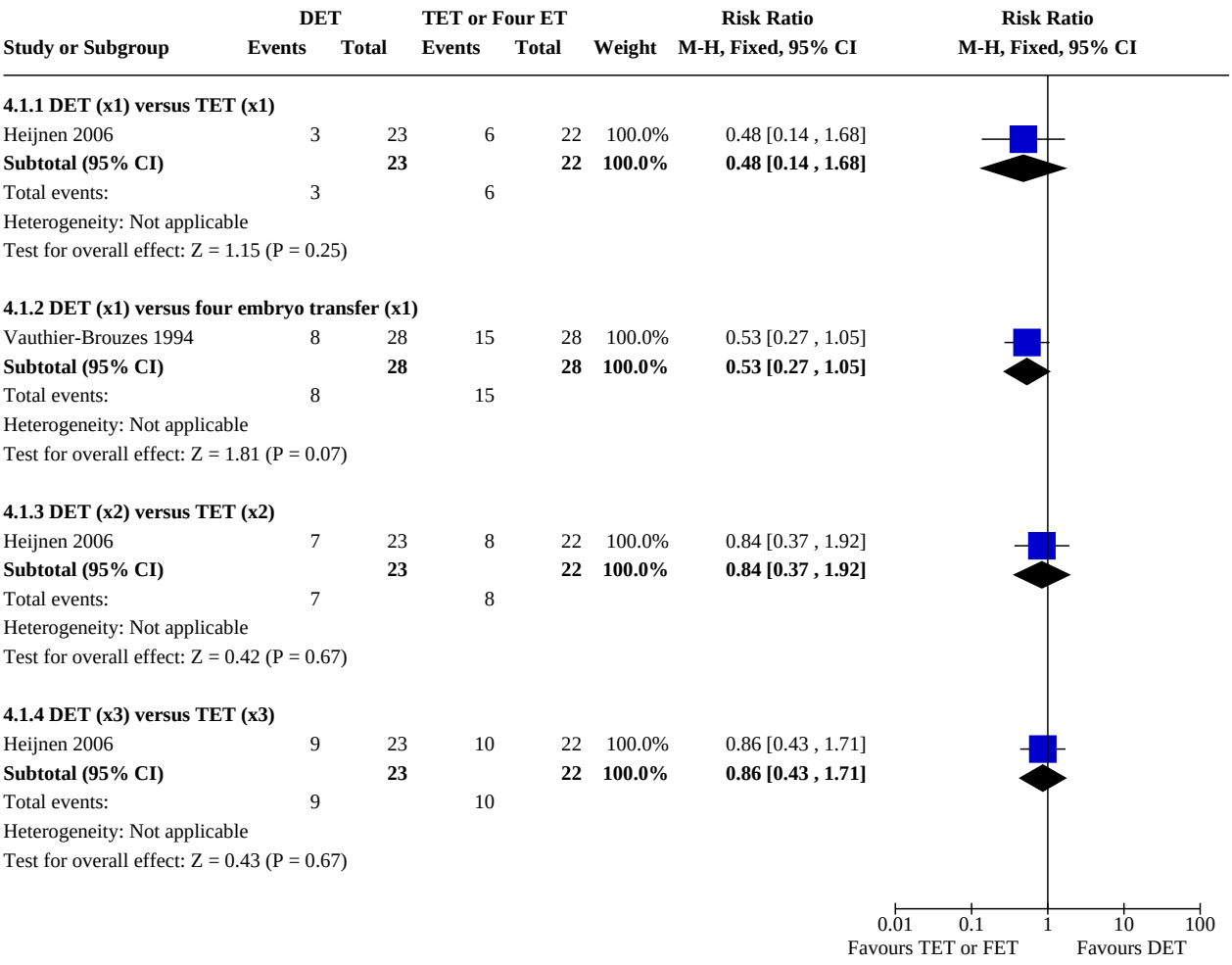
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2.2 DET versus four embryo transfer	1	56	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.11, 1.88]
4.3 Clinical pregnancy	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 DET (x1) versus TET (x1)	2	343	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.53, 1.06]
4.3.2 DET (x1) versus four embryo transfer (x1)	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.47, 1.26]

