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Elective Single Embryo Transfer Following In Vitro Fertilization

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Key Words: Embryo transfer, elective single embryo transfer, in vitro fertilization, intracytoplasmic sperm injection, assisted reproductive technologies, blastocyst, multiple pregnancy, twins

Abstract

Objective: To review the effect of elective single embryo transfer (eSET) compared with double embryo transfer (DET) following in vitro fertilization (IVF), and to provide guidelines on the use of eSET in order to optimize live birth rates and minimize twin pregnancies.

Options: Rates of live birth, clinical pregnancy, and multiple pregnancy following eSET and DET are compared.

Outcomes: Live birth, clinical pregnancy, and multiple pregnancy rates, and cost-effectiveness.

Evidence: Published literature was retrieved through searches of PubMed, Medline, and The Cochrane Library in 2009, using appropriate controlled vocabulary (e.g., elective single embryo transfer) and key words (e.g., embryo transfer, in vitro fertilization, intracytoplasmic sperm injection, assisted reproductive technologies, blastocyst, and multiple pregnancy). Results were restricted to English language systematic reviews, randomized controlled trials/controlled clinical trials, and observational studies. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to November 2009. Additional references were identified through searches of bibliographies of identified articles and international medical specialty societies. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: Available evidence was reviewed by the Joint Society of Obstetricians and Gynaecologist of Canada–Canadian Fertility and Andrology Society Clinical Practice Guidelines Committee and the Reproductive Endocrinology and Infertility Committee of the Society of Obstetricians and Gynaecologists of Canada, and was qualified using the evaluation of evidence criteria outlined in the report of the Canadian Task Force on Preventive Health Care.

Benefits, Harms, and Costs: This guideline is intended to minimize the occurrence of twin gestations while maintaining acceptable overall live birth rates following IVF-ET.

Summary Statements

1. Indiscriminate application of eSET in populations with less than optimal prognosis for live birth will result in a significant reduction in effectiveness compared with DET. (I)
2. In women aged 38 years and over, eSET may result in a significant reduction in live birth rate compared with DET. (II-2)
3. Selective application of eSET in a small group of good-prognosis patients may be effective in reducing the overall multiple rate of an entire IVF population. (II-3)
4. Given the high costs of treatment, uptake of eSET would be enhanced by public funding of IVF treatment. (II-2)

Recommendations

1. Patients should be informed of the reductions in both multiple pregnancy rate and overall live birth rate after a single fresh eSET when compared with DET in good-prognosis patients. (I-A)
2. Because the cumulative live birth rate after fresh eSET followed by transfer of a single frozen-thawed embryo is similar but not equivalent to the rate after fresh DET in good-prognosis patients, the eSET strategy should be used in order to avoid multiple pregnancy. (I-A)
3. Women aged 35 years or less, in their first or second IVF attempt, with at least 2 good quality embryos available for transfer should be considered good-prognosis patients. (I-A)
4. In order to maximize cumulative live birth rates following eSET, effective cryopreservation programs should be in place. (I-A)
5. In order to maintain the reduction in the rate of multiples achieved by fresh eSET, eSET should be performed in subsequent frozen-thawed embryo transfer cycles. (II-2A)
6. Because blastocyst stage embryo transfer generally increases the chance of implantation and live birth compared with cleavage stage embryo transfer, eSET should be performed in good-prognosis patients who have good quality blastocysts available. (I-A)
7. In women aged 36 to 37 years, eSET should be considered in good-prognosis patients with good quality embryos, particularly when blastocysts are available for transfer. (II-2A)
8. In oocyte donor–recipient cycles when the donor has good prognosis and when good quality embryos are available, eSET should be performed. (II-2B)
9. In women with medical or obstetrical contraindications to twin pregnancy, eSET should be performed. (III-B)
10. In order to achieve successful uptake of eSET, it is essential to provide patient and physician education regarding the risks of twin pregnancy and regarding the similar cumulative live birth rate following an eSET strategy and DET. (III-C)
11. When considering both direct health care and societal costs, it should be noted that live birth following eSET is significantly less expensive than DET in good-prognosis patients. (I-A) Therefore, from a cost-effectiveness perspective, eSET is indicated in good-prognosis patients. (III-A)

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ABBREVIATIONS

ART	assisted reproductive technology
DET	double embryo transfer
eSET	elective single embryo transfer
FET	frozen-thawed embryo transfer
fzSET	frozen single embryo transfer
ICER	incremental cost-effectiveness ratio
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilization
OHSS	ovarian hyperstimulation syndrome
RCT	randomized controlled trial
SET	single embryo transfer

INTRODUCTION

In Canada in 2006, 46% of all children born after embryo transfer were a result of multiple pregnancies, and 93.8% of these were twins (Table 1). Elective single embryo transfer was performed in 2.8% of all cycles, while DET occurred in 55.8% of cycles.[1] More frequent application of eSET is required in order to reduce the incidence of twin pregnancies. However, indiscriminate application of eSET regardless of prognosis will unnecessarily reduce the chance of live birth for many couples. The greatest benefit of eSET will be derived from its selective application to those women who have a good prognosis for pregnancy and are at risk for twins.

This guideline reviews the available data on eSET. Recommendations regarding the application of eSET are presented with the aim of reducing the incidence of twin pregnancies in at-risk populations while maintaining acceptable live birth rates. The quality of evidence reported in this guideline has been described using the evaluation of evidence criteria outlined in the report of the Canadian Task Force on Preventative Health Care (Table 2).[2]

THE BURDEN OF MULTIPLE PREGNANCY

The rate of multiple births in Canada has increased substantially in the last 3 decades, as it has in other western countries.[3] From 1995 to 2004, the Canadian multiple birth rate rose steadily from 2.2% to 3.0%, translating into an additional 900 multiple births per year.[4] The rate of twin pregnancies has increased by 50% to 60% since the mid-1970s, and the rates of higher order (triplet or more) multiple pregnancies have increased by 300% to 700%.[3] Although 25% to 33% of this increase in multiple pregnancies is attributable to a contemporaneous increase in maternal age, 30% to 50% of twin pregnancies, and at least 75% of triplet pregnancies, occur after infertility treatment.[3]

