A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI

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BACKGROUND: Single embryo transfer (SET) is the sole strategy with which to reduce the incidence of twins following assisted reproductive technology (ART), but SET may increase the number of ART cycles needed per live-born child. Its cost-effectiveness compared with double embryo transfer (DET) is therefore unknown.

METHODS: A decision-analytic model comparing SET with DET was developed. Estimates were obtained from literature, national pregnancy registers and local hospital records. A sensitivity analysis was performed, using pregnancy rates from four published studies. The outcome measure was the cost per child born, calculated from IVF procedure-related, pregnancy-related and neonatal care costs. Neonatal mortality and long-term morbidity costs were not taken into account.

RESULTS: Independently of the pregnancy rates used, the SET cost per child born was in all instances the same as with DET, varying from €9 520 (SET) versus €9 511 (DET) to €12 254 (SET) versus €12 934 (DET).

CONCLUSIONS: More ART cycles are required to obtain the same numbers of children born following SET compared with DET. Because SET allows the avoidance of twins and thus diminishes pregnancy-related and neonatal care costs, there is no difference in the cost per child born between SET and DET. The real advantage of SET is the avoidance of the very high long-term costs resulting from the increased morbidity of twins after birth.

Key words: cost-effectiveness/decision-analytic model/health-economics/IVF–ICSI/single embryo transfer

Introduction

Infertility is an important issue for health-economic evaluation because of the high impact on society (Philips et al., 2000). The demand for infertility treatment is still increasing and both patients and insurance companies want to know how much a given treatment will cost. A less efficacious but relatively cheap treatment (e.g. no treatment or intrauterine inseminations) may be preferred over a more efficacious but more expensive technique (e.g. IVF, ICSI) (Mol et al., 2000). New and more successful drugs may be more expensive than older, less successful ones and the decision for reimbursement undoubtedly requires an economic evaluation. The studies comparing urinary and recombinant gonadotrophins are a recent example of the importance of health-economics in assisted reproduction. Several meta-analyses, published a couple of years ago, have demonstrated the superiority of recombinant gonadotrophins over the older urinary products (Out et al., 1996; Daya and Gunby, 1999). Recently the same groups published a cost-effectiveness study showing that recombinant gonadotrophins may be more expensive, but due to their superiority, are more cost-effective than the urinary products (Daya et al., 2001; Sykes et al., 2001; Silverberg et al., 2002).

The cost-effectiveness studies of recombinant gonadotrophins illustrate the methodology used in health-economics. Since a prospective economic evaluation of a sufficiently large group of real patients is almost impossible to perform in practice, a mathematical simulation is used. A decision-analytic model, called a Markov model (Briggs and Sculpher, 1998) consists of a tree structure in which each arm corresponds to a certain outcome occurring with a certain probability. Probabilities for each arm as well as estimates of costs for each particular outcome are obtained from meta-analyses, randomized trials, national registries, insurance data and expert opinions. A computer program allows a high number of virtual patients enter the tree model and calculates the final outcomes and corresponding costs. Since the input parameters can be varied, the impact of each individual parameter on the output can be studied. This so-called sensitivity analysis has the limitation that only one parameter can be varied at a time, in contrast to the Monte Carlo method (Doubilet et al., 1985) where distributions of all parameters are taken into account at once.

We developed a simple reproducible decision-analytic model in Microsoft Excel to investigate the cost-effectiveness of single embryo transfer (SET). Elective SET unquestionably is the only effective measure to reduce the incidence of twins following assisted reproduction techniques (ART) (Dhont,
2001; Gerris et al., 2001). Although this principle has already been acknowledged both from a medical and an ethical point of view (ESHRE Campus Course Report, 2001), the cost-effectiveness of SET has not yet been established using real pregnancy rates. Wølner-Hanssen and Rydhstroem have calculated the cost-effectiveness of SET using hypothetical pregnancy rates, no exact data on the success of SET being available at that time (Wølner-Hanssen and Rydhstroem, 1998).

