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A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles

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BACKGROUND: We analysed the difference in maternal, neonatal and total costs after single (SET) versus double day 3 embryo transfer (DET). METHODS: We performed a two-centre prospective study of women in their first IVF/ICSI cycle choosing between SET or DET. Infertility treatment data were gathered from a database; maternal and neonatal outcome data from a case report form (CRF); health economic data from medical acts registered in the CRF for the outpatient part and from hospital bills. SET was performed in 206/367 (56.1%) and DET in 161/367 (43.9%) women. RESULTS: In all, 367 transfers yielded 186 positive pregnancy tests, 148 ongoing pregnancies and 136 live deliveries (50.7, 40.3 and 37.1% per embryo transfer) of which 15 (11.0%) were twins. Live birth rate was 37.4% for SET, 36.6% for DET. Intention-to-treat analysis showed differences for: duration of pregnancy (SET: 39.0 ± 1.4 versus DET: 38.3 ± 2.2 weeks; $P = 0.055$), percentage prematurity (8.5 versus 23.8%; $P = 0.033$), percentage of neonates hospitalized (5.7 versus 17.9%; $P = 0.121$) and duration of neonatal hospitalization (6.3 ± 2.2 versus 10.3 ± 10.1 days; $P = 0.01$). Total cost after DET was higher (SET: €4700 ± 3239 versus DET: €8613 ± 10 105; $P = 0.105$), due to significantly higher neonatal costs (€451 ± 957 versus €3453 ± 8154; $P < 0.001$) and not to differences in maternal costs (€4250 ± 2882 versus €5160 ± 4106; $P = 0.152$). CONCLUSIONS: This prospective health economic study shows that transfer of a single top quality embryo is equally effective as, but substantially cheaper than, double embryo transfer in women <38 years of age in their first IVF/ICSI cycle.

Key words: assisted reproductive technology/health economic analysis/single embryo transfer/single versus two-embryo transfer

Introduction

There has been a global increase in the incidence of multiple pregnancies, which is mainly due to the widespread application of assisted reproductive technologies. It is estimated that IVF and ICSI account for half of the increase while non-IVF treatments are responsible for the other half. According to national reports, the incidence of multiple pregnancy after IVF varies between 20 and 30%. Approximately 500 000 IVF/ICSI cycles are performed in the whole world each year (Nygren and Nyboe-Andersen, 2002). These result in ~100 000 ongoing pregnancies; a large number of the children resulting from these pregnancies are part of a set of twins or high order multiples (HOM). To give a rough estimate, if the global incidence for post-IVF/ICSI twinning is assumed to be 25% and for HOM to be 3%, these ~100 000 ongoing pregnancies will result in 72 000 singletons, 50 000 twin children and 9000 triplet children for a total of 131 000 children. Assuming an incidence of ~10% of severe complications and sequelae per child belonging to a set of twins or HOM (Wennerholm and Bergh, 2000), this means that each year, IVF/ICSI alone is responsible for ~6000 severely disabled children. In addition, non-IVF treatments are responsible for at least a similar number of multiples. Apart from severe complications, e.g. cerebral palsy, there are other physical and mental complications, as well as non-medical problems, such as educational, emotional, (neuro)linguistic, financial, familial and sexual consequences that usually accompany the raising of twins (Dhont *et al*., 1999). A reasonable solution to the recent epidemic of twins would be to transfer only one embryo. However, the pressure on both doctors and patients to increase the success rate of an expensive and stressful treatment has made the transfer of two or more embryos the standard of care. Many clinicians are reluctant to introduce single embryo transfer (SET) because of fear of lowering their results.

However, the judicious application of elective single embryo transfer is a feasible option which has been demonstrated to

reduce substantially the high incidence of twins following IVF/ICSI (Gerris *et al*., 2002; De Sutter *et al*., 2003a and b; Tiitinen *et al*., 2003). It has been shown that the combination of strict embryo selection with single embryo transfer in twin-prone patients, i.e. women <38 years of age in their first treatment cycle, can decrease the twinning rate to <50% of its current incidence without reducing the overall efficacy of the programme. Easily applicable selection criteria for both twin-prone patients and for good quality embryos with a putative high competence for implantation used to this effect have been described and validated in both retrospective and prospective studies (Gerris *et al*., 1999; Van Royen *et al*., 1999, 2001; Strandell *et al*., 2000).