In 2006 in Canada, there were 12 052 assisted reproductive technology treatment cycles, including IVF and ICSI with both autologous and donor oocytes, and FET. In 24.9% of cycles, these treatments resulted in births, of which 28.1% were twins and 1.2% were triplets.[1] While the higher order multiple delivery rate has maintained its decline since 2001, the twin rate remains unchanged.[5,6]

The most substantial problem resulting from multiple pregnancies relates to newborn immaturity subsequent to preterm birth. In 2004, preterm births (< 37 weeks) in Canada occurred in 6.7% of singletons, 57.0% twins, and 96.1% of higher order multiple gestations.[7] In ART singleton and twin births, the frequency of preterm birth was higher: 15.9% of singletons and 69.1% of twins (Table 1).[1] The increased risks associated with twin gestations are

Table 1. 2006 Canadian ART birth outcomes[1]

Plurality	Number of neonates	Perinatal mortality rate	Median GA at delivery, wks	Preterm birth, %	Very preterm birth, %	Low birth weight, %	Extremely low birth weight, %
Single	2123	11.8	39	15.9	4.6	9.7	0.9
Twin	1692	30.1	36	69.1	21.0	51.6	3.0
≥Triplet	112	44.6	32	100	77.8	96.2	19.8

Perinatal mortality rate (per 1000 births); GA: Gestational age; preterm: < 37 weeks; very preterm: < 34 weeks; low birth weight: < 2500 g; extremely low birth weight: < 1000 g.

Table 2. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well–designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[2]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[2]

well documented. They include significantly increased rates of perinatal mortality[1,8] and a 5-fold increased risk of cerebral palsy.[9] Although much of the mortality and cerebral palsy risk is attributable to higher rates of preterm delivery, even at term, twins are at increased risk for these complications compared with singletons.[8,9] Preterm delivery is also associated with higher rates of bronchopulmonary dysplasia, visual complications including blindness, and necrotizing entercolitis.[9] Following birth, multiples suffer from increased rates of learning difficulties and perceptual disabilities.[10] Growth-restricted twins are at increased risk of poor postnatal growth and speech and behavioural problems compared with their appropriately grown siblings.[11] Further, the differences in locomotive, hearing, speech, and practical reasoning scores increase with the degree of birth weight discordance.[12] Similarly, increased morbidity and mortality has been reported in IVF twins compared with IVF singletons.[13] Compared with IVF singletons, IVF twins have a 10-fold increased risk of preterm (< 37 weeks) delivery, a 7-fold increased risk of delivery before 32 weeks' gestation, and a 12-fold and 5-fold increased risk of birth weight < 2500 g and < 1500 g, respectively. The risk of stillbirth is doubled.[13] However, incidence of neurological sequelae appears to be similar.[14]

It is also well established that maternal morbidity is increased with multiple pregnancies. In a recent Canadian review of spontaneously conceived multiples,[15] preeclampsia, myocardial infarction, heart failure, pulmonary edema, venous thromboembolism, Caesarean section, hysterectomy, and blood transfusion were all significantly more common than in singleton pregnancies. There was a trend toward an increase in maternal death.[15] Maternal depression and parenting stress,[16,17] decreased quality of life, and difficulty in meeting basic material needs were significantly more common for parents of IVF multiples than for parents of singletons.[18]

A meta-analysis of 11 case–control and 3 cohort studies identified an increased risk of preterm birth between 32 and 36 weeks' gestation (OR 1.48; 95% CI 1.05 to 2.10) and an increased rate of Caesarean section (OR 1.33; 95% CI 1.06 to 1.67) in IVF twins, compared with their spontaneously conceived counterparts.[19] However, significant differences in perinatal mortality, low birth weight, or congenital malformations were not identified. On the contrary, it is widely reported that singletons born following IVF have increased risks of adverse perinatal outcomes such as low birth weight, preterm delivery, small for gestational age, NICU admission and perinatal mortality compared with spontaneously conceived singletons.[20–23] The risks for IVF singletons are also higher than for singletons conceived through non-IVF methods.[24]

Several studies have examined outcomes of singleton gestations following single embryo transfer and double embryo transfer. Although some studies reported increased incidences of adverse outcomes for singletons following DET, such as low birth weight, preterm delivery, placental abruption, and cerebral palsy,[25–27] others have not found significant differences between the groups.[26,28] The reported incidence of vanishing twins following DET has been similar among the studies, ranging from 7% to 12%.[25,26,29,30] On the other hand, 2 recent studies comparing IVF singletons born from spontaneously reduced twin pregnancies with those from singleton pregnancies have demonstrated significant increases in the incidences of low birth weight, preterm delivery,[30] and small for gestational age babies[31] in the vanishing twin cohort. Other studies,[20,32] but not all,[29] have reported similar findings. One study has shown that singletons born following eSET in good-prognosis patients have incidences of low birth weight and very preterm birth (< 32 weeks) comparable with those of their spontaneously conceived counterparts.[33]

ELECTIVE SINGLE EMBRYO TRANSFER

Elective single embryo transfer is effective in reducing the rate of twin gestations following IVF. In 7 published RCTs comparing eSET with DET, rates of multiple pregnancy were significantly lower after eSET (Table 3).[34–40] Six of these trials were conducted using predominantly cleavage stage embryos; those cultured in vitro for 2 or 3 days. A Cochrane review including 4 of these trials found an odds ratio of 23.55; 95% CI 8.00 to 69.29 ($P < 0.001$) for multiple pregnancy following DET compared with eSET.[41]

However, eSET is also associated with reductions in overall pregnancy/live birth rates compared with DET, even in good-prognosis patients. Although several observational studies have reported no difference in pregnancy rates in good-prognosis patients undergoing eSET,[42–54] 6 of 7 RCTs found that eSET resulted in lower pregnancy/live birth rates than DET (Table 3). Five of the 7 eSET RCTs were conducted in patients with characteristics that are thought to impart optimal prognosis (Table 4). Participants were, on average, aged 36 years or less and undergoing their first or second IVF-ET attempt. In these studies, the mean number of oocytes retrieved was > 9, with a high number of embryos available for transfer.[35–40] In all but the Lukassen et al. trial,[36] the inclusion criteria specified that at least 2 of the available embryos should be of good quality.

