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Guidelines for the Number of Embryos to Transfer Following In Vitro Fertilization

This guideline was reviewed by the Reproductive Endocrinology and Infertility Committee and the Maternal-Fetal Medicine Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada and the Board of the Canadian Fertility and Andrology Society.

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Abstract

Objective: To review the effect of the number of embryos transferred on the outcome of in vitro fertilization (IVF), to provide guidelines on the number of embryos to transfer in IVF-embryo transfer (ET) in order to optimize healthy live births and minimize multiple pregnancies.

Options: Rates of live birth, clinical pregnancy, and multiple pregnancy or birth by number of embryos transferred are compared.

Outcomes: Clinical pregnancy, multiple pregnancy, and live birth rates.

Evidence: The Cochrane Library and MEDLINE were searched for English language articles from 1990 to April 2006. Search terms included embryo transfer (ET), assisted reproduction, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), multiple pregnancy, and multiple gestation. Additional references were identified through hand searches of bibliographies of identified articles.

Values: Available evidence was reviewed by the Reproductive Endocrinology and Infertility Committee and the Maternal-Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada and the Board of the Canadian Fertility and Andrology Society, and was qualified using the Evaluation of Evidence Guidelines developed by the Canadian Task Force on the Periodic Health Exam.

Benefits, Harms, and Costs: This guideline is intended to minimize the occurrence of multifetal gestation, particularly high-order multiples (HOM), while maintaining acceptable overall pregnancy and live birth rates following IVF-ET.

Recommendations

The recommendations made in this guideline were derived mainly from studies of cleavage stage embryos—those cultured for two or three days.

1. Individual IVF-ET programs should evaluate their own data to identify patient-specific, embryo-specific, and cycle-specific determinants of implantation and live birth in order to develop embryo transfer policies that minimize the occurrence of multifetal gestation while maintaining acceptable overall pregnancy and live birth rates. (III-B)
2. In general, consideration should be given to the transfer of fewer blastocyst stage embryos than cleavage stage embryos, particularly in women with excellent prognoses and high-quality blastocysts. (I-A)

Summary Statement

The following recommendations are generally intended for cleavage stage embryos transferred on day two or three. Because

Table 1. Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from 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 support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.[55]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.[55]

blastocyst stage embryos have higher implantation rates than cleavage stage embryos, fewer blastocyst stage embryos may need to be transferred. (II)

Recommendations (continued)

3. In women under the age of 35 years, no more than two embryos should be transferred in a fresh IVF-ET cycle. (II-2A)
4. In women under the age of 35 years with excellent prognoses, the transfer of a single embryo should be considered. Women with excellent prognoses include those undergoing their first or second IVF-ET cycle or one immediately following a successful IVF-ET cycle, with at least two high-quality embryos available for transfer. (I-A)
5. In women aged 35 to 37 years, no more than three embryos should be transferred in a fresh IVF-ET cycle. In those with high-quality embryos and favourable prognoses, consideration should be given to the transfer of one or two embryos in the first or second cycle. (II-2A)
6. In women aged 38 to 39 years, no more than three embryos should be transferred in a fresh IVF-ET cycle. (III-B) In those with high-quality embryos and favourable prognoses, consideration should be given to the transfer of two embryos in the first or second cycle. (III-B)
7. In women over the age of 39 years, no more than four embryos should be transferred in a fresh IVF-ET cycle. (III-B) In those older women with high-quality embryos in excess of the number to be transferred, consideration should be given to the transfer of three embryos in the first IVF-ET cycle. (III-B)
8. In exceptional cases when women with poor prognoses have had multiple failed fresh IVF-ET cycles, consideration may be given to the transfer of more embryos than recommended above in subsequent fresh IVF-ET cycles. (III-C)
9. In donor–recipient cycles, the age of the oocyte/embryo donor should be used when determining the number of embryos to transfer. (II-2B)
10. In women with obstetrical or medical contraindication to multifetal gestation, fewer embryos should be transferred to minimize the chance of multifetal gestation. In such cases, pre-treatment consultation with a maternal-fetal medicine specialist should be pursued. (III-C) Whenever reasonable, consideration should be given to the transfer of a single embryo. (II-3B)
11. Couples should be adequately counselled regarding the obstetrical, perinatal, and neonatal risks of multifetal gestation to facilitate informed decision making regarding the number of embryos to transfer. (II-3B) Emphasis on healthy singleton live birth as the measure of success in IVF-ET may be beneficial in promoting a reduction in the number of embryos transferred. (III-C)
12. A strategy for public funding of IVF-ET must be developed for the effective implementation of guidelines limiting the number of embryos transferred. In the context of this strategy, total health care costs would be lower as a result of reductions in the incidence of multifetal pregnancies and births. (III-C)
13. Efforts should be made to limit iatrogenic multiple pregnancies resulting from non–IVF-ET ovarian stimulation through the development of suitable guidelines for cycle cancellation and the removal of financial barriers to IVF-ET. (III-B)

Validation: This guideline was reviewed by the Reproductive Endocrinology and Infertility Committee and the Maternal-Fetal Medicine Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada and the Board of the Canadian Fertility and Andrology Society.

Sponsor: Society of Obstetricians and Gynaecologists of Canada.

The quality of evidence reported in this document has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table 1).

