Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis

Ann Thurin Kjellberg1, Per Carlsson2 and Christina Bergh1,3

1Reproductive Medicine, Department of Obstetrics and Gynaecology, Institute for Health of Women and Children, Sahlgrenska Academy, SU/S SE-413 45 Göteborg and 2Center for Medical Technology Assessment, Linköping University, SE-581 83 Linköping, Sweden
3To whom correspondence should be addressed. E-mail: christina.bergh@vgregion.se

BACKGROUND: Transfer of several embryos after IVF results in a high multiple birth rate associated with increased morbidity and high costs for the neonatal care. In a previous randomized trial we demonstrated that a single embryo transfer (SET) strategy, including one fresh single embryo transfer and, if no live birth, one additional frozen–thawed SET, resulted in a live-birth rate that was not substantially lower than after double embryo transfer (DET) but markedly reduced the multiple birth rate. METHODS: We compared costs for maternal health care and productivity losses and paediatric costs for the SET and DET strategies. In addition, maternal and paediatric outcomes between the two groups were compared. RESULTS: The SET strategy resulted in lower average total costs from treatment until 6 months after delivery. There were a few more deliveries with at least one live-born child in the DET group. The incremental cost per extra delivery in the DET alternative was high, €71 940. The rates of prematurely born and low birthweight children were significantly lower with the SET strategy. There were also markedly fewer maternal and paediatric complications in the SET group. CONCLUSIONS: The SET strategy is superior to the DET strategy, when number of deliveries with at least one live-born child, incremental cost-effectiveness ratio and maternal and paediatric complications are taken into consideration. The findings do not support continuing transfers of two embryos in this group of patients.

Key words: cost-effectiveness/IVF/multiple births/randomized controlled trial/single embryo transfer

Introduction
An important issue in IVF is how many embryos should be transferred for each individual couple. A number of variables must be considered, i.e. prognosis for a live birth, the health risks for the children, the costs to the couples and to society. The multiple births after IVF (ASRM/SART, 2004; Nyboe-Andersen, 2004) and the associated prematurely born children (Bergh et al., 1999; Schieve et al., 2002; Helmerhorst et al., 2004; Jackson et al., 2004; Wennerholm and Bergh, 2004) often result in increased neonatal morbidity. Elective single embryo transfer (eSET) has recently been introduced (Gerris et al., 1999; Martikainen et al., 2001; Thurin et al., 2004) as a method for achieving the objective of successful treatment with less neonatal morbidity. A few health economic analyses have previously evaluated eSET versus double embryo transfer (DET). A Swedish study (Wölner-Hansen and Rydström, 1998) used estimates of hypothetical values to compare costs per successful pregnancy. One Belgian model analysis (De Sutter et al., 2002) was based on literature data, including randomized as well as observational studies. Another more recent Belgian study (Gerris et al., 2004) compared the costs per delivery with live birth after patient’s choice of eSET or DET. These studies suggested lower costs per delivery for eSET. No health economic analysis has yet been published with costs based on a large population randomized between eSET and DET. We have previously reported from a randomized controlled trial performed on SET versus DET. It showed a cumulative live-birth rate in the SET group that was not substantially lower than the DET group (Thurin et al., 2004). The protocol stated that if no live birth occurred in the fresh SET cycle, a transfer of a thawed single embryo transfer was performed. The aim of the present study was to calculate and compare the outcomes and total costs to society for two IVF strategies, cumulative SET and DET, until 6 months after delivery, and to conduct a partial cost-effectiveness analysis by relating costs to delivery with at least one live birth.

Materials and methods
Study design
The study population consisted of 661 women, all aged <36 years, undergoing their first or second IVF cycle and having at least two good quality embryos available, randomized to eSET or DET. The original protocol stipulated that the patient had to be aged <35 years and have at least three good quality embryos available, but these criteria were modified in an amendment after the first 215
patients were enrolled in the study, owing to a change in usual clinical practice in Sweden. Eleven Scandinavian clinics, public as well as private, participated in the trial. Approvals from the ethics committees were obtained, and all patients signed informed consent.

