Cost-effectiveness of a mild compared with a standard strategy for IVF: a randomized comparison using cumulative term live birth as the primary endpoint

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BACKGROUND: Conventional ovarian stimulation and the transfer of two embryos in IVF exhibits an inherent high probability of multiple pregnancies, resulting in high costs. We evaluated the cost-effectiveness of a mild compared with a conventional strategy for IVF. METHODS: Four hundred and four patients were randomly assigned to undergo either mild ovarian stimulation/GnRH antagonist co-treatment combined with single embryo transfer, or standard stimulation/GnRH agonist long protocol and the transfer of two embryos. The main outcome measures are total costs of treatment within a 12 months period after randomization, and the relationship between total costs and proportion of cumulative pregnancies resulting in term live birth within 1 year of randomization. RESULTS: Despite a significantly increased average number of IVF cycles (2.3 versus 1.7; \(P<0.001\)), lower average total costs over a 12-month period (8333 versus €10 745; \(P=0.006\)) were observed using the mild strategy. This was mainly due to higher costs of the obstetric and post-natal period for the standard strategy, related to multiple pregnancies. The costs per pregnancy leading to term live birth were €19 156 in the mild strategy and €24 038 in the standard. The incremental cost-effectiveness ratio of the standard strategy compared with the mild strategy was €185 000 per extra pregnancy leading to term live birth. CONCLUSIONS: Despite an increased mean number of IVF cycles within 1 year, from an economic perspective, the mild treatment strategy is more advantageous per term live birth. It is unlikely, over a wide range of society’s willingness-to-pay, that the standard treatment strategy is cost-effective, compared with the mild strategy.

Keywords: GnRH antagonist; mild ovarian stimulation; single embryo transfer; IVF

Introduction
The increasing success of IVF in the 1990s did not just result in an increased pregnancy rate, but especially in an increase in the incidence of multiple births (Fauser et al., 1999, 2005). Several cost studies have demonstrated the impact of multiple births on health care resources (Callahan et al., 1994; Gerris et al., 2004; Kjellberg et al., 2006). Conventional ovarian stimulation along with the transfer of two embryos in IVF exhibits an inherent high probability of multiple pregnancies, resulting in high costs due to intensive antenatal surveillance, increased chances for complications of both mother and child with associated hospital admissions, a higher chance for caesarian section and perinatal and postpartum care (Wolner-Hanssen and Rydhstroem, 1998; Gerris et al., 2004; Lukassen et al., 2004). The financial burden of multiple births on health care resources has been calculated to be greater than the costs of IVF treatment itself (Collins et al., 2000). There is a growing awareness that the high rate of multiple pregnancies can be greatly reduced by a single embryo transfer (SET) policy (Thurin et al., 2004; Fauser et al., 1999, 2005; Papanikolaou et al., 2006). However, SET results in a reduced live birth rate per IVF treatment cycle, which can to some extent be overcome by cryopreservation of supranumerary embryos (Thurin et al., 2004; Pandian et al., 2005). There is a clear need for the further evaluation of efficacy and economic consequences of different approaches in IVF, including SET.

The introduction of GnRH antagonists into clinical practice has enabled the development of novel milder ovarian stimulation protocols (Fauser et al., 1999, 2005; Macklon et al., 2006). Mild stimulation might be advantageous when evaluated over an entire (multiple cycle) treatment period, since
the amount of time needed to complete a single IVF cycle is reduced, the costs of stimulation are lower (Hohmann et al., 2003; Tarlatzis et al., 2006), patient discomfort and chances for complications may be reduced and the patient dropout rate may decrease. Milder treatment strategies including SET may allow for more IVF cycles in the same period of time and therefore result in a similar term live birth rate per treatment period compared with standard stimulation protocols with the transfer of two embryos (Heijnen et al., 2004; Eijkemans et al., 2006). Such a mild treatment strategy may also reduce costs by eliminating multiple pregnancies. As reported recently, a mild approach in IVF results in a similar 1-year cumulative proportion of pregnancies leading to term live birth compared with a standard treatment strategy (standard ovarian stimulation protocol, including GnRH agonist long protocol co-treatment and the transfer of two embryos) in women less than 38 years of age, while greatly reducing multiple pregnancy rates (Heijnen et al., 2007). Consequently, the total costs of treatment (including the obstetric and post-natal period) were significantly reduced (Heijnen et al., 2007). The aim of the current paper is to provide additional information concerning the economic consequences of two different treatment strategies in IVF involving ovarian stimulation protocols and embryo transfer policies during consecutive treatment cycles.

