Economic evaluations of single- versus double-embryo transfer in IVF

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Multiple pregnancies lead to complications and induce high costs. The most successful way to decrease multiple pregnancies in IVF is to transfer only one embryo, which might reduce the efficacy of treatment. The objective of this review is to determine which embryo-transfer policy is most cost-effective: elective single-embryo transfer (eSET) or double-embryo transfer (DET). Several databases were searched for (cost* or econ*) and (single embryo* or double embryo* or one embryo* or two embryo* or elect* embryo or multip* embryo*). On the basis of five exclusion criteria, titles and abstracts were screened by two individual reviewers. The remaining papers were read for further selection, and data were extracted from the selected studies. A total of 496 titles were identified through the searches and resulted in the selection of one observational study and three randomized studies. Study characteristics, total costs and probability of live births were extracted. Besides this, cost-effectiveness and incremental cost-effectiveness were derived. It can be concluded that DET is the most expensive strategy. DET is also most effective if performed in one fresh cycle. eSET is only preferred from a cost-effectiveness point of view when performed in good prognosis patients and when frozen/thawed cycles are included. If frozen/thawed cycles are excluded, the choice between eSET and DET depends on how much society is willing to pay for one extra successful pregnancy.

Key words: systematic review/cost-effectiveness/single embryo transfer

Introduction

In 2001, of all children born in Europe, 0.2–3.9% were born following assisted reproduction treatment (ART) (Andersen et al., 2005). During recent decades, the multiple pregnancy rate and especially the twin pregnancy rate has increased markedly due to ART. Of all IVF pregnancies, 24.0% were twin pregnancies in 2001 (Andersen et al., 2005), compared with 1.2% being twin pregnancies after natural conception (ESHRE Capri Workshop Group, 2000). Multiple pregnancies are considered high-risk pregnancies for both the mother and infants, due to the relative high incidence of maternal, perinatal and neonatal morbidity and mortality (Land and Evers, 2003). The most successful way to decrease twin pregnancies in IVF is to transfer only one embryo (Gerris, 2005). By now several randomized studies have been performed in which transfer of one embryo is compared to the transfer of two embryos (Gerris et al., 1999; Martikainen et al., 2001; Gardner et al., 2004; Thurn et al., 2004; Lukassen et al., 2005; Van Montfoort et al., 2006), and clinical outcomes such as pregnancy rates, ongoing pregnancy rates and numbers of live-born children or live births are reported. However, nowadays not only the clinical outcome of medical interventions is relevant to decision makers. Information concerning the cost-effectiveness of interventions is input to the decision whether or not implementation of a health care technology is opportune (Van Velden et al., 2005). In this respect, IVF is no exception, and therefore, the question of whether transfer of one embryo is efficient needs to be answered. In this study, we will review the empirical cost-effectiveness studies published so far on elective single-embryo transfer (eSET) versus double-embryo transfer (DET). The objective of this review is to determine the cost-effectiveness of eSET versus DET.

Cost-effectiveness analysis: concepts and methods

An economic evaluation is defined as ‘the comparative analysis of alternative courses of action in terms of both their costs and consequences’ (Drummond et al., 2005). Besides full economic
evaluations, Garceau and co-workers defined costing studies and economic benefit studies (Garceau et al., 2002). A costing study is a form of an economic study in which the cost of one or more treatment options is estimated. An economic benefit study is a form of an economic study in which patient preferences for health care interventions are valued using several economic techniques (Garceau et al., 2002). Regarding a full economic evaluation, two criteria have to be met. First, two or more alternative strategies for patient management have to be compared. Second, an economic evaluation must deal with both the consequences (outcome) and the costs (investment) of the treatment alternatives being compared (Drummond et al., 2005). This principle makes it possible to determine the efficiency of a new, experimental treatment compared with existing ones. There are four forms of a full economic evaluation (Gold et al., 1996; Drummond et al., 2005):

(i) Cost-minimization analysis: two or more alternatives are compared. This analysis is done if outcomes of alternative strategies are equal or irrelevant and therefore only costs are compared.

(ii) Cost-effectiveness analysis: both costs and consequences of two or more alternatives are compared. Outcomes are measured in natural or physical units such as successful pregnancy or live-born child.

(iii) Cost-utility analysis: a refinement of cost-effectiveness analysis, it focuses particular attention on the quality of the health outcome produced by health programmes or treatments. The most commonly used outcome measure is ‘quality adjusted life years’ (QALYs; combining the number of life years gained with the quality of that life). Nowadays, the term cost-effectiveness analysis is often used for cost-utility analysis.

