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Single embryo transfer: a mini-review

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This paper provides a concise review of single embryo transfer (SET) in cycles using fresh embryos as well as in cycles using frozen–thawed embryos. Relevant studies were identified by a computerized search in PubMed for the period 1995–2004. The pregnancy rates, delivery rates and multiple pregnancy/birth rates were evaluated after fresh or frozen embryo transfer as well as cumulative delivery rates after fresh and frozen SET. The results of four randomized controlled trials (RCT) and seven observational studies using fresh embryo transfers are analysed. No RCT with SET in freezing–thawing cycles was identified, while one observational study was identified. The effects of a change in the rules from the National Board of Health and Welfare in Sweden in 2003 regarding the implementation of SET in Sweden are summarized.

Key words: frozen embryo transfer/multiple pregnancy/pregnancy rates/randomized controlled trials/single embryo transfer

Introduction

IVF has become the most successful treatment of infertility, both of female and male origin. Since the pioneering report of the first IVF child (Steptoe and Edwards, 1978), $>1 \times 10^6$ children have been born after IVF. In several countries, IVF children represent 2–4% of children born yearly (Nyboe-Andersen *et al.*, 2004). It is also obvious from national as well as from international registries that the success rate assessed as pregnancy per cycle has gradually increased. Despite this high success, European and American registries of assisted reproduction indicate a high multiple pregnancy rate after IVF and ICSI (ASRM/-SART, 2004; Nyboe-Andersen *et al.*, 2004). The multiple birth rates have stayed fairly constant during the last decade and were according to the latest reports 26.4 and 35.4% for Europe and the USA respectively (ASRM/-SART, 2004; Nyboe-Andersen *et al.*, 2004).

It is well known from numerous publications that IVF children have a less favourable obstetric outcome compared to children born from spontaneous conception (Gissler *et al.*, 1995; Bergh *et al.*, 1999; Westergaard *et al.*, 1999; Schieve *et al.*, 2002; Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Wennerholm and Bergh, 2004) including higher risks of prematurity, low or very low birthweight, and perinatal death. The increased risk of prematurity is primarily due to the greatly increased rate of multiple birth even though an adverse outcome for IVF singletons is also found more frequently than among children born after spontaneous conception (Gissler *et al.*, 1995; Bergh *et al.*, 1999; Westergaard *et al.*, 1999; Schieve *et al.*, 2001; Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Wennerholm and Bergh, 2004). In a large Swedish study, an increased risk of neurological sequelae was noted in IVF children, particularly among multiple birth babies (Strömberg *et al.*, 2002). However, in a recent Danish registry study, similar rates of neurological sequelae were observed for assisted reproduction technology twins, assisted reproduction technology singletons and spontaneous twins (Pinborg *et al.*, 2004). Concerning congenital malformations, controlled studies have shown a slight increase for IVF children compared to spontaneous controls (Ericson and Källén, 2001; Anthony *et al.*, 2002; Hansen *et al.*, 2002; Ludwig and Katalinic, 2002).

The most important factor influencing the rate of multiple births is the number of embryos transferred. In Sweden, starting in 1993, there was a voluntary reduction in the number of embryos transferred from three to two, which resulted in an almost complete elimination of triplets, while the twin rate remained fairly unchanged at ~25% per delivery. The overall pregnancy and delivery rates stayed fairly unaffected at ~35 and 25% per embryo transfer (National Board of Health and Welfare, 2004).

It is quite obvious that a strategy using transfer of only one embryo would result mainly in singletons but might also result in a considerable decline in the overall birth rate. Several studies have tried to identify patients suitable for single embryo transfer (SET) (Coetsier and Dhont, 1998; Strandell *et al.*, 2000). These studies identified woman's age and quality of embryos to be predictive for multiple births.

The first report of SET came from Finland (Vilska *et al.*, 1999). Still rather few studies have been published

on SET, some observational studies and a few randomized controlled trials.

The aim of this article is to review briefly studies concerning SET in cycles with transfer of fresh embryos as well as in cycles with transfer of frozen–thawed embryos.