Costs for health care
The costs of IVF treatment, drugs, complications with the IVF treatment and the costs of pregnancy losses were calculated individually for each patient. The obstetric and paediatric outcomes were assessed by means of two prospective self-reporting questionnaires, submitted after delivery and 6 months postpartum, and from records for the IVF treatment, antenatal care and hospital care for mothers (n = 270) and children (n = 318).

For hospital services we used Nord DRG (diagnosis-related-groups) which is an adaptation for Nordic countries of the American DRG system. Nord DRG is used in all three countries.

All hospital services were estimated on the basis of DRG points at Sahlgrenska University Hospital, Göteborg, Sweden (National Board of Health and Welfare) and calculated for the year 2004 in euro (€). Standard IVF was set to €2933, ICSI to €3386 and a frozen–thawed cycle to €994. We used Swedish sales prices for drugs in the calculations. Adding the cost for down-regulation for 4 weeks with a GnRH agonist, the average cost for ovariain stimulation with FSH and the cost for ovulation induction with 10 000 IU of HCG and the cost for luteal support for 3 weeks with progesterone administered by vaginal route, gave an average cost for drugs of €1241 per patient, irrespective of group. The costs for miscarriages were divided into three categories: biochemical (€310), early miscarriages, not demanding curettage (€621) and late miscarriages, demanding curettage (€1215). The cost for antenatal care was calculated based on its organization in Göteborg, Sweden; including laboratory tests, appointment with a midwife, and one appointment with a physician and was estimated to €545 (nulliparous) or €460 (parous women). Additional costs were: €68 or 136 for more check-ups with the midwife or physician, €97 for an ultrasound examination around gestational week 17, €310 for twin pregnancies and €497 for patients with diabetes.

Costs of productivity losses
Working status and the number of days of absence from work were assessed for each patient by means of questionnaires and from medical records. Absence from work during pregnancy was divided into sick leave, maternity leave and parental insurance leave. Aware of the methodological difficulties, we chose a rough method to estimate productivity losses. We added 50% for the employer’s contribution to national social insurance systems to the mean daily income in 2004 for all Swedish losses. We added 50% for the employer’s contribution to national social insurance systems to the mean daily income in 2004 for all Swedish losses. We added 50% for the employer’s contribution to national social insurance systems to the mean daily income in 2004 for all Swedish losses. We added 50% for the employer’s contribution to national social insurance systems to the mean daily income in 2004 for all Swedish losses.

Cost-effectiveness
A correct cost-effectiveness analysis should take all relevant costs and effects during a certain time horizon into consideration. In this case it would be lifetime costs and effects for the children and their parents. Here we present a partial cost-effectiveness analysis, up to age 6 months for the children, by calculating the incremental cost-effectiveness ratio (Karlsson and Johannesson, 1996).

Quality of life
We assessed the quality of life of the mothers in order to determine whether there were any differences that should be included in the economic analysis. The patients were asked to answer two well-known and validated questionnaires, SF-36 (Ware et al., 1993; Sullivan and Karlsson, 1994) and SPSQ (Swedish Parenthood Stress Questionnaire) (Abidin, 1990; Östberg et al., 1997) 6 months after the delivery. For Danish and Norwegian women the questionnaires were in their languages.

Statistical analysis
The statistical analysis was done according to intention to treat, i.e. strict analysis according to randomization group. Comparison of costs was performed with Student’s t-test. For other continuous or discrete variables Mann–Whitney U-test was used and for comparison of proportions Fisher’s exact test. Mean, SD, median and range were used for descriptive statistics, and for main outcomes the 95% CI for the difference were calculated. All tests were two-tailed and significance was accepted at P < 0.05.

SPSS version 12.0 and SAS version 2.0 were used.