(iv) Cost-benefit analysis: costs and outcomes are both expressed in monetary units. The most commonly used method to give a monetary value to health outcome is the ‘willingness to pay’ approach.

Although these four types of economic evaluations are generally distinguished, in case it is impossible to define all cost and consequences of patient management within one of these frameworks, a strict method may be found in the cost-consequence analysis (Mauskopft et al., 1998). Using this approach, the impact of a new treatment on lifetime resource use, costs (including specific health care service use and costs and productivity losses) and health outcomes (including disease symptoms, life expectancy and quality of life) for an individual or group of individuals is estimated and presented.

Each type of economic evaluation serves its own purpose. The usefulness of cost-minimization analysis is strictly limited to situations where alternative patient management strategies are known to be equal regarding the consequences of medical treatment (Briggs and O’Brien, 2001). Cost-effectiveness analyses using disease-specific outcome measures are useful for detecting disease-relevant differences between patient management strategies, but for decision makers who should decide whether or not a health technology should be used in daily health care practice cost-utility analyses are most valuable (Dowie, 2002).

An economic evaluation can be performed from several perspectives, and the most commonly used are hospital perspective, health care perspective, third party payer perspective and societal perspective (Gold et al., 1996; Drummond et al., 2005). From the hospital perspective, only actual hospital costs are included in the analyses. The health care perspective includes actual hospital costs and other health care related costs, for example, costs of a general practitioner or costs of midwifery care. From the third party payer perspective, the health care costs for patient management are reflected by the payments made (tariffs), regardless of the actual costs. The societal perspective includes all actual health care costs and cost outside health care, such as out-of-pocket costs and costs associated with productivity losses due to an inability to work. Productivity costs may contribute substantially to total societal costs of patient management. How to measure and value productivity losses is however controversial (Koopmanschap et al., 2005). The choice of a particular perspective is dictated by the goal of the analysis and the question or decision at hand (Macones et al., 1999). However, the societal perspective is considered the most appropriate because all relevant costs and benefits are included (Weinstein et al., 1996; Macones et al., 1999).

In the past, costs and benefits were classified as direct or indirect. Direct costs and benefits would include resources in health care (direct medical cost) or patients’ out-of-pocket expenses, for example, over-the-counter medication and travel costs (direct non-medical cost). Indirect costs and benefits would denote the time costs or productivity losses, that is, productivity costs (indirect non-medical costs) (Drummond et al., 2005). However, the use of these terms is not consistent across studies, which sometimes causes confusion. Therefore, nowadays four other categories of costs are identified. First, health care resources consumed consist of the costs of organizing and operating a health care programme, including dealing with the adverse events caused by the programme (for example, the time of health professionals and overheads). Second, patient and family resources consumed include out-of-pocket expenses incurred by patient or family members as well as the value of any resources that they contribute to the treatment process, such as informal care. Third, when patients or family members lose time from work while seeking treatment or participating in a health care programme, there could be productivity losses. Although controversy exists whether this should be reflected in quality of life (Brouwer et al., 1997), the inability to work due to illness is an important cause of the existence of productivity costs. Fourth, resources can be consumed in other sectors, such as social worker visits. These costs may however be insignificant for many health care programmes.

Besides disease- or treatment-specific outcomes, in most cost-effectiveness analyses, two types of outcome measures are reported: years of life saved and quality adjusted life years (QALYs) gained (Johannesson et al., 1996; Anell and Norinder, 2000). However, in IVF, live births (i.e. a pregnancy resulting in at least one live-born child, twins are considered as one live birth) or live-born children (i.e. twins are considered as two live-born children) are mostly used as outcome measure (Garceau et al., 2002). The measure used to express the results of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER). To obtain the ICER, the following formula is applied: (Total costs strategy A – Total costs strategy B)/ (Effect strategy A – Effect strategy B). An ICER compares a strategy to the next most effective strategy and eliminates strategies that are dominated, that is, have higher costs and lower effectiveness. However, dominancy is not common in economic evaluations, because in most cases more effective treatments are also more costly (Johannesson, 1995; Weinstein et al., 1996). Whether an ICER is cost-effective depends on the maximum amount of money that society is prepared to pay for a gain in effectiveness, which is called the ceiling ratio (Eichler et al., 2004).
### Methods

