

Elective single-embryo transfer

Practice Committee of the Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine

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As in vitro fertilization implantation rates have improved, the practice of transferring multiple embryos must be evaluated. The purpose of this document is to reassess the literature on elective single-embryo transfer, to provide guidance for patient selection, and to discuss barriers to utilization. (Fertil Steril® 2012;97:835–42. ©2012 by American Society for Reproductive Medicine.)

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Numerous publications have investigated the practice of elective single-embryo transfer (eSET) (1–27). Single-embryo transfer after in vitro fertilization (IVF) has been advocated as the only effective means to avoid multiple pregnancy in IVF cycles (28). Elective SET is defined as the transfer of a single embryo at either the cleavage or blastocyst stage of embryo development that is selected from a larger number of available embryos. It is defined in the Society for Assisted Reproductive Technologies (SART) reporting guidelines as “an embryo transfer in which more than one high-quality embryo exists but it was decided to transfer only one embryo.”

Historically, to compensate for low rates of implantation for individual embryos and achieve “acceptable” pregnancy rates, multiple embryos have been transferred to the majority of IVF patients. Consequently, IVF carries a high risk of multiple pregnancy and its associated adverse effects on mothers and children, as detailed in the ASRM Practice Committee Document titled, *Multiple gestation associated with infertility therapy* (29). However, as implantation rates (IRs) have improved, the practice of transferring multiple embryos must be reassessed. There are many issues that

must be addressed in order to maximize the efficacy of eSET and improve its acceptability and utilization among clinicians and patients.

APPLICATION OF ESET

In 2000, more than two-thirds of all IVF transfer procedures in the United States were of three or more embryos. Practice guidelines from SART and the American Society for Reproductive Medicine (ASRM) recommending maximum numbers of embryos to transfer were first published in 1998 and have been periodically revised and adjusted downward as implantation rates improved, most recently in 2009 (30–32). With the release of these guidelines, the frequency of transfers of three or more embryos has declined steadily (Fig. 1) (33). In the 10-year period from 1999 to 2008, the proportion of transfers with three or more embryos declined from 70% to 39%, with transfers of four or more embryos declining by more than one-half from 36% to 14%. Before 2002, only 1% of transfers were eSET (33). Concomitant with evolving SART/ASRM guidelines, eSET rates among patients under 35 years of age increased by approximately 1%–2% each year since 2002, accounting for approximately 10% of all transfers to patients less than 35

years old in 2009. These trends have resulted in an increased number of double-embryo transfers (DETs), leading to a reduction in number of triplet gestation but an unchanged rate of twin gestation (Fig. 2) (32, 34–41).

Gradual increase in eSET rates over time is a general worldwide pattern, but the United States has lagged behind much of the rest of the world in adoption of eSET (42). Across Europe in 2005, 20% of all transfers were of single embryos. Rates vary considerably within Europe, with the highest reported eSET rates in Sweden (69%), followed by Finland (50%), Belgium (48%), Denmark (33%), and Slovenia (30%). High rates of eSET use in Australia and New Zealand (57% in 2006) and Japan (46% in 2007) also have been reported. A variety of factors contribute to international differences in eSET rates, including whether IVF coverage is mandated, patient populations, legislation, guideline recommendations, and culture.

EFFICACY OF ESET VERSUS DET

Randomized Controlled Trials

Studies evaluating efficacy of eSET and DET include trials of both cleavage-stage and blastocyst-stage embryos. Several randomized controlled trials (RCTs) have compared birth rates between transfers of one versus two embryos (6, 8, 14, 23, 43–45). The largest and best-controlled among these studies is a double-blinded multicenter trial among 11 clinics in Sweden that randomized 661 patients to either eSET or

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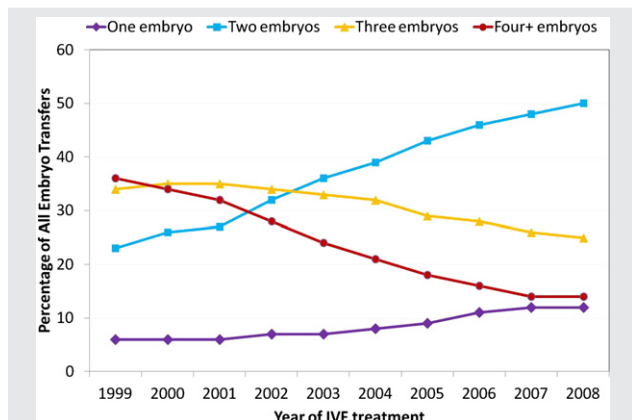
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FIGURE 1