Materials and Methods

Study design
The study protocol was approved by the ethics review board of both participating University Medical Centers (Utrecht and Rotterdam). Patients were recruited from February 2002 until March 2004 (Eijkemans et al., 2006). Patients with a regular indication for IVF or IVF/ICSI (tubal, male and unexplained), female age <38 years, normal menstrual cycle (cycle length between periods 25–35 days) and without severe obesity or underweight (body mass index 18–28 kg/m²) were eligible for the study. Patients were randomly assigned to undergo either mild ovarian stimulation with GnRH agonist co-treatment combined with SET (mild strategy, n = 205), with reimbursement of a maximum of four treatment cycles, or a ‘standard’ ovarian stimulation protocol (n = 199) where pituitary down-regulation was achieved using a GnRH agonist long-protocol combined with the transfer of a maximum of two embryos (standard strategy), with reimbursement of up to three treatment cycles. Full details of the trial design, interventions and clinical outcomes have been reported elsewhere (Eijkemans et al., 2006; Heijnen et al., 2004, 2007).

The endpoint for this study was defined as mean total costs of IVF treatment per couple within 12 months after randomization, including costs of resulting pregnancy and post-natal costs of the mother and the infant(s) up to 6 weeks after the expected date of delivery. A summary of the mean total costs has been published earlier (Heijnen et al., 2007). In the current paper, the extended cost analysis will be addressed, including costs per completed IVF treatment and cost per term child born. To make a full economic comparison of the two treatment strategies, the difference between the two groups in mean total costs will be related both to the difference in the proportion of pregnancies leading to term live birth within 1 year of randomization and to the difference in the number of term born children.

Cost calculations
The economic analysis was performed from a societal perspective. The costs of the two IVF strategies were assessed in two stages. First, the cost of IVF treatment itself, starting with the first IVF cycle and ending with the outcome of the last IVF-cycle within 1 year (pregnant, no pregnancy or dropout). Second, the costs of antenatal, peripartum and post-partum care were analysed in women who became pregnant after IVF treatment.

Medical costs were calculated by multiplying the volumes of health care use with the corresponding unit prices. The costs apply to the financial year 2004. The costs of IVF treatment were distinguished into medical costs in the hospital (intramural), extramural medical costs and non-medical costs. Medical costs in the hospital consist of scheduled and unscheduled outpatient visits, number of IVF cycles, personnel time per cycle, use of GnRH analogues and recombinant FSH, costs of ultrasound and hormone monitoring, the embryo transfer procedure and costs associated with complications. Extramural medical costs consist of general practitioner consultations, and social worker. Non-medical costs are associated with travel and absence from work/sick leave due to the treatment or associated complications. Cost volumes in the treatment stage were recorded with case record forms, hospital-based management and budgetary information systems, patient questionnaires and literature (Fig. 1).

The costs of pregnancy and obstetric care were distinguished into medical costs in the hospital (secondary obstetric care) and medical costs outside the hospital (e.g. primary obstetric care, general practitioner care, etc.). Pregnant patients received several questionnaires regarding health care use each covering a 3 month period of their pregnancy. The final questionnaire covered the period around the calculated term date, until 6 weeks thereafter. This means that the neonatal costs are covered for a 6-week period post-term. For preterm births, the post-natal period is therefore longer and costs higher than for term births (Bollen et al., 2003). In order to receive medical

Figure 1: Timing of the economic evaluation assessments, during IVF treatment itself, and at three time points during pregnancy and the perinatal period
information regarding birth, questionnaires were sent to the responsible obstetrician.