However, it has not been shown, until now, whether and by how much the application of SET will turn out to be more economic than systematic two-embryo transfer. In the present prospective impact study, we provide both clinical and health economic outcome data concerning patients of <38 years of age in their first IVF/ICSI cycle who were offered the choice between SET of one high quality embryo versus double embryo transfer (DET), irrespective of embryo quality, in their first IVF/ICSI cycle.

Materials and methods

Inclusion criteria

Patients were recruited in two IVF/ICSI programmes including all accepted indications for this treatment. They had to fulfil the following inclusion criteria: <38 years of age at the time of embryo transfer; first IVF/ICSI treatment ever or after a previous delivery, whether or not that pregnancy was the result of an infertility treatment.

Sample size

Prior to the initiation of the study, a calculation of the study group size was made using a Monte Carlo analysis for 10 000 patients entered into the model using figures from the only (theoretical) economic evaluation model comparing SET with DET available at the time the study was conceived (Clark, 1997; Wølner-Hanssen and Rydstroem, 1998). In this model, the cost of one treatment cycle applying both SET or DET was estimated at €2000; the average cost for a singleton pregnancy at €1625; the cost for a twin-complicated pregnancy at €4500; and neonatal costs were estimated at €7000 per twin child and at €2125 for a singleton. In our pre-study estimate, an ongoing pregnancy rate per cycle of 40% was used, based on prior published data (Gerris *et al*., 1999). The Monte Carlo evaluation provided an estimate of the SD of the expected cost. Based on this estimation, an alpha value of 0.05 and a power of 90%, the required sample size was calculated.

It was calculated that a total number of 50 patients in each group would be sufficient to demonstrate a significant cost difference with $P < 0.05$. However, anticipating a lower than usual (25–30%) incidence of twins in the study of ~15%, it was calculated that a total number of patients of ~350 would be needed, even when unequally distributed (e.g. 25/75%) between both study arms. The present study sample of 367 patients eligible for analysis corresponds to these target numbers.

Clinical and laboratory protocols

All IVF/ICSI cycles were performed according to accepted standard protocols of pituitary suppression, ovarian stimulation, oocyte retrieval, gamete handling and embryo culture techniques, embryo transfer and luteal supplementation, as described in previous papers from our groups (Gerris *et al*., 1999, 2002; De Sutter *et al*., 2003b).

The SET versus DET procedure was well explained and understood prior to the initiation of treatment. An informed consent document was read and signed. Transfers were all intended to be performed on day 3 after fertilization. Patients were given the choice between the transfer of one (SET) or two (DET) embryos. SET would be performed exclusively on the condition that the morphology of the transferred embryo corresponded to strict morphological criteria of a putative high competence (PHC) embryo: 4 or 5 blastomeres with <20% fragmentation on day 2; ⩾7 blastomeres with <20% fragmentation on day 3 after fertilization, and no multinucleation observed at any stage of embryo development (Van Royen *et al*., 1999). These criteria were used taking into account further refinements published later stressing the importance of multinucleation (Van Royen *et al*., 2001, 2003). If no high quality embryo was available, patients who had chosen SET received two embryos, except if only one embryo was available. Some patients ($n = 31$) who had chosen SET but who had not produced a high quality embryo, maintained their wish to have only one embryo transferred.

The study was approved by the Institutional Review Board of both participating centres.