Results
Maternal health care costs and outcome up to 6 months after delivery (Tables I and II)
Treatment costs were significantly higher in the SET group (P < 0.0001) owing to the additional costs for the frozen cycles. The major complication in IVF was ovarian hyperstimulation syndrome (OHSS) of which 29 cases were reported in the SET group and 37 in the DET group; of the total, 27 (4.1%) cases were severe, requiring hospitalization. Three other severe complications occurred: one case of ovarian torsion and two patients with thrombosis. A total of 34 cases of pregnancy loss befell the SET group and 33 the DET group. In each group one case of extrauterine pregnancy and one case of a singleton intraterine fetal death after week 22 occurred. The costs of maternal antenatal health care and delivery were significantly lower for the SET group. Preterm labour (P < 0.001), preterm premature rupture of the membranes (P = 0.003) and severe haemorrhage (P = 0.039) were significantly more common in the DET group. The rate of Caesarean section was considerably higher in the DET group (P < 0.0001). One twin pregnancy occurred in the SET group and 48 twin pregnancies and one triplet pregnancy in the DET group. Significantly more women experienced severe complications during pregnancy and delivery in the DET group [69/142 (48.6%)] compared to the SET group [39/128 (30.5%)] (P = 0.003). More patients had multiple complications in the DET group: 27/142 (19.0%) as compared with 6/128 (4.7%) in the SET group (P = 0.003). In the SET group 14/128 (10.9%) of the pregnant women were smokers and in the DET group 7/142 (4.9%) (P = 0.08). The mean total maternal health care cost was €6857 in the SET group and €6767 in the DET group (P = 0.677).

Costs of productivity losses
The women in the SET group had on average significantly fewer days of sick leave during pregnancy as compared with the DET group (14.1 versus 23.0; P = 0.031) and also a significantly lower total mean cost for absence from work (€1602 versus €2359; P = 0.022).

Paediatric costs and outcome, first 6 months of life (Tables III and IV)
Median gestational age and median birthweight were significantly lower in the DET versus the SET group (both P < 0.0001).
The preterm rate (<37 weeks) and the rate of low birthweight infants (<2500 g) were both significantly higher in the DET group (P = 0.002 and P < 0.0001 respectively). The median birthweights for singletons in the DET and SET groups were 3405 and 3550 g respectively (P = 0.198). The median gestational ages for singletons in the DET and SET groups were 282 days and 280 days (P = 0.256). A lower percentage of children in the SET group suffered severe neonatal complications, demanding neonatal care in hospital [23/129 (17.8%) versus 64/189 (33.9%); P = 0.003] and the hospitalization of the children in the SET group in the neonatal ward lasted a significantly lower number of days (P = 0.002). Morbidity also seemed more severe and complex in the DET group where 46/189 children (24.3%) had two or more complications, as compared to the SET group 10/129 (7.8%) (P = 0.0001). Mortality during the first 6 months was zero in the SET group and two in the DET group. In eight children major malformations were present at birth (SET, n = 5; DET, n = 3) and in eleven children there were minor malformations (SET, n = 5; DET, n = 6).

The mean health care cost per randomized woman for paediatric care and cost for readmission to the hospital during the first 6 months for her child/children, was significantly lower for the SET group (€2445 versus €5551; P < 0.0001). Costs per live-born child

The DET strategy resulted in 60 more live-born children, many of them twins, and the cost calculated per live-born child was €21572 in the DET group (4 077 155/189) and €23 798 (3 069 989/129) in the SET group if excluding costs for loss of productivity.

Effectiveness of the two IVF strategies

The rate of pregnancies resulting in at least one live-born child was 128/330 (38.8%) in the cumulative SET group...
Cost-effectiveness of SET and DET

Cost-effectiveness analysis

Total health care cost in the SET group was €3,069,989 and in the DET group when adjusted to 330 women €4,064,837 (4077.155 × 330/331) and the mean health cost per randomized woman was €99309 in the SET group and €12,318 in the DET group (P = 0.002). The difference, i.e. the additional cost for the DET group, was €994,848. The difference in number of deliveries with at least one live-born child was, if adjusted to 330 women, 13.957 (330/331 × 14). Thus, the incremental cost-effectiveness ratio (ICER) was €73,307 per extra delivery with live-born child. If the calculation includes productivity losses, the ICER is €91,702 per extra delivery.

The mother’s quality of life, 6 months after delivery

(Figure 1)

The SF-36 and the SPSQ questionnaires were each answered by 265/270 (98.1%) of the patients. No significant differences between the SET and DET groups were observed for either questionnaire.

Sensitivity analysis

A sensitivity analysis was performed where the mean actual treatment cost for IVF/ICSI (€3134) was doubled (€6269). The total health care cost per participating woman was thereby increased but was still lower in the SET group (€12,437 versus €15,452, P = 0.003). Similar results were found when production loss was included in the analysis (SET: €14,039 versus DET: €17,811: P = 0.001). The ICER was €73,315 per extra delivery, when health care costs were included, and €91,722 with costs for production loss also included.