Materials and methods

A computerized search in PubMed for the period 1995–2004 was conducted to identify relevant studies published in English. The following search strategy was used: IVF (1), in-vitro fertilization (2), intracytoplasmic sperm injection (3), ICSI (4), 1 or 2 or 3 or 4, and single embryo transfer (SET) (5), cryopreservation (6), and 5 or 5 and 6. In addition, reference lists were searched for cross-references, and abstracts from relevant meetings were checked. The latest search was done in November 2004. When it was obvious that multiple publications reported data for the same study subjects, the most recent publication was selected. The objectives were to evaluate: (i) the pregnancy rate, the delivery rate and the multiple pregnancy/birth rates after SET and double embryo transfer (DET) in cycles with fresh embryos; (ii) the pregnancy rate, the delivery rate and the multiple pregnancy/birth rates after SET and DET in cycles with frozen–thawed embryos; (iii) the cumulative delivery rate after fresh and frozen–thawed SET.

Results

Randomized controlled studies

Four randomized controlled studies (RCT) were identified (Table I): Martikainen *et al.* (2001) and Thurin *et al.* (2004) report delivery/live birth rate while the other two studies (Gerris *et al.*, 1999; Gardner *et al.*, 2004) report ongoing pregnancy rate. The Belgian study from Gerris *et al.* is a small RCT including 53 good prognosis patients (<34 years of age, 1st IVF cycle, at least two top quality embryos). A significantly higher ongoing pregnancy rate was achieved in the DET group (74.1%) versus the elective SET (eSET) group (38.5%) respectively ($P = 0.013$, RR = 1.9, 95% CI 1.13–3.23). In the Finnish four-centre study (Martikainen *et al.*, 2001), 144 women were randomized to SET or DET. The inclusion criteria in this study were: women's age <36 years, 1st or 2nd IVF cycle and at least four good quality embryos. The ongoing pregnancy rate was 24/74 (32.4%) versus 33/70 (47.1%) in the eSET group and the DET group respectively, which did not differ significantly ($P = 0.09$). However, the 95% confidence interval (CI) for the difference was wide (−0.01 to 0.31), making firm conclusions difficult to draw. As for the Belgian study, no proper sample size calculation was presented and neither was it clear if the design of these studies aimed for equivalence or superiority. While both these trials included day 2 or day 3 transfers, in a recent publication from Gardner *et al.* (2004) single blastocyst transfers were compared with double blastocyst transfers in 48 good prognosis women. In the single blastocyst group 14/23 (60.9%) and in the double blastocyst group 19/25 (76%) of the women achieved an ongoing pregnancy (not significant; 95% CI for the difference: −0.11 to 0.41). In the large multicentre trial from Scandinavia (Thurin *et al.*, 2004), 661 women were randomized to elective SET or DET. The aim of this study was to show equivalence concerning live birth between the two strategies; one fresh single embryo + one frozen–thawed SET versus one fresh DET. A further hypothesis was that the multiple birth rate would be less in the SET group. Equivalence was defined as: the upper limit of the 95% CI for the difference in live birth rates should not be >10%. A 30% live birth rate was assumed in both groups. The study showed that the live birth rate in the eSET group was not substantially lower than that in the DET group, although equivalence could not be declared according o the above definition of equivalence. Second, the multiple birth rate was sharply decreased in the single embryo group. Third, the live birth rate after only fresh embryo transfers was significantly lower in the eSET group (27.6 versus 42.9%) ($P < 0.001$) i.e. ~50% higher live birth rate was achieved with DET compared to single embryo transfer, if frozen–thawed embryo transfer cycles were not taken into account. The price for this higher live birth rate in the DET group was the high multiple birth rate (33.1%). The rationale behind the Thurin study was that both groups should have the possibility of receiving two embryos; in one group both were transferred immediately; in the other group one embryo was transferred at a time. This design would seem a more 'fair' comparison if the aim was to show equivalence. The results of this trial emphasize the high importance of a well-functioning freezing programme.