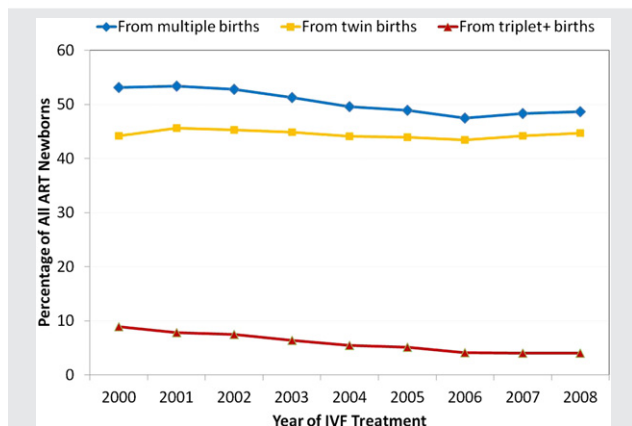


Proportions of transfers of one, two, three, or four or more embryos among all IVF cycles performed in the United States, 1999–2008.

Practice Committee. eSET. *Fertil Steril* 2012.

DET, 98% of them performed with cleavage-stage embryos (8). Eligibility requirements included age <36 years, first or second IVF cycle, and at least two good-quality embryos. Subjects randomized to the eSET group but not achieving a birth from their fresh cycle underwent a subsequent transfer of a single frozen-thawed embryo (FET). Thus the maximum possible number of embryos transferred to subjects was identical between treatment groups, with the only difference being whether they were both transferred at the same time while fresh or one at a time in two separate cycles (fresh then frozen, if necessary). Birth rates were significantly lower after fresh transfer of one versus two embryos (28% vs. 43%; risk ratio [RR] 0.64; $P < .001$). After factoring in the contribution of a single FET after unsuccessful fresh SET, the cumulative birth rates were not statistically different between the treatment groups (39% vs. 43%; RR 0.90; $P = .30$).

FIGURE 2



Proportions of all liveborn children resulting from assisted reproductive technologies in the United States that were members of multiple births.

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Three recent meta-analyses combining results from RCTs comparing cleavage-stage eSET and DET all reached similar conclusions. Birth rates after fresh eSET or DET were 26% and 43%, respectively; however, the effect of subsequent transfer of cryopreserved embryos was not included in the analyses, which therefore likely overestimated the benefit of DET (46–48).

In a study evaluating blastocyst transfer, patients were randomized to eSET or DET. The ongoing pregnancy rates for eSET versus DET were 61% versus 76% (RR 0.80; $P = \text{NS}$) (6).

Among the RCTs of cleavage-stage transfers, approximately 30% of all pregnancies and births resulting from DET were twins, whereas only 1%–2% of SET were multiples, arising from monozygotic twinning (8, 14, 23, 43–48). In the RCT of blastocyst transfer, the twin rate was 47% after DET and 0% after eSET (6).

Nonrandomized Trials

In addition to the randomized trials described above, several nonrandomized trials provide good comparisons of outcomes between eSET and DET at the cleavage and blastocyst stages. Collectively, these well controlled nonrandomized comparisons of eSET versus DET are consistent with and reinforce the conclusions of the RCTs (Table 1) (2, 9, 11, 24, 49).

Three of the nonrandomized trials compared cumulative live birth (LBR) or cumulative pregnancy (PR) rates including both fresh embryo transfers and subsequent FET. The FETs, however, were a combination of single- and double-embryo transfers, more commonly the latter. In all three studies, the cumulative outcomes were nearly identical for the eSET-FET and DET treatment groups: 43% versus 45% LBR (49), 65% versus 64% LBR (11), and 83% versus 83% PR (9). Thus both RCTs and these well controlled nonrandomized comparisons consistently demonstrate that when subsequent FET is factored in, cumulative PRs per oocyte retrieval are similar with eSET or DET.

Clinical Experience

Multiple reports of increased eSET utilization have confirmed the reduction of multiple gestation rate and maintenance of pregnancy and birth rates. One study evaluated the voluntary

TABLE 1

Summary of nonrandomized controlled trials.

