Single or multiple embryo transfer following in vitro fertilisation for improved neonatal outcome: a systematic review of the literature
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CRD summary
This review concluded that transferring one embryo during in vitro fertilisation does not alter the likelihood of a singleton pregnancy or birth compared with transferring two or more embryos, whilst transferring one or two embryos decreases the risk of a multiple pregnancy, pre-term birth and low birth weight. Given the variation and poor design and quality of the studies, the authors' conclusions may not be reliable.

Authors' objectives
To establish whether single versus two or more embryos, or double versus three or more embryos, transferred during in vitro fertilisation (IVF) maximises the likelihood of pregnancy, while minimising the likelihood of multiple pregnancy and adverse sequelae.

Searching
The Cochrane Controlled Trials Register, PubMed, MEDLINE, Current Contents and ACP Journal Club were searched up to 10 July 2003; the search terms were reported. In addition, citation lists of relevant publications, review articles and included studies were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), quasi-randomised trials and cohort studies were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing different IVF protocols (transferring one embryo compared with two or more embryos, or two embryos with three or more) were eligible for inclusion. IVF was defined as the transfer of fresh embryos to the uterus or fallopian tubes, transfer of frozen or thawed embryos, use of donor oocytes and intracytoplasmic sperm injection (ICSI). Studies of gamete intrafallopian transfer were excluded.

Participants included in the review
Studies including women who had received IVF treatment because the couple had proven infertile (with the origin of infertility being female or male) were eligible for inclusion. The infertility may also have arisen from immunological conditions where either partner was unresponsive to conventional treatment.

Outcomes assessed in the review
A range of outcome measures were eligible for inclusion. The primary outcome measures were live birth of a healthy baby at term (at least 37 weeks' gestation), normal birth weight for gestational age, normal childhood development at 2 years, and the costs of care. The secondary outcomes included a range of pregnancy, infant, maternal and health service outcomes.

How were decisions on the relevance of primary studies made?
Three reviewers selected studies for inclusion in the review, with any disagreements resolved by consensus.

Assessment of study quality
The included trials were allocated a quality score on the basis of allocation concealment, completeness of follow-up and blinding of the outcome assessment. The authors did not state how many reviewers performed the validity assessment.
Data extraction

Three authors extracted data from the included studies using predefined methods. Dichotomous outcomes were reported as relative risks (RRs) with 95% confidence intervals (CIs).

Methods of synthesis

How were the studies combined?
Studies with dichotomous data were combined in a random-effects meta-analysis and pooled RRs with 95% CIs were reported.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. The studies were grouped according to study design and the number of embryos transferred. Sensitivity analyses were used to assess the effects of maternal age, quality of the embryos, type of infertility and study design, where relevant.

Results of the review

Twenty studies (number of participants unclear) were included in the review: 3 RCTs and 17 cohort studies.

RCTs.

When one embryo was transferred, compared with two, fewer women had a clinical pregnancy (RR 0.69, 95% CI: 0.51, 0.93). However, the risk of twin or multiple pregnancy (RR 0.12, 95% CI: 0.03, 0.48) and low birth weight (RR 0.17; 95% CI: 0.04, 0.79) was reduced. When two rather than four embryos were transferred (in a single RCT), no differences on any of the reported outcomes were found.

Cohort studies comparing single embryo transfer with the transfer of two or more embryos.

Single embryo transfer was associated with lower rates of clinical pregnancy (7 studies; RR 0.17, 95% CI: 0.43, 0.90), multiple pregnancy (8 studies; RR 0.03, 95% CI: 0.01, 0.09) and multiple birth (2 studies; RR 0.02, 95% CI: 0.00, 0.13), twin pregnancy (7 studies; RR 0.03, 95% CI: 0.01, 0.09) and twin birth (2 studies; RR 0.02, 95% CI: 0.00, 0.15). One study reported a reduced incidence in low birth weight for SET compared with double embryo transfer (RR 0.22, 95% CI: 0.08, 0.57).

Cohort studies comparing double embryo transfer with the transfer of three or more embryos.

Double embryo transfer was associated with a lower incidence of live birth at term of a healthy baby (6 studies; RR 0.84, 95% CI: 0.74, 0.96, p=0.011), clinical pregnancy (8 studies; RR 0.82, 95% CI: 0.71, 0.94), multiple pregnancy (8 studies; RR 0.59, 95% CI: 0.41, 0.85, p=0.044) and multiple birth (4 studies; RR 0.46, 95% CI: 0.31, 0.69, p=0.021), twin birth (4 studies; RR 0.58, 95% CI: 0.40, 0.83), triplet or higher order pregnancy (4 studies; RR 0.11, 95% CI: 0.03, 0.47), and triplet or higher order birth (5 studies; RR 0.07, 95% CI: 0.04, 0.12). One study reported a lower risk of pre-term birth (<37 weeks) (RR 0.41, 95% CI: 0.21, 0.79), while another reported a reduced incidence in low birth weight for double embryo transfer compared with the transfer of three or more embryos (RR 0.48, 95% CI: 0.29, 0.79).

Authors’ conclusions

Information on neonatal and maternal outcomes was limited. The transfer of one embryo did not affect the likelihood of a singleton pregnancy or birth compared with the transfer of two or more embryos. The transfer of one or two embryos decreased the risk of a multiple pregnancy, pre-term birth and low birth weight.

CRD commentary

The review question was supported by appropriate inclusion criteria relating to the participants, interventions, study designs and outcomes. A search of multiple electronic databases and supplementary sources was undertaken, although it was unclear whether this search was limited to publications in English or not. Multiple reviewers were involved in selecting studies for inclusion, but similar processes to minimise error and bias at the validity assessment stage were not
reported.

Very few details of the individual studies in the review were available, so it was not possible to establish the relevance of the included studies and the extent of variation in their clinical characteristics. Consequently, although the authors' conclusion about the limited high-quality evidence on neonatal and maternal outcomes appears appropriate, it is difficult to assess the reliability of their other conclusions.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that further large, well-designed randomised trials are required to provide long-term maternal and neonatal outcomes of relevance to a couple undergoing IVF.

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