Summarizing the results from RCT shows that in good prognosis patients satisfactory delivery rates can be achieved with eSET. The delivery rate is, however, significantly lower after eSET compared to DET but might be restored with the addition of frozen–thawed embryo transfers (Thurin *et al.*,

Table I. Elective single embryo transfer (eSET) versus double embryo transfer (DET): results from randomized controlled trials (fresh cycles)

Study	*n*	eSET			DET		
		Pregnancy rate[a]	Delivery rate	Twin rate[b]	Pregnancy rate[a]	Delivery rate	Twin rate[b]
Gerris *et al.*, 1999	53	10/26 (38.5)	NA	1/10	20/27 (74.0)	NA	6/20 (30.0)
Martikainen *et al.*, 2001[c]	144	24/74 (32.4)	22/74 (29.7)	1/24	33/70 (47.1)	28/70 (40.0)	11/28 (39.3)
Gardner *et al.*, 2004	48	14/23 (60.9)	NA	0	19/25 (76.0)	NA	9/19 (47.4)
Thurin *et al.*, 2004[c]	661	94/330 (28.5)	91/330 (27.6)	1/91 (1.1)	146/331 (44.1)	142/331 (42.9)	47/142 (33.1)
Total	906	142/453 (31.3)	113/404 (28.0)	3 (2.0)	218/453 (48.1)	170/401 (42.4)	73/209 (34.9)

Values in parentheses are percentages.
[a]Defined as clinical pregnancy rate per transfer, i.e. fetal sacs with cardiac activity.
[b]Calculated as the number of twins per delivery if delivery rate is available, otherwise twins per ongoing pregnancy.
[c]The Martikainen trial reports delivery rate and the Thurin trial reports live birth rate.
NA = not applicable.

Table II. Elective single embryo transfer (eSET) (1 + 1) versus double embryo transfer (DET) (2 + 0): results from randomized controlled trials

Study	*n*	eSET			DET		
		Pregnancy rate[a]	Live birth rate	Twin rate	Pregnancy rate[a]	Live birth rate	Twin rate
Thurin *et al.*, 2004	661	131/330 (39.7)[b]	128/330 (38.8)	1/330	145/331 (43.8)	142/331 (42.9)	47/142 (33.1)
Van Montfoort *et al.*, 2004	200	34/100 (34)[b]		1 (2)	36/100 (36)		12/36 (33)

Values in parentheses are percentages.
[a]Defined as clinical pregnancy rate per transfer, i.e. fetal sacs with cardiac activity.
[b]In the Thurin study, frozen–thawed SET was also performed, in the Van Montfoort trial the number of frozen–thawed embryos transferred was routinely two.

Table III. Elective single embryo transfer (eSET) versus double embryo transfer (DET): results from observational studies of fresh cycles

Study	*n*	eSET			DET		
		Pregnancy rate[a]	Delivery rate	Twin rate[b]	Pregnancy rate[a]	Delivery rate	Twin rate[b]
Vilska *et al.*, 1999	816	22/74 (29.7)	18/74 (24.3)	0	218/742 (29.4)	NA	52/218 (23.9)
Tiitinen *et al.*, 2003	1494	162/470 (34.4)	128/470 (27.2)	2/128 (1.6)	376/1024 (36.7)	275/1024 (26.9)	76/275 (27.6)
Gerris *et al.*, 2002	1152	105/299 (35.1)	NA	1/105 (0.9)	309/853 (36.2)	NA	109/309 (35.3)
De Sutter *et al.*, 2003	2898	163/579 (28.2)		1/163 (0.6)	734/2319 (31.7)		223/734 (30.4)
Catt *et al.*, 2003	385	49/111 (44.1)		1/49 (2.0)	161/274 (58.8)		71/161 (44.1)
Gerris *et al.*, 2004	367	83/206 (40.3)	77/206 (37.4)	0	65/161 (40.4)	59/161 (36.6)	20/59 (30.8)
Martikainen *et al.*, 2004	1111	107/308 (34.7)	86/308 (27.9)	1/86	255/803 (31.8)	NA	NA
Total	8263	691/2047 (33.8)	309/1058 (29.2)	6/626 (1.0)	2118/6176 (34.3)	334/1185 (28.2)	551/1756 (31.4)

Values in parentheses are percentages.
[a]Defined as clinical pregnancy rate per transfer, i.e. fetal sacs with cardiac activity.
[b]The twin rate is calculated as the number of twins per delivery if delivery rate is available, otherwise twins per ongoing pregnancy.
NA = not applicable.