Analysis 4.1. Comparison 4: Double embryo transfer versus more than two embryos transferred, Outcome 1: Live or cumulative live birth



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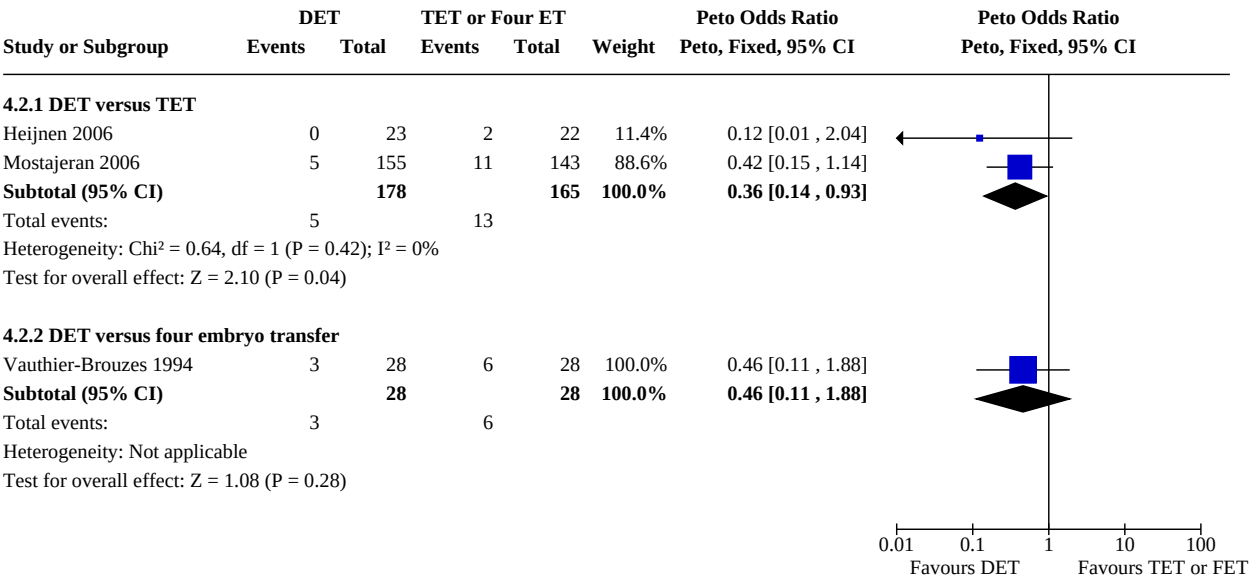
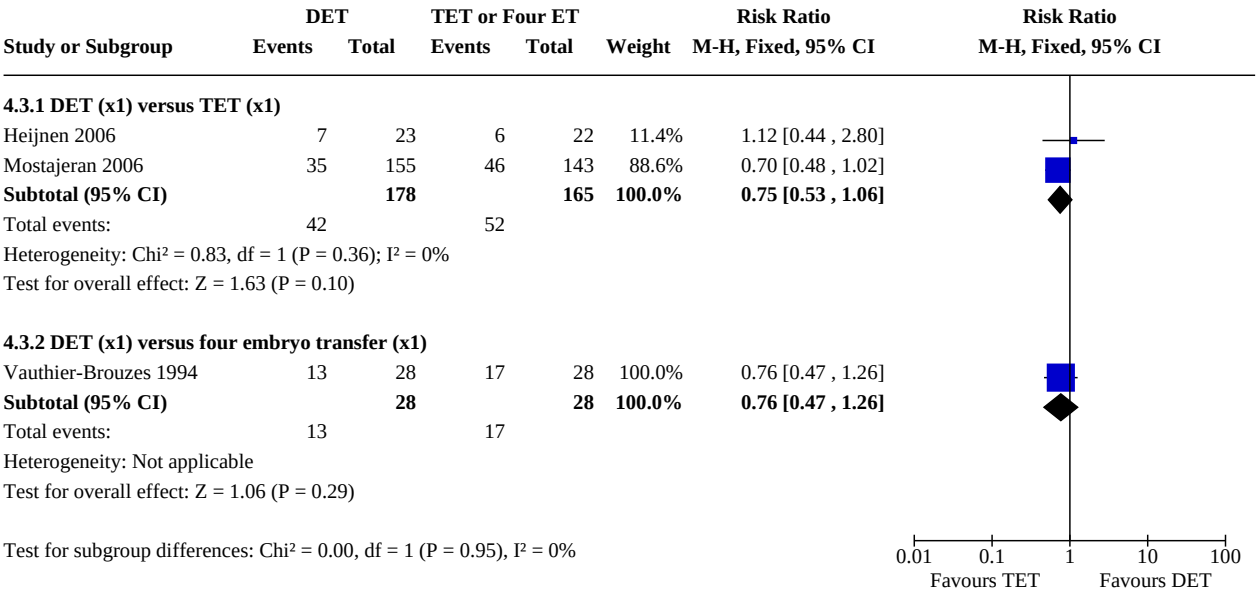
Analysis 4.2. Comparison 4: Double embryo transfer versus more than two embryos transferred, Outcome 2: Multiple pregnancy