A second sensitivity analysis where the NICU costs were increased by 50% was also performed. The total health care costs per participating woman were thereby increased for both groups but to a higher extent in the DET group (SET: €11,052 versus DET: €15,097: P = 0.004). The ICER was €98,361 per extra delivery when health care costs were included.

Table I. Severe obstetric complications, requiring hospital treatment; mode of delivery

<table>
<thead>
<tr>
<th></th>
<th>SET(n = 128)</th>
<th>DET(n = 142)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td>1</td>
<td>5</td>
<td>0.217</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>9</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td>Preterm labour</td>
<td>2 (1.6)</td>
<td>22 (15.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Preterm premature rupture of the membranes</td>
<td>1 (0.8)</td>
<td>12 (8.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Severe haemorrhage before, during or after delivery</td>
<td>21 (16.4)</td>
<td>39 (27.5)</td>
<td>0.039</td>
</tr>
<tr>
<td>Severe psychological complications</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrombo-embolic complications</td>
<td>1</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Obstetric infections</td>
<td>7</td>
<td>14</td>
<td>1.0</td>
</tr>
<tr>
<td>Total no. of complications (n)</td>
<td>43</td>
<td>106</td>
<td></td>
</tr>
</tbody>
</table>

| No. (%) of patients with | | |
| ≥1 diagnosis | 39 (30.5) | 69 (48.6) | 0.003 |
| ≥2 diagnoses | 6 (4.7) | 27 (19.0) | 0.0003 |
| ≥3 diagnoses | 0 | 9 (6.3) |
| ≥4 diagnoses | 0 | 2 (1.4) |

| Mode of delivery [n (%)] | | |
| Vaginal, spontaneous | 81 (63.3) | 57 (40.1) |
| Vaginal, instrumental | 16 (12.5) | 15 (10.6) |
| Caesarean section, total | 31 (24.2) | 70 (49.3) | < 0.0001 |
| Section, elective | 7 | 28 |
| Section, emergency | 24 | 42 |

Table II. Severe neonatal complications, requiring neonatal ward (each child can have more than one complication)

<table>
<thead>
<tr>
<th></th>
<th>SET group (n = 129)</th>
<th>DET group (n = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity*</td>
<td>12 (9.3)</td>
<td>47 (24.8)</td>
</tr>
<tr>
<td>Low birthweight*</td>
<td>10 (7.8)</td>
<td>43 (22.8)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>11 (8.5)</td>
<td>24 (12.7)</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>2 (1.6)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Septis or pneumonia</td>
<td>5 (3.9)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>3 (2.3)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>20</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Malformations*</td>
<td>4 (3.1)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>Other complications</td>
<td>0</td>
<td>2 (1.1)</td>
</tr>
</tbody>
</table>

Values are n (%).

*Only children treated in the neonatal ward are included in this table. The total number of children with low gestational age, low birthweight or malformations are presented in Table IV.

The SF-36 and the SPSQ questionnaires were each answered by 265/270 (98.1%) of the patients. No significant differences between the SET and DET groups were observed for either questionnaire.

Sensitivity analysis

A sensitivity analysis was performed where the mean actual treatment cost for IVF/ICSI (€3134) was doubled (€6269). The total health care cost per participating woman was thereby increased but was still lower in the SET group (€12,437 versus 15,452, P = 0.003). Similar results were found when production loss was included in the analysis (SET: €14,039 versus DET: €17,811: P = 0.001). The ICER was €73,315 per extra delivery, when health care costs were included, and €91,722 with costs for production loss also included.

A second sensitivity analysis where the NICU costs were increased by 50% was also performed. The total health care costs per participating woman were thereby increased for both groups but to a higher extent in the DET group (SET: €11,052 versus DET: €15,097: P = 0.004). The ICER was €98,361 per extra delivery when health care costs were included.