#### Literature search

The search of trials to be included in this review on eSET and DET was conducted using the following databases: Medline, PubMed, CINAHL (Cumulative Index of Nursing and Allied Health Literature), EMBASE, CDSR (Cochrane database of systematic reviews), NHS CRD DARE (UK NHS Centre for Reviews and Dissemination Database of Abstracts of Review of Effectiveness) Central, NHS CRD HTA (UK NHS Centre for Reviews and Dissemination Health Technology Assessment), NHS CRD NHS EED (UK NHS centre for Reviews and Dissemination NHS Economic Evaluation Database), OHEHEED (Office of Health Economics Health Economic Evaluation Database), INAHTA Clearing House (International Network of Agencies for Health Technology Assessment; http://nzhta.chmeds.ac.nz/inahta/inahta.htm), CCOHTA (Canadian Coordinating Office for Health Technology Assessment; http://www.ccohta.ca), SBU (Swedish Council for Health Technology Assessment; http://www.sbu.se), AHRQ (US Agency for Healthcare Research and Quality; http://wwwahrq.gov) and NICE (National Institute for Health and Clinical Excellence; http://www.nice.org.uk).

The search was performed in February 2006 for all available papers, and the articles selected had to be written in English. The free text search terms (cost* or econ*) and (single embryo* or double embryo* or one embryo* or two embryo* or elect* embryo or multip* embryo*) were used.

#### Study selection

Two reviewers (A.F. and J.S.) assessed independently all studies for inclusion or exclusion in the review. As a first step, titles were screened and a high sensitivity of the selection was aimed for; thus, only studies that were certainly not of interest were excluded. Studies were excluded if it was clear from the title that one of the following exclusion criteria was fulfilled: the study was not based on human subjects or the study clearly did not deal with eSET and/or DET. Furthermore, three other criteria were used to determine whether the study was not relevant for inclusion in our economical review: non-comparative studies, studies not reporting both the consequences (outcome) and the costs (investment) of the alternatives being compared and studies not reporting original, empirical data. Of the titles that were not excluded based on these criteria, the abstracts were read. The criteria mentioned above were also used to assess the abstracts, again aiming at a high sensitivity of selection. In case of doubt, the final selection of the studies was reached by consensus of the two separate reviewers after having read the full paper.

#### Data extraction and analysis

Data extraction is the process by which reviewers obtain the information they need from what is reported by primary investigators (York, 2006). Using a data extraction form, data were collected from all included studies by one reviewer (A.F.). In case of doubt, the second reviewer was consulted.

To re-verify study eligibility at the time of data extraction, specific information is needed about the study population, the exact form and delivery of the intervention, the outcome measures and the study design. In addition, information should be recorded about any differences in characteristics of the population and interventions on which the assessment of heterogeneity will be based (Drummond et al., 2005; York, 2006). Consequently, the following study characteristics were extracted: research objectives/question, design of the study, type of economic evaluation, comparison, outcome measure, perspective of the study, time horizon, cost components used, year of costing, inclusion criteria, exclusion criteria, inclusion or exclusion of frozen/thawed cycles, number of patients or cycles included for eSET and DET, mean age of the female patients and country of origin.

For all studies included in the review, costs, effects, costs per effect and an ICER were reported, if calculated in the original article. It was most ideal if an ICER was given in the original article. If no ICER was given, it was best for costs and effects to be reported separately, because costs per effect and the ICER could then be calculated. Otherwise, total costs, effects and the ICER could be deduced from the average costs per effect of both strategies. To enhance the comparability of the individual study results based on the data reported in the articles, we re-calculated the costs and effects related to one cycle of eSET and one cycle of DET. The outcome measures were, if necessary, re-calculated to a live birth (i.e. a pregnancy resulting in at least one live-born child). Finally, all costs were re-calculated towards the year 2005 (CBS, 2006) and were given in euros. For example, if the effect and the average costs per effect were given, the costs could be derived by costs per effect/effect. Then, the ICER could be calculated by difference in costs/difference in effect. The ICERS presented in this review reflect one cycle of DET versus one cycle of eSET, meaning that an ICER is calculated by using the following formula: (mean total costs DET – mean total costs eSET)/(proportion of live births DET – proportion of live births eSET). Cost-effectiveness calculations were done from both the health care perspective and the societal perspective.

#### Results

#### Literature search

Figure 1 shows the process of inclusion and exclusion of studies. The search of all databases identified a total of 496 titles, of which 88 were duplicates. Of the remaining 408 titles, 382 were excluded as being not relevant to the subject of the present review. Of these excluded titles, 286 did not deal with eSET or DET, 69 were non-human studies, 23 studies were non-comparative and in four studies cost and outcome were not assessed simultaneously. In case of any doubt, studies were included for further review. Of the remaining 26 articles, the abstracts were read, and based on the given criteria, finally four studies were included in the review (Gerris et al., 2004; Lukassen et al., 2005; Fiddelers et al., 2006; Thurin Kjellberg et al., 2006).