Study or Subgroup	DET Events	DET Total	TET or Four ET Events	TET or Four ET Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
4.2.1 DET versus TET						
Heijnen 2006	0	23	2	22	11.4%	0.12 [0.01 , 2.04]
Mostajeran 2006	5	155	11	143	88.6%	0.42 [0.15 , 1.14]
Subtotal (95% CI)		**178**		**165**	**100.0%**	**0.36 [0.14 , 0.93]**
Total events:	5		13			
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
4.2.2 DET versus four embryo transfer						
Vauthier-Brouzes 1994	3	28	6	28	100.0%	0.46 [0.11 , 1.88]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**0.46 [0.11 , 1.88]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						

Analysis 4.3. Comparison 4: Double embryo transfer versus more than two embryos transferred, Outcome 3: Clinical pregnancy



Study or Subgroup	DET Events	DET Total	TET or Four ET Events	TET or Four ET Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 DET (x1) versus TET (x1)						
Heijnen 2006	7	23	6	22	11.4%	1.12 [0.44 , 2.80]
Mostajeran 2006	35	155	46	143	88.6%	0.70 [0.48 , 1.02]
Subtotal (95% CI)		**178**		**165**	**100.0%**	**0.75 [0.53 , 1.06]**
Total events:	42		52			
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
4.3.2 DET (x1) versus four embryo transfer (x1)						
Vauthier-Brouzes 1994	13	28	17	28	100.0%	0.76 [0.47 , 1.26]
Subtotal (95% CI)		**28**		**28**	**100.0%**	**0.76 [0.47 , 1.26]**
Total events:	13		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						

ADDITIONAL TABLES

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Table 1. Prognostic factors in included studies