142/331 (42.9%) in the DET group (95% CI for the difference: 3.4–11.6) (Thurin et al., 2004).
Table IV. Neonatal outcome

<table>
<thead>
<tr>
<th></th>
<th>SET (n = 129)</th>
<th>DET (n = 189)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>276 (16.7)</td>
<td>265 (26.0)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>280 (200–298)</td>
<td>274 (168–304)</td>
<td></td>
</tr>
<tr>
<td>Low gestational age (&lt;37 weeks) [n (%)]</td>
<td>15 (11.6)</td>
<td>55 (29.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Very low gestational age (&lt;32 weeks) [n (%)]</td>
<td>4 (3.1)</td>
<td>49 (34.5)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3439 (721)</td>
<td>2938 (850)</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3545 (1190–4915)</td>
<td>3020 (505–5400)</td>
<td></td>
</tr>
<tr>
<td>Low birthweight (&lt;2500 g) [n (%)]</td>
<td>10 (7.8)</td>
<td>52 (27.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Very low birthweight (&lt;1500 g) [n (%)]</td>
<td>5 (3.9)</td>
<td>14 (7.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Treated in neonatal ward (days) [n (%)]</td>
<td>23 (17.8)</td>
<td>64 (33.9)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.9 (15.3)</td>
<td>9.9 (24.3)</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0–75)</td>
<td>0 (0–189)</td>
<td></td>
</tr>
<tr>
<td>1–10 days (n)</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>11–29 days (n)</td>
<td>3</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>&gt;29 days (n)</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>CPAP/respirator [n (%)]</td>
<td>8 (6.2)</td>
<td>21 (11.1)</td>
<td>0.166</td>
</tr>
<tr>
<td>Children with ≥2 diagnoses (%)</td>
<td>10 (7.8)</td>
<td>46 (24.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Apgar score [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min &lt;4</td>
<td>9 (7.0)</td>
<td>9 (4.8)</td>
<td></td>
</tr>
<tr>
<td>5 min &lt;7</td>
<td>4 (3.1)</td>
<td>8 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Neonatal mortality (n)</td>
<td>0</td>
<td>2*</td>
<td></td>
</tr>
<tr>
<td>Multiple births [n (%)]</td>
<td>1 (0.8)</td>
<td>49 (34.5)*</td>
<td></td>
</tr>
</tbody>
</table>

*aCalculated with Mann–Whitney U-test.
*bBoth infants died within the first day of life.
*cIn three twin pregnancies one of the two fetuses died in utero [delivery in week 24.0 in two cases and in week 27.1 (acrania) in one case]. In Sweden a stillborn fetus born before 28 full gestational weeks is not considered a child according to the law. One set of triplets was born, all alive.

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

Discussion

In the present cost-effectiveness analysis effectiveness was defined as ‘delivery with at least one live-born child’. Of course this definition of effectiveness can be discussed. However, we think that this definition of success after IVF can be accepted by most IVF clinicians. An alternative definition of success, the BESST endpoint, defined as ‘birth of a singleton child at term’ was recently suggested by Min et al. (2004). However, according to the following debate in Human Reproduction this more strict definition of success did not seem to be accepted by a majority of the readers. One major concern with this definition is that it raises huge problems how to define a healthy child (Wennerholm and Bergh, 2004a).

The study has a high degree of generality since the patients were recruited from 11 IVF units in three Scandinavian countries, with meticulous registration of care. The protocol also stated that patients should be treated according to ordinary routines. Costs for particular services were calculated from one centre. The strength of such an approach is that it gives a good view of relative costs for different services during the treatment, while the weakness may be that this particular clinic is not representative of all hospitals providing IVF in Scandinavia or other centres worldwide. However, checking some key cost items with another hospital indicated slightly higher costs at that centre. Thus, we have no support for an overestimation of medical costs in our analysis. The costs of productivity losses were difficult to calculate owing to methodological issues, and assumptions and average costs in Swedish society have been used. The costs of sick leave also vary, depending on the particular social welfare system in each country. These costs are probably higher in Scandinavia, with its state-supported social security system, than in many other parts in the world. As we have only estimated costs of productivity losses for employed women, and as we used the average income for all women, we may have underestimated this cost. Some costs were not included in the analysis, but probably affected the SET and DET groups equally, such as the costs of absence from work for complications and pregnancy loss for the patients not achieving a live birth, and transportation costs.