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INTRODUCTION

In Canada, 1645 deliveries resulted from embryo transfer following in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) in 2001.[1] Of these, 31.5% were multiple births. Data from the Canadian Fertility and Andrology Society (CFAS) show that the incidence of multiple deliveries after IVF-embryo transfer (ET) had

Table 2. IVF-ET Births

Region	No. deliveries	Singletons (%)	Twins (%)	Triplets/+ (%)
Canada, 2003[2]*	1780	69.0	29.4	1.6
Europe, 2002[3]†	42827	75.5	23.2	1.3
USA, 2003[4]†	25775	65.8	31.0	3.2

* all embryo transfers

† fresh, non-donor embryo transfers

Table 3. Canadian 2001 IVF-ET birth outcomes[1]

Plurality	Number of neonates	Perinatal mortality rate	Mean GA at delivery (weeks)	Preterm birth	Very preterm birth	Low birth weight	Extremely low birth weight
Single	1141	2.3	39	15.7%	5.4%	10.4%	1%
Twin	958	3.7	36	65.5%	28.6%	52.7%	3.5%
Triplet	132	6.8	33	97.6%	6.7%	94.3%	16.4%
Quad	16	18.8	32	100%	100%	100%	0%

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

remained unchanged to 2003.[2] The incidence of multiple delivery after IVF-ET in Canada was closer to that of the United States (34.2%) than to the incidence in Europe (24.5%)[3,4] (Table 2). The proportion of multifetal gestations attributed to IVF-ET is higher than after spontaneous conception. In the United States, IVF-ET contributed to 1.1% of all infants born in 2002 but accounted for 17.1% of all multiple births and 43.8% of high-order (triplet or more) deliveries.[5] The incidence of twin and high-order multiple (HOM) births after IVF-ET was 14-fold and 54-fold greater than after spontaneous conception, respectively.[6]

It is well established that multifetal gestations are associated with a significantly greater incidence of complications than singleton gestations; most of these complications are directly related to increased rates of prematurity.[7–11] More than 50% of twins and 90% of triplets are born preterm (< 37 weeks' gestation) and low birth weight (< 2500 g).[12] Compared with singletons, twins are born an average of three weeks earlier and 1000 g lighter, and triplets are born more than six weeks earlier and weigh 1600 g less.[12] The rates of very preterm and very low birth weight infants are disproportionately higher in multiples, and perinatal mortality increases with increasing plurality of birth[1,5,13,14] (Table 3).

Twin gestations are associated with increased rates of maternal morbidity, including hypertensive disorders,[15,16] Caesarean section,[16–20] and postpartum hemorrhage,[15] resulting in increased sick leave and antepartum hospitalization.[15,17] Even after adjustment for prematurity, twin neonates are more often admitted to NICU and require longer stays.[19,21] They also suffer from increased rates of congenital malformations,[11,19,22] some cognitive development difficulties,[22–24] childhood hospitalization, and surgeries.[25,26] Unlike in spontaneous cohorts, the increased incidence of cerebral palsy has not been consistently found with IVF-ET twin deliveries.[27,28] Finally, IVF-ET multiple births may be associated with increased parental stress, marital discord, and financial hardship in comparison with singleton births.[23,29–34]

Although there have been reductions in the incidence of high-order multiples with IVF-ET, twin delivery rates have remained unchanged.[3,5] In Canada in 2001, almost one half of all children born after IVF-ET were from multifetal gestations, 86.6% of which were twins[1] (Table 3). Although it is recognized that twin gestations suffer increased rates of adverse neonatal and maternal outcomes when compared with singletons, there is still some debate among IVF-ET practitioners regarding the need to limit iatrogenic twin pregnancy.[7,35–40] Given that twins are by far the most common multiple after IVF-ET, the bulk of excess morbidity and mortality attributable to IVF-ET conceptions occur in twin gestations.[11,41–43] Furthermore, there is recent evidence that IVF-ET births associated with vanishing fetuses are at increased risk for perinatal and long-term neurological morbidity.[44–49]

The excess occurrence of multifetal gestation following IVF-ET has resulted directly from the replacement of multiple embryos per transfer.[1,3,5] According to an analysis of United States registry data from 1996 to 2002, there has been a decrease in the transfer of three or more embryos with a corresponding increase in double embryo transfer (DET). Over the same period, the overall pregnancy rate has increased from 33.7 to 42.2%, owing to an improvement in embryo implantation rates. Unfortunately, in most age groups, the multiple gestation rates after DET in 2002 were comparable with those following triple embryo transfer (TET) in 1996. Consequently, while there has been a decline in high-order multiples, the proportion of multiple pregnancies has actually increased from 46.5 to 49.9% because of a concurrent increase in twins.[43] In the United States in 2003, three or more embryos were transferred in 56.2% of fresh cycles.[5] In Canada in 2001, at least three embryos were transferred in 50.6% of fresh IVF-ET cycles.[1] However, by 2004, only one or two embryos were transferred in 66% of cycles.[2]

Multifetal reduction can be used to decrease the occurrence of HOM delivery; however, reduction of twins to a singleton is generally not performed. The risk of pregnancy loss after reduction performed in experienced centres ranges from 4.5% to 15.4%.[50] Moreover, morbidity may be higher for twins resulting from multifetal reduction than for non-reduced twins.[51–53] Psychologically, elective reduction is often difficult for couples who have achieved pregnancy after a long duration of infertility. For some, the process can be highly stressful, and long-term guilt may follow.[54] For others, reduction may not be an option for ethical or religious reasons. Furthermore, the need for travel to centres with expertise in reduction can result in additional burdens for the couple. Ideally, primary prevention of HOM pregnancy is preferable, and the need for multifetal reduction should be minimized.