It can be anticipated that by performing SET the number of ART cycles needed to obtain a pregnancy will be increased. Of paramount importance, therefore, is the question to what extent SET would influence the success rate of ART. Only a health-economic analysis taking into account all possible variables can answer this question (Meltzer, 2001). Another aspect is that many infertile couples deliberately opt for a twin pregnancy to short-cut their costly and unpredictable efforts to establish a family. In comparing SET with double embryo transfer (DET), there are various costs to consider: direct and indirect; short and long-term; and those that are measurable and non-measurable. These latter costs are especially difficult to calculate.

**Materials and methods**

For our model we developed a spreadsheet tree model as depicted in Figure 1. A probability must be attributed to each branch of the tree and looping must be possible. After each failed treatment cycle we allowed each patient to stop or to continue, with a fresh or thaw cycle, depending on whether embryos remained frozen. A pregnancy may end in a miscarriage and in our model the most important outcome events are of course premature birth and the costs of neonatal intensive care. When a computer simulation is used one has the choice to define the end-point as the birth of two healthy children and the model could then calculate how many cycles of SET as compared with DET are required and at what overall cost.

Of course the results of this modelling exercise strongly depend on the estimates used, and the value of the conclusions therefore depends on the reliability of the data used for input. Pregnancy rates in particular may vary widely between centres and therefore influence the analysis. Also the cost of the IVF procedure itself may vary extensively and finally the real costs of premature twin births are difficult to estimate correctly.

In our model we had to agree on certain presumptions. Every patient remained in the group to which she was originally assigned (all SETs or all DETs but no mixing of SET and DET) and the pregnancy rates remained constant for each cycle. In the model we also put the limit at one successful pregnancy, except when embryos are frozen (they belong to the original cycles and all should be used to calculate the cost/effectiveness of the procedure). We also assumed that pregnancies obtained by frozen-thawed embryos are all singletons. We restricted our exercise to three cycles, relying on the fact that the pregnancy rates remained constant during at least the first three treatment cycles (Croucher et al., 1998). Finally, we also selected a group of patients with a good prognosis because all available data on SET have been obtained in young patients with good embryo quality. We therefore assumed that there were no cancelled stimulation cycles, no retrievals without oocytes and no fertilization failures, and that in this patient population all women had a transfer. This is a very important point to realize, since this model therefore does not allow the ability to test a realistic situation, in which the transfer of one or two embryos may be chosen depending on patients age, number of previous cycles, and embryo quality.

Our model therefore strictly compared SET and DET in the same patient group and cannot be used to evaluate an ‘optimal and individualized transfer strategy’.

Our model started running at the time of embryo transfer and ended with the birth of the child. For simplicity’s sake we entered 1000 women in each group.

Table I summarizes the estimates used in the model. These estimates were obtained from the literature where available. The cost of course is a very local variable and we based our estimates on the costs from

![Figure 1. Decision-analysis tree model used for the comparison of SET and DET.](https://academic.oup.com/humrep/article-abstract/17/11/2891/635311/71/12891635311)
the Gent University Hospital in 2001. IVF costs in Table I are the
global costs (both patients’ and societal), calculated from our own
programme, averaging all cycles performed in 2001 (both IVF and
ICSI), including the stimulation by a short protocol with urinary
gonadotrophins, ultrasound monitoring and oocyte retrieval procedure.
Pregnancy costs are calculated from an average number of prenatal
consultations and hospitalization, whereas vaginal delivery and
Caesarean section costs include both the procedure and hospital stay.
We do not account for perinatal mortality and morbidity, but rather
for the number of days of admission in a neonatal care unit. Costs
of neonatal intensive care are also obtained from our own university
hospital (2001). Pregnancy outcome data are taken from the regional
register of perinatal activities in Flanders (SPE, 2000).