We used Student’s t-test when comparing arithmetic means of costs. t-Tests and confidence intervals are advocated for cost comparison even if the results are skew when the sample size is moderately large (Thompson and Barber, 2000) as in the current study. The robustness and the generality of the results were supported by the sensitivity analyses. In particular, in the USA the treatment costs are considerably higher than in Europe. Doubling the treatment costs did not change the overall results when comparing SET and DET, and the costs of the SET strategy were still significantly lower than for DET, and the ICER for an extra delivery in the DET group was high. We included two kinds of quality of life questionnaires, which were answered by almost all women achieving a live birth. It has previously been found that mothers of multiple birth babies suffer a considerable social burden (Cook et al., 1998; Bryan, 2003). The results from both questionnaires, however, indicated a high quality of life in both groups. As there were no differences in quality of life between the groups, this aspect was not further taken into account in the economic analysis. The reason for following children and including costs up to the...
Cost-effectiveness of SET and DET

Figure 1. (a) Comparison of the SF-36 questionnaire between the single embryo transfer (SET) and double embryo transfer (DET) study groups: physical functioning (PF; $P = 0.885$); role physical (RP; $P = 0.708$); bodily pain (BP; $P = 0.835$); general health (GH; $P = 0.197$); vitality (VT; $P = 0.736$); social functioning (SF; $P = 0.304$); role emotional (RE; $P = 0.492$), mental health (MH; $P = 0.594$). Higher values indicate better health. A comparison with a Swedish normal population of women 30–35 years of age is also shown. Reasons for not responding were as follows. The SET group (three patients): one woman who gave birth to a severely impaired child has still not recovered well enough to be asked; one patient has moved abroad and cannot be reached; the SF-36 was not filled in by one patient, because of a new pregnancy, and she felt the answers would be misleading. The DET group (two patients): one of the patients does not have any living child, both died at birth. One patient decided not to fill in the questionnaires for social reasons; one patient, the triplet mother, did not fill in the SPSQ due to attention a clinical decision-making problem that is present in many countries. Before a final conclusion can be drawn concerning policy recommendations, modelling of the expected lifetime costs for the two alternatives should be performed. Still not all costs for long-term complications are included. Put in a broader health policy context, when ICER for new treatments around or above €50,000 per extra life-year with full health is debated, then €72,000 per extra delivery seems to be a low value as the number of expected life-years per newborn might be 75 years. However, it is not obvious that the number of expected life-years gained really should be included in the analysis. The debate in Sweden and other countries about the reimbursement of IVF clearly indicates that society does not perceive the outcome of IVF in terms of life-year gain equal to life-year gained in treatment of severe diseases such as cancer or coronary infarction. We have brought to attention a clinical decision-making problem that is present in many countries. Before a final conclusion can be drawn concerning policy recommendations, modelling of the expected lifetime costs for the two alternatives should be performed.

In conclusion, with a defined budget and demand exceeding supply in IVF treatments, the SET strategy is perceived as superior to DET, when number of deliveries with at least one complications were observed in the DET group mainly due to a higher rate of multiple births and thus a higher number of prematurely born children. The long-term medical prognosis for the children cannot yet be predicted at the age of 6 months and the future costs for these children, in some cases severely ill, will probably be very large. It is known that cerebral palsy and major malformations are more common in children born in a multiple gestation (Petterson et al., 1999; Strömberg et al., 2002; Källén et al., 2005). The median birthweight for singletons in the DET and SET groups did not differ significantly although a median difference of 145 g was noted in favour of the SET singletons. Singletons after SET might have a better obstetric outcome than singletons after IVF in general. In a recent Belgian study, SET singletons were found to compete favourably with spontaneously conceived singletons (De Neubourg et al., 2005). Singletons after transfer of two or more cleaved embryos have in several publications been shown to have a worse outcome than spontaneously conceived singletons (Bergh et al., 1999; Schieve et al., 2002; Helmerhorst et al., 2004; Jackson et al., 2004; Wennerholm and Bergh, 2004b), which at least partly might be due to competition between embryos at implantation.