Study	Gerris (2)	le Lannou (49)	Henman (11)	Criniti (9)	Stillman (24)
Embryo stage	CLV	CLV	Blast	Blast	Donor blast
SET IR (%)	35.1	27.6	45	76	63
SET PR (%)	35.1	27.6	45	76	63
DET IR (%)	36.5	23.8	42	66	59
DET PR (%)	50	37	57	79	71
Twin rate (%)	41	37	44	62	54

Note: Blast = blastocyst; CLV = cleavage; DET = double-embryo transfer; IR = implantation rate; PR = pregnancy rate; SET = single-embryo transfer.

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adoption of eSET over a 6-year period (3). Single-embryo transfer was recommended to patients <37 years old undergoing their first or second attempt if they had at least two good-quality embryos. Treatment outcomes were compared between 1997–1998 (when 1.5% of all transfers were eSET) and 1999–2002 (when 17% of all transfers were eSET). Despite the more than tenfold rise in the use of eSET, both IRs (18% vs. 18%) and clinical PRs (32% vs. 31%) were not statistically different between these two time periods, while the multiple gestation rate dropped significantly from 31% to 23%. Multiple subsequent studies have reproduced these findings (10, 16, 18, 22, 50, 51).

Cost-Effectiveness Analyses

The economic costs relating to the excess perinatal and maternal morbidity and mortality associated with multiple births resulting from assisted reproductive technologies (ART) are substantial and include both the immediate costs of maternal hospitalization and neonatal intensive care and the potential lifetime costs of care for chronic illness, rehabilitation, and special education. Whereas the immediate costs associated with multiple births can be estimated from hospital charges, the lifetime costs are more difficult to determine but have been estimated in several studies from Europe, Canada, and the United States. Compared with singleton pregnancy and birth, the known costs associated with twin pregnancy and their sequelae are increased fourfold, and for triplet pregnancy and birth by tenfold. In 2004, approximately 4% of all preterm births in the United States resulted from ART, with associated costs reaching \$1 billion (52, 53).

Published studies of the cost-effectiveness of eSET are limited to cost of treatment to achieve a pregnancy and do not account for postnatal and childhood costs. Not surprisingly, these studies report increased costs for eSET over DET for this end point (14, 54–57). For example, two independent studies from The Netherlands, conducted at around the same time, calculated costs per birth among patients randomized to either single- or double-embryo transfer (14, 54). In both studies, the observed LBRs for eSET were similar (23% and 21%) as were those for DET (36% and 40%). Both studies calculated financial costs over about the same time period (IVF treatment through 4 or 6 weeks, respectively, after delivery). One study (14) considered only direct medical costs and estimated very similar costs per delivery for eSET and DET (14). The other study considered indirect costs, such as loss of productivity (e.g., sick leave and maternity leave), and estimated costs per delivery to be higher for eSET compared with DET (54).

INDICATIONS FOR ESET

Elective SET is most beneficial when selectively applied according to patient characteristics and embryo quality. It is most appropriate for those with a good prognosis: age <35 years, more than one top-quality embryo available for transfer, first or second treatment cycle, previous successful IVF, and recipient of embryos from donated eggs.

Elective SET is most applicable to transfers of blastocyst-stage embryos, because these tend to have higher IRs than

those at the cleavage stage (58–60). However, even embryos transferred at the cleavage stage, if morphologically high quality (with 7 or 8 cells, no multinucleation, and minimal fragmentation), may implant at rates of 50% or more (61, 62). Transfer of even two embryos of this quality puts patients at high risk of multiple gestation.

Multiple gestation rates near 50% (6, 63) and in excess of 60% (9, 64) have been reported for transfers of two top-quality blastocysts. Triplet gestation rates of 2%–5% have been reported for transfers of two cleavage- or blastocyst-stage embryos (2, 24), demonstrating that with the transfer of two high-quality embryos there is also a small but significant risk of high-order multiple gestation. The monozygotic twin rate has been reported to be 2–5-fold higher for blastocyst- versus cleavage-stage transfers (65, 66).

Patients using donor oocytes have the best prognosis and are at highest risk for multiple gestation. Multiple gestation rates of 40% or more are typical for transfers of embryos derived from donated oocytes (24, 33, 38). Even with the transfer of only two cleavage-stage embryos derived from donor oocytes, multiple gestation rates near 40% can be expected (67), and multiple gestation rates may be greater than 50% with transfer of two blastocyst-stage embryos (24).