Study author and year	Age Eligibility criteria (mean participant age, where stated)	Duration of infertility	Previous failed cycle	Frozen cycles	Prim/Sec infertility	FSH	Quality of embryo
Prados 2015	Under 38 years (mean age 33)	Mean 2.6 to 3.2 years	First IVF/ICSI cycle.	Frozen cycles included	Not stated	Not stated	Good
Gerris 1999	less than 34 years	Average duration of infertility 3.5 years.	First IVF/ICSI cycle.	Not included	Unclear	Not mentioned	Good
Heijnen 2006	38 to 45 years (mean age 41)	Average duration of infertility in DET group was 3.7(± 2.5) and in TET group was 3.2(± 2.4) years	First cycle and previous successful cycle	Not included	Yes	Not mentioned	Good
Komori 2004	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Good
Lukassen 2005	< 35 years (mean age 30 to 31)	Not stated	First IVF/ICSI cycle or after previous successful cycle .	Not included	Yes	FSH < 10IU/L.	Good
Martikainen 2001	various, no age criteria, ranged between 22 to 40 years (mean age 31)	Not stated	women who had / not had more than 1 previous failed treatment.	Frozen cycles included	Yes, but not mentioned	Not mentioned	good
Mostajeran 2006	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Good
Thurin 2004	< 36 years (mean age 31)	0 to 12 years	First or second IVF cycle	Frozen cycles included	Yes	Not mentioned	Good, blastocysts included
Thurin 2005 Unpublished trial, pilot study, part of a thesis	≥ 36 years	0 to 12 years	First or second IVF/ICSI cycle	Frozen cycles included	Yes	Not mentioned	At least 2 good-quality embryos available

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Table 1. Prognostic factors in included studies *(Continued)*

van Montfoort 2006	Various ages, no criteria (mean age 33)	SET- 3.3 ± 1.8, DET- 3.3 ± 2.1 years	First IVF cycle	Not included	Yes	Not mentioned	Good
Vauthier-Brouzes 1994	≤ 35 years	Not mentioned	First or previous successful cycle	Frozen cycles included	Yes	Not mentioned	good
ASSETT 2003 unpublished trial	Female age < 35 if no previous ART pregnancy, < 40 if previous ART pregnancy.	Not mentioned	First or previous successful cycle	Frozen cycles included	Yes	Not mentioned	At least 4 good-quality embryos or at least 3 if previous ART pregnancy successful
ECOSSE 2006 unpublished trial	≤ 37 years	Not mentioned	First or second cycle of treatment	Frozen cycles included	Yes	Not mentioned	4 or more good quality embryos available at the time of embryo transfer
Abuzeid 2017	< 35 years	SET - 2.6 ± 1.6 years DET - 3.2 ± 2.4 years	No more than 1 previous ART failure	Frozen cycles performed but not included in the analysis	Yes	Mentioned	At least 2 good-quality blastocysts were available,
Clua 2015	oocyte donor recipients aged 18-50 years	not mentioned	Undergoing first or second synchronised oocyte donation cycle	Frozen cycles performed but not included in the analysis	Not mentioned	Not mentioned	Minimum of 5 embryos with at least 2 good-quality embryos on day 3 after oocyte retrieval
López-Regalado 2014b	< 38 years	SET - 3.1 ± 1.1 DET - 3.1 ± 1.0	First or second cycle with previous attempt with positive pregnancy test	Frozen cycles included	Not mentioned	Not mentioned	good

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APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register search strategy

PROCITE platform

Searched 16 March 2020

Keywords CONTAINS "Number of blastocysts" or "number of blastocysts transferred" or "number of embryos" or "number of embryos transferred" or "triple embryos transfer" or "single blastocyst transfer" or "single embryo transfer" or "single vs multiple" or "single vs multiple transfer" or "double embryo transfer" or "triple embryos transfer" or "three embryos transfer" or "SET" or "two embryos" or Title CONTAINS "Number of blastocysts" or "number of blastocysts transferred" or "number of embryos" or "number of embryos transferred" or "triple embryos transfer" or "single blastocyst transfer" or "single embryo transfer" or "single vs multiple" or "single vs multiple transfer" or "double embryo transfer" or "triple embryos transfer" or "three embryos transfer" or "SET" or "two embryos"
AND
Keywords CONTAINS "ivf" or "ICSI" or "subfertility" or Title CONTAINS "ivf" or "ICSI" or "subfertility"
(1250 records)