For the most important cost items, unit prices were determined by following the micro-costing method (Gold et al., 1996), which is based on a detailed inventory and measurement of all resources used. During the determination of unit prices, two embryos were transferred in the majority of cycles. Therefore, all unit prices are determined for the transfer of two embryos. The calculation of the unit price of the IVF treatment consisted of detailed measurement of investments in manpower, equipment, materials, housing and overhead. The salary schemes of hospitals and other health care suppliers were used to estimate costs per hour for each caregiver. Taxes, social securities and vacations were included, as well as the costs of the time that could not be assigned to other patients. The costs of equipment included those of depreciation, interest and maintenance. Costs for inpatient days in hospital were calculated from real, basic costs per day using detailed information from the financial department of the hospital. For the unit price per inpatient day in hospital, a distinction was made between general and university hospitals. These estimates included overhead and indirect costs. Other charges associated with inpatient and outpatient care were derived from previous publications (Oostenbrink et al.), in order to render our results more comparable with other research and to make these unit costs independent from the specific hospital prices. For these items, we used charges as a proxy of real costs. In the Netherlands, a ‘fee for service’ system is used for the reimbursement of medical interventions and diagnostic procedures. In order to calculate the costs for medication, we used pharmacotherapeutic charges. Costs caused by loss of economic productivity due to absence from work were also taken into account, using charges (Oostenbrink et al.). Discounting was not applied because of the limited time horizon. Table I provides an overview of the cost categories and data used in the cost calculations.

### Statistical analysis

Analysis was carried out according to the intention-to-treat principle. For a pragmatic (or effectiveness) trial, the focus should not be the cost per cycle but rather the overall cost that a patient may expect over a given treatment period (including cycles in which cryopreserved embryos were transferred) (Vail and Gardener, 2003). Therefore, we elected to base the analysis on a 1-year treatment period allowing sufficient time for most patients to complete all IVF treatment cycles. Differences in mean costs between the two strategies were tested by a two-sample t-test. Effectiveness, measured by the proportion of cumulative pregnancies resulting in term live birth within 1 year after randomization, was estimated by the Kaplan–Meier method. The time period of analysis started from the moment of randomization, to avoid post-randomization selective dropout (Eijkemans et al., 2006).

Cost-effectiveness was assessed by calculating the incremental cost-effectiveness ratio, defined here as the difference in average costs between the two strategies divided by the difference in average effects. The sampling distribution (i.e. uncertainty) of costs and effects was investigated by bootstrapping. From this distribution, a cost-effectiveness acceptability curve was constructed (Glick et al., 2001), which shows the probability that the standard treatment is cost-effective for a range values of the maximum monetary expenditures.

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**Table I.** Cost categories and data used in cost calculations.

<table>
<thead>
<tr>
<th>Cost category</th>
<th>Parameter</th>
<th>Data collection volume of care</th>
<th>Cost estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CRF (physician)</td>
<td>Questionnaires patient</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRH analogues</td>
<td>Strategy</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Recombinant FSH</td>
<td>Days</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>hHCG/Progesteron</td>
<td>Days</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Technical procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oocyte retrieval</td>
<td>Strategy</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Laboratory procedures</td>
<td>Strategy</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Embryo transfer</td>
<td>Strategy</td>
<td>*</td>
<td></td>
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<tr>
<td>Intramural care</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hospital (academic)</td>
<td>Days</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Hospital (general)</td>
<td>Days</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>NICU/MCU</td>
<td>Days</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Physician</td>
<td>Visits</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Number</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Prenatal screening</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Other therapy</td>
<td>Number</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td>Category</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Obstetrician</td>
<td>Visits</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>General practitioner</td>
<td>Visits</td>
<td>*</td>
<td></td>
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<tr>
<td>General practitioner</td>
<td>Visits</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Social worker</td>
<td>Visits</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Maternity nurse</td>
<td>Days</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Non-medical costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travel costs</td>
<td>Distance</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Absence from work</td>
<td>Days</td>
<td>*</td>
<td></td>
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</tbody>
</table>