This guideline reviews available data on pregnancy, live birth, and multiple pregnancy and birth rates following fresh embryo transfer after conventional IVF/ICSI. Recommendations regarding the number of embryos to transfer are presented with the principal aim of reducing the occurrence of multifetal gestation while maintaining acceptable clinical pregnancy and live birth rates. These recommendations are not specifically applicable to frozen-thawed embryo transfer cycles, or to embryos derived from previously cryopreserved or in vitro-matured oocytes.

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 the Periodic Health Exam (Table 1).[55]

LIMITING THE NUMBER OF EMBRYOS TO TRANSFER IN IVF-ET

The existing literature on the number of embryos to transfer in IVF-ET is difficult to translate into strict guidelines. There are few randomized controlled trials providing robust evidence. Conclusions are difficult to draw from observational studies given that comparison groups generally differ in prognosis and are often not contemporary. Furthermore, comparisons among studies are confounded by heterogeneous methodology, insufficient reporting of key prognostic variables, and differences in baseline performance of individual IVF-ET programs. Finally, improvements in implantation rates over time often render all but the most current studies outdated.

Nevertheless, several observational studies have identified threshold values for the number of embryos transferred, above which pregnancy and live birth rates do not increase, although multiple pregnancy rates do.[56–59] Furthermore, many programs have reported maintenance of pregnancy and birth rates with reductions in multiple and HOM rates when decreasing the number of embryos routinely transferred, particularly in young patients with favourable prognoses.[60–64]

Although the most effective strategy to reduce the incidence of IVF-ET multiples is to limit the number of embryos transferred per attempt, indiscriminate application of such policies would unnecessarily reduce the chance of pregnancy for many couples. Instead, decisions limiting the number of embryos transferred should be made according to the relevant probabilities of pregnancy and multifetal gestation.[65,66] Several studies have characterized determinants of pregnancy and embryo implantation potential,[59,67–71] and others have generated prediction models to minimize HOM and twin gestations.[72–74]

However, it is difficult and not always appropriate to generalize the results of individual studies to IVF-ET programs with heterogeneous patient populations and embryo implantation rates. Furthermore, there is currently no consensus regarding acceptable rates of twin and HOM gestations after IVF-ET. The determination of acceptable Canadian rates should be a priority for researchers and practitioners in reproductive medicine, as well as other stakeholders. In the absence of such consensus targets, and with recognition of the varying performance of individual IVF-ET programs, the following recommendations have been made based upon the existing, worldwide published literature. Given the rapidity of advances in IVF-ET,[43] it must be acknowledged that these recommendations will require regular revision to accurately reflect ongoing improvements in implantation rates.

Recommendation

1. Individual IVF-ET programs should evaluate their own data to identify patient-specific, embryo-specific, and cycle-specific determinants of implantation and live birth, in order to develop embryo transfer policies that minimize the occurrence of multifetal gestation while maintaining acceptable overall pregnancy and live birth rates. (III-B)

Cleavage Stage Versus Blastocyst Stage Embryos

The recommendations made in this guideline were derived mainly from studies of cleavage stage embryos—those cultured for two or three days. Although a recent meta-analysis did not demonstrate a difference in live birth and multiple pregnancy rates between the transfer of cleavage stage embryos and blastocyst embryos cultured for five or six days,[75] several studies have shown higher implantation rates following blastocyst culture, particularly for high-quality blastocysts.[68,76–81] A recently published randomized controlled trial of elective single embryo transfer in young women with good prognosis demonstrated a significant improvement in live birth rate following blastocyst compared with cleavage stage transfer.[82] Consequently, consideration should be given to the transfer of fewer blastocyst stage embryos than of comparable quality cleavage stage embryos.

Recommendation

2. In general, consideration should be given to the transfer of fewer blastocyst stage embryos than cleavage stage embryos, particularly in women with excellent prognoses and high-quality blastocysts. (I-A)

WOMEN UNDER THE AGE OF 35 YEARS

A small (n = 56) randomized controlled trial published more than 10 years ago compared DET with transfer of four embryos (QET) in good prognosis patients under the age of 35 years. DET resulted in lower live birth (28.6% vs. 53.6%) and multiple pregnancy rates (10.7% vs. 21.4%). HOM pregnancies did not result from DET, and four of five multiples after QET were triplet.[83] A more recent randomized controlled trial comparing DET with TET in 212 women found the live delivery rate was similar for DET and TET (30.1% vs. 24.5%), and multiple (15.0% vs. 41.4%, $P < 0.05$) and HOM pregnancies (0% vs. 6.9%) were substantially decreased for DET compared with TET.[84]

Several observational studies have reported comparable pregnancy rates, with an accompanying maintenance or reduction in multiples, for DET compared with TET in young women with good prognoses. Although a significant incidence of HOM was reported after TET in all studies (3.9–18.0%), none resulted from DET in these series.[85–89] In women with lower quality embryos but otherwise similar prognoses, TET has resulted in higher pregnancy rates than DET; however, rates were not as high as with DET of good embryos.[86,87,89] Although TET in women with lower quality embryos resulted in multiple rates similar to DET in women with good embryos, HOM rates were still higher after TET.[86,89] Compared with DET in good prognosis patients, TET in patients with poorer prognoses resulted in similar or lower pregnancy rates, with increased multiple and HOM rates.[90,91]