2004) (Table II). Elective SET results in a dramatically decrease in the rate of multiple birth.

Observational studies

Table III summarizes results from observational studies. In the Finnish study from Vilska *et al.* (1999) the pregnancy rate after eSET (at least two good embryos available for transfer) was 29.7% which was similar to the pregnancy rate after DET from the same time period. In 94 other cycles where only one embryo was available the pregnancy rate was 20.2%. Several other studies have indicated that the pregnancy rate is poor when only one embryo is available for transfer, i.e. non-eSET (Giorgetti *et al.*, 1995). The indication for eSET in the Finnish study was a mixture of medical reasons, risk of ovarian hyperstimulation syndrome and patients wishes. The study of Tiitinen *et al.* (2003) is a retrospective survey over the years 1997–2001 at Helsinki University Hospital. Elective SET was performed if, on day 2, at least two embryos of good quality were available. About one-third of all cycles were performed as eSET and pregnancy and delivery rates were similar between eSET and DET. Gerris *et al.* (2002) described retrospective results for a 4 year period 1998–2001. About one-quarter of cycles were performed as eSET which was offered to women with at least one top quality embryo. The authors concluded that, if applying eSET to approximately one-third of all patients, it would be possible to halve the multiple birth rate without a decrease in ongoing pregnancy rate. In the later study from the same group (Gerris *et al.*, 2004), 367 women chose either eSET (206 women) or DET (161 women). Live birth rate was 37.4% for eSET and 36.6% for DET. The choice between SET and DET was mainly based on embryo morphology. If a high competence embryo was present, patients generally received eSET; if no high competence embryo was available then DET was performed. The third Belgian study (De Sutter *et al.*, 2003) summarizes a 5 year period 1997–2002 from a Belgian unit, altogether 2898 cycles. Similar pregnancy rates were achieved in the eSET and DET group while the twinning rate was high in the DET group. Finally, an Australian study (Catt *et al.*, 2003) also shows encouraging results for SET.

The results from observational studies indicate that similar pregnancy and delivery rates are achieved with eSET and DET. The reason for achieving similar results is of course that the two groups are not strictly comparable; good prognosis women receive eSET while poor prognosis women receive DET. Should all patients have received DET, the overall pregnancy and delivery rates would have been higher but at the price of a high multiple birth rate.

Single embryo transfers in freezing–thawing cycles

No RCT with SET in freezing–thawing cycles was identified. One observational study from Finland was identified (Tiitinen *et al.*, 2001), which is a small trial reporting a live birth rate after SET of 10.9% and after DET of 32.5% (Table IV). In a later Finnish study (Hyden-Granskog, 2004), more encouraging results have been reported after frozen–thawed SET.

Table IV. Single embryo transfer (SET) versus double embryo transfer (DET): results from observational studies on frozen–thawed cycles

Study	*n*	SET			DET		
		Pregnancy rate[a]	Live birth rate	Twin rate	Pregnancy rate[a]	Live birth rate	Twin rate
Tiitinen *et al.*, 2001	129	8/46 (17.4)	5/46 (10.9)	0	31/83 (37.3)	27/83 (32.5)	4/27 (14.8)

Values in parentheses are percentages.
[a]Defined as clinical pregnancy rate per transfer, i.e. fetal sacs with cardiac activity.

Cumulative delivery rate

Only one randomized study has compared the live birth rate between eSET combined with a frozen–thawed SET and DET (Thurin *et al.*, 2004) (Table II). This trial showed a live birth rate after cumulative eSET (1 + 1) that is not substantially lower than the live birth rate after DET (2 + 0). Preliminary results from the ongoing Dutch study (Van Moortfort *et al.*, 2004) were recently reported. However, in that trial two embryos were often transferred in the frozen cycles.