In 3 of the eSET RCTs, the reductions in pregnancy/live birth rates were both clinically and statistically significant.[34,38,39] In 3 other trials, the lower pregnancy/live birth rates following eSET were not found to be statistically significant. Lukassen et al.[36] reported a non-significant reduction in live birth rate with eSET compared with DET, 25.9% versus 35.8%; however, this trial was powered to detect only a large absolute difference of 20% between the groups.[36] In the Martikainen et al.[35] trial, a 10.3% reduction in live birth rate with eSET (29.7%) compared with DET (40.0%) was clinically but not statistically significant. Again, this study was underpowered and would have required more than double the number of participants to detect a clinically significant absolute difference of 10% in the live birth rate between groups.[35] Similarly, the sample size in the Gardner et al. trial was insufficient to find the 15.1% lower pregnancy rate in the eSET group to be a significant reduction.[37] In contrast, Moustafa et al. found no difference in live birth rate between the groups: 30.0% after eSET and 31.7% after DET.[40] Nevertheless, a meta-analysis of 4 RCTs, including 2 of the trials showing non-significant differences,[34–36,38] found the pregnancy rate (OR 2.16; 95% CI 1.65 to 2.82, $P < 0.001$) and live birth rate (OR 1.94; 95% CI 1.47 to 2.55, $P < 0.001$) to be significantly higher after DET than after eSET.[41] These data suggest that even in good-prognosis patients, one fresh eSET cycle results in significantly lower pregnancy and live birth rates than one fresh DET cycle.

CUMULATIVE LIVE BIRTH RATE: THE VALUE OF CRYOPRESERVATION

In order for eSET pregnancy/live birth rates to approach those of DET, additional fresh or frozen embryo transfer cycles are required. In the Lukassen et al. trial, the cumulative live birth rate following 2 fresh eSET cycles (41%) was similar to the rate following a single fresh DET cycle (36%).[36] In the largest eSET trial, women in the eSET group who failed to achieve a live birth after the fresh embryo transfer were subsequently eligible for transfer of a single frozen-thawed embryo. This study was designed to demonstrate equivalence between the 2 transfer strategies. While the cumulative live birth rate with the eSET strategy was similar to that with

Table 3. Elective single versus double embryo transfers: randomized controlled trials

		Ongoing pregnancy*/Live birth†		Multiples	
Trial	n	eSET %	DET %	eSET %	DET %
Gerris et al[34]	53	38.5 (10/26)	74.1 (20/27)	10‡ (1/10)	30.0‡ (6/20)
Martikainen et al[35]	144	29.7‡ (22/74)	40.0‡ (28/70)	4.5 (1/22)	39.3 (11/28)
Gardner et al[37]	48	60.9‡ (14/23)	76.0‡ (19/25)	0 (0/14)	47.4 (9/19)
Thurin et al[38]§	634	29.6 (91/307)	43.4 (142/327)	1.1 (1/91)	33.1 (47/142)
Lukassen et al[36]‖	107	25.9‡ (14/54)	35.8‡ (19/53)	0 (0/14)	36.8 (7/19)
van Montfoort et al[39]	308	21.4 (33/154)	40.3 (62/154)	0 (0/33)	21.0 (13/62)
Moustafa et al[40]	81	30.0 (12/40)	31.7 (13/41)	0 (0/13)	31.3¶ (5/16)

*Ongoing pregnancy rate per transfer: Gerris et al[34] (12 weeks), Gardner et al[37] (6.5 weeks), and van Montfoort et al[39] (7 weeks)

†Live birth rate per transfer: Martikainen et al,[35] Thurin et al,[38] Lukassen et al,[36] Moustafa et al.[40]

‡Not significant

§Per protocol analysis

‖First fresh eSET cycle only

¶Recalculated from original data

Table 4. Eligibility criteria for eSET trials

Trial	Patient	Attempt no.	Embryos
Gerris et al[34]	Age < 34 years	1	≥ 2 top quality available; 4 or 5 cells on day 2 and ≥ 7 cells on day 3, no multinucleation and < 20% fragmentation
Martikainen et al[35]	Age < 36 years in 43 of 144, no age criterion in 101 of 144	1 in 43, 1 or 2 in 101	≥ 4 available; even-sized blastomeres and < 20% fragmentation on day 2
Gardner et al[37]	FSH ≤ 10 IU/L, E_2 < 80 pg/mL, normal cavity, ≥ 10 follicles >12 mm at hCG	Not specified	≥ 2 available; blastocysts
Thurin et al[38]	Age < 36 years (< 35 for initial recruitment)	1 or 2	≥ 2 available; < 20% fragmentation and 4–6 cells on day 2 or 6–10 cells on day 3 or expanded blastocysts on day 5/6 (≥ 3 for initial recruitment period)
Lukassen et al[36]	Age < 35 years, FSH ≤ 10 IU/L	1	≥ 2 available, at least one good or excellent (≤ 10% fragmentation) on day 3
van Montfoort et al[39]	Any	1	≥ 2 normally fertilized embryos
Moustafa et al[40]	Age ≤ 30 years	Not specified	≥ 1 good quality embryo available for transfer on day 2 or 3

FSH: follicle stimulating hormone; hCG: human chorionic gonadotropin

fresh DET (38.8% vs. 43.4%, NS, per-protocol analysis), it was not found to be equivalent, because the upper limit of the relative difference in cumulative live birth rates between groups exceeded the pre-specified 10% needed to find the strategies equivalent. However, multiple births were virtually eliminated with the eSET strategy (0.8% vs. 33.1%, $P < 0.001$).[38]

Le Lannou et al.[55] reported the findings of a case–control study examining cumulative live birth rates in couples initially receiving a fresh eSET or DET. The live birth rate after DET was 31.5%, compared with 26.1% after fresh eSET, with a significantly lower multiple pregnancy rate after eSET (0% vs. 37%). In the subset of women who received the transfer of a single frozen-thawed embryo if they failed to achieve a live birth after fresh eSET, the cumulative live birth rate of 33% was similar to that after fresh DET.[55] Other observational studies have also found that the cumulative live birth rate after fresh eSET and FET cycles is similar to that following fresh DET. However, in several of these studies, the near elimination of multiples following fresh eSET was lost because of subsequent double FETs.[54,56,57] The Le Lannou et al. study found no increase in the cumulative multiple pregnancy rate (0% vs. 29.4%)

because the majority of FETs (84.3%) were single in the eSET group.[55] Similarly, others have found that the maintenance of eSET in the majority of FET cycles preserves the reduction in multiples with fresh eSET, while providing a similar cumulative live birth rate to DET.[58]