Based upon 44 236 cycles performed in the United Kingdom from 1991 to 1995, when the legislated maximum number of embryos transferred was three, Templeton and Morris generated estimates for live birth and multiple birth rates standardized for nulliparious women with tubal infertility and one to three prior IVF attempts. In women aged 30 years with greater than four fertilized eggs, DET resulted in the same live birth rate as TET (21.3% vs. 21.1%) with a significantly lower multiple birth rate (28.6% vs. 39.4%, $P < 0.001$). Similar findings were reported in women with only three or four fertilized eggs.[59]

Schieve et al.[92] reported a retrospective analysis of 35 554 fresh, non-donor embryo transfers performed in the United States in 1996. Unlike in the United Kingdom, there was no legislated maximum number of embryos permitted for transfer. In women aged 30 to 34 years, there were significant increases in both live birth rates (35.1% vs. 19.4%, $P < 0.01$) and multiple birth rates (39.8% vs. 19.7%, $P < 0.01$) after TET compared with DET, and the transfer of four or more embryos resulted in increased multiple births, particularly high order (6.7%), without substantial improvement in live birth rates. Similar findings were noted in women aged 20 to 29 years.[92] Reflecting significant improvement in embryo implantation rates, analysis of 2002 United States registry data found that in unmatched women aged under 35 years, DET gave similar live birth rates to TET (46.3% vs. 43.7%) with lower multiple (36.1% vs. 42.3%) and HOM (0.8% vs. 7.2%) rates.[5]

SUMMARY STATEMENT

The following recommendations are generally intended for cleavage stage embryos transferred on day two or three. Because blastocyst stage embryos have higher implantation rates than cleavage stage embryos, fewer blastocyst stage embryos may need to be transferred. (II)

Recommendation

3. In women under the age of 35 years, no more than two embryos should be transferred in a fresh IVF-ET cycle. (II-2A)

Table 4. eSET versus DET: randomized controlled trials

		Ongoing Pregnancy* / Live Birth†		Multiples	
Trial	n	eSET %	DET %	eSET %	DET %
Gerris 1999[94]	53	38.5 (10/26)	74.1 (20/27)	10‖ (1/10)	30.0‖ (6/20)
Martikainen 2001[96]	144	29.7‖ (22/74)	40.0‖ (28/70)	4.5 (1/22)	39.3 (11/28)
Gardner 2004[93]	48	60.9‖ (14/23)	76.0‖ (19/25)	0 (0/14)	47.4 (9/19)
Thurin 2004[97‡]	634	29.6 (91/307)	43.4 (142/327)	1.1 (1/91)	33.1 (47/142)
Lukassen 2005[95§]	107	25.9‖ (14/54)	35.8‖ (19/53)	0 (0/14)	36.8 (7/19)
van Montfoort 2005[98]	308	21.4 (33/154)	40.3 (62/154)	0 (0/33)	21.0 (13/62)
Total	1294	28.8 (184/638)	44.2 (290/656)	1.6 (3/184)	32.1 (93/290)

n: number; eSET: elective single embryo transfer; DET: double embryo transfer.

* Ongoing pregnancy rate per transfer: Gerris 1999 (> 12 weeks), Gardner 2004 (> 6.5 weeks), and van Montfoort (> 7 weeks).

† Live birth rate per transfer: Martikainen 2001, Thurin 2004, and Lukassen 2005.

‡ per protocol analysis

§ First fresh eSET cycle only

‖Not significant

ELECTIVE SINGLE EMBRYO TRANSFER

To date, six randomized controlled trials have compared pregnancy, live birth, and multiple rates following DET with those following elective single embryo transfer (eSET)[93–98] (Table 4). When at least two embryos were available for transfer in fresh IVF-ET cycles, DET resulted in a higher pregnancy or live birth rate than eSET. Although some studies failed to demonstrate a statistically significant difference,[93,95,96] a systematic review of four of these trials confirmed that DET resulted in significantly higher clinical pregnancy rates (odds ratio [OR] 2.16; 95% confidence interval [CI], 1.65–2.82) and live birth rates (OR 1.94; 95% CI 1.46–2.55) per woman than eSET.[99] Multiple pregnancy rates were also significantly increased with DET (OR 23.55; 95% CI, 8.00–69.29).[99] Elective eSET was effective in preventing HOM and reducing the incidence of twins to that of monozygotic twinning associated with IVF-ET.[100,101] There was a 1.6% rate of twins in the eSET groups, and 2.2% of multiples in the DET groups were triplets (Table 4).

Participation in four of the six eSET randomized controlled trials was restricted to patients with optimal prognosis (Table 5). In the five trials that provided demographic data, participants on average were aged under 34 years and undergoing their first or second IVF-ET attempt. The mean number of oocytes retrieved was greater than nine, with a high number of embryos available for transfer.[93,95–98] In the Martikainen et al. trial, older age was not a specific exclusion criteria for 70% of participants, however the mean age of participants was 31 years.[96] The van Montfoort et al. trial was specifically conducted in a population with a more heterogeneous prognosis. Although the participants were also young (mean age 32.5), only 42% had at least one good quality embryo available for transfer. The ongoing pregnancy rate was twice as high after DET than after eSET (40.2% vs. 21.4%, $P < 0.05$).[98] Moreover, the ongoing pregnancy rate in the eSET group was the lowest of all randomized controlled eSET trials (Table 4).