The risk of multiple gestation among women using their own oocytes declines with increasing age, but it still remains high for women through the age of 40 years. Multiple birth rates for transfers of two embryos to patients <35 years, 35–37 years, and 38–40 years were 40%, 33%, and 28%, respectively, when additional embryos were cryopreserved (35). Although the probability of multiple gestation is reduced among older IVF patients, the risks associated with carrying multiples increase with age. Although these patients are much less likely to produce embryos able to develop into high-quality blastocysts in vitro, those that do may achieve IRs and PRs similar to those of younger patients (68). Viable PRs of >50% have been reported for single-blastocyst transfers to patients aged 36–42 years (69) and 38–40 years (24).

The risks of multiples are reduced, yet still significant, with the transfer of cryopreserved embryos (35). Decisions regarding eSET of cryopreserved embryos should take into consideration prognosis, embryo quality, and success rates of the individual cryopreservation program.

OUTCOME ISSUES

Although cleavage-stage embryos and blastocysts can be transferred, more groups are utilizing transfer of blastocysts owing to higher success rates. Concerns have been raised—though unsubstantiated by any data—regarding the effects that longer durations of culture may have on the risks of epigenetic mutations in offspring resulting from ART (70–74), although other studies appear reassuring (75), particularly regarding the blastocyst stage (see ASRM Practice Committee document titled “Blastocyst culture and transfer in clinical-assisted reproduction”) (76). Furthermore, children born from blastocyst transfer may be at a slightly increased risk for adverse neonatal outcomes compared with children conceived naturally (odds ratio [OR] 1.53, 95% CI 1.23–1.90) (77). There appears to be less of risk in children

conceived following cleavage-stage transfer compared with natural conception: OR 1.11, 95% CI 1.02–1.21 (77). The clinical significance of any small increased risk with blastocyst transfer is unclear.

PROMOTING SET

Challenges to increased use of eSET exist. These include provider and patient education, financial considerations, embryo selection, and successful cryopreservation. Stakeholders should recognize that the optimal outcome of an IVF cycle is the birth of a healthy singleton.

One particular difficulty in promoting fresh eSET with FET one at a time in subsequent cycles is the way that IVF clinic data are reported in the United States. Pregnancy rates are reported per cycle initiated or per transfer and do not capture cumulative success rates of subsequent transfer of frozen embryos derived from the same cycle. Therefore, clinics promoting eSET may be at a disadvantage because they appear to have lower “success” rates than those utilizing DET, even though the total “success” rates are similar. Physicians and patients will require additional education to understand that the data now reported do not necessarily accurately reflect the likelihood of pregnancy. Changes in methods of IVF clinic data reporting may clarify this.

Physician/Staff Education

Clinicians are often reluctant to encourage SET for their patients because of concern that PRs will suffer as a result (78, 79). Providers at all levels of patient interaction would benefit from a knowledge of the literature demonstrating that high cumulative PRs can be maintained with eSET (and subsequent FET as appropriate) for selected patients. Familiarity with this information will encourage clinicians to be strong advocates of eSET when counseling their patients.

Clinicians have a professional and ethical obligation to optimize the chance of a singleton birth for prospective parents whose preferences and choices may be clouded by feelings of desperation to achieve a pregnancy.

Patient Education

Patient education is vital for accepting eSET and presents a particular challenge. Not only are patients understandably concerned about potential reductions in PRs with SET, but numerous studies have found that clear majorities of patients would actually prefer twin pregnancies over singleton pregnancies (80–84). Such attitudes may be due to misconceptions that underestimate the efficacy of eSET and of the risks and health consequences associated with multiple pregnancies.

Increased education has been shown to make eSET more acceptable (18, 85–87). In one study, patients’ preferences for twin pregnancy were reduced by one-half after education comparing risks to maternal, fetal, and neonatal health between singleton and twin pregnancies (18). Another study reported that after presentation of the associated risks, the desire for twin pregnancy declined significantly among both men and women, and eSET became the preferred option

(87). Use of written patient education materials that outlined the advantages of eSET and the risks of DET led to a tripling of eSET in 1 year (86).

A randomized trial demonstrated that a DVD was more effective than a written brochure presenting the same facts contrasting success rates and risks associated with eSET versus DET, with the DVD resulting in significantly better understanding of multiple pregnancy risks and stronger preference for eSET (88).