Table I. Estimates used for the decision-analytic model comparing SET with DET

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>% cycles with freezing</td>
<td>80</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>% pregnancy rate SET</td>
<td>See text</td>
<td></td>
</tr>
<tr>
<td>% pregnancy rate DET</td>
<td>See text</td>
<td></td>
</tr>
<tr>
<td>% twins after DET</td>
<td>35</td>
<td>(calculated from Martikainen et al., 2001)</td>
</tr>
<tr>
<td>% of SET/thaw cycles</td>
<td>113.5</td>
<td>(calculated from Martikainen et al., 2001)</td>
</tr>
<tr>
<td>% of DET/thaw cycles</td>
<td>80</td>
<td>(calculated from Martikainen et al., 2001)</td>
</tr>
<tr>
<td>% PR frozen/thawed embryos</td>
<td>15</td>
<td>(Martikainen et al., 2001)</td>
</tr>
<tr>
<td>% miscarriage rate singleton &lt; 12 weeks</td>
<td>20</td>
<td>(Tummers et al., 2002)</td>
</tr>
<tr>
<td>% complete miscarriage twin &lt; 12 weeks</td>
<td>5</td>
<td>(Tummers et al., 2002)</td>
</tr>
<tr>
<td>% partial miscarriage twin &lt; 12 weeks</td>
<td>12</td>
<td>(Tummers et al., 2002)</td>
</tr>
<tr>
<td>% drop-outs if not pregnant</td>
<td>27–33–36</td>
<td>(De Vries et al., 1999)</td>
</tr>
<tr>
<td>% drop-outs after miscarriage</td>
<td>10</td>
<td>(estimate after Croucher et al., 1998)</td>
</tr>
<tr>
<td>% ongoing singletons &gt; 37 weeks</td>
<td>93.8</td>
<td>(SPE, 2000)</td>
</tr>
<tr>
<td>% ongoing twins &gt; 37 weeks</td>
<td>44.1</td>
<td>(SPE, 2000)</td>
</tr>
<tr>
<td>Days NN care/baby born &lt; 37 weeks</td>
<td>20</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>% Caesarean section for singleton</td>
<td>15.8</td>
<td>(SPE, 2000)</td>
</tr>
<tr>
<td>% Caesarean section for twins</td>
<td>48.8</td>
<td>(SPE, 2000)</td>
</tr>
<tr>
<td>Direct costs of one IVF cycle (€)</td>
<td>2250</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of a freezing cycle (€)</td>
<td>250</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of a thawing cycle (€)</td>
<td>250</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of a miscarriage * (€)</td>
<td>1000</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of pregnancy singleton (€)</td>
<td>1000</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of pregnancy twin (€)</td>
<td>4000</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of vaginal delivery (€)</td>
<td>2500</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of Caesarean section (€)</td>
<td>4000</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
<tr>
<td>Cost of neonatal stay/day (€)</td>
<td>500</td>
<td>(University Hospital Gent, 2001)</td>
</tr>
</tbody>
</table>

PR = pregnancy rate.
NN = neonatal.
*Including sick leave and curettage.

Results
As an example we will discuss in detail the results of the
model using the Martikainen et al. (2001) data. If 1000 women
are included in the SET group for one cycle, this yields 368
singleton pregnancies (including the pregnancies occurring
after the transfer of all frozen–thawed embryos), 165 failed
cycles from patients who do not start a second cycle and 495
failed cycles from patients who continue their treatment. In
all, 92 miscarriages will have to be accounted for. Using the
same estimates, except for a higher drop-out rate (De Vries
et al., 1999), the 495 couples starting a second cycle will
obtain a total (fresh and frozen–thawed) of 182 ongoing
singleton, 46 miscarriages, and 99 failures who drop-out,
leaving 228 couples starting for a third time. The third
cycle yields 84 singleton pregnancies and 21 miscarriages. In
conclusion, after three cycles, 634 ongoing singleton pregnan-
cies are obtained and 159 miscarriages. Using the cost estimates
from Table I, a cost of €11 805 per child born was obtained
(Table II). This cost does not increase with the cycle number,
since all estimated costs remain constant throughout the three cycles.

If 1000 women are included in the DET model, the figures become quite different. After one cycle 341 singletons and 137 twins, yielding a total of 615 children are obtained, with 89 miscarriages, 137 drop-outs and 416 patients who will start again. In the second cycle 256 children (142 singletons and 57 twins) and 37 miscarriages are obtained; 69 patients drop-out and 161 patients continue. In the third cycle 99 children are born (55 singletons and 22 twins) and 14 miscarriages.