Several observational studies have also reported the efficacy of eSET in minimizing twin gestations (Table 6). Unlike the randomized trials, the majority of these studies found similar clinical pregnancy rates after eSET and DET, likely reflecting the heterogeneity in embryo quality and patient prognosis in the DET groups.[91,102–112] Analysis of the 2002 US registry data supports the application of eSET in good-prognosis patients. In women aged under 35 years with excess embryos "set aside for future use," eSET resulted in a 47.4% live birth rate per transfer with no multiples. DET was associated with a higher live birth rate (51.8%) but high twin (38.8%) and HOM birth rates (0.9%).[5]

Cumulative rates including contributions of cryopreserved embryos

In the largest eSET randomized controlled trial published by Thurin et al., women in the eSET group who did not achieve a live birth after the fresh embryo transfer were subsequently eligible for the transfer of a single frozen-thawed embryo.[97] The per protocol analysis demonstrated an insignificantly lower cumulative live birth rate with the eSET strategy than in the fresh DET group (38.8% vs. 43.4%),

Table 5. Eligibility criteria for eSET trials

Trial	Patient	Attempt No.	Embryos
Gerris 1999[94]	Age < 34 y	1st	≥ 2 available; 4 or 5 cells on day 2 and ≥ 7 cells on day 3, no multinucleation and < 20% fragmentation
Martikainen 2001[96]	Age < 36 y in 43 of 144, no age criteria in 101 of 144	1st in 43, 1st or 2nd in 101	≥ 4 available; even-sized blastomeres and < 20% fragmentation on day 2
Gardner 2004[93]	FSH ≤ 10 IU/L, E_2 < 80 pg/mL, normal cavity, ≥ 10 follicles > 12mm at hCG	Not specified	≥ 2 available; blastocysts
Thurin 2004[97]	Age < 36 y (< 35 for initial recruitment)	1st or 2nd	≥ 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 2005[95]	Age < 35 y, FSH ≤ 10 IU/L	1st	≥ 2 available; < 10% fragmentation
van Montfoort 2005[98]	Any	1st	≥ 2 normally fertilized embryos

eSET: elective single embryo transfer; FSH: follicle stimulating hormone; E_2: estradiol; hCG: human chorionic gonadotropin

while maintaining a significant reduction in multiple rates (0.8% vs. 33.1%, $P < 0.001$).[97] A few cohort studies have also demonstrated the benefit of cryo-augmentation. With the inclusion of pregnancies from frozen-thawed embryos, pregnancy rates per woman following eSET were similar to those after fresh DET, with minimal increases in multiple pregnancies resulting from the transfer of more than one frozen-thawed embryo.[102,103,111–113]

It is noteworthy that 17% of women eligible for frozen-thawed embryo transfer in the Thurin et al. trial[97] did not receive a transfer because cryopreserved embryos did not survive the thaw. It is likely that at least a portion of these women would have achieved a pregnancy if they had received a fresh DET.[114] This suggests that assessment of a clinic's embryo cryopreservation program is important when contemplating eSET.[93,102,115,116]

Estimated Impact of eSET

It was estimated that application of eSET in 25% to 30% of all IVF-ET cycles in Europe would result in a reduction of multiple births from 25–50% to 12–15%.[35] However, the 2002 European registry data suggest eSET has yet to have significant impact.[3] A few programs with young patient populations have reported a significant uptake of eSET (41–65%). These European programs have demonstrated that multiple pregnancy rates can be minimized (7–11%) while maintaining acceptable clinical pregnancy rates (29–42%).[101,117–120] Finland remains the only nation to demonstrate a reduction in multiple birth in IVF-ET.[117] It has been estimated that about 30% of IVF-ET cycles performed in the United States are in young, good-prognosis patients who would be eligible for eSET.[114]

Recommendation

4. In women under the age of 35 years with excellent prognoses, the transfer of a single embryo should be considered. Women with excellent prognoses include those undergoing their first or second IVF-ET cycle or one immediately following a successful IVF-ET cycle, with at least two high-quality embryos available for transfer. (I-A)

WOMEN AGED 35 TO 39 YEARS

Schieve et al. published an analysis of 1996 IVF-ET registry data from the United States.[92] Among women aged 35 to 39 years, live birth rates increased with the transfer of increasing numbers of embryos, peaking at four. Transfer of four embryos (QET) resulted in a higher live birth rate than TET (33.3% vs. 23.0%, $P < 0.01$). Multiple birth rates (37.5% vs. 29.4%, $P < 0.01$) and HOM birth rates (5.4% vs. 2.2%, $P < 0.01$) were also higher after QET than after TET. Although DET decreased the occurrence of multiple births (11.6%) and eliminated HOM births, the decrease in the live birth rate was substantial (14.0%).[92]

In 1222 unmatched transfer cycles, Svendsen et al. in 1996 found non-significant increases in ongoing and multiple pregnancy rates with up to four embryos transferred.[121] Clinical pregnancy and multiple pregnancy rates with QET were 23.4% and 24.2% respectively. A similar proportion of HOM pregnancies occurred following TET (3.2%) and QET (3.9%), and none followed DET.[121] Hu et al. in 1998 reported a similar analysis of 224 unmatched transfers of up to five embryos.[122] With poor quality embryos, pregnancy