Embryo assessment

Culture medium on the day of oocyte retrieval was Ménézo B2 in 25 µl (Laboratoire CCD, France) droplets under oil (Sigma no. M8410; Sigma-Aldrich, Belgium). Oocytes were inseminated, each in a separate droplet with 20 000 sperm having a linear motility >22 µm/s in the case of IVF. In the case of ICSI, up to 10 injected oocytes were incubated together in a 10 µl Ménézo B2 droplet under oil. On day 1, zygotes were examined for the appearance of two pronuclei and up to 10 zygotes were cultured together in a 10 µl Ménézo B2 droplet under oil. On day 2, embryos were rinsed and transferred to individual 10 µl droplets of Medi-Cult M3 medium (Medi-Cult, Denmark) under oil in order to follow their further individual development. All transfers in the analysis were performed on day 3. A maximum of two embryos was transferred in the first two attempts in women <38 years of age. All embryos were scored for three parameters on day 2 (41–44 h after insemination/injection) and again on day 3 (66–71 h post insemination/injection): (i) fragmentation: F1, <10% of anucleated fragments; F2, 10–20% anucleated fragments; (ii) number of blastomeres; (iii) number of multinucleated blastomeres (MNB). The two participating centres used the same morphological criteria for defining a PHC embryo (Van Royen *et al*., 1999, 2001).

Data collection

Clinical data pertaining to the infertility treatment and laboratory data of each treatment cycle were entered in a specially designed database used by both centres. These data comprised: indication for treatment; type of infertility (primary, secondary); suppression/stimulation protocol; type of gonadotrophin used; type of ovulation trigger and of luteal supplementation (progesterone, hCG); method of fertilization (IVF versus ICSI); and number of oocytes retrieved, of normally fertilized 2PN zygotes, of (PHC) embryos (transferred), and of embryos cryopreserved.

Clinical data pertaining to the pregnancy and health economic data regarding pregnancy were collected using case report forms (CRF), given to each patient at the time of the first sonography of their pregnancy. Each contained an antenatal, an obstetric and a neonatal section recording all consultations, sonographies, blood examinations, medications taken during the pregnancy, amniocentesis and other examinations. These CRF were sent to us upon completion of the observation period (3 months after delivery) together with all bills the

patient had received during that period. Each patient permitted us in writing to obtain from the hospital administrative staff all bills pertaining to prenatal hospitalizations, delivery and neonatal hospitalizations of mother and child(ren).

Similarly, patients were requested to return information for medical acts performed in the neonates during their postnatal hospitalization period, contained in the CRF on the day their child or children had reached the age of 3 months. Whenever needed, active measures were taken to obtain as many data as possible by telephoning and writing to the patients.

Statistical analysis

For the analysis of antenatal costs, the number of medical acts was multiplied by the cost per unit for each different act performed. For the analysis of the hospitalization phase, use was made of procured hospital bills. In total, a complete cost analysis could be performed for 118 women, 71 choosing SET and 47 choosing DET. Missing ambulatory or hospital costs were calculated from the average costs adjusted for length of stay. For 30 patients, insufficient health economic data were available.

For comparing maternal, neonatal and total costs between the SET and the DET groups, both a non-parametric test (Wilcoxon rank test) and an unpaired *t*-test were applied. Costs of the IVF/ICSI procedure itself were included in a secondary analysis in order to obtain a better estimate of the total health care costs. This cost per cycle represents a calculated average of €2426 from the Belgian health insurance perspective and is virtually the same for all patients. It is obtained by adding the cost for: (i) the IVF/ICSI laboratory procedure of €1187; (ii) gonadotrophins of 714 (based on a calculated average of 42 ampoules of 75 IU each multiplied with an average unit cost of 17 per ampoule—both urinary and recombinant gonadotrophins being used 50/50; (iii) medical costs of 500 (five consultations, five sonographies, oocyte puncture and embryo transfer) and (iv) 25 for paramedical acts (injections, blood sampling), leading to a total of €2426.

For patient characteristics and clinical outcome variables, differences between SET and DET were evaluated using Student's *t*-test for continuous variables and the χ^2-test for categorical variables. Two-sided $P < 0.05$ for differences was considered significant.

The data analysis was performed on an intention-to-treat analysis, not on an as-treated analysis. This approach allows an analysis from an *a priori* point of view of the patient and is independent of the availability of the desired top quality embryo at the time of transfer.

