

# The likelihood of live birth and multiple birth after single versus double embryo transfer at the cleavage stage: a systematic review and meta-analysis

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**Objective:** To determine whether a policy of elective single-embryo transfer (e-SET) lowers the multiple birth rate without compromising the live birth rate.

**Design:** Systematic review and meta-analysis.

**Setting:** Tertiary referral center for reproductive medicine and IVF unit.

**Patient(s):** None.

**Intervention(s):** Searches of the Cochrane Controlled Trials Register, Meta-register for Randomized Controlled Trials (RCTs), EMBASE, MEDLINE, and SCISEARCH with no limitation on language and publication year, 1974 to 2008. Selection criteria: randomized, controlled trials comparing e-SET with double-embryo transfer (DET) for live birth and multiple birth rates after in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI). Nonrandomized trials and studies that included only patients who had blastocyst transfer were excluded.

**Main Outcome Measure(s):** The likelihood of live birth per patient and multiple birth per total number of live births. Other outcomes included implantation rate, pregnancy rate, miscarriage and ectopic pregnancy rates, clinical pregnancy rate, ongoing pregnancy rate per patient, and preterm delivery rate per live birth.

**Result(s):** Six trials (n = 1354 patients) were included in the meta-analysis. Compared with DET, the e-SET policy was associated with a statistically significant reduction in the probability of live birth (RR 0.62; 95% CI, 0.53–0.72) and multiple birth (RR 0.06; 95% CI, 0.02–0.18).

**Conclusion(s):** Elective-SET of embryos at the cleavage stage reduces the likelihood of live birth by 38% and multiple birth by 94%. Evidence from randomized, controlled trials suggests that increasing the number of e-SET attempts (fresh and/or frozen) results in a cumulative live birth rate similar to that of DET. Offering subfertile women three cycles of IVF will have a major impact on the uptake of an e-SET policy. (Fertil Steril® 2010;94:936–45. ©2010 by American Society for Reproductive Medicine.)

**Key Words:** Double embryo replacement, double embryo transfer, IVF, live birth, multiple birth, single embryo replacement, single embryo transfer

The transfer of two embryos after in vitro fertilization (IVF) leads to a high probability of multiple pregnancy, mainly dizygotic twins (1). Multiple birth is the single biggest risk to the health and welfare of children born after IVF. There is no doubt that twin pregnancies are associated with a significantly higher risk of complications for both the mother and the child (2, 3). The main risk to the fetus is prematurity, which is responsible for the high perinatal mortality and morbidity as well as the increased incidence of long-term neurologic complications (3–5). The considerable emotional impact of the adverse effects of prematurity is also an issue for the parents. Henceforth, it is of paramount importance to identify possible ways of preventing this iatrogenic yet serious complication of IVF.

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A policy of elective single-embryo transfer (e-SET) is a logical approach to reduce the incidence of multiple birth after IVF, particularly in young women with good prognosis. In the past few years, different strategies have been proposed to implement a policy of e-SET without compromising the overall pregnancy and live birth rates. The principle of any balanced strategy is based on selecting the best quality embryo for transfer and freezing any surplus embryos to be used in subsequent treatment cycles. Although the number of attempts needed to achieve equivalent live birth rates is higher in women who have only one embryo transferred, the marked decrease in twin pregnancy makes e-SET a safer, more desirable and cost-effective option (6). Moreover, the increasing use of the less costly, milder treatment protocols allows for more IVF treatment cycles to be performed during the same period of time, thus achieving a similar cumulative live birth rate (7).

Although fewer embryos per cycle were transferred by clinicians in Europe in 2004, the pregnancy rates gradually but consistently increased, and the twin birth declined to 21.7% of all deliveries after IVF and intracytoplasmic sperm

injection (ICSI) (1). Similar trends have been witnessed in the United States, where the twin pregnancy rates decreased from 24.3% in 2004 to 20.3% in 2006 (8). The latter data are indeed interesting and lend to speculation on the value of practice guidelines and the introduction of single blastocyst transfer in assisted conception clinics in the two continents, where practices vary slightly.

A previous Cochrane review of four randomized, controlled trials (RCTs) concluded that e-SET statistically significantly reduces the risk of multiple pregnancies but also decreases the chance of live birth in a fresh IVF cycle (9). In light of data from more recent publications and the growing public interest in this subject, our aim was to perform an updated systematic review and meta-analysis to determine the effect of e-SET on the likelihood of live birth and multiple birth in IVF.