#### Study characteristics

The study characteristics of the four included studies are given in Table I. Although the research objectives/questions of the studies were quite different, costs and effects of eSET and DET were reported in all studies. Of all studies included, three studies were randomized clinical trials (RCTs) (Lukassen et al., 2005; Fiddelers et al., 2006; Thurin Kjellberg et al., 2006), and one study was an observational comparative study (Gerris et al., 2004). Cost-effectiveness analysis was the type of economic evaluation used in all four studies.
Furthermore, three studies compared total costs for one fresh cycle eSET versus one fresh cycle DET (Gerris et al., 2004; Fiddelers et al., 2006; Thurin Kjellberg et al., 2006), whereas the other study determined total costs for two fresh cycles eSET versus one fresh cycle DET (Lukassen et al., 2005). Additionally, Thurin Kjellberg et al. (2006) compared total costs for one fresh and frozen cycle eSET versus one fresh cycle DET. When estimating cost-effectiveness, in three studies the costs per live birth were calculated, considering twins as one effect (i.e. one live birth) (Lukassen et al., 2005; Fiddelers et al., 2006; Thurin Kjellberg et al., 2006). In the other study however, the cost per live-born child was given, and twins were considered as two effects (i.e. two live-born children) (Gerris et al., 2004). One study performed an economic evaluation both from the societal perspective and from the health care perspective (Thurin Kjellberg et al., 2006). One study only used the societal perspective (Fiddelers et al., 2006), whereas the two remaining studies only used the health care perspective (Gerris et al., 2004; Lukassen et al., 2005). As can be seen from Table I, the studies differed with respect to the time horizon, varying from a maximum of one IVF cycle to two IVF cycles. All studies calculated costs during IVF treatment, pregnancy, delivery and post-natal period. However, the duration of follow-up after delivery (1–6 months after delivery) differed between the studies. The year of costing varied from 2001 until 2004. The inclusion criteria differed considerably between studies. In one observational study, patients <38 years of age were included and offered the choice for eSET in case one good quality embryo was available versus DET irrespective of embryo quality (Gerris et al., 2004). In two RCTs in patients <36 years of age, at least two embryos had to be available of which one or two had to be of good quality (Lukassen et al., 2005; Thurin Kjellberg et al., 2006). Finally, in the other RCT, two embryos also had to be available, and eSET and DET were performed in an unselected study population, irrespective of age and embryo quality (Fiddelers et al., 2006). Only two studies reported exclusion criteria (Lukassen et al., 2005; Fiddelers et al., 2006). Only one study included frozen/thawed cycles (Thurin Kjellberg et al., 2006). The number of patients included in the studies varied from 107 to 661, and the mean age of the female patients was comparable for three studies (30.2–30.9 years of age), whereas in the one study that did not select for age, the mean age was 32.7 years. Finally, one study was performed in Scandinavia (Thurin Kjellberg et al., 2006), one in Belgium (Gerris et al., 2004) and two in the Netherlands (Lukassen et al., 2005; Fiddelers et al., 2006).

**Reported outcomes**

Table II shows costs, effects, costs per effect and the ICER of all included studies, as and if reported in the original articles. The cost-effectiveness analyses of the four studies included in the review were performed quite differently. First, in the study of Gerris et al. (2004), total health care costs and effects were given for one fresh cycle eSET and DET. Second, Lukassen et al. (2005) reported effects and health care costs per effect of two fresh cycles eSET versus one fresh cycle DET. Third, Thurin Kjellberg et al. (2006) reported effects including frozen/thawed cycles, total health care costs as well as societal costs and the ICER based on health care costs as well as societal costs. Fiddelers et al. (2006) reported total societal costs, effects, total costs per live birth, and the ICER based on societal costs.