The costs per child born amounts to €10 966 These results are summarized in Table II.

Table III shows the different results using pregnancy rates for SET and DET as obtained from the four studies discussed above. Whichever pregnancy rate is used in the model, there are no substantial differences regarding the costs per child born between the four data sets. Statistical comparison of these figures is impossible since we have not used the Monte Carlo simulation in which confidence intervals around the estimates are entered in the model.

**Discussion**

The results of these calculations, using pregnancy rates from four different studies, may seem surprising, since intuitively one assumes that pregnancy rates are of absolute importance in determining the cost-effectiveness of the treatment. Of course, when the pregnancy rates are elevated, the child per cycle rate is also elevated, but that is not the subject of our analysis. Using the data from the two randomized trials (which yield higher pregnancy rates with DET than with SET), the SET procedure is equally (Gerris et al., 1999) or only slightly more (7%, Martikainen et al., 2001) cost-effective than the DET procedure. Using the data from the two non-randomized studies (Vilska et al., 1999; De Sutter et al., 2000), SET is 5–6% cheaper than DET per child born.

It is probable that the differences in the figures obtained by the four different studies are due to the nature of the studies themselves. The study by Gerris et al. used very rigorous criteria to perform SET (only when at least two top quality embryos were available) (Gerris et al., 1999). Criteria to perform SET were different in the Martikainen study (Martikainen et al., 2001), and the two other studies comparing SET with DET (Vilska et al., 1999; De Sutter et al., 2000) were not randomized, but left the choice to the couple. Therefore, in the two latter studies SET was performed on demand, even when no top quality embryos were available. It is clear that both the level of counselling and the evaluation of the embryo quality (Van Royen et al., 1999, 2001) will influence the degree of application of SET in an IVF programme. A distinction should therefore be made between these studies and a theoretical model, such as discussed, which tests a virtual population of 100% good prognosis patients (in whom top quality embryos will be available). In reality, embryo transfer strategy will be individualized, taking into account patient’s prognostic factors and the availability of one or more top quality embryos. In each cycle the choice between SET and DET will be made in order to obtain the ideal trade-off between a maximum chance of pregnancy and a minimal risk for a twin pregnancy. An optimized strategy implies that SET will be performed when at least one top quality embryo is available, and DET when no top quality embryos are obtained.

An important question is whether changing the cost of the IVF procedure itself and of neonatal intensive care would influence the results of the analysis. Performing a sensitivity analysis for different ranges of costs of the IVF procedure on the one hand, and of neonatal care on the other hand, the differences in cost-effectiveness between SET and DET never exceed 10% (data not shown). Of course, in doing this exercise, we assume that in countries where IVF is more expensive, neonatal critical care is more expensive as well, and vice versa.

Many cost-effectiveness studies on ART have been published previously. One study (Neumann et al., 1994) calculated the cost of a successful delivery after IVF (independent of the fact whether it was a singleton or a multiple pregnancy) to be US$66 667 for the first cycle up to US$114 286 by the sixth cycle. These seemingly high costs can be explained by the fact that the data used in this study dated from the pre-ICSI era when delivery rates for IVF were lower than today (from 12% in the first cycle to 7% in the sixth). It has been estimated (Collins, 2001) that for 2001 the median projected cost for an IVF delivery would be US$56 419 in the US and US$20 522 in other countries. Another study (Callahan et al., 1994) showed that hospital charges (per baby) are doubled for twins compared with singletons, both for the mother and the child(ren). All studies show that the cost of ART is significantly increased by multiple pregnancies. It is