Two cohort studies compared outcomes of SET and DET specifically in FET cycles. Hyden-Granskog et al.[59] found a significantly lower multiple delivery rate (2.0% vs. 21.9%, $P < 0.001$) and live birth rate (19.2% vs. 25.7%, $P < 0.005$) with obligatory and elective SET than with DET. However, when the analysis was restricted to women with more than one frozen-thawed embryo available for transfer, the live birth rate of 28.6% after eSET was comparable to the rate for women receiving DET, while the reduction in multiples (0%) was maintained.[59] Similarly, Yanaihara et al. found no difference in clinical pregnancy (40.7% vs. 46.0%) and live birth rates (29.1% vs. 35.3%), but a significant reduction in twins (2.3% vs. 15.9%, $P < 0.05$) after eSET compared with DET of frozen-thawed blastocyst stage embryos.[60] In the RCT of Moustafa et al.,[40] assignment to eSET or DET was maintained for subsequent FET cycles. After one year, the cumulative live birth rates from the initial fresh embryo transfer were identical at 33.3% per transfer, and 45.0% versus 46.3% per woman for the eSET and DET groups, respectively. Meanwhile, there were no multiple pregnancies in the eSET group, compared with 33.0% in the DET group.[40] Published studies show that the cumulative live birth rate following an eSET strategy is similar to that after fresh DET. Successful implementation of an eSET program may be improved by the presence of an effective cryopreservation program.[61,62] However, if eSET is not applied in the frozen-thawed transfer cycle, the magnitude of the reduction in multiples following fresh eSET may be lost.

Recommendation

1. Patients should be informed of the reductions in both multiple pregnancy rate and overall live birth rate after a single fresh eSET when compared with DET in good-prognosis patients. (I-A)
2. Because the cumulative live birth rate after fresh eSET followed by transfer of a single frozen-thawed embryo is similar but not equivalent to the rate after fresh DET in good-prognosis patients, the eSET strategy should be used in order to avoid multiple pregnancy. (I-A)
3. Women aged 35 years or less, in their first or second IVF attempt, with at least 2 good quality embryos available for transfer should be considered good-prognosis patients. (I-A)
4. In order to maximize cumulative live birth rates following eSET, effective cryopreservation programs should be in place. (I-A)
5. In order to maintain the reduction in the rate of multiples achieved by fresh eSET, eSET should be performed in subsequent frozen-thawed embryo transfer cycles. (II-2A)

BLASTOCYST STAGE EMBRYOS

Five of the 7 RCTs comparing eSET and DET examined cleavage stage embryos, those cultured for 2 or 3 days after oocyte retrieval.[34–36,39,40] In the Thurin et al. trial, 97.6% of transfers were performed at the cleavage stage.[38] Only the Gardner et al. trial[37] specifically examined eSET in blastocyst stage embryos, those cultured for 5 or 6 days after oocyte retrieval. The reported implantation rates were higher than in the other trials. Two recent meta-analyses compared blastocyst and cleavage stage embryo transfers.[63,64] Both found the live birth rate significantly higher with blastocyst transfer, with odds ratios of 1.39 (95% CI 1.10 to 1.76, $P = 0.005$)[63] and 1.35 (95% CI 1.05 to 1.74).[64] Both meta-analyses included an RCT of elective single blastocyst compared with cleavage stage embryo transfer in good-prognosis patients, those in their first or second IVF cycle, 36 years or less, with day 3 FSH < 12IU/L. In an intention to treat analysis, the delivery rate was 56% after blastocyst transfer compared with 38% after cleavage stage transfer (RR 1.49; 95% CI 1.05 to 2.12).[65] This finding resulted in early termination of the study at a planned interim analysis. It is well documented that good quality blastocysts have better implantation potential than cleavage stage embryos, and consequently, eSET should be applied more readily with blastocyst stage embryos.

Recommendation

6. Because blastocyst stage embryo transfer generally increases the chance of implantation and live birth compared with cleavage stage embryo transfer, eSET should be performed in good-prognosis patients who have good quality blastocysts available. (I-A)

eSET IN OTHER POPULATIONS

Five of the 7 eSET RCTs were conducted in patients with characteristics that are thought to impart optimal prognosis (Table 4).[35,37–40] Only the van Montfoort et al. trial[39] was specifically conducted in a population with a more heterogeneous prognosis. Although the participants were young (mean age 32.5 years), 58% of women did not have good quality embryos available for transfer. The ongoing pregnancy rate was twice as high after DET than after eSET (40.2% vs. 21.4%, $P < 0.05$).[39] Moreover, the ongoing pregnancy rate in the eSET group in this trial was lowest of all randomized controlled eSET trials (Table 3).

Summary Statement

1. Indiscriminate application of eSET in populations with less than optimal prognosis for live birth will result in a significant reduction in effectiveness compared with DET. (I)

OLDER WOMEN

Although eSET may not be appropriate in all patients, some women aged over 35 years still have good prognoses for live birth after IVF and are at significant risk of multiples. According to 2006 Canadian ART outcomes, 27.6% of fresh embryo transfers from non-donor egg cycles in women aged 35 to 39 years resulted in multiple pregnancies.[1] With 48.4% of embryo transfers in Canada being DET,[1] there is likely to be a role for eSET in this older patient population. Of the 7 eSET RCTs, only the Gardner et al. trial[37] did not have age as an inclusion criterion. The oldest participant was 43 years; however, the mean ages of the eSET and DET groups were 33.5 ± 0.9 years and 34.2 ± 0.7 years, respectively, and stratification of results by age was not reported.[37] No other RCTs of eSET have included patients over 35 years, and there are few descriptive studies of eSET in this older population.