Elective single embryo transfer (eSET)

The definition of eSET seems to be a confusing issue. In the first observational studies and in all RCT, eSET was defined as transfer of one good quality embryo in cases where at least two good quality embryos were available. This definition is also stated in a recent review (Gerris, 2004). Some publications use the term eSET when only one good quality embryo exists and others when the reason for eSET only is the patient's own wish. Even if good results have also been achieved in the group of patients where only one good quality embryo is available, it should be pointed out that all randomized trials are based on the above definition and it is from these trials that we have the highest evidence.

Health economics of eSET versus DET

A few health economic analyses have evaluated eSET versus DET, including treatment costs, maternal and delivery costs and neonatal costs (Wölner-Hanssen and Rydström, 1998; De Sutter *et al.*, 2002; Gerris *et al.*, 2004). The Swedish study (Wölner-Hanssen and Rydström, 1998) used estimates of hypothetical figures to compare costs per successful pregnancy after transfer of one or two embryos. The first Belgian study (De Sutter *et al.*, 2002) based their cost analysis on a decision-analytic model where randomized as well as observational studies were included. The most recent Belgian trial (Gerris *et al.*, 2004) compared the costs per liveborn delivery after eSET and DET. The patients included in that study were offered the choice between eSET and DET. No health economic analysis has yet been published where costs are based on a large population randomized between eSET and DET. Nonetheless, cost analyses performed so far have been in favour of eSET.

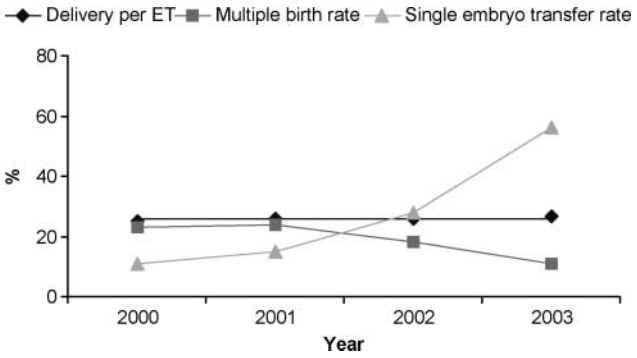

Figure 1. National data for delivery rates, multiple birth rates and single embryo transfer rates in Sweden 2000–2003. For the year 2003, results are given for 13/15 IVF clinics (with permission from P.O.Karlström).

Implementation of SET in Sweden

In Sweden, in parallel with the multicentre study and following results from registry studies concerning obstetric outcome and follow-up of children, an intensive debate has taken place in recent years among paediatricians, obstetricians, IVF physicians and politicians concerning the number of embryos to transfer. This debate ended in new rules from the National Board of Health and Welfare, which, from the beginning of 2003, declared that SET should be the normal routine and that two embryos could be transferred only occasionally when the twinning risk was considered low. Whether the law is the right way to go is not in the scope of this review. However, the implementation of SET in Sweden has been a lot easier than one might imagine. Figure 1 shows the delivery rate, the SET rate and the multiple birth rate in Sweden in recent years. From the data it seems possible to decrease the multiple birth rate considerably, while keeping the overall delivery rate fairly constant by performing SET, in a large proportion of the patients. Preliminary data for 2004 indicates a further increased SET rate, an unchanged delivery rate and a multiple birth rate below 10%. Similar results have been reported from Finland (Tiitinen *et al.*, 2004) and Belgium (De Neubourg and Gerris, 2003; Gerris, 2004). Since RCT show lower pregnancy and delivery rates after SET compared to DET, one would have expected a decline in the overall delivery rate. However, since no remarkable decline in delivery rates is notable, a better selection of embryos for transfer ought to have taken place and/or better prognosis women have been treated. Thus, the price which has to be paid for

the decrease in the multiple birth rate seems to be a slight decrease or the absence of an increase in the delivery rate. This means that women have to go through some more cycles to achieve a live birth and the associated inconvenience and psychological stress should be borne in mind. However, if these additional cycles can be restricted to some freezing–thawing cycles not requiring ovarian stimulation and oocyte retrieval, this stress would be regarded as minor and must be balanced against the much higher risk of multiple pregnancy after DET.

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