Results

Patient characteristics

A total of 408 patients was included in the study at the end of the inclusion period which ran from January 1, 2000 until December 31, 2001; there were 262 in centre A and 146 in centre B. In 33 patients there was no transfer either because there were no embryos available or because no embryos of sufficient quality to transfer were available. There were also eight protocol violations: patients in whom embryo transfer was not performed on day 3 (in three patients it was performed on day 2 and in five patients on day 5); these were excluded from further analysis. Thus, a total of 375 (91.9%) patients had embryo transfer, of whom 367 (89.9% of the total number of cycles included) were analysed. These resulted in either no ongoing pregnancy (biochemical pregnancy, miscarriage, extrauterine pregnancy, late pregnancy loss) (62.9% of all treatment cycles) or in a live birth of one or two children reaching the age of 3 months on December 31, 2002 at the latest (37.1% of all treatment cycles).

Table I. Overall clinical outcome of 367 IVF/ICSI cycles

	n	%
No conception	181	49.3
Total conception	186	50.7
Biochemical conception	21	5.7
Early pregnancy loss (<12 weeks)	14	3.8
Extrauterine pregnancy	3	0.8
Late pregnancy loss (>12 weeks)	12	3.3
Live-born delivery	136	37.1

Women were on average 30.9 ± 3.6 years of age and men 33.7 ± 5.4 years of age. Infertility was primary in 63% and secondary in 37% of cases. There were no differences in age or in the distribution of indications for treatment between both centres.

Choice for SET or DET

The baseline choice was for SET in 66.2% and for DET in 33.8% of all cases. There was no significant difference in the baseline choice between both centres (A: 63.5% SET and 36.5% DET; B: 71.4% SET and 28.6% DET). The final distribution of actual transfers at the time of transfer was also not different between both centres (A: 52.3% for SET and 47.7% DET; B: 63.5% SET and 36.5% DET). The percentage change between the baseline choice and the final transfer was as follows: 19% of patients ($n = 47$) who chose for SET finally obtained DET; 8.1% of patients who chose for DET finally received SET. In the group choosing for SET but receiving DET, this change was due either to the fact that no top quality embryo was available ($n = 37$) but also to protocol violations ($n = 10$): patients who had opted for SET at the baseline, who did produce at least one top quality embryo but who nevertheless requested and received two embryos at the time of transfer. Three of the ongoing twins occurred in this subgroup. Conversely, patients who had requested DET received only one embryo ($n = 10$) either because they produced only one embryo or because they insisted on receiving only one embryo. In total, 243 patients (66.2%) chose SET of 1 PHC embryo and 124 (33.8%) chose DET irrespective of embryo quality; 206 patients received SET (56.1%) (175×1 PHC embryo, 31×1 non-PHC embryo) and 161 received DET (43.9%) (51×2 PHC embryos, 28×1 PHC + 1 non-PHC embryo, 82×2 non-PHC embryos).

Clinical treatment outcome

Infertility treatment outcome

Overall clinical data regarding the outcome of infertility treatment are shown in Table I. In total, 186/367 (50.7%) transfers were followed by a positive pregnancy test (two subsequently rising serum hCG values of >5 mIU/ml each, attesting to the presence of at least one implanting embryo). Of these, 136 (37.1%) ended in a live birth. On the basis of an as-

Table II. Clinical results after SET and DET as a function of the type of embryo(s) transferred (as-treated analysis)

	SET	DET			Total	
		2 PHC	1 PHC	0 PHC	Total DET	
No. of cases	206	51	28	82	161	367
No. of ongoing pregnancies (%)	83 (40.3)	29 (56.9)	13 (46.4)	23 (28.1)	65 (40.4)	148 (40.3)
No. of live births (%)	77 (37.4)	28 (54.9)	13 (46.4)	18 (22.0)	59 (36.6)	136 (37.1)
No. of twins (%)	0	12 (41.4)	5 (38.5)	3 (13.0)	20 (30.8)	20 (13.5)

SET = single embryo transfer; DET = double embryo transfer; PHC = putative high competence embryos.