Table 6. Elective single versus double embryo transfers: observational studies

	Pregnancy Rate*		Multiples†	
Study	eSET %	DET %	eSET %	DET %
Vilska 1999[102]	29.7 (22/74)	29.4 (218/742)	0 (0/22)	23.9 (52/218)
Catt 2003[103]	44.1‡ (49/111)	58.8† (161/274)	2.0 (1/49)	44.1 (71/161)
Gerris 2002[91]	35.1 (105/299)	36.2 (309/853)	1.0 (1/105)	35.3 (109/309)
De Sutter 2003[104]	28.2 (163/579)	32.7 (734/2319)	0.7 (1/163)	30.4 (223/734)
Kovacs 2003[105]	31.8 (54/170)	33.5 (816/2436)	0 (0/54)	33.1 (244/737)§
Soderstrom-Anttila 2003[106]	40.8 (20/49)	41.0 (32/78)	0 (0/20)	36.0 (9/35)
Tiitinen 2003[107]	34.5 (162/470)	36.7 (376/1024)	1.2 (2/162)	30.1 (113/376)
Gerris 2004[108]	40.3 (83/206)	40.4 (65/161)	0 (0/83)	30.8 (20/65)
Martikainen 2004[109]	34.7 (107/308)	31.8 (255/803)	0.9 (1/107)	na
Criniti 2005[111]	75.6 (31/41)	78.8 (52/66)	3.2 (1/31)	61.5 (32/52)
Henman 2005[112]	44.6† (54/121)	57.9† (163/285)	1.9 (1/54)	44.2 (72/163)
van Montfoort 2005[110]	31.6 (35/111)	29.0 (119/410)	0 (0/35)	33.6 (40/119)
Total	34.9 (885/2539)	34.9 (3300/9451)	0.9 (8/885)	33.2 (985/2969)

eSET: elective single embryo transfer; DET: double embryo transfer.

* per transfer

† all comparisons statistically significant

‡ $P < 0.05$

§ data available for 737 of 816 cases

rates increased after QET. With fair quality embryos, pregnancy rates did not increase after TET. With good quality embryos, transfer of five embryos (5ET) resulted in the highest pregnancy rate, but the HOM rate was significant at 40%. In this subgroup, HOM appeared with the transfer of three or more embryos. When only fair quality embryos were transferred, HOM pregnancies were first noted with QET, and when poor quality embryos were transferred, HOM pregnancies were first noted with 5ET.[122]

In a review of 138 unmatched transfers in women aged 35 to 39 years, Giannini et al. in 2004 found TET resulted in a higher clinical pregnancy rate (42.0% vs. 34.2%) than DET, but a similar multiple pregnancy rate (16.7% vs. 15.4%).[123] In 814 fresh and frozen transfers in women aged 37 years and over, Elsner et al. in 1997 reported increasing live birth rates with the transfer of greater numbers of embryos up to three.[57] TET resulted in significantly higher live birth rates than DET (34.5% vs. 16.0%, $P < 0.05$). However, multiple pregnancy (29.1% vs. 8.0%, $P < 0.05$) and HOM (1.3% vs. 0%) rates were also higher after TET.[57] Similarly, Salha et al. in 2000 published outcomes of women aged over 35 years undergoing their first cycle with at least six embryos available for transfer.[86] In 95 women with three good quality embryos remaining after transfer, TET compared with DET resulted in higher clinical pregnancy rates (37.7% vs. 20.0%, $P < 0.05$) and higher live birth rates (30.6% vs. 20.0%, $P < 0.05$). Twin birth rates were similar (3.8% vs. 0%) and there were no HOM in either group.[86] Matson et al. in 1999 reported similar clinical pregnancy rates in 355 cycles after DET (24%) and TET (20%), without significant difference in multiple gestations.[88]

Based on data from the 1996 United Kingdom registry, Templeton and Morris estimated that a woman aged 35 years with more than four fertilized eggs had the same probability of live birth after DET as after TET (17.0% vs. 16.9%); however, the risk of multiple birth was significantly reduced (25.6% vs. 32.6%, $P < 0.001$) after DET.[59] United States registry data from 2002 demonstrated that in women aged 35 to 37 years, live birth rates (39.7% vs. 37.7%) multiple birth rates (36.6% vs. 29.2%) and HOM birth rates (4.4% vs. 0.8%) were higher after TET than after DET.[5] When limited to cycles with surplus embryos remaining after transfer, there was no benefit in live birth rate with TET over DET, and HOM rates remained higher after TET.[5] However, in unselected women aged 38 to 40 years, live birth rates improved after TET compared with DET (28.9% vs. 23.3%), with a corresponding increase in multiple (24.3% vs. 18.8%) and HOM births (2.6% vs. 0%). In

those with excess embryos following transfer, the birth rate was highest after DET (43.1%).[5]

Although some eSET studies have included a few older women (typically under 38 years),[101,103,110–112,119] the application of eSET in older women has not been extensively reported. In 862 women aged 35 to 39 years with at least four good quality embryos available for transfer, a 2003 study found that the clinical pregnancy rate after eSET was not significantly different from the rate after DET (26.7% vs. 30.5%).[105] Other observational studies have also reported similar pregnancy rates after eSET in small numbers of older women.[107,113,117,124]