A Finnish study reported live birth rates following eSET of cleavage stage embryos in 335 women aged 36 to 39 years performed between 2000 and 2003. Women eligible for eSET had a good response to stimulation, with at least one top quality embryo and at least one additional embryo of sufficient quality to freeze. The mean age of the women was 37.5 ± 1.1 years. The live birth rate was 26.0%, with no multiples,[66] similar to the rates reported after eSET in the Martikainen et al.[35] and Thurin et al.[38] eSET trials. Of 585 women in the same age group (mean age 37.6 ± 1.1 years) receiving DET, largely because of the absence of any good quality embryos, the live birth rate was not significantly lower (22.4%) but with a higher twin rate (17.7%).[66] In a small series of 45 women over 35 years (mean age 37.3 ± 2.0 years) receiving eSET of a blastocyst, the ongoing pregnancy rate was 51.1%, with no multiples. This was a highly selected cohort of patients with a mean of 12.5 embryos on day 3, and 5 blastocysts frozen after transfer.[67] A larger study reported outcomes of 784 eSET cycles in good-prognosis patients with at least 2 blastocysts available for transfer. Among 153 women aged 35 to 40 years, the viable pregnancy rate was 52.9%. In comparison, in women less than 35 years, the viable pregnancy rate was significantly higher at 65.8% ($P = 0.005$).[68] Another large series in 406 women under 38 years, with at least 3 blastocysts available for fresh transfer found similar live birth rates (41% vs. 53%) and cumulative live birth rates (65.3% vs. 64.2%) after eSET and DET.[56] Unfortunately, with the exception of the age cut-off for inclusion, detailed demographic data were not provided. In a recent retrospective cohort study, Kalu et al.[54] reported live birth rates following SET and DET of blastocyst embryos in women aged 27 to 37 years and those aged 38 to 43 years. In 248 women aged less than 38 years with excess cryopreserved embryos, live birth rates were similar following eSET (62.8%) and DET (60.5%), while significantly fewer twins resulted from eSET (1.2% vs. 50.0%).[54] Again, neither age-specific live birth rates nor mean age of the cohort were reported. Cumulative live birth rates were similar in the eSET (72.8%) and DET (67.2%) groups; however, the reduction in multiples with fresh eSET was not maintained, with a 23.1% twin rate after FET cycles in the eSET group.[54] In 78 women aged 38 years or more, eSET resulted in a significantly lower live birth rate than DET (23.8% vs. 63.2%). However, the twin birth rate was similar between the groups because of a high monozygotic twining rate (20.0%) in the eSET group. The cumulative live birth rates were also significantly lower in the eSET group (28.6% vs. 68.4%), although not all women who failed to conceive in their fresh embryo transfer had yet to have a frozen-thawed attempt. No additional multiple pregnancies resulted from the FET attempts.[54]

Summary Statement

2. In women aged 38 years and over, eSET may result in a significant reduction in live birth rate compared with DET. (II-2)

Recommendation

7. In women aged 36 to 37 years, eSET should be considered in good-prognosis patients with good quality embryos, particularly when blastocysts are available for transfer. (II-2A)

DONOR OOCYTES

The potential for live birth and multiple pregnancy following oocyte-donor IVF is higher than predicted by the age of the recipient, because of the frequent use of optimal quality oocytes from young, healthy donors. In addition, the high cost of treatment may contribute to the choice of DET over eSET by recipients and clinicians alike. However, the evidence for eSET in oocyte-donor recipients is encouraging. In a retrospective comparison of 2 time periods with differing emphasis on eSET in oocyte donor-recipient cycles, a Finnish program reported maintenance of delivery rates with significant reduction in multiple pregnancy rates.[45] During the period when 17% of transfers were eSET, the delivery rate was 31.6% with a 29% twin rate. When the proportion of eSET increased to 61%, the delivery rate was similar at 33.9%, with reduction of the twin rate to 10%.[45] The same group reported a retrospective analysis of

outcomes following SET and DET in oocyte donor–recipient cycles. Delivery rates were similar after SET (30.4%) and DET (33.3%), with significant reductions in the twin rate: 0% with SET and 40% after DET.[69] More recently, an American group reported a comparison of eSET and DET at the blastocyst stage in oocyte donor–recipient cycles. While eSET resulted in a lower live birth rate (54.2% vs. 64.0%, $P = 0.012$), there was also a dramatic reduction in the multiple rate (2.5% vs. 54.2%, $P < 0.001$).[68]

Recommendation

8. In oocyte donor–recipient cycles when the donor has good prognosis and when good quality embryos are available, eSET should be performed. (II-2B)

MEDICALLY OR OBSTETRICALLY INDICATED eSET

Obstetrical or medical contraindications for multiple pregnancy include severe maternal diseases (diabetes mellitus, cardiovascular disease), morbid obesity, uterine malformation, history of cervical incompetence or hysterotomy, previous preterm delivery, indication for specific prenatal diagnosis, and risk of ovarian hyperstimulation syndrome.[70] A retrospective analysis reported outcomes following eSET in 74 women. Compared with an unselected cohort receiving DET, eSET had similar clinical pregnancy rates (29.7% vs. 29.4%) with a significant reduction in twins (0% vs. 23.9%). The pregnancy rate in those with medically indicated eSET was lower (24.1%) than in those receiving eSET for OHSS risk (35.3%).[52] A similar pregnancy rate (30.6%) has been reported in a series of 72 women over 37 years, some of whom received eSET for medical or obstetrical indications.[71]

Recommendation

9. In women with medical or obstetrical contraindications to twin pregnancy, eSET should be performed. (III-B)

INTERNATIONAL EXPERIENCE

The European IVF-monitoring Consortium reported 19.1% of all embryo transfer cycles were SET in 2004. The rate of SET in individual countries ranged from 7.5% to 67.4%. While it is not possible to determine the proportion of these transfers that were elective, it is likely the increase is due to a rise in eSET. The proportion of SET cycles has increased steadily from 12% in 2001. In 2004, 6 European countries reported more than 25% of transfers being SET. The highest rates were in Finland (47%), Belgium (49%), and Sweden (67%). The multiple delivery rates in these countries were 13.4%, 10.4%, and 5.6%, respectively.[72]