**Cost-effectiveness calculations**

In Table III, calculated costs, difference in costs, effects, difference in effects, costs per effect and ICERs are given, based on the reported outcomes as stated in Table II. Cost-effectiveness calculations are given both for the health care perspective and for the societal perspective. All data were based on one fresh cycle eSET and one fresh cycle DET, or one fresh and frozen cycle eSET and one fresh cycle DET. The outcome measures were calculated to live birth (i.e. a pregnancy resulting in at least one live-born child). On the basis of the costs and effects reported in Gerris et al. (2004), costs per effect and the ICER were calculated. Although an intention to treat analysis was performed, it is possible that both groups were not comparable because of a non-randomized design (i.e. confounding by indication). In Lukassen et al. (2005), effects were also reported for one cycle eSET, and total costs could be re-calculated for one cycle eSET. On the basis of these numbers, costs per effect and the ICER were calculated. On the basis of the data reported in Thurin Kjellberg et al. (2006), costs per effect were calculated.
Finally, on the basis of the data reported in Fiddelers et al. (2006), total health care costs, total health care costs per effect and the ICER based on health care costs was calculated. DET was the most expensive strategy when either the health care perspective or the societal perspective was used. Total health care costs of two studies were high compared with the other studies (Gerris et al., 2004; Thurin Kjellberg et al., 2006). In the study by Gerris et al. (2004), costs were high because of very high costs related to twins in both groups, as the costs were determined until 3 months after delivery. For the study by Thurin Kjellberg et al. (2006), relatively high costs in both strategies can be explained by the fact that costs were determined until 6 months after delivery. Concerning the effects, the study of Gerris et al. (2004) cannot be compared validly with the other three studies, because it was a non-randomized trial in which the choice for eSET or DET was left to the patients. In case no good quality embryos were available, patients who chose eSET received DET. The effects of eSET and DET were similar. For the other studies (Lukassen et al., 2005; Fiddelers et al., 2006; Thurin Kjellberg et al., 2006), effects of DET were higher compared with effects of eSET when only fresh cycles were included. The difference in effect was much smaller when frozen/thawed cycles were included in the eSET group (Thurin Kjellberg et al., 2006). The ICERs of the three randomized studies were almost comparable if only fresh cycles were included. The difference in effect was much smaller when frozen/thawed cycles were included in the analyses, irrespective of the perspective used. If frozen/thawed cycles were included in the analyses, the ICERS increased, in favour of eSET. In the study of Gerris et al. (2004), the ICER showed that DET was dominated by eSET, because DET was more expensive and less effective compared with eSET.

### Table I. Main characteristics of the selected studies

<table>
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<tr>
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<tbody>
<tr>
<td>What is the cost-effectiveness of eSET and DET in patients &lt;38 years of age who were offered the choice between eSET of one high quality embryo versus DET irrespective of embryo quality?</td>
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<tr>
<td>What is the live birth rate after two consecutive cycles eSET and one cycle DET?</td>
<td>What are the outcomes and total costs of cumulative eSET and DET, until 6 months after delivery, and what is the cost-effectiveness of eSET and DET?</td>
<td>What are the costs and cost-effectiveness of one cycle eSET and one cycle DET?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design of the study</td>
<td>Observational study</td>
<td>Randomized clinical trial, single-centre</td>
<td>Cost-effectiveness analysis</td>
<td>Cost-effectiveness analysis</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-effectiveness analysis</td>
<td>Cost-effectiveness analysis</td>
<td>Cost-effectiveness analysis</td>
<td>Cost-effectiveness analysis</td>
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<tr>
<td>Comparison</td>
<td>One fresh IVF cycle eSET versus one fresh IVF cycle DET</td>
<td>Two fresh IVF cycles eSET versus one fresh IVF cycle DET</td>
<td>One fresh IVF cycle eSET and one frozen SET versus one fresh IVF cycle DET</td>
<td>One fresh IVF cycle eSET versus one fresh IVF cycle DET</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>Total costs per live-born child</td>
<td>Total costs per live birth</td>
<td>Total costs per live birth</td>
<td>Total costs per live birth</td>
</tr>
<tr>
<td>Study’s perspective</td>
<td>Health care perspective</td>
<td>Health care perspective</td>
<td>Societal as well as health care perspective</td>
<td>Societal perspective</td>
</tr>
<tr>
<td>Time horizon</td>
<td>A maximum of one fresh IVF cycle</td>
<td>A maximum of two fresh IVF cycles eSET and one fresh IVF cycle DET</td>
<td>A maximum of one fresh and one frozen IVF cycle eSET and one fresh IVF cycle DET</td>
<td>A maximum of one fresh IVF cycle</td>
</tr>
<tr>
<td>Cost components used</td>
<td>IVF procedure, pregnancy, delivery, post-natal period until 3 months after delivery</td>
<td>IVF procedure, pregnancy up to 6 weeks after delivery</td>
<td>IVF procedure, pregnancy up to 6 months after delivery</td>
<td>IVF procedure, pregnancy up to 4 weeks after delivery</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>&lt;38 years of age, first IVF cycle ever or after a previous pregnancy, irrespective whether that pregnancy was the result of infertility treatment or not</td>
<td>&lt;35 years of age, first IVF cycle ever or after a previous pregnancy, FSH &lt;10 IU/L, at least two embryos available with at least one of excellent or good quality</td>
<td>&lt;36 years of age, first or second IVF cycle, at least two good quality embryos available</td>
<td>First IVF, transfer policy irrespective of female age and embryo quality</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Not stated</td>
<td>Patients with a medical reason for eSET</td>
<td>Not stated</td>
<td>Patients applying for PGD, medical reason for eSET and patients who could not give informed consent</td>
</tr>
<tr>
<td>Inclusion or exclusion of frozen/thawed cycles</td>
<td>Exclusion frozen/thawed cycles</td>
<td>Exclusion frozen/thawed cycles</td>
<td>Inclusion and exclusion frozen/thawed cycles</td>
<td>Exclusion frozen/thawed cycles</td>
</tr>
<tr>
<td>Number of patients/ cycles included for eSET and DET</td>
<td>eSET: 206; DET: 161</td>
<td>eSET: 54; DET: 53</td>
<td>eSET: 330; DET: 331</td>
<td>eSET: 154; DET: 154</td>
</tr>
<tr>
<td>Mean female age (years)</td>
<td>30.9</td>
<td>eSET: 30.2; DET: 31.2</td>
<td>eSET: 30.9; DET: 30.8</td>
<td>eSET: 32.7; DET: 32.4</td>
</tr>
<tr>
<td>Country of origin</td>
<td>Belgium</td>
<td>The Netherlands</td>
<td>Sweden/Scandinavia</td>
<td>The Netherlands</td>
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</table>