Recommendations

5. In women aged 35 to 37 years, no more than three embryos should be transferred in a fresh IVF-ET cycle. In those with high-quality embryos and favourable prognoses, consideration should be given to the transfer of one or two embryos in the first or second cycle. (II-2A)

6. In women aged 38 to 39 years, no more than three embryos should be transferred in a fresh IVF-ET cycle. (III-B) In those with high-quality embryos and favourable prognoses, consideration should be given to the transfer of two embryos in the first or second cycle. (III-B)

WOMEN AGED OVER 39 YEARS

Compared with younger women, women over 39 years have lower pregnancy, delivery, and multiple rates for any given number of embryos transferred.[5] An unmatched retrospective review published in 1997 of 525 ICSI cycles in women over 39 years found that the transfer of four or more embryos resulted in significant improvement in the clinical pregnancy rate (20.4% vs. 10.0%, $P < 0.005$), and higher twin rates (17.2% vs. 11.1%) than the transfer of one to three embryos.[125] In an unmatched comparison of 320 embryo transfers, Svendsen et al. in 1996 found that TET in these older women resulted in a higher ongoing pregnancy rate than DET (14.4% vs. 3.2%), and HOM did not occur in this series.[121]

When the maximum number of embryos transferred was restricted to three, Templeton and Morris estimated that women aged 40 years with more than four fertilized eggs had the same probability of live birth (13.5% vs. 13.3%) and multiple birth (22.8% vs. 26.5%) after DET and TET, respectively. With only three or four fertilized eggs, TET improved the live birth rate without increasing multiples in this group of women.[59]

In women aged 41 to 42 years using fresh embryos, the most recent unadjusted registry data from the United States showed increasing live birth and multiple birth rates with the transfer of more embryos. In women receiving five or more embryos, live birth, multiple birth, and HOM birth rates were 21.8%, 22.1%, and 2.5%, respectively. The corresponding rates resulting from transfer of four embryos were 16.6%, 15.0%, and 0.9%, respectively.[5] When restricted to women with excess embryos remaining after transfer, live birth rates were similar after transfer of two (27.9%) and five or more embryos (29.1%), but the transfer of five or more embryos compared with DET resulted in considerably higher rates of multiple birth (28.0% vs. 16.7%) and HOM birth (8.0% vs. 0%).[5]

Recommendation

7. In women over the age of 39 years, no more than four embryos should be transferred in a fresh IVF-ET cycle. (III-B) In those older women with high-quality embryos in excess of the number to be transferred, consideration should be given to the transfer of three embryos in the first IVF-ET cycle. (III-B)

POOR PROGNOSIS

In 1995, Azem et al. reported a significant improvement in pregnancy rates following the transfer of six or more embryos compared with five embryos in women with at least four prior failed IVF-ET attempts.[126] Aside from this single study, there is no published evidence demonstrating improvements in pregnancy or live birth rates after the transfer of more embryos in subsequent IVF-ET cycles than the number transferred in previous failed cycles. Nevertheless, the transfer of greater numbers of embryos in women with multiple fresh IVF-ET failures is not uncommon. This practice has also been extended to women predicted to have a poor probability of conception on the basis of other prognosticators such as embryo quality, also with little supportive evidence regarding efficacy.[122] Although the preceding recommendations are not intended to be punitive for women with poorer prognoses for conception, caution and sound clinical judgement must be exercised when exceeding their prescribed maximums.

Recommendation

8. In exceptional cases when women with poor prognoses have had multiple failed fresh IVF-ET attempts, consideration may be given to the transfer of more embryos than recommended above in subsequent fresh IVF-ET cycles. (III-C)

DONOR–RECIPIENT CYCLES

Licciardi et al. reported a retrospective analysis of outcomes of 449 donor–recipient cycles.[127] With embryos derived from young donors (aged 21 to 30 years), DET versus TET resulted in similar clinical pregnancy (57.5% vs. 55.8%) and

multiple pregnancy (40.5% vs. 51.0%) rates. However, DET versus TET resulted in significantly lower HOM rates (0% vs. 13.7%, $P < 0.01$).[127] In another unmatched retrospective study, eSET of good quality embryos resulted in similar live birth rates to those achieved after DET of unknown quality embryos (32.6% vs. 32.1%), with a significant reduction in twins (0% vs. 36.0%, $P < 0.01$).[106] More recently, a small retrospective study reported a clinical pregnancy rate of 88% without any multiple gestations following single blastocyst transfer.[111]

Recommendation

9. In donor–recipient cycles, the age of the oocyte/embryo donor should be used when determining the number of embryos to transfer. (II-2B)

MEDICAL SINGLE EMBRYO TRANSFER

In circumstances that make the avoidance of multifetal gestation more important than usual, it may be prudent to limit the number of embryos transferred, regardless of a possible reduction in the chance of achieving pregnancy. Obstetrical indications or medical conditions that may be exacerbated by multifetal gestation include severe maternal disease (e.g., 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.[101] In a retrospective analysis, Vilska et al.[102] reported outcomes following eSET in 74 women with contraindications to multifetal gestation. Compared with an unselected cohort receiving DET, the women receiving eSET had similar clinical pregnancy rates (29.7% vs. 29.4%) with a significant reduction in twins (0% vs. 23.9%).[102] A similar pregnancy rate (30.6%) has been reported in a series of 72 women aged over 37 years receiving eSET for medical or obstetrical indications.[117]