Only 2 countries mandate SET: Sweden and Belgium. In Sweden, the uptake of eSET was largely physician driven, starting in 1999, prior to any legislation. However, in 2003, the Swedish National Board of Health and Welfare decreed that SET should be routinely performed in IVF cycles in general, with DET applied only in exceptions when the risk of twins was considered low.[73,74] Although the legislation is vague, eSET is generally applied in women under 38 years with at least one good quality embryo available for transfer.[75] The Swedish rate of eSET increased from 21.2% in 2002 to 51% in 2004. Multiple birth rates decreased from 19.4 to 5.7%, while live birth rate per embryo transfer remained stable from 26.8 to 25.0%.[75] Similar findings have been reported for an individual IVF program.[73] It is noteworthy that about one half of all IVF cycles in Sweden are publicly funded. In Belgium, legislation regulating the number of embryos transferred was implemented on July 1, 2003. In exchange for reimbursement for a maximum of 6 IVF cycles, in women aged 35 and under, SET was mandated in the first cycle. In the second cycle, DET was permitted if poor quality embryos were available for transfer, otherwise SET was performed. In subsequent attempts, a maximum of 2 embryos were allowed for transfer. In women aged 36 to 39 years, the transfer of up to 2 embryos is permitted in the first 2 treatment cycles, with a maximum of 3 in subsequent attempts.[76] In 2006, SET was performed in 49% of all cycles. The live birth rate per transfer was 21.1% in all cycles, with a 13.4% multiple delivery rate. In women aged 35 years and under, the SET rate was 61.1%, the live birth rate was 24.4%, and the multiple birth rate was 12.2%.[77] Several Flemish IVF programs have reported supporting outcomes.[44,76,78,79] In Finland, the uptake of SET has been voluntary. In 2006, 54.7% of fresh and 55.0% of frozen- thawed embryo transfers were of single embryos. The eSET rate was 37.1%, resulting in a 25.8% live birth rate, while DET gave similar live birth rate of 24.1%. The multiple birth rate was 11.0%.[80]

THE CANADIAN EXPERIENCE

In Canada, eSET is infrequently practised. Only 2.8% of all embryo transfer cycles were eSET in 2006. These 205 transfers represented only 26% of all SET cycles.[1] The clinical pregnancy rate was 52.2% after eSET compared with 12.8% when only one embryo was available. For eSET performed on day 3 (33% of eSETs), the clinical pregnancy rate was 41.2%. For eSET preformed on day 5 (64% of eSETs), the clinical pregnancy rate was 59.1%.[1] In 2001, eSET occurred in only 31 cycles, or 0.7% of all transfer cycles.[81] In 2006, the live birth rate after IVF with non-donor oocytes was 27.1% per cycle started, and the multiple delivery rate was 30.3%. The number of elective DET cycles was 2029, and 67% of these cycles were performed in women less than 35 years of age. The multiple birth rate in this age group was 33.7%.[1] This group represents the obvious target for eSET.

SELECTIVE APPLICATION OF eSET RESULTS IN SIGNIFICANT DECLINES IN MULTIPLES FOR AN ENTIRE PROGRAM

Many IVF practitioners are hesitant to implement eSET at all[82]; however, even modest increases in eSET can result in significant reductions in multiples. In a retrospective report of the effect of targeted eSET at the blastocyst stage in a highly selected subset of patients, Khalaf et al. reported maintenance of pregnancy rates with a significant reduction in multiples in a British IVF program that routinely transferred up to 3 embryos.[83] Women with at least four 8-cell embryos with less than 10% fragmentation on day 3, representing 9% of cycles in the program, were offered blastocyst culture, with eSET subsequently offered to those with at least one high quality blastocyst available for transfer. Comparing the 18 months before and after institution of this eSET strategy, the mean number of embryos transferred in the entire population was similar (1.9 vs. 1.8); however, the rate of eSET increased significantly from 0.3% to 10.0% of all transfers. The clinical pregnancy rate increased from 27% to 32% ($P = 0.015$), because of increased implantation rates in women receiving blastocyst transfer, while the multiple rate was almost halved, from 32% to 17% ($P < 0.001$).[83]

Summary Statement

3. Selective application of eSET in a small group of good-prognosis patients may be effective in reducing the overall multiple rate of an entire IVF population. (II-3)
4. Given the high costs of treatment, uptake of eSET would be enhanced by public funding of IVF treatment. (II-2)

BARRIERS TO eSET

A high proportion of infertility patients express a desire for twin over singleton pregnancies, ranging from 20%[84,85] to 90% of patients surveyed.[86] While many are either unaware of the risks of twin pregnancies or underestimate them,[84,87,88] some of the reasons given for this preference include a desire to minimize number of IVF cycles, pregnancies, and deliveries and an awareness of the effects of advancing reproductive age.[89] Several studies have examined barriers to patients' choice of eSET. Of patients surveyed at a Danish clinic, a majority of respondents (78.5%) desired DET. Even in those who preferred one child at a time, 81.2% planned to have DET.[89] Some studies have shown that the choice of eSET increases when patients are educated about the risks of multiples.[42,88–90] However, others have found that many still choose DET over eSET, accepting the higher risks associated with twins to maximize pregnancy rates.[82,84,90–93] In a British study, most couples identified failed treatment as the most serious adverse outcome of IVF.[92] Another study found that "some women waiting for IVF treatment view severe child disability outcomes associated with double embryo transfer as being more desirable than having no child at all."[93] In a Dutch survey, if eSET was presented as having even a 1% reduction in pregnancy rate, there was a significant increase in the proportion of patients preferring DET.[85] DET was also preferred when eSET was presented as providing an equivalent success rate but requiring one more IVF cycle.[89] Finally, patients with prior IVF experience, and even those with prior success, often favour DET.[91,94,95]

Presentation and promotion of eSET by the IVF practitioner can have a positive influence on the uptake of eSET by the patient.[94] However, there are also barriers to physician uptake of eSET. Among Dutch IVF physicians, these included a perceived reduction in pregnancy rate with eSET and increased burden to the patient of additional cycles to achieve a pregnancy rate equivalent to the rate with DET, and inferior cryopreservation programs with poor success rates of FETs.[62,82] Further, there are some IVF physicians who do not endorse the drive to reduce the incidence of twins,[96] perhaps because they are often removed from the obstetrical care, delivery, and neonatal outcomes of twins.[62,82] Other practical reasons for not promoting eSET include lack of a prediction model to help select appropriate patients for eSET and a lack of a clinic protocol for eSET that would support the physician's promotion of eSET.[82]

Recommendation

10. In order to achieve successful uptake of eSET, it is essential to provide patient and physician education regarding the risks of twin pregnancy and regarding the similar cumulative live birth rate following an eSET strategy and DET. (III-C)

THE IMPORTANCE OF FUNDING

To achieve similar live birth rates with eSET compared to DET, eSET requires additional embryo transfer cycles,[38,58] resulting in added costs, inconvenience, time commitment, and medical risks. This is one of the main barriers to the adoption of eSET for both physicians and patients.[82] Fortunately, cryopreservation has reduced the burden of additional treatment considerably. Nevertheless, not all frozen embryos will survive the thawing process. In the Thurin et al. trial, 17% of eligible women did not receive a FET, because the embryo did not survive the thaw.[38] It is likely that some of these women would have achieved a live birth had they received a fresh DET instead of eSET. Instead, they would have to undergo another ovarian stimulation and oocyte retrieval to have another attempt at conception. In Canada, where IVF treatment is predominantly

unfunded, eSET will also result in additional costs and burden of treatment for the patient.