## MATERIALS AND METHODS

### Search Strategy

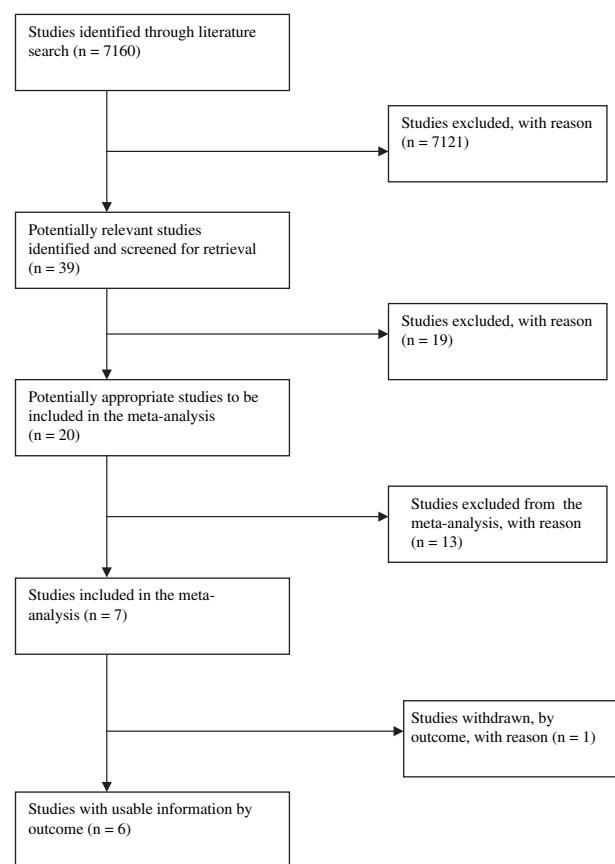
We searched the MEDLINE, EMBASE, and SCISEARCH databases for relevant studies published between January 1974 and September 2008. The search strategy used terms such as “single or one embryo transfer or replacement,” “double or two embryo transfer or replacement,” “twin or multiple pregnancy,” “IVF,” and “ICSI.” We also searched the Cochrane Library, the Intercollegiate Study Institute (ISI) Proceedings for conference abstracts, the International Standard Randomized Controlled Trial Number (ISRCTN) Register, and the Meta-register for Randomized Controlled Trials (mRCT) for ongoing and archived trials and used the same key words. The references of retrieved articles together with the proceedings of relevant conferences were hand-searched to identify other potentially eligible studies for inclusion in the analysis that had been missed by the initial search or any unpublished data. Articles frequently cited were used in the Science Citation Index to identify additional citations. The literature search was independently undertaken and verified by two investigators (TAG and IT). Institutional review board approval was not required according to the design of the analysis.

### Selection Criteria

Criteria for inclusion/exclusion of the studies were established before the literature search. All RCTs that evaluated the effects of e-SET versus double-embryo transfer (DET) on pregnancy or live birth rate and on multiple birth rate in women undergoing IVF with or without ICSI were included in the current systematic review and meta-analysis, irrespective of the type of protocol used, the type of gonadotropins used for ovarian stimulation, or the type and dose of luteal phase support. We excluded nonrandomized studies, those that included only women who had blastocyst transfer, and those that compared single blastocyst to double early cleavage embryo transfer. There was no language restriction.

**FIGURE 1**

### Quality of Reporting of Meta-analyses (QUOROM) statement flowchart.



Gelbaya. IVF outcomes after e-SET or DET. *Fertil Steril* 2010.

### Data Extraction and Quality Assessment

Data extraction was performed independently by two investigators (TAG and IT). Descriptive tables for population and study characteristics for all eligible studies were generated. For each eligible study, the first author, publication year, journal title, sample size, characteristics of study and control groups, type of interventions, ovarian stimulation protocol, and all relevant outcomes were recorded. The quality of the studies was assessed with respect to allocation concealment, blinding, and intention to treat analysis. Where appropriate, the investigators were contacted in an attempt to obtain missing and/or additional data.

### Outcomes

The main outcome measures were the live birth rate per patient and the multiple birth rate per total number of live births. Other outcome measures included implantation rate, pregnancy rate, miscarriage and ectopic pregnancy rates, clinical pregnancy rate, ongoing pregnancy rate per patient, and pre-term delivery rate per live birth.

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