Recommendation

10. In women with obstetrical or medical contraindication to multifetal gestation, fewer embryos should be transferred to minimize the chance of multifetal gestation. In such cases, pre-treatment consultation with a maternal-fetal medicine specialist should be pursued. (III-C) Whenever reasonable, consideration should be given to the transfer of a single embryo. (II-3B)

ATTITUDES TOWARDS MULTIFETAL GESTATION

Despite the significant body of evidence, many patients are unaware that twin pregnancies are associated with increased risks of adverse maternal and neonatal outcomes.[32,35,128,129] For many patients suffering from long-term infertility, multiple birth is an acceptable and even desired outcome of fertility treatment.[95,128–132] Some data suggest that counselling regarding the risks of twins may be inadequate.[133] Consultation with a specialist in maternal-fetal medicine may be helpful in providing a more accurate understanding of the risks associated with multifetal gestations, particularly with higher order multiples. Murray et al. found that even when informed about these risks, although two thirds of couples would prefer singletons, less than 10% would be deterred by the prospect of twins.[132] Emphasis on healthy singleton live birth rather than simply achieving pregnancy as a measure of success would be beneficial in promoting reductions in the numbers of embryos transferred.

Recommendation

11. Couples should be adequately counselled regarding the obstetrical, perinatal, and neonatal risks of multifetal gestation to facilitate informed decision making regarding the number of embryos to transfer. (II-3B) Emphasis on healthy singleton live birth as the measure of success in IVF-ET may be beneficial in promoting a reduction in the number of embryos transferred. (III-C)

ECONOMIC CONSIDERATIONS

Many patients and physicians are reluctant to reduce the number of embryos transferred for fear of a reduction in the probability of pregnancy.[66,93–95,97,134] This is particularly relevant when patients assume the costs of IVF-ET treatments and may not be able to afford multiple attempts. In this context, respect for patient autonomy should be observed.[135]

Studies in the United States have demonstrated reductions in the number of embryos transferred per attempt with subsequent decreases in multiple and HOM rates in jurisdictions providing insurance coverage for IVF.[136,137] Surveys have also suggested that the uptake of eSET would increase with greater reimbursement of subsequent treatment attempts.[129,132] In Belgium, limits on the number of embryos transferred per attempt, including eSET in good prognosis patients, have been legislated; however, these policies are appropriately tied to state reimbursement of IVF-ET costs.[118,138,139]

Direct maternal and early neonatal costs are significantly elevated by plurality of birth.[140,141] Although eSET results in a lower birth rate than DET, [93–97] analyses including the costs of IVF treatment have shown the cost per baby born to be comparable after eSET and DET.[95,108,141,142] When considering the long-term costs associated with higher morbidity in children born from multifetal gestations, public funding of IVF-ET may prove to be a cost-effective strategy through improved participation in eSET and other strategies to reduce the incidence of iatrogenic multiple pregnancy.

Recommendation

12. A strategy for public funding of IVF-ET must be developed for the effective implementation of guidelines limiting the number of embryos transferred. In the context of this strategy, total health care costs would be lower as a result of reductions in the incidence of multifetal pregnancies and births. (III-C)

NON–IVF-ET INFERTILITY TREATMENTS AND MULTIFETAL GESTATION

A significant proportion of multiple pregnancies and births are derived from non–IVF-ET fertility treatments, particularly superovulation. In 2000, 21% of twin and 40% of HOM births in the United States were attributed to ovarian stimulation without IVF-ET.[6] Similar statistics have been reported from other jurisdictions.[3,143] Although the efficacy of superovulation is significantly less than that of IVF-ET,[144] superovulation is also much less expensive, and it therefore remains a frequently employed treatment modality. Although control over the occurrence of multifetal, and especially HOM, gestations can be exercised through limits on the number of embryos transferred in IVF-ET, control over multiples from superovulation is not as simple to achieve.[8,145]

In order to maximize any reduction in multifetal gestation resulting from infertility therapy, the contribution of non-IVF-ET fertility treatments should also be addressed. One strategy is the formulation of appropriate guidelines for the cancellation of superovulation cycles.[146] Another is to reduce the use of superovulation in favour of IVF-ET.[147] Removing the financial barriers to IVF-ET through public funding could reduce the incidence of iatrogenic multifetal gestation while increasing the overall efficacy infertility treatment.

Recommendation

13. Efforts should be made to limit iatrogenic multiple pregnancies resulting from non–IVF-ET ovarian stimulation, through the development of suitable guidelines for cycle cancellation and the removal of financial barriers to IVF-ET. (III-B)

SUMMARY

The desired outcome of infertility treatment is the birth of a healthy child. As multifetal gestations are associated with higher rates of morbidity and mortality, their disproportionately high occurrence after IVF-ET should be minimized. The transfer of fewer embryos per attempt should be employed as primary prevention. However, indiscriminate application of limitations upon the number of embryos transferred would be inappropriate until accurate predictors of successful implantation can be determined. Decisions on the number of embryos to transfer should be based upon prognosis determined by variables including the woman's age, prior outcomes, and the number and quality of embryos available for transfer, and should be made to minimize the risk of multifetal gestation while maintaining a high probability of healthy live birth.

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