Appendix 2. CENTRAL Register of Studies Online (CRSO) search strategy

Web platform

Searched 16 March 2020

#1 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 1072
#2 (Embryo* adj5 Transfer*):TI,AB,KY 3969
#3 (blastocyst* adj5 Transfer*):TI,AB,KY 472
#4 #1 OR #2 OR #3 4087
#5 (one adj2 embryo*):TI,AB,KY 136
#6 (single adj2 embryo*):TI,AB,KY 295
#7 (single adj2 blastocyst*):TI,AB,KY 119
#8 (one adj2 blastocyst*):TI,AB,KY 32
#9 (two adj2 embryo*):TI,AB,KY 238
#10 (double adj2 embryo*):TI,AB,KY 224
#11 (double adj2 blastocyst*):TI,AB,KY 2
#12 (two adj2 blastocyst*):TI,AB,KY 46
#13 (three adj2 embryo*):TI,AB,KY 109
#14 (triple adj2 embryo*):TI,AB,KY 3
#15 (triple adj2 blastocyst*):TI,AB,KY 0
#16 (three adj2 blastocyst*):TI,AB,KY 3
#17 (multiple adj2 blastocyst*):TI,AB,KY 3
#18 (multiple adj2 embryo*):TI,AB,KY 41
#19 (SET or DET or TET):TI,AB,KY 26970
#20 (SBT or DBT or TBT):TI,AB,KY 756
#21 (four adj2 embryo*):TI,AB,KY 39
#22 (four adj2 blastocyst*):TI,AB,KY 1
#23 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 28576
#24 #4 AND #23 882

Appendix 3. MEDLINE search strategy

OVID platform

Searched from 1946 to 16 March 2020

1 Embryo Transfer/ (15557)
2 (Embryo$ adj5 Transfer$).tw. (18859)
3 (blastocyst$ adj5 transfer$).tw. (2479)
4 exp embryo, mammalian/ or exp blastocyst/ (93114)
5 or/1-4 (112678)
6 (two adj2 embryo$).tw. (3566)
7 (double adj2 embryo$).tw. (643)
8 DET.tw. (1117)
9 (three adj2 embryo$).tw. (1944)

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10 (triple adj2 embryo$).tw. (45)
11 TET$.tw. (450651)
12 (two adj2 blastocyst$).tw. (273)
13 (double adj2 blastocyst$).tw. (34)
14 (three adj2 blastocyst$).tw. (122)
15 (triple adj2 blastocyst$).tw. (4)
16 DBT.tw. (2494)
17 TBT.tw. (1746)
18 (one adj2 embryo$).tw. (2295)
19 (single adj2 embryo$).tw. (2109)
20 SET.tw. (510321)
21 (one adj2 blastocyst$).tw. (236)
22 (single adj2 blastocyst$).tw. (388)
23 SBT.tw. (2058)
24 (four adj2 embryo$).tw. (962)
25 (four adj2 blastocyst$).tw. (80)
26 FET.tw. (3167)
27 FZET.tw. (0)
28 (multiple$ adj2 embryo$).tw. (727)
29 (multiple$ adj2 blastocyst$).tw. (22)
30 (quadruple adj2 embryo$).tw. (5)
31 (quadruple adj2 blastocyst$).tw. (1)
32 or/6-31 (972810)
33 5 and 32 (9191)
34 randomized controlled trial.pt. (501858)
35 controlled clinical trial.pt. (93575)
36 randomized.ab. (473201)
37 placebo.tw. (211687)
38 clinical trials as topic.sh. (190393)
39 randomly.ab. (329293)
40 trial.ti. (215152)
41 (crossover or cross-over or cross over).tw. (83825)
42 or/34-41 (1305981)
43 exp animals/ not humans.sh. (4678649)
44 42 not 43 (1200138)
45 33 and 44 (479)