**Notes:**
- Obstetrician: obstetrics/gynaecology.
- bFor the costs of medication, mean costs were used per couple.
- cEmbryo transfer for SET €233 and for double embryo transfer €283.
- dNeonatal intensive care unit/medium care unit.
- ePhysician visits: costs for an inpatient visit at the IVF department are €50 and telephonically consults are €28.
- fDelivery costs depend on delivery at home/in hospital, with or without complications, delivery with caesarean section (with or without complications).
- fData used in the cost calculations.
that society would be willing to pay for an extra pregnancy that leads to a term live birth. By way of sensitivity analysis, we determined costs, term live birth rate and cost-effectiveness, based on all treatment cycles that patients went through instead of the limited 12 months time frame. In addition, the outcome of term live birth was relaxed to all live births, to make a comparison possible with other studies that did not take into account the toll involved in multiple pregnancies as a result of the transfer of two embryos.

Missing cost items arising due to non-response to the questionnaires were imputed, and stratified by randomization arms to avoid the loss of data. For this purpose, the AregImpute method in S-plus (MathSoft Inc., Seattle, WA, USA, version 2000) was used. A comparison of the costs between both treatment strategies was performed with the independent group t-test.

Results

Costs per cycle
The response rate of the economic evaluation questionnaires during treatment was 81% for all IVF cycles and did not differ significantly between the two treatment strategies. Almost 75% of the pregnant women responded to at least two of the three economic evaluation questionnaires during pregnancy and the neonatal period. The mean direct medical costs per IVF cycle were lower for the mild strategy (1559 versus €1977; P = 0.001), mainly due to lower costs for medication and technical procedures (Table II). Per cycle, women in the mild treatment strategy had on average fewer days of sick leave during pregnancy when compared with the standard treatment strategy (23 versus 30; P = 0.029).

Clinical outcomes and costs per 12-months
An extensive description of the clinical outcomes and total costs per patient within 1 year was presented in our earlier publication (Heijnen et al., 2004, 2007). In Table III, the most relevant outcomes are summarized.

For the mild strategy, the duration between cycles was shorter (88 ± 49 versus 109 ± 38 days; P < 0.001), yet more frozen cycles were performed (54 versus 30; P = 0.016). The cumulative treatment costs of the standard treatment strategy were higher in the first 4 months. However, over the complete 12-months period, treatment costs of the mild treatment strategy were comparable with those of the standard strategy (Fig. 2).

IVF treatment, pregnancy and the neonatal period revealed lower total costs for the mild strategy (8333 versus €10 745; P = 0.006), as reported previously (Heijnen et al., 2007). The costs of intramural care during IVF treatment was significantly higher for the mild strategy (750 versus €576; P = 0.006) (Heijnen et al., 2007), which is due to the higher mean total number of cycles within 1 year. The medical costs during pregnancy for the mild strategy were half the costs of the standard strategy (530 versus €1061; P = 0.03), due to the requirement for more medical care (outpatient visits, hospital admissions). Furthermore, the costs of the obstetric and post-natal period per ongoing pregnancy were significantly higher for the standard strategy (4136 versus €1947; P < 0.001), due to more hospital admissions and more prolonged duration in hospital for mother and child.

Within 12 months after randomization there were 16 pregnancies leading to preterm live birth (<37 weeks) in the standard treatment group, versus 6 in the mild treatment group (P = 0.02) (Heijnen et al., 2007). Early preterm live birth (<32 weeks gestation) resulted in relatively low costs of pregnancy and perinatal period, primarily due to a low neonatal survival rate. Late preterm live birth (32–37 weeks gestation) did result in relatively high costs, especially in case of twin pregnancies (Fig. 3).