Reducing Financial Disincentives

Financial considerations may also motivate patients to desire transfer of multiple embryos. The prospect of limiting the high costs of multiple IVF treatment cycles may be a powerful incentive to transfer more than one embryo and risk multiple gestation (85). Again, patient education may play a crucial role in responding to this motivation by making patients aware that when the longer-term costs of carrying and delivering a multiple pregnancy are considered, transferring embryos one at a time may be a more cost-effective way of building a family than transferring multiple embryos at once.

Increased availability of insurance coverage for infertility treatment could also help to reduce financial disincentives to eSET, because insurance coverage would mitigate patients’ out-of-pocket costs for repeated treatment cycles. Increased availability of insurance coverage has been associated with fewer embryos per transfer and lower rates of multiple and high-order multiple gestations (24, 89–92). Patients opted for eSET over DET 50% more often when they had insurance coverage than when they did not (24).

Studies show that in the absence of insurance coverage for infertility treatment, financial disincentives to eSET can be reduced if IVF providers offer ethically rigorous refund guarantee programs in which patients only pay for treatment if the result is a live birth (93). Like insurance coverage, such “shared-risk” programs can mitigate the costs of repeated IVF cycles that may be needed to achieve a successful pregnancy, and they have been shown to result in significantly greater use of eSET (24). As with insurance coverage, patients chose eSET over DET 50% more frequently when they participated in a refund guarantee program than when they did not (24, 93).

Improving Embryo Selection

Successful implementation of eSET depends on the ability to select the most viable embryos in any cohort. The selection of the best embryo(s) for transfer continues to rely on morphologic evaluation, which has recognized shortcomings. Many morphologically high-quality embryos fail to implant, and some seemingly poor-quality embryos result in healthy live births.

Noninvasive biochemical assays, including emerging technologies such as proteomic and metabolomic analysis of embryo culture media, may eventually prove to be valuable complements to morphologic assessments (94–101). Genomic evaluation through preimplantation genetic screening has the theoretic potential to increase the ability to identify the most competent embryos and consequently increase treatment

success rates; however, prospective trials to date have failed to demonstrate any benefit.

Optimizing Embryo Cryopreservation

A successful embryo cryopreservation program is critical to practical application of eSET. Without the ability to store viable embryos for later use, eSET would be difficult to support. With effective cryopreservation that results in little or no damage to embryos, cumulative birth rates per retrieval should, in theory, be highest when embryos are transferred individually.

SUMMARY

- Utilization of eSET has increased over the past decade. Use of eSET in the United States has lagged behind that of many other countries. In the United States during this time, the use of DET has increased and twin pregnancy rates have remained essentially unchanged.
- RCTs comparing cleavage-stage eSET and subsequent FET with DET have demonstrated similar PRs and LBRs with a substantial reduction in multiple gestations.
- An RCT comparing eSET and DET of blastocyst-stage embryos demonstrated no statistical difference in PRs and a reduction in multiple gestation rate from 47% to 0%.
- There is evidence from well controlled nonrandomized trials and clinical reports that if the contribution of cryopreserved embryo transfers is included, cumulative success rates per retrieval are similar for eSET and DET.
- Published studies of the cost-effectiveness of eSET versus DET have included only costs to achieve a pregnancy or through 4–6 weeks postpartum.
- Elective SET is most appropriate for those with a good prognosis: age <35 years, more than one top-quality embryo available for transfer, first or second treatment cycle, previous successful IVF, and recipients of embryos from donated eggs.
- Women aged 35–40 years may be considered for eSET if they have top-quality blastocyst-stage embryos available for transfer.
- Decisions regarding eSET of cryopreserved embryos should take into consideration prognosis, embryo quality, and success rates of the individual cryopreservation program.
- Challenges to increased use of eSET exist. These include provider and patient education, financial considerations, embryo selection, and successful cryopreservation. Stakeholders should recognize that the optimal outcome of an IVF cycle is the birth of a healthy singleton.
- Reduced financial burdens for IVF through insurance coverage or risk-sharing programs have been shown to improve patient acceptance of eSET.
- Selection and successful cryopreservation of the embryos with the highest IR will facilitate wider use of eSET.

CONCLUSIONS

- Elective SET should be offered to patients with a good prognosis and to recipients of embryos from donated eggs.
- IVF centers should promote eSET when appropriate through provider and patient education.

- Improvements in embryo selection should further increase the application of eSET.

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