Appendix 4. Embase search strategy

OVID platform

Searched from 1980 to 16 March 2020

1 Embryo Transfer/ (29832)
2 (Embryo$ adj5 Transfer$).tw. (29099)
3 (blastocyst$ adj5 transfer$).tw. (4752)
4 exp embryo, mammalian/ or exp blastocyst/ (28866)
5 or/1-4 (59994)
6 (two adj2 embryo$).tw. (4269)
7 (double adj2 embryo$).tw. (999)
8 DET.tw. (1537)
9 (three adj2 embryo$).tw. (2348)
10 (triple adj2 embryo$).tw. (65)
11 TET$.tw. (473237)
12 (two adj2 blastocyst$).tw. (406)
13 (double adj2 blastocyst$).tw. (102)
14 (three adj2 blastocyst$).tw. (161)
15 (triple adj2 blastocyst$).tw. (5)
16 DBT.tw. (3402)
17 TBT.tw. (2248)
18 (one adj2 embryo$).tw. (3129)
19 (single adj2 embryo$).tw. (3734)
20 SET.tw. (649215)

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21 (one adj2 blastocyst$).tw. (410)
22 (single adj2 blastocyst$).tw. (896)
23 SBT.tw. (3782)
24 (four adj2 embryo$).tw. (1078)
25 (four adj2 blastocyst$).tw. (105)
26 FET.tw. (4510)
27 FZET.tw. (0)
28 (multiple$ adj2 embryo$).tw. (1063)
29 (multiple$ adj2 blastocyst$).tw. (46)
30 (quadruple adj2 embryo$).tw. (7)
31 (quadruple adj2 blastocyst$).tw. (1)
32 or/6-31 (1140425)
33 5 and 32 (11074)
34 Clinical trial/ (956829)
35 Randomized controlled trials/ (175321)
36 Random Allocation/ (82227)
37 Single-Blind Method/ (36164)
38 Double-Blind Method/ (142855)
39 Cross-Over Studies/ (50639)
40 Placebos/ (277114)
41 Randomi?ed controlled trial$.tw. (222841)
42 RCT.tw. (36001)
43 Random allocation.tw. (1981)
44 Randomly allocated.tw. (34385)
45 Allocated randomly.tw. (2509)
46 (allocated adj2 random).tw. (810)
47 Single blind$.tw. (24170)
48 Double blind$.tw. (199664)
49 ((treble or triple) adj blind$).tw. (1107)
50 Placebo$.tw. (298020)
51 Prospective Studies/ (480306)
52 or/34-51 (2020914)
53 Case study/ (67370)
54 Case report.tw. (394310)
55 Abstract report/ or letter/ (1084934)
56 or/53-55 (1536415)
57 52 not 56 (1964442)
58 animal/ (1323785)
59 human/ (20095580)
60 58 not 59 (958622)
61 57 not 60 (1932644)
62 33 and 61 (1211)

Appendix 5. PsycINFO search strategy

OVID platform

Searched from 1806 to 16 March 2020

1 exp Infertility/ or exp Reproductive Technology/ (3474)
2 (Embryo$ adj5 Transfer$).tw. (175)
3 (blastocyst$ adj5 transfer$).tw. (6)
4 or/1-3 (3551)
5 (two adj2 embryo$).tw. (41)
6 (double adj2 embryo$).tw. (16)
7 DET.tw. (166)
8 (three adj2 embryo$).tw. (15)
9 (triple adj2 embryo$).tw. (0)
10 (two adj2 blastocyst$).tw. (0)
11 (three adj2 blastocyst$).tw. (0)
12 (one adj2 embryo$).tw. (34)
13 (single adj2 embryo$).tw. (30)
14 (four adj2 embryo$).tw. (9)

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15 or/5-14 (300)
16 4 and 15 (24)