Cost-effectiveness analysis
The cost per ongoing pregnancy leading to term live birth was €19 200 (€8333/0.434) in the mild strategy and €24 000 (€10 745/0.447) in the standard strategy and the costs per term live born child were €19 200 (€8333/0.434) in the mild strategy and €20 197 (€10 745/0.447 + 0.085) in the standard strategy. The incremental cost-effectiveness ratio of the standard strategy compared with the mild strategy was €185 000 per extra pregnancy leading to term live birth (Heijnen et al., 2007) and €24 600 per term live born child (Table IV). The uncertainty in both costs and effects, as assessed by 5000 bootstrap samples, is depicted in Fig. 4 (upper panel), and the corresponding cost-effectiveness acceptability curve Fig. 4 (lower panel). The latter curve shows that there is only a 20% probability that the standard treatment strategy is cost-effective up to a ceiling ratio of €50 000 per extra pregnancy leading to term live birth and at a ceiling ratio of €100 000, this probability does not exceed 40%. The dotted line shows the acceptability curve when effectiveness is expressed as term live born child instead of term live birth. The probability that the standard treatment strategy is cost-effective reaches 80% from a ceiling ratio of €60 000 onwards.

Sensitivity analyses
The drop-out rate per cycle was significantly lower in the mild treatment group compared with the standard group [odds ratio (OR) = 0.53; P = 0.04, Heijnen et al., 2007]. Further, there

Table II. Intramural medical costs (€) per cycle for the standard and mild IVF treatment.

<table>
<thead>
<tr>
<th></th>
<th>Mild (mean ± SD)</th>
<th>Standard (mean ± SD)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRH analogue*</td>
<td>155 ± 71</td>
<td>235 ± 70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH</td>
<td>585 ± 236</td>
<td>816 ± 337</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Technical procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oocyte retrieval/</td>
<td>323 ± 210</td>
<td>352 ± 184</td>
<td>0.038</td>
</tr>
<tr>
<td>laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryo transfer</td>
<td>151 ± 112</td>
<td>222 ± 110</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Embryo cryo transfer</td>
<td>17 ± 68</td>
<td>14 ± 60</td>
<td>NS</td>
</tr>
<tr>
<td>Intramural care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>151 ± 69</td>
<td>157 ± 94</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>26 ± 167</td>
<td>72 ± 471</td>
<td>0.059</td>
</tr>
<tr>
<td>Visits</td>
<td>42 ± 51</td>
<td>43 ± 59</td>
<td>NS</td>
</tr>
<tr>
<td>Laboratory</td>
<td>108 ± 123</td>
<td>65 ± 82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total costs per cycle</td>
<td>1559 ± 608</td>
<td>1977 ± 803</td>
<td>0.001</td>
</tr>
</tbody>
</table>

■CRF: case record form.
■cryo: cryopreservation.
*■Independent groups t-test.
were 12 patients (6%) in the mild strategy group and 15 patients (8%) in the standard strategy who switched to the other stimulation protocol or embryo-transfer strategy. Censoring these patients at the moments of switching resulted in 1-year estimates of term live birth of 43.2% in the mild and 44.6% in the standard group (Heijnen et al., 2007), very similar to the results of the base-case analysis (Table IV).

The results of the sensitivity analysis are summarized in Table IV. The number of patients still in treatment after 12 months was 72 and 68 in the mild and standard groups, respectively. The sensitivity analysis on all available treatment cycles (including cycles performed after the 12 months period, and including cycles in excess of the three or four cycles that
were refunded) revealed that in the mild strategy, a total of 114 term live births occurred (56\% of patients) versus 103 (52\%) in the standard strategy (\(P = 0.4\)). The mean number of started IVF cycles was significantly higher in the mild strategy (2.80 versus 2.05; \(P < 0.001\)), but the mean total costs per patient were significantly lower compared with the standard strategy (\(\text{€}12 657 \pm 12 791\) versus \(\text{€}10 033 \pm 5869\); \(P = 0.009\)). Therefore, the mild strategy is dominant in the cost-effectiveness analysis, i.e. it is both cheaper and more effective than the standard strategy.