**CET**, double-embryo transfer; eSET, elective single-embryo transfer.
Discussion

In all studies, DET was the most expensive strategy. Furthermore, DET was more effective, unless eSET was performed in good prognosis patients (i.e. young patients with good quality embryos), and frozen/thawed cycles were included. After recalculation, DET was dominated by eSET in one study (Gerris et al., 2004). In the other studies, the ICERs, because of the health care perspective, comparing one fresh cycle DET with one fresh cycle eSET varied from €8399 to €30 571, meaning that each additional live birth in the DET group will need an investment ranging from €8399 to €30 571 (Lukassen et al., 2005; Fiddelers et al., 2006; Thurin Kjellberg et al., 2006). Inclusion of frozen/thawed cycles caused a higher ICER of DET versus eSET compared with exclusion of frozen/thawed cycles, meaning that eSET was more favourable if frozen/thawed cycles were included. This could be explained by the fact that inclusion of frozen/thawed cycles usually cause relatively more live births for eSET than for DET, because more and better quality embryos are left for freezing after

Table II. Reported outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Costs (€)</th>
<th>Effects (%)</th>
<th>Costs per effect (€)</th>
<th>ICER (DET versus eSET)</th>
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</thead>
<tbody>
<tr>
<td>Gerris et al. (2004)</td>
<td>eSET (one cycle)</td>
<td>7126</td>
<td>37.4</td>
<td>NR^</td>
</tr>
<tr>
<td>Lukassen et al. (2005)</td>
<td>eSET (two cycles)</td>
<td>NR^</td>
<td>40.7</td>
<td>13 438</td>
</tr>
<tr>
<td>Thurin et al. 2006^</td>
<td>DET (one cycle)</td>
<td>12 318</td>
<td>42.9</td>
<td>28 712</td>
</tr>
<tr>
<td>Thurin et al. 2006^</td>
<td>eSET (one cycle)</td>
<td>9309</td>
<td>38.8</td>
<td>23 984</td>
</tr>
<tr>
<td>Fiddelers et al. 2006^</td>
<td>DET (one cycle)</td>
<td>7334</td>
<td>20.8</td>
<td>35 260</td>
</tr>
</tbody>
</table>