Appendix 6. CINAHL search strategy

EBSCO platform

Searched from 1961 to 16 March 2020

S47 S23 AND S46 219
S46 S45 NOT S44 634,392
S45 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 663,188
S44 S42 NOT S43 168,310
S43 MH (human) 2,045,086
S42 S39 OR S40 OR S41 191,371
S41 TI (animal model*) 2,899
S40 MH (animal studies) 111,330
S39 MH animals+ 87,856
S38 AB (cluster W3 RCT) 327
S37 MH (crossover design) OR MH (comparative studies) 259,647
S36 AB (control W5 group) 100,230
S35 PT (randomized controlled trial) 87,859
S34 MH (placebos) 11,654
S33 MH (sample size) AND AB (assigned OR allocated OR control) 3,787
S32 TI (trial) 100,205
S31 AB (random*) 284,114
S30 TI (randomised OR randomized) 98,224
S29 MH cluster sample 4,074
S28 MH pretest-posttest design 39,788
S27 MH random assignment 57,798
S26 MH single-blind studies 13,185
S25 MH double-blind studies 43,656
S24 MH randomized controlled trials 91,194
S23 S4 AND S22 873
S22 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 3,454
S21 TX TBT or TX DBT 796
S20 TX TET or TX DET 1,244
S19 TX (single N2 embryo*) 453
S18 TX (single N2 blastocyst*) 114
S17 TX (one N2 blastocyst*) 39
S16 TX (double N2 blastocyst*) 4
S15 TX (two N2 blastocyst*) 29
S14 TX (three N2 blastocyst*) 22
S13 TX (four N2 blastocyst*) 13
S12 TX (multiple N2 blastocyst*) 3
S11 TX (multiple N2 embryo*) 170
S10 TX (four N2 embryo*) 102
S9 TX (triple N2 embryo*) 5
S8 TX (three N2 embryo*) 247
S7 TX (one N2 embryo*) 270
S6 TX (double N2 embryo*) 98
S5 TX (two N2 embryo*) 329
S4 S1 OR S2 OR S3 3,283
S3 TX (blastocyst* N5 Transfer*) 401
S2 TX (Embryo* N5 Transfer*) 3,191
S1 (MM "Embryo Transfer") 1,122

WHAT'S NEW

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Date	Event	Description
18 May 2020	New citation required but conclusions have not changed	The addition of 3 new trials added more strength to existing data but overall conclusions did not change.
18 May 2020	New search has been performed	The review was updated in March 2020. MSK lead a new team of authors including MM and RK. Previous author SB provided important inputs to the current update. Three new trials were added in this review: López-Regalado 2014b; Clua 2015; Abuzeid 2017. We have presented the results and conclusions as per latest Cochrane editorial guidelines.Risk of bias for older studies changed. We used risk ratio instead of odds ratio for dichotomous outcomes and Peto odds ratio for outcomes that were associated with low event rates.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 4, 2004

Date	Event	Description
1 June 2014	Amended	Analyses of single embryo transfer versus double embryo transfer changed so that single embryo transfer is now regarded as the intervention and double embryo transfer as the control, in order to make the nature of the comparison more clinically appropriate. Text and summary of findings table edited accordingly. Errors in display of some of tables of analysis corrected in order to show OR consistently. Assessed as up to date and Search dates corrected.
25 July 2013	New search has been performed	The search was updated to July 2013 Comparisons of different numbers of blastocysts were added (previously only cleavage-stage embryo comparisons were included) Seven extra completed studies were included (ASSETT 2003, Gardner 2004, Komori 2004, Thurin 2005, ECOSSE 2006, Mostajeran 2006, Manuel-Fernandez 2012) The structure of the table of comparisons was reformatted
25 July 2013	New citation required but conclusions have not changed	No change to conclusions
29 August 2011	New search has been performed	Review updated Aug 2011. Objective- wording has been changed Three unplished trials (ASSETT 2003; Thurin 2005; ECOSSE 2006) have been added to comparison 1 Comparison 2 has been changed to DET vs SET (2 or more cycles), the sub comparisons now include DET vs 2 fresh SET, DET vs SET plus 1FZET, DET plus FZET vs SET +FZET and has additional data from 2 unpublished trials. The original Comparison 3 from previous review has therefore been deleted and included in