This analysis shows lower total costs with the SET strategy as compared with DET. Moreover, the SET strategy results in a marked reduction in the rate of prematurely born children and days in neonatal ward for the children, and a reduction in severe maternal and paediatric complications. The fact that the DET strategy results in a few more deliveries of at least one live-born child, of a high incremental cost, makes it difficult to interpret the results from a policy-making perspective without bringing two conditions into the analysis. It is reasonable from a clinical perspective to assume that we have a fixed budget for IVF care, e.g. €4 million, comparable to the total health care cost for DET in this study, and an extensive list of couples waiting for IVF treatment. If we choose the DET strategy, 331 women will be treated, resulting in 142 deliveries with at least one live-born child (€28,712 per delivery). With the same budget, the SET strategy will allow for treatment of 437 women, resulting in 170 deliveries (€23,984 per delivery). The cost per extra delivery was €71,940 and €89,940 if productivity costs are included. Still not all costs for long-term complications are included. Put in a broader health policy context, when ICER for new treatments around or above €50,000 per extra life-year with full health is debated, then €72,000 per extra delivery seems to be a low value as the number of expected life-years per newborn might be 75 years. However, it is not obvious that the number of expected life-years gained really should be included in the analysis. The debate in Sweden and other countries about the reimbursement of IVF clearly indicates that society does not perceive the outcome of IVF in terms of life-year gain equal to life-year gained in treatment of severe diseases such as cancer or coronary infarction. We have brought to attention a clinical decision-making problem that is present in many countries. Before a final conclusion can be drawn concerning policy recommendations, modelling of the expected lifetime costs for the two alternatives should be performed.

In conclusion, with a defined budget and demand exceeding supply in IVF treatments, the SET strategy is perceived as superior to DET, when number of deliveries with at least one

child’s age of 6 months was to include costs of neonatal and early childhood complications. We assessed paediatric morbidity in collaboration with neonatologists at the local hospitals, blinded to the randomization group. More severe and complex
live-born child and complications are considered. Thus, our findings do not support continuing transfers of two embryos in this group of patients.

Acknowledgements

The following investigators participated in the study: Sweden: A.Thurin Kjellberg, L.Nilsson, C.Bergh, G.Westlander, E.Ekeroth, A.Cerne, L.Lindborg, A.K.Lind, I.Wikander, G.Borg (Reproductive Medicine, Sahlgrenska University Hospital, Göteborg); M.Wikland, T.Hillensjö, M.Wood, J.Olofsson, K.Borg (Fertility Center Scandinavia, Carlendarska Hospital, Göteborg); L.Marsk, K.G.Nygren, M.Steffensson (IVF Clinic, Sophiahemmet, Stockholm); B.Jablownowska, S.Kjellberg, A.Johansson, M.Wallström (Reproductive Medicine Center, University Hospital, Linköping); S.Nilsson, U.Walenström, M.Blennborn (IVF Clinic, Falun Hospital, Falun); Norway: J.Hausken, E.Oldland Anunden (Fertility Clinic, Hauessund Hospital, Hauessed); V.von During (Fertility Clinic, Sankt Olav University Hospital, Trondheim); Denmark: A.Pinborg, A.Loft, A.Nyboe Andersen (Fertility Clinic, Rigshospitalet, Copenhagen); K.Erb, P.E.Rasmussen (Fertility Clinic, University Hospital, Odense); A.L.Mikkelsen, R.Lindberg, H.U.Dengaard (Fertility Clinic, Herlev Hospital, Copenhagen); H.Ejdrup Braedkjer, M.L.Gröndahl (Fertility Clinic, Hvidovre Hospital, Copenhagen). We are indebted to Professor O.Finnström, Department of Paediatrics, Linköping University Hospital, for help with assessment of neonatal and infant outcome; and to N.G.Pehrsson and G.Ekeroth for statistical support. This study was supported by a grant from Serono Nordic, by the Göteborg Medical Society and by the Hjalmar Svensson Foundation.

References


Ware JE, Snow KK, Kosinski M and Gandek B (1993) SF-36 Health Survey Manual and Interpretation Guide. New England Medical Center, The Health Institute, Boston, MA, USA.


Wennerholm U-B and Bergh C (2004b) What is the most relevant standard of success in assisted reproduction? Singleton live births should also include preterm births. Hum Reprod 19,1943–45.


Submitted on May 28, 2005; resubmitted on July 20, 2005; accepted on July 25, 2005.