Table III. Calculated costs, effects, costs per effect and cost-effectiveness of the studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Costs (€)</th>
<th>Difference in costs (DET – eSET) (€)</th>
<th>Effects (%)</th>
<th>Difference in effects (DET – eSET) (%)</th>
<th>Costs per effect (€)</th>
<th>ICER (DET versus eSET)</th>
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<tbody>
<tr>
<td>Health care perspective</td>
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<td>including frozen/thawed cycles</td>
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<tr>
<td>Thurin et al. 2006^</td>
<td>eSET (one cycle)</td>
<td>9467</td>
<td>38.8</td>
<td>24 399</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gerris et al. 2004^</td>
<td>DET (one cycle)</td>
<td>12 527</td>
<td>3060</td>
<td>42.9</td>
<td>4.1</td>
<td>29 200</td>
</tr>
<tr>
<td>Lukassen et al. 2005^</td>
<td>eSET (one cycle)</td>
<td>3396</td>
<td>25.9</td>
<td>32 815</td>
<td>DET dominated by eSET</td>
<td></td>
</tr>
<tr>
<td>Thurin et al. 2006^</td>
<td>DET (one cycle)</td>
<td>5176</td>
<td>1780</td>
<td>35.8</td>
<td>9.9</td>
<td>14 378</td>
</tr>
<tr>
<td>Fiddelers et al. 2006^</td>
<td>eSET (one cycle)</td>
<td>7618</td>
<td>27.6</td>
<td>28 651</td>
<td>15.3</td>
<td>30 571</td>
</tr>
<tr>
<td>Societal perspective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>including frozen/thawed cycles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thurin et al. 2006^</td>
<td>DET (one cycle)</td>
<td>6518</td>
<td>39.6</td>
<td>28 651</td>
<td>18.8</td>
<td>34 792</td>
</tr>
<tr>
<td>Societal perspective</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>excluding frozen/thawed cycles</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thurin et al. 2006^</td>
<td>eSET (one cycle)</td>
<td>11 094</td>
<td>38.8</td>
<td>28 593</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiddelers et al. 2006^</td>
<td>DET (one cycle)</td>
<td>14 925</td>
<td>3831</td>
<td>28 386</td>
<td>4.1</td>
<td>34 792</td>
</tr>
</tbody>
</table>

DET, double-embryo transfer; eSET, elective single-embryo transfer; ICER, incremental cost-effectiveness ratio.

^aNR means not reported in the original publication.

^bHealth care perspective.

^cSocietal perspective.

^dEffects were given, total health care and societal costs, costs per effect and ICERs were obtained by Professor C. Bergh, personal communication.

^eTotal health care and societal costs, effects, total costs/live birth and the ICER based on societal costs were given; ICER based on health care costs was calculated.
eSET (Bergh, 2005; Van Montfoort et al., 2006). In the study of Thurin Kjellberg et al. (2006) however, frozen cycles were only included in the eSET group and not in the DET group. Furthermore, in case the implantation rate rises, the conclusion that eSET is more favourable than DET will become stronger in case frozen/thawed cycles are included, because the relative merits of eSET rise extremely fast as the probability of multiple pregnancy in DET, with its complications will also rise.

The choice between offering couples one cycle eSET or one cycle DET depends on what society is prepared to pay for one extra live-born child (i.e. ceiling ratio). Within the field of IVF, there is currently no agreement on an appropriate ceiling ratio for one extra live birth. Therefore, on the basis of the results of this review, it cannot be concluded whether eSET or DET is more cost-effective. Given the fact that currently DET is considered the strategy of first choice one should realize that eSET, although less costly, indicates loss of effectiveness. Whether society is willing to give up effectiveness for the individual patient remains to be seen (Severens et al., 2005). Furthermore, in deciding on the preferred strategy, the long-term consequences of eSET and DET should also be considered. Inclusion of the long-term costs in the cost-effectiveness analysis, such as costs due to premature births, would probably result in a substantially higher ICER, making DET less attractive from a long-term economic point of view. However, to obtain a balanced estimate of the long-term cost-effectiveness of eSET versus DET, both long-term costs and effects in terms of QALYs should be considered. For practical reasons, this has not been included in any study so far. Therefore, it is difficult to provide a fair estimate of the long-term cost-effectiveness.