treated analysis, in the group of patients actually receiving SET, there were 77/206 (37.4%) singleton live births and no twins; in the group receiving DET, there were 59 live births (36.6%) (Table II). The intention-to-treat analysis, on the basis of what the patients had chosen prior to the initiation of treatment, is shown in Table III. On this basis, the live birth rate was 35.4% for those who initially chose SET and 40.3% for those who initially chose DET. Of all ongoing pregnancies (n = 148), 20 started off as twin pregnancies (13.5%), three in the SET group and 17 in the DET group. In two cases, one amniotic sac spontaneously vanished during the first trimester resulting in a total of 18/148 (12.1%) clinically ongoing twins. Of these 18 twins, there was one spontaneous expulsion at 22 weeks of gestation after premature rupture of the membranes and two selective reductions to singletons, one because of trisomy 21 in one fetus and one because of cystic fibrosis in one fetus, leading to a total of 15/136 (11.0%) live-born twins (30 twin children).

A comparison between IVF and ICSI cycles showed no difference between the percentage of cycles in which SET was performed (IVF: 55.2% versus ICSI: 56.6%) nor in the percentage of cycles in which two PHC embryos were transferred (13.5 versus 13.2%).

Obstetric and neonatal outcome

A comparison of major obstetric and neonatal outcome variables between the SET and DET groups, based on an intention-to-treat analysis, is shown in Table IV. There was no significant difference between SET and DET in the number of days of antenatal hospitalization, the number of prenatal consultations, the number of blood samples analysed, the number of sonographies performed and the number of days women were absent from work prior to 34 weeks of gestation, which is the usual onset of antenatal home rest in Belgium. Mean birthweight for the SET children was 3226 ± 499 versus 3132 ± 634 g for the DET children (not significant). There was a difference in the duration of the pregnancies (SET: 39.0 ± 1.4 weeks versus DET: 38.3 ± 2.2 weeks; P = 0.055); in the incidence of prematurity (SET: 8.5% versus DET: 23.8%; P = 0.033); in the percentage of children with postpartum hospitalization in an neonatal intensive care (NIC) unit (SET: 5.7% versus DET: 17.9%; P = 0.121); and in the mean duration of hospitalization (SET: 6.3 ± 2.2 versus DET: 10.3 ± 10.1 days) (P = 0.018) of children admitted to a NIC unit.

Table III. Clinical results according to initial choice for SET or DET (intention-to-treat analysis)

	SET	DET
No. of cases	243	124
No. (%) of of SET	196 (80.7)	10 (8.1)
No. (%) of of DET	47 (19.3)	114 (91.9)
No. (%) of positive pregnancy tests	119 (49.0)	67 (54.0)
No. of (%) live births	86 (35.4)	50 (40.3)
No. of twins	3 (2.5)	17 (25.4)

SET = single embryo transfer; DET = double embryo transfer.

Health economic results

The health economic analysis was performed on a total of 118 out of 148 ongoing pregnancies (79.7%), 71 choosing SET and 47 choosing DET. Of the total of 15 ongoing twins, 12 provided data for the health economic evaluation.

This health economic intention-to-treat analysis (Table V) showed a higher total (for mother plus children) cost after DET than after SET: €4700 ± 3239 (SET) versus €8613 ± 10 004 (DET) (Wilcoxon rank test: P = 0.105; unpaired t-test: P = 0.013), entirely due to significantly higher neonatal costs after DET due to some very expensive twins: €451 ± 957 (SET) versus €3453 ± 8154 (DET) (Wilcoxon rank test: $P < 0.001$; unpaired t-test: P = 0.016) and not to minor differences in maternal costs: 4250 ± 2882 (SET) versus €5160 ± 4106 (DET) (Wilcoxon rank test: P = 0.152; unpaired t-test: P = 0.191). When including the initial cost of IVF/ICSI, the total cost becomes €7126 ± 3239 and €11 039 ± 10 004 for SET and DET respectively (Wilcoxon rank test: P = 0.105; unpaired t-test: P = 0.013).

Discussion

Although increasing numbers of clinicians subscribe to the idea of transferring only one embryo in 'twin prone' patients who produce a top quality embryo, the final and most convincing proof of the value of single embryo transfer has to come from a prospective health economic evaluation, which is not yet available (Garceau *et al.*, 2002). In the present prospective study, the health economic outcome was the primary study outcome. We therefore compared the maternal, the neonatal and the total costs of first SET versus DET IVF/ICSI cycles.