In total, there were 116 term born children in the mild strategy versus 124 in the standard strategy. The incremental cost-effectiveness ratio of the standard strategy compared with the mild strategy is therefore \(\text{€}46 035\) per term live born child and \(\text{€}19 097\) for all live born children for all cycles.

**Discussion**

We have previously published the clinical outcomes of this trial, which showed that in women below 38 years of age, a mild strategy in IVF results in a similar proportion of cumulative pregnancies resulting in term live birth within 1 year of randomization compared with a standard strategy, while greatly reducing the multiple pregnancy rate (Heijnen et al., 2007). In the current study, we assessed in detail the consequences of both IVF treatment strategies in terms of costs in order to provide an integrated evaluation of the health economics of the two treatment strategies. The overall costs resulting from treatment up until 12 months after randomization (including costs associated with resulting pregnancies and delivery) were lower for the mild strategy compared with the standard strategy, despite a higher average number of IVF cycles for the mild strategy. This is mainly due to a reduction of multiple pregnancies and preterm births in the mild strategy. The costs per extra term live birth of the standard compared with the mild strategy are unacceptably high.

The real advantage of the mild strategy is the anticipated added long-term quality of life and the avoidance of the very high long-term costs resulting from the increased morbidity of twins after birth (De Sutter et al., 2002; Adashi et al., 2003; Wennerholm 2004). In the current study, the neonatal costs were covered until 6 weeks after expected date of delivery. The long-term medical prognosis for the children born in this study period cannot be predicted but the future costs for these (in some cases severely ill) children are likely to be very large (Petrou et al., 2001). The incidence of disabilities is markedly increased in multiple pregnancies, and the associated long-term costs would
certainly have impact on cost analysis because indirect long term costs will outweigh perinatal costs (Petrov et al., 2001; Wennerholm 2004). This strengthens our conclusion that the mild treatment strategy with SET is distinctly more cost-effective. Recently published randomized trials comparing the costs of IVF with the transfer of one or two embryos (Lukassen et al., 2004; Kjellberg et al., 2006; Fiddelers et al., 2006), differed from our study in that costs were calculated on first treatment cycles only and only standard ovarian stimulation protocols with GnRH agonist long protocol co-treatment were employed. Our study combined a SET strategy with a GnRH antagonist stimulation protocol. A seeming advantage of standard over mild stimulation is that more fresh embryos will be obtained and therefore more embryos available for cryopreservation, which is important in compensating for the reduced chances of SET (Thurin et al., 2004; Pandian et al., 2005). However, this advantage might be counterbalanced by having relatively more good quality embryos after mild stimulation: a recent study of our group shows that embryos obtained after mild stimulation are euploid more often than after standard stimulation (Baart et al., 2007). Nevertheless, findings of these studies were consistent with the results of the present study, showing lower total costs with SET compared with the transfer of two embryos (Kjellberg et al., 2006; Fiddelers et al., 2006). The costs of paediatric health care were markedly reduced due to a considerable reduction of multiple pregnancies (Kjellberg et al., 2006). Another randomized trial concluded that one cycle SET was less expensive, but also less effective compared with one cycle with the transfer of two embryos. It depends on the society’s willingness to pay for one extra IVF cycle, whether the transfer of one or two embryos is preferred from a cost-effectiveness point of view (Fiddelers et al., 2006). Other studies comparing different embryo transfer policies were not randomized controlled trials. Instead, theoretical extrapolations or decision-analytic calculations were used (Wolner-Hanssen and Rydhstroem, 1998; De Sutter et al., 2002; Garceau et al., 2002).