Funding of IVF is associated with reductions in the incidence of multiples[97,98] and the numbers of embryos transferred.[97,99] An American study reported that uptake of eSET was significantly higher in patients with insurance than in those without (24% vs. 16%, $P = 0.14$), and that the use of eSET declined significantly as patients' expenses increased.[68] Similarly, a New Zealand program found significantly higher acceptance of SET by women with fully funded treatment that included the costs of cryopreservation and subsequent FET (63.0%) than by those who were fully responsible for the costs of treatment themselves (29.6%).[100] Also, a survey of Dutch patients, who receive up to 3 fully funded cycles of IVF, found that lack of IVF funding would be a barrier to a patient's choosing eSET.[82] In a survey of couples from the UK, 55% to 65% were more inclined to accept eSET if the cost of treatment was fixed to include all subsequent FET cycles from a single oocyte retrieval procedure.[92]

ECONOMIC CONSIDERATIONS

It is known that the cost of care of a twin pregnancy is significantly higher than that of a singleton pregnancy.[101–103] In 1994, Callahan et al. estimated that the total hospital cost of an IVF twin delivery, even when expressed per child born, was twice that of an IVF singleton delivery: US$18 974 compared with US$9845.[101] In the UK, the total estimated annual cost to the National Health Service of all IVF babies up to the end of the first year of life was £33 239 595 in 2000/2001. Although IVF singletons accounted for 73% of the total number of live births, they incurred only 46% of the total costs. In contrast, IVF twins represented 25% of total births and 43% of the costs, and triplets accounted for only 2% of live births but 10.6% of the costs.[102] In 2000, it was evident that the costs of caring for multiple births resulting from infertility treatment in Canada exceeded the direct costs of the care itself.[103] Despite this, IVF has remained largely unfunded in Canada, and multiple birth rates have been stable at around 30% over the last 5 years (J. Gunby, personal communication, 2008). There have been several economic and cost-effectiveness studies comparing eSET and DET that generally provide support for eSET, at the very least in patients with good prognosis.

Gerris et al.[47] reported a cost comparison of women achieving live birth after SET or DET. In this observational study, women aged 38 years or less were undergoing their first IVF cycle or their first cycle after a live birth. Although the mean age of participants was 30.6±3.6 years, not all SET cycles were elective and the SET and DET groups may not have been comparable as women were encouraged to undergo eSET or DET depending on the quality of available embryos.[47] Based on economic data from 79.7% of the births in the study population, with 71 women choosing SET and 47 choosing DET, and considering costs of IVF treatment, pregnancy, and neonatal care to 3 months postpartum, the total costs per live born child were €7126 after SET and €11039 with DET, with the majority of the cost difference due to the high cost of twins.[47] A true cost-effectiveness analysis was not conducted in this study, since costs were compared only for those women achieving pregnancies, and not for all 367 women undergoing treatment. However, given the similar live birth rates between the groups—37.4% after SET and 36.6% following DET—it is unlikely that adding the costs of unsuccessful cycles would significantly alter the cost estimates. In a secondary analysis of these data, it was found that SET was always more cost-effective than DET, since it always cost less and had a higher live birth rate than DET.[104]

A cost-effectiveness analysis[105] of eSET was conducted based upon the RCT of van Montfoort et al.[39] comparing eSET with DET in women in their first IVF attempt with at least 2 embryos of any quality available for transfer.[39] This trial was not strictly limited to patients with good prognosis. While the mean age of the population was 32.6 years, with only 14 women aged 38 years or over, only 42% of participants had at least one good quality embryo available for transfer. Included in the analysis were direct costs of health care, including IVF treatment and medications, and societal costs, such as those resulting from productivity losses of both female and male partners. Cost estimates were included from the start of IVF treatment to one month postpartum.[105] The cost of a live birth following an eSET cycle (€7334) was significantly less than a DET cycle (€10924), with 40% of the difference due to direct hospital costs and 32% from productivity losses. The effectiveness of eSET was also significantly reduced. The live birth rate was 20.5% following eSET compared with 39.6% after DET. However, no multiple pregnancies followed eSET, compared with a 19.6% twin rate following DET. The incremental cost-effectiveness ratio, which is calculated as:

$$\frac{\textbf{mean total cost of DET} - \textbf{mean total cost of eSET}}{\textbf{proportion of successful pregnancies after DET} - \textbf{proportion of successful pregnancies after eSET}}$$

or the cost of one additional live birth from DET compared with eSET was estimated at €19 096.[105]

Lukassen et al. reported the first cost-effectiveness analysis conducted specifically in good-prognosis patients, on the basis of their RCT of eSET and DET.[36] Costs were derived from a database of IVF singleton and twin births[106] and included the costs of IVF treatment (€2532), antenatal care, delivery, and hospital admissions of the mother and

neonate(s) to 6 weeks postpartum (€2550 for singletons and €13 469 for twin births). DET was more effective than eSET: 19 live births resulted from 53 DET cycles, and 22 live births occurred after 94 eSET cycles. For every live birth, 1.5 more eSET cycles were needed than DET cycles. Subsequently, the direct cost of IVF cycles per live birth was €10 888 after eSET and €7090 after DET. No multiples resulted from eSET, but 7 of 19 births were of multiples in the DET group, with 6 sets of twins and one set of triplets. Although the costs of pregnancy and neonatal care were higher after DET (€6590) than after eSET (€2550), the total cost per live birth was similar between the groups: €13 438 after eSET and €13 680 following DET.[36] In a secondary analysis, without the inclusion of societal costs or any costs beyond 6 weeks postpartum, ICER for an additional live birth after DET was estimated at €17 804.[104]