Table IV. Comparison of clinical outcome variables in SET versus DET and singleton versus twin pregnancies (intention-to-treat analysis)

	SET	DET	*P*	Within DET		
	(*n* = 56)	(*n* = 45)		Singleton (*n* = 33)	Twins (*n* = 12)	*P*
Pregnancy						
Antenatal hospitalization (%)	26.7	29.3	0.774	20.0	55.5	0.031**
Working incapacity (%) (*n* = 84 with job)	45.8	41.0	0.644	34.5	60.0	0.157
Special sonography (%)	37.0	48.6	0.281	37.0	87.5	0.012**
Amniocentesis (%)	22.8	18.4	0.607	17.9	20.0	0.881
Duration pregnancy (weeks) (SD)	39.0 (± 1.4)	38.3 (± 2.2)	0.055*	39.3 (± 1.2)	35.9 (± 2.3)	< 0.001**
Partus						
Prematurity (<37 weeks) (%)	8.5	23.8	0.033**	3.4	69.2	< 0.001**
Low birth weight (<2500 g) (%)	9.3	15.8	0.342	3.6	50.0	0.001**
Primary Caesarean section (%)	17.5	17.9	0.773	13.8	30.0	0.205
Secondary Caesarean section (%)	2.1	5.7	0.238	0.0	25.0	0.020**
Birthweight (g), mean (SD)	3226 (± 499)	3132 (± 634)	0.430	3357 (± 442)	2501 (± 648)	< 0.001**
Hospitalization NIC unit (%)	5.7	17.9	0.121*	3.7	50.0	0.001**
Hospitalization (days), mean (SD)	6.3 (± 2.2)	10.3 (± 10.1)	0.018**	6.1 (± 1.6)	20.2 (± 14.2)	0.006**
Postpartum 3 months						
Body weight (g), mean (SD)	5975 (± 622)	5828 (± 759)	0.327	5984 (± 571)	5224 (± 1105)	0.123

**Significant differences; *marginally significant differences.
SET = single embryo transfer; DET = double embryo transfer; NIC = neonatal intensive care.

Table V. Absolute cost (€) ± SD for the average maternal, neonatal and total expenditure in the group choosing SET versus DET (intention-to-treat analysis), excluding and including IVF/ICSI treatment cost

	SET (*n* = 71)[a]		DET (*n* = 47)[a]			
			Singleton		Twin (per child)	
	Outpatient	Hospital	Outpatient	Hospital	Outpatient	Hospital
Mother	521 ± 266 4250 ± 2882	3728 ± 2832	560 ± 186 4791 ± 4213 5160 ± 4106	4232 ± 4244	663 ± 247 7477 ± 3009	6814 ± 3029
Child	451 ± 957		309 ± 687 3453 ± 8154		12 728 ± 12 361	
Total follow-up	4700 ± 3239		8613 ± 10 105			
Grand total (including IVF/ICSI)	7126 ± 3239		11 039 ± 10 105			

Maternal data are split up for the outpatient and the hospitalization phase; DET data are split up for singletons and twins.
[a]IVF/ICSI: 2426.
SET = single embryo transfer; DET = double embryo transfer.

The clinical results of this study corroborate what is already known but still in need of further confirmation: there is no difference in the ongoing clinical pregnancy rate and the live delivery rate between good prognosis patients receiving one top quality embryo versus patients receiving two embryos (Vilska *et al*., 1999; ESHRE Campus Course Report, 2001; Tiitinen *et al*., 2001, 2003; Gerris *et al*., 2002; De Neubourg *et al*., 2002; De Sutter *et al*., 2003a). This is due to the fact that in the DET group, the very high pregnancy rate in patients receiving two high competence embryos is balanced by the low pregnancy rate in patients receiving two low competence embryos.