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Date	Event	Description
		comparison 2. Comparison 5 from previous review has also been deleted and added to comparison 4 of the updated review. This updated review will have 3 comparisons.
8 May 2008	New search has been performed	A new literature search was performed on 30/03/2008 by two reviewers independently (ZP, OO). Five new trials were identified using the Cochrane search strategy for identifying new trials.Search redesigned and run March 2008. Three new trials were added to the review. One trial (Thurin 2004) included blastocyst transfers. Blastocyst transfers were excluded from the data analysed. Two trials (Thurin2004 and van Montfoort 2006) compared one embryo transfer versus two embryo transfer. One trial (Thurin 2004) also compared one embryo transfer followed by a frozen-thawed single embryo transfer versus two embryo transfer. Livebirth rates from Van Montfoort 2006 study was derived from another publication from the same study and appears as van Montfoort* 2006 in the review and references. A single trial (Heijnen 2006) compared two embryo transfer versus three embryo transfer. The trial also determined the cumulative effect of multiple transfers of two and three embryos. A trial included in the original review (Lukassen 2002) that compared single embryo transfer versus double embryo was updated and published in 2005. This review has also been updated with this trial. Two trials (Komori 2004; Mostajeran 2006) that compared three embryo transfer versus two embryo transfer were identified with the new literature search but were excluded as the method of randomisation was unclear in both trials. The review has been converted into the new Rev man 5 format. The order of appearance of the comparisons have been changed. Two additional tables (1, 2) has been added.
8 May 2008	Amended	Converted to new review format.
12 June 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Mohan S Kamath: checked the updated literature search, study selection, data extraction, quality assessment, entered and checked data, completed the 'Risk of bias' tables and wrote the first draft of the review.

Mariano Mascarenhas: checked the updated literature search, study selection, data extraction, checked data and checked the draft.

Richard Kirubakaran: study selection, data extraction and data synthesis, 'Risk of bias' tables.

Siladitya Bhattacharya: study selection, quality assessment, responsible for final draft of the review.

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DECLARATIONS OF INTEREST

MSK, MM, RK and SB have no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics & Gynaecology, University of Aberdeen, UK
- Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India, Other

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The structure of the comparisons was reformatted to prioritise comparisons of repeat single embryo transfer. Live birth and cumulative live birth rates were amalgamated as a single primary outcome.

Studies of blastocyst transfer were added (previously only cleavage-stage transfers included).

At the 2020 update:

We planned subgroup analysis for the following prognostic factor: cleavage stage versus blastocyst stage transfer.

Sensitivity analysis: for the previous update, the planned sensitivity analysis restricted to studies at lower risk of bias (i.e. with clearly reported methods of randomisation and allocation concealment and not at high risk of bias in any of the domains assessed); for the current update, eligibility for lower risk of bias was restricted to studies without high or unclear risk of bias in any domain;

Risk of bias: in previous update, open label trials were categorised as unclear risk of bias for performance bias. For the current update, we categorised studies at high risk of performance bias for lack of blinding. Awareness of group allotment is likely to influence clinicians behaviour and performance; however, for detection bias we categorised them at low risk of bias since the outcomes were objective in nature.

Measurement of treatment effect: we used risk ratio instead of odds ratio for dichotomous outcomes as it is more intuitive and easier to understand. However, we used Peto odds ratio for dichotomous outcomes that were associated with low events rate.

We have added two more clinical outcomes in the 'Summary of findings' tables (clinical pregnancy and miscarriage rates) for the current update.

INDEX TERMS

Medical Subject Headings (MeSH)

Blastocyst; Cleavage Stage, Ovum [transplantation]; Embryo Transfer [*adverse effects] [*methods]; *Fertilization in Vitro; *Pregnancy Rate; Pregnancy, Multiple; Randomized Controlled Trials as Topic; Sperm Injections, Intracytoplasmic

MeSH check words

Female; Humans; Pregnancy

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