Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials


CRD summary
This individual patient data meta-analysis concluded that there was a lower pregnancy rate with elective fresh single embryo transfer compared to double transfer; this difference was overcome by an additional frozen single embryo transfer cycle. The multiple pregnancy rate following single embryo transfer was comparable to that in spontaneous pregnancies. The authors' conclusions are likely to be reliable.

Authors' objectives
To assess the effectiveness of elective single embryo transfer compared with double embryo transfer on live birth, multiple live birth, miscarriage and perinatal outcomes following fresh embryo transfer and on the outcomes of cumulative live birth and multiple live birth following fresh and frozen embryo transfer.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to 2008 without language restrictions. Several trial registers and bibliographies of relevant studies and reviews were searched. Experts were contacted to identify further studies.

Study selection
Randomised controlled trials (RCTs) that compared elective single to double cleavage stage embryo transfer after fresh or frozen in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) were included. Studies were required to have similar protocols for all aspects of the intervention except the number of embryos transferred. Only women who used their own oocytes were included. Primary outcomes of interest were live births and multiple live births after the initial embryo transfer and cumulative multiple live births after fresh and frozen embryo transfers that accrued from a single oocyte retrieval.

All the included studies compared one fresh cycle of single embryo transfer to one fresh double transfer cycle. In addition, two trials compared a fresh elective single transfer followed by a single frozen embryo transfer to a fresh double embryo transfer. Most trials included women with good prognoses (younger women receiving their first or second IVF treatment cycle with good quality embryos). Inclusion criteria for age varied among the studies. There was some variation in the treatment protocols used.

The authors did not state how many researchers were involved in the selection of studies.

Assessment of study quality
Individual patient data were obtained from all the trials included in the review. Standard range and internal consistency checks were used to assess the accuracy of the data and the original trialists were contacted to resolve any data queries.

Studies were assessed for adequacy of randomisation (sequence generation and allocation concealment), baseline comparability of groups, use of blinding and intention-to-treat analysis, completeness of follow-up, a priori sample size estimation and generalisability. Authors were contacted where further clarification was required.

Data extraction
Individual patient data were obtained for the outcomes of interest to enable calculation of odds ratio (OR) and 95% confidence intervals (CI). With the exception of one characteristic, more than 95% of the data was complete.

Methods of synthesis
A one-stage meta-analysis of individual patient data was undertaken. A logistic model was used to compare single
versus double embryo transfer adjusted for trial and separately for several population and study characteristics: duration of infertility, primary cause of infertility, type of infertility, type of treatment (IVF or ICSI), the woman's age and body mass index, number of embryos available for transfer, day of transfer and quality of embryos transferred. Covariates with p<0.3 were included in a backward stepwise logistic regression model. All analyses were based on intention-to-treat data.

Statistical heterogeneity between trials was assessed using the $I^2$ statistic based on a meta-analysis of aggregate data. Heterogeneity was explored by excluding the relevant trials. Subgroup analyses were used to explore whether the effect of single versus double embryo transfer differed by woman's age (<33 versus ≥33), duration of fertility and embryo quality.

The possibility of publication bias was assessed using funnel plots and the Horbold-Egger test.

**Results of the review**

Eight RCTs were included (n=1,367). All used an adequate randomisation method, six explicitly described adequate allocation concealment and six used at least single blinding. For all studies there was at least 80% follow-up and groups were comparable at baseline. The results reported below are unadjusted unless otherwise stated.

**Primary outcomes**: The odds of a live birth were significantly lower in the single than in the double embryo transfer group (adjusted OR 0.50, 95% CI 0.39 to 0.63); live birth rate was 27% with single and 42% with double embryo transfer. The multiple live birth rate was significantly lower in the single than in the double embryo transfer group (OR 0.04, 95% CI 0.01 to 0.12); the rate was 2% with single and 29% with double embryo transfer. An additional frozen single embryo transfer following the initial fresh single embryo transfer (data available from two trials) resulted in a similar cumulative live birth rate to one fresh double embryo transfer (OR 0.85, 95% CI 0.62 to 1.15); the rate was 38% in the consecutive single embryo transfer group and 42% with double embryo transfer. The cumulative risk of multiple live birth was minimal. The woman's age, duration of fertility and embryo quality did not alter the results for live and multiple live births.

**Perinatal outcomes**: There was a significantly reduced odds of delivering at least one low birth weight baby (<2,500g) (OR 0.26, 95% CI 0.14 to 0.48) with single embryo transfer compared to double transfer; a reduced odds of preterm birth with single embryo transfer at ≤37 weeks (OR 0.33, 95% CI 0.20 to 0.55) as well as at ≤34 and ≤32 weeks and a greater odds of a term singleton birth (>37 weeks) after single embryo transfer compared to double embryo transfer (OR 4.93, 95% CI 2.98 to 8.18).

There was no evidence of significant between trial-heterogeneity or publication bias, based on live birth and multiple live birth outcomes.

**Authors’ conclusions**

There was a higher chance of delivering a term singleton live birth following elective single fresh embryo transfer compared to double embryo transfer. There was a lower pregnancy rate with single embryo transfer compared to double transfer; this difference is almost completely overcome by an additional frozen single embryo transfer cycle. After elective single embryo transfer the multiple pregnancy rate was comparable to that observed in spontaneous pregnancies.

**CRD commentary**

This was a well-conducted individual patient data meta-analysis. Use of individual patient data had the benefit of allowing checking of the original data, standardised outcomes and subgroups, use of intention-to-treat data and consistent analysis across trials. It is considered superior to meta-analysis of aggregate data. A number of appropriate sources were searched without language restrictions for published and unpublished data; it was unclear how many researchers were involved in study selection. Individual patient data were available for all the included studies. The analysis seemed appropriate. Clinical and statistical heterogeneity were investigated.

The authors' conclusions are likely to be reliable. They highlighted that the results may not be generalisable beyond women with "good prognoses" (such as those in the included studies) and cleavage stage embryo transfer.
Implications of the review for practice and research

**Practice:** The authors stated that elective single embryo transfer should be the default position where there is the opportunity for undertaking a single frozen embryo transfer in a subsequent cycle to an elective fresh single embryo transfer.

**Research:** The authors stated that future trials comparing elective single and double embryo transfer should focus on women with different prognostic profiles, such as older women. National databases should be examined to identify which women and embryos could benefit from a policy of single transfer.

**Funding**
Wellcome Trust.

**Bibliographic details**

**PubMedID**
21177530

**DOI**
10.1136/bmj.c6945

**Original Paper URL**
http://www.bmj.com/content/341/bmj.c6945.abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Abortion, Spontaneous; Adult; Embryo Transfer /methods; Female; Fertilization in Vitro; Humans; Live Birth; Maternal Age; Pregnancy; Pregnancy Rate; Pregnancy, Multiple /statistics & numerical data; Randomized Controlled Trials as Topic

**AccessionNumber**
12011000230

**Date bibliographic record published**
12/01/2011

**Date abstract record published**
19/01/2011

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.