Performing more SET will increase the number of cycles needed to obtain the same number of children when compared with a standard policy of DET. Using a decision-analytic model, it has been shown that, irrespective of the level of the costs and irrespective of the level of performance of an IVF/ICSI centre, the cost per child born in a programme judiciously applying elective SET (eSET) is comparable with the cost per child in a programme with a standard DET policy (De Sutter *et al*., 2002). This is explained by the fact that the higher pre- and neonatal cost due to the twin pregnancies arising after DET is balanced by the higher cost for more SET cycles needed to obtain the same number of children. Clearly, this in itself is an argument in favour of applying eSET, because twins cause higher postnatal long-term morbidity leading to a long-lasting supplementary financial burden after birth. However, no direct evidence is available to date as to the real difference in costs when comparing eSET with DET. All available evidence stems from theoretical extrapolations or from decision-analytical calculations (Wølner-Hanssen and Rydstroem, 1998; Garceau *et al*., 2002; De Sutter *et al*., 2002).

Therefore the important conclusion of this real-life study is that the total cost, based on a prospective collection of data from adequate primary sources, and taking into account all costs up to the age of 3 months of the children, for cycles in

which DET is performed is substantially higher than the total cost for cycles in which SET is performed. When we compare costs for singletons born after SET versus DET, absolutely no difference is found. The difference in cost between SET and DET is entirely due to the higher cost of the twin pregnancies occurring in the DET group (Table V). Moreover, the increased cost per child in the twin pregnancies is entirely due to the extremely elevated cost in some very expensive twins, which cannot be predicted.

Interestingly, the mere fact of starting a strict study protocol comparing SET with DET appears to result in a spectacular reduction in the total twinning rate of the programme: only 15/136 = 11% of all deliveries concerned twins. Theoretically, in a series of 400 first IVF/ICSI trials in which DET is the standard policy of transfer and 40% is the ongoing pregnancy rate, 160 pregnancies would be expected, of which an estimated 25% would be 40 twins (80 twin children). In the present study, only 20 twins were initiated, of which 15 led to the live delivery of 30 children. Nevertheless, the study sample size remains sufficiently large to show significant differences between the SET and the DET groups. This was anticipated prior to the initiation of the study. Moreover, the hypothetical ongoing pregnancy rate of ~40% appeared in retrospect very near the observed ongoing pregnancy rate in the present study (40.4% for DET and 40.3% for SET).

The actual cost per IVF/ICSI cycle in Belgium of €2426 may seem relatively low. However, the difference in cost between SET and DET is independent of the absolute cost, since a sensitivity analysis shows that if one of the cost variables varies, the others will vary in the same direction (De Sutter *et al*., 2003b). The average cost for a child born after DET in this study is ⩾50% than the average cost for a child after SET independent of the absolute cost, as well as of who is paying. The theoretically calculated difference between a SET child and a DET child was higher in the Wølner-Hanssen–Rydhstroem study, where it was ~3-fold higher for a DET child. This difference in our study is based on an intention-to-treat analysis; on the basis of an as-treated analysis, where a comparison is made on the basis of what is actually transferred (one or two embryos) and not on the basis of what is decided prior to the initiation of the cycle, the difference is ~2-fold (data not shown).

The additional effect of cryopreservation must also be taken into consideration in assessing the overall value of eSET, because it has been shown that on average one more embryo can be cryopreserved after SET than after DET (Tiitinen *et al*., 2001, 2003; De Neubourg *et al*., 2002). From a health economic point of view, it is very likely that a cryo-augmentation effect will prove to be an additional tool in the prevention of multiple pregnancies (Gerris *et al*., 2003).

In conclusion, we believe that this prospective health economic study has shown that the total (maternal + neonatal) cost per child up to 3 months of age born after a first IVF/ICSI treatment is substantially higher when DET is applied than when SET is applied. The difference in total costs between children born after SET versus DET was significant (Student's unpaired *t*-test: $P = 0.013$) and completely due to the twins after DET. Keeping in mind that subsequent costs for raising twin children further increase the difference in cost, this study shows that not only for purely medical but also for health economic reasons, SET should be applied when a putative high competence embryo is available in a first treatment cycle. It is very likely that the same is true for higher treatment ranks, but this remains to be proven. Given the importance for the practice of IVF/ICSI worldwide, more studies are needed to confirm these conclusions.

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