Our study shows a robust finding about the cost-effectiveness from a societal perspective, when combining SET with a mild stimulation regime compared with double embryo transfer with a standard stimulation regime and analysing a complete treatment course over a 12 month time frame. Two recent reviews have identified several problems in achieving a definitive assessment of the cost-effectiveness of SET (Fiddelers et al., 2007; Scotland et al., 2007). Inconsistencies between studies in definitions of outcomes and time horizon, in- or exclusion of frozen/thawed embryos and differences in economic perspective made comparisons difficult (Fiddelers et al., 2007). By way of sensitivity analysis, we determined costs, effectiveness and cost-effectiveness, based on other definitions of outcomes to make comparisons possible with other studies. The cost-advantage of the mild strategy remained significant in a sensitivity analysis that included all cycles, irrespective of time frame, and the cost-effectiveness results were even more in favour of the mild strategy in that analysis.

When calculating the chance of term live birth per couple, twin live births were counted as being equivalent to one live birth. It may be argued that a term-born twin should count as two live births. Defining preterm born children as success and counting a twin as two live born children will be more in favour of the effectiveness of the standard strategy. However, the cost-effectiveness ratio is still in favour for the mild strategy, even after relaxing term live birth to all live born children. A term born twin may be perceived as a positive outcome, reducing the need for subsequent IVF treatments. However, in addition to the increased perinatal morbidity, mortality and long term health consequences associated with twin pregnancies, parents of multiple pregnancies have been shown to be at greater risk of depression and anxiety (Leonard 1998; Baor et al., 2004). Furthermore, when weighing the benefits of the transfer of one or two embryos, account should also be taken of the live births which may occur following the subsequent transfer of surplus embryos (El Toukhy et al., 2003), of which more will remain when just one fresh embryo is transferred. The drop-out rate per cycle was significantly lower in the mild treatment group compared with the standard group (OR = 0.53; P = 0.04, Heijnen et al., 2004, 2007). Thus, although more cycles are needed with the mild strategy, they are better tolerated by patients. Further, there were 12 patients (6%) in the mild strategy group and 15 patients (8%) in the standard strategy who switched to the other stimulation protocol or embryo-transfer strategy. Censoring these patients at the moments of switching resulted in 1-year estimates of term live birth of 43.2% in the mild and 44.6% in the standard group (Heijnen et al., 2004, 2007), very similar to the results of the base-case analysis. These data show that the results of the trial are not biased by the fact that patients were in a randomized controlled trial instead of in a real-life situation. We have chosen not to perform a separate sensitivity or scenario analysis excluding these patients, since the impact on results would be trivial.

Standard effectiveness outcomes in economic evaluation studies such as quality adjusted life-years were not employed, because their use in certain pregnancy situations can be difficult to interpret and sometimes misleading (Ganiats, 1996).

In general, a greater acceptance of mild treatment strategies in IVF will increase the number of cycles needed to achieve the same number of live births. Despite this higher average number of cycles for the mild strategy (and therefore higher treatment costs), we found in our study that overall costs per term live birth were lower compared with the standard treatment strategy. This is mainly due to the health economic benefit of the reduction of multiple pregnancies in the mild stimulation approach. The impact of multiple gestations and their associated complications on costs is dramatic.

This study may contribute to the more widespread introduction of mild ovarian stimulation along with a SET policy in IVF. Clinicians, health care providers and patients should be aware that an extra treatment cycle might be considered a low price for the prevention of the lifelong compromised quality of life of offspring. If structured, written information about risks and complications of multiple pregnancies and the consequences of the transfer of fewer embryos is provided, patients may become more inclined to the transfer of one embryo rather than two (Murray et al., 2004; Bhattacharya and Templeton, 2004). An adequate reimbursement system is a vital point to make SET work (Saldeen and Sundstrom, 2005). Society will carry a large part of the costs for the complications associated with
multiple pregnancy and birth. Governments therefore might have regulatory interest in how IVF is performed. By funding IVF, they will accrue costs in the short term, but might also be able to establish guidelines for the number of embryos transferred. The possible need for a higher number of treatment cycles to achieve pregnancy after SET, might increase treatment costs. However, in the long run, governments will profit by saving the costs of complications associated with multiple pregnancies.

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References


Hohmann FP, Macklon NS, Fauser BC. A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GNRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol. J Clin Endocrinol Metab 2003;88:166–173.


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