Given the reduced effectiveness of a single fresh eSET compared with DET in randomized controlled trials (Table 3), additional cycles with eSET are required to achieve the same number of live births as DET. However, cryopreservation allows for a more practical provision of these additional cycles than fresh embryo transfer attempts. An analysis of the Thurin et al. trial[38] examined the contribution of a single FET in patients who fail to achieve a live birth with fresh eSET.[28] Costs were calculated from a societal perspective, including the costs of IVF treatment, antenatal care, and maternal and neonatal costs to 6 months postpartum, taking the costs of maternal productivity losses into consideration. The mean cost of IVF treatment was significantly higher in the eSET group because of the additional FET cycles (€3675 vs. €3142). However, the total mean maternal health care costs were similar between the groups: €6857 for eSET and €6767 for DET, owing to the increased incidence of obstetrical complications in the DET group. Pediatric costs and the cost of lost maternal productivity were also higher in the DET group, resulting in a total cost per live child of €23 798 after eSET compared with €21 572 after DET, with 60 more live born children after DET.[28] When expressed per live birth, the total cost is €28 115 after the eSET strategy compared with €34 210 after DET. The ICER was €91 702 per extra delivery with a live born child after DET.[28] Excluding the contribution of FET cycles, the ICER falls to €38 121,[104] demonstrating that an eSET strategy is more cost-effective when frozen-thawed transfer cycles are included. It is noteworthy that the total costs per delivery and ICER are higher in this study than in any other because of a slightly longer duration of follow-up.

A Finnish analysis[107] of the cost-effectiveness of an eSET policy in everyday clinical practice was recently published, and unlike prior studies, which generally compared eSET cycles with DET cycles, this study reported the impact on birth rates and costs of treatment over an entire IVF program in periods with differing proportions of eSET utilization. Fresh and frozen-thawed transfer cycles were compared during a 4-year period when eSET was used infrequently (4.2%) and a 4-year period when it was used routinely (46.2%) in a total of 1510 women under 40 years of age. Including all FET cycles, the cumulative live birth rate per egg retrieval (32.5% vs. 27.3%, $P = 0.007$) and term cumulative live birth rate (28.0% vs. 22.5%, $P = 0.001$) were higher in the period of routine eSET use, with a significant decline in the cumulative multiple birth rate (8.7% vs. 18.7%, $P < 0.001$). The total numbers of fresh and frozen embryo transfers performed per woman were similar; 2.5±1.7 in the period of routine eSET use and 2.4±1.6 in the DET dominated period.[107] Considering the costs of medication and treatment cycles only, the ICER was –€19 889, indicating that €19 889 was saved per term live birth in the period of high eSET use compared with the period dominated by DET, a finding that was consistent throughout multiple sensitivity analyses. It should be noted that the lower treatment costs with routine use of eSET were independent of consideration of the high costs of neonatal care, which would have further increased the ICER because of the increased multiple rate in the DET dominated period.[107] This study demonstrated that with increasing implementation of eSET cycles, the probability of term live birth for an entire program improved.

Unlike cost-effectiveness analyses based on outcomes of trials comparing eSET and DET, economic analyses based upon modelling of outcomes have reported varying results. Wolner-Hanssen and Rydhstroem[108] found the cost of a live birth following DET was 4 times higher than after SET when considering the cost of treatment, hospital care, delivery, sick leave, neonatal care, and disability.[108] On the other hand, De Sutter et al. reported similar costs per child born after eSET and DET in good-prognosis patients; however, cost drivers did not take into consideration the costs associated with long-term morbidity.[109,110] When expressed per live birth, the cost after DET was approximately 20% higher than after eSET. More recently, Dixon et al. modelled costs after SET, SET with frozen-thawed, SET in those failing to achieve a live birth following the fresh transfer (SET + fzSET), and DET.[111] Cost drivers included antenatal, maternal, and neonatal care, pediatric care to 5 years of age, and adverse events. Unlike previous studies, this study found DET to be more effective and less costly than SET + fzSET for any age group, and SET was always more cost-effective than SET + fzSET.[111] This result is explained by the low live birth rates used for all groups to more accurately estimate outcomes in an entire IVF population, rather than in studies that considered only good-prognosis patients.

With currently reported implantation rates in good-prognosis patients (Table 3), additional cycles of eSET will be required to achieve similar live birth rates to those achieved with DET. However, the modest costs of additional FET cycles pale in comparison with the high direct and societal costs associated with twin births.[107] Further, even the study finding the highest ICER limited costs to 6 months postpartum,[105] grossly underestimating the long-term costs related to the increased morbidity experienced by twins. With inclusion of such ongoing costs, the ICER will be even higher. As implantation rates improve, the difference in effectiveness between eSET and DET decreases substantially, and eSET rapidly becomes more cost-effective than DET, particularly when frozen-thawed cycles are included. Under such circumstances, ICER rises quickly as the incidence of multiples rise in the DET group.[104] Ultimately, whether eSET or DET is deemed to be more cost-effective depends on the value placed upon an additional live birth.[104,111] From a societal perspective, an eSET strategy with the contribution of cryopreserved embryos appears to be more cost-effective than DET, at least in good-prognosis patients. When considering the long-tem costs associated with higher morbidity in children born from multiple pregnancies, public funding of IVF with eSET in twin-prone patients would to be a cost-effective strategy. The cost savings could be used to fund a number of additional IVF cycles.

Recommendation

11. When considering both direct health care and societal costs, it should be noted that live birth following eSET is significantly less expensive than DET in good-prognosis patients. (I-A) Therefore, from a cost-effectiveness perspective, eSET is indicated in good-prognosis patients. (III-A)

SUMMARY

In 2006, a Canadian expert panel on ART multiples concluded that with adequate funding and improved access to treatment it would be possible to reduce IVF multiple pregnancies by 50%.[112] Although the Canadian ART higher order multiple delivery rate has declined significantly in recent years to 1.5% in 2006, the incidence of twins has remained unchanged at approximately 30%.[1] The evidence supports successful reduction in the twin rate with eSET in appropriate patients with a minimal reduction in the live birth rate. Economic analyses point to significant cost reductions per live birth after eSET compared with DET. Given the high long-term costs of twins, the significant cost savings resulting from a decrease in the rate of twin pregnancies could be used to fund many cycles of IVF with eSET. In order to promote the uptake of eSET, public funding of IVF should therefore be provided.

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