The results of the three RCTs included in this review were confirmed by two other studies (Wolner-Hanssen and Rydhstroem, 1998; De Sutter et al., 2002, 2003), which had the same research question but used a modelling approach, and could therefore not be included in our review (Donaldson et al., 2002). In case an empirical study is infeasible or impracticable for economic evaluation, modelling techniques can be used to simulate experiments and to explore alternative scenarios (Gold et al., 1996; Buxton et al., 1997; Brennan and Akehurst, 2000). The study of Wolner-Hanssen and Rydhstroem (1998) was a cohort study combined with model calculations. For eSET, a theoretical live birth rate was given. The study of De Sutter et al. (2002) used a Markov model in which live birth rates from four other studies were attributed. The first two studies (study 1 and 2) were RCTs, whereas the other two studies (study 3 and 4) were observational studies. According to the study of Wolner-Hanssen and Rydhstroem (1998) and study 1 and 2 of De Sutter et al. (2002), costs of DET were higher than costs of eSET (range of difference in costs €2610 to €4453) and the effect of DET was also higher than the effect of eSET (range of difference in effect 11.0 to 20.0%). The ICERs varied from €21 999 to €37 099. Furthermore, study 3 and 4 of De Sutter et al. (2002) confirm the results of the study of Gerris et al. (2004) that costs of DET were higher than costs of eSET and that the effect of eSET was comparable with the effect of DET. Other studies, in which eSET was also performed in good prognosis patients and with DET performed in the remaining patients, only compared effects of eSET and DET (Tiittinen et al., 2001, 2003; Gerris et al., 2002; Martikainen et al., 2004; Van Montfoort et al., 2005). They also showed that eSET and DET were equally effective. Because costs always turned out to be higher for DET than for eSET, and an ICER is calculated by difference in costs/difference in effects, these studies also confirm the results found in Gerris et al. (2004) that DET was dominated by eSET, meaning that eSET was the most favourable strategy. However, because of a non-randomized design, it is possible that eSET and DET were not comparable because of confounding by indication.

Because only few studies were considered for inclusion in this review, no selection was made based on quality of the studies, which is normally necessary to check (Jefferson et al., 2002; Evers et al., 2005). However, discussion remains about the validity regarding this quality assessment (Juni et al., 1999). Furthermore, heterogeneity occurred between the included studies (difference in patient population, perspective of the study, inclusion criteria and inclusion or exclusion of frozen/thawed cycles). Therefore, it was not possible to validly pool total costs, effects and the ICERs of the included studies.

In this review, only point estimates of the ICERs were presented. Nowadays, it is standard procedure to calculate uncertainty rates around cost differences and ICERs by using the bootstrap method. The bootstrap method estimates the sampling distribution of a statistic through many simulations, based on sampling replacement from the original data (Briggs et al., 1997). However, in this review, only one study performed bootstrap simulations (Fiddelers et al., 2006).

To compare economic evaluations alongside clinical studies, it is necessary that the same methods are used (Gold et al., 1996; Drummond et al., 2005). Until recently the quality of most economic evaluations in the field of obstetrics and gynaecology had important shortcomings and did not adhere to the guidelines for economic evaluations that exist in different countries (Smith and Blackmore, 1998). In cases where guidelines and reporting formats for economic evaluations are followed (Drummond and Jefferson, 1996), it is easier for any reader to judge the validity and usefulness of economic evaluations for their own decision-making (Severens, 2001). Therefore, it is useful to develop a reference case for the economic evaluations of ART in general or embryo transfer strategies in particular. In such a reference case, an instruction is given of how to perform an economic evaluation and to standardize methods for economic evaluations. A reference case-based economic evaluation would adhere to specific settings with regard to outcomes, comparators, modelling techniques and use of costs to facilitate comparisons among economic evaluations performed with the same objective (Maetzel et al., 2003). Although this might be new within the assessment of ART patient management, a good example of a reference case exists in the field of rheumatoid arthritis (Gabriel et al., 2003; Maetzel et al., 2003).

Conclusion

Despite the diversity in the material and methods of four empirical economic evaluations of embryo transfer in IVF, from our review, we can conclude that today DET is always more expensive than eSET. Furthermore, DET is always more effective, but the difference in effectiveness decreases substantially when eSET including frozen/thawed cycles is performed in good prognosis patients (i.e. young patients with good quality embryos). eSET is only preferred from a cost-effectiveness point of view in these cases. In all other
patients it depends on how much society is willing to pay for one extra successful pregnancy, whether one cycle eSET or one cycle DET is preferred from a cost-effectiveness point of view.

Acknowledgements

The authors wish to thank professor Christina Bergh (Department of Obstetrics and Gynaecology, Institute for Health of Women and Children, Sahlgrenska University Hospital, Göteborg, Sweden) for the additional cost calculations she performed referring to the Thurin trial (Thurin Kjellberg et al., 2006). Our study was supported by a research grant (number 945-12-014) from the Dutch Organization for Health Research and Development (ZonMw) and the Dutch Health Insurance Board (CvZ) in a joint research programme on health technology assessment of infertility.

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Economic evaluations of eSET versus DET


Submitted on March 30, 2006; resubmitted on October 10, 2006; accepted on October 12, 2006