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**Table III. Cost-effectiveness of SET versus DET after three consequent cycles, with 1000 couples entering the model, using the figures from Gerris et al., 1999 (1); Martikainen et al., 2001 (2); Vilska et al., 1999 (3); and De Sutter et al., 2000 (4).**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of cycles</th>
<th>Pregnancy rate</th>
<th>Children born</th>
<th>Twin pregnancies</th>
<th>Child/cycle</th>
<th>Cost/child (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>DET</td>
<td>1533</td>
<td>1723</td>
<td>1749</td>
<td>1635</td>
<td>1303</td>
<td>1577</td>
</tr>
<tr>
<td></td>
<td>0.538</td>
<td>0.324</td>
<td>0.297</td>
<td>0.420</td>
<td>0.777</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>826</td>
<td>634</td>
<td>606</td>
<td>727</td>
<td>1257</td>
<td>970</td>
</tr>
<tr>
<td></td>
<td>826</td>
<td>634</td>
<td>606</td>
<td>727</td>
<td>669</td>
<td>538</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>294</td>
<td>216</td>
</tr>
<tr>
<td></td>
<td>0.54</td>
<td>0.37</td>
<td>0.35</td>
<td>0.44</td>
<td>0.96</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>9 520</td>
<td>11 805</td>
<td>12 254</td>
<td>10 563</td>
<td>9 511</td>
<td>10 966</td>
</tr>
</tbody>
</table>
well known from the literature that twins lead to a higher maternal and neonatal morbidity and mortality, (The ESHRE Capri Workshop Group, 2000; for review). When comparing ART pregnancies with spontaneous controls, we have previously shown that for ART pregnancies the incidence of Caesarean section is significantly increased (Dhont et al., 1999). Moreover, some authors have demonstrated that ART twin pregnancies have more pregnancy complications and a more adverse perinatal outcome than spontaneous twins (Bernasko et al., 1997; Daniel et al., 2000; Lynch et al., 2002). For all these reasons the cost of an ART twin pregnancy is a multiple of that of an ART singleton pregnancy, which is already much more expensive than a spontaneous singleton pregnancy. The ESHRE Capri Workshop Group calculated the cost of a twin delivery after ART to be four times higher than that of an ART singleton delivery (ESHRE Capri Workshop Group, 2000). Obviously, the differences between all these data and the costs used in the present study do not only depend on local economical variables, but also on the success rates of IVF used to calculate these costs.

Regarding SET and DET, only one group has calculated the theoretical costs of pregnancies after SET compared with DET (Wölsner-Hanssen and Rydstroem, 1998). The method they used to calculate the costs was different from ours and in 1998 no data from trials comparing SET with DET were available. However, these authors reached a similar conclusion to ours, namely that although more treatments might be needed to achieve a similar take-home baby rate after transfer of one compared with two embryos, the lower twin pregnancy rate of the former approach causes it to be more cost-efficient than the latter.

Very recently a prediction model for selecting patients for SET in IVF has been published (Hunault et al., 2002). In this study, in common with other studies (Coetsier and Dhont, 1998; Strandell et al., 2000; Engmann et al., 2001), which also ran a database analysis, they conclude that applying SET in a good-prognosis subgroup of patients drastically diminishes the twin rate without compromising singleton pregnancy rates. It seems that more and more authors are becoming convinced of the value of SET, at least on the basis of theoretical speculations. The present analysis suggests that the SET strategy is defendable not only medically and ethically, but also economically.

In conclusion, our calculations show that the cost per child born is not different whether the SET or the DET approach is used. DET is more effective in terms of child per cycle rate, but SET is as cost-effective per child born. It is clear that the twins originating from DET increase the indirect and long-term costs, which are not calculated in the present model. Twins have a perinatal mortality of 25/1000 versus singletons 6/1000 (SPE, 2000) and it is well documented that the long-term morbidity is much higher with twins than with singletons (Wölsner-Hanssen and Rydstroem, 1998). There is more need for hospitalization, special education and training due to cerebral palsy and other handicaps following preterm birth (Peterson et al., 1990). Twins have a 6-fold increased risk of mortality (Luke and Keith, 1992) and a 13-fold increased risk of handicap (Yokoyama et al., 1995). The present model only calculates the economic costs of neonatal care, but does not cipher the economic impact of mortality and long-term morbidity. The message is clear: although DET leads to more children in fewer cycles, economically SET and DET are break-even; and in the long-term SET is definitely more advantageous than DET. The final validity of all these assumptions remains to be proven in a health-economic impact study comparing SET with DET in a real clinical setting.

References