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

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared a single embryo transfer (SET) strategy, including one fresh single embryo transfer and, if no live birth, one additional frozen-thawed SET, with double embryo transfer (DET).

Type of intervention
Other: in vitro fertilisation (IVF).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women aged younger than 36 years, undergoing their first or second IVF cycle and having at least two good-quality embryos available.

Setting
The study setting was secondary care. The economic study was carried out in Sweden.

Dates to which data relate
The dates to which the effectiveness and resource use data referred were not reported in this paper, although the details of the clinical study were published in 2004 (Thurin et al. 2004, see 'Other Publications of Related Interest' below for bibliographic details). The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
The methods and results of the effectiveness study had been published elsewhere (Thurin et al. 2004). Consequently, the authors only provided a brief summary of the methods used in the effectiveness study.

The authors reported that 661 women meeting the inclusion criteria (see 'Study Population' section) were randomised. Of these, 330 were randomised to the SET group and 331 to the DET group.
Study design
This was a multi-centred randomised controlled study that was undertaken in 11 Scandinavian clinics (public and private). The patients were followed up until 6 months postpartum. The method used to randomise the patients was not reported in this paper. Some of the outcomes were reported to have been assessed blinded, although the method of blinding used was not reported.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome was the rate of pregnancies resulting in at least one live-born child. The authors also assessed the quality of life of the mothers. In order to measure quality of life, patients were asked to answer the SF-36 and the Swedish Parenthood Stress Questionnaire (SPSQ) 6 months after the delivery. Other obstetric and paediatric outcomes (i.e. severe obstetric complications requiring hospital treatment and severe neonatal complications requiring the neonatal ward) were also assessed. These were evaluated through two prospective self-reporting questionnaires, submitted after delivery and 6 months postpartum, and from records for the IVF treatment, antenatal care and hospital care.

Effectiveness results
The rate of pregnancies resulting in at least one live-born child was 128 (38.8%) of 330 in the cumulative SET group and 142 (42.9%) of 331 in the DET group (95% confidence interval for the difference, CI: 3.4 to 11.6).

The results of the effectiveness study also showed that there were significantly fewer severe obstetric complications in the SET group than in the DET group, including:
- preterm labour (1.6% versus 15.5%; p<0.0001),
- preterm premature rupture of the membranes (0.8% versus 8.5%; p=0.003),
- severe haemorrhage before, during or after delivery (16.4% versus 27.5%; p=0.039), and
- the number of women requiring Caesarean section (24.2% versus 49.3%; p<0.0001).

In a similar fashion, SET was also associated with significantly lower neonatal complications than DET (17.8% versus 33.9%; p=0.003).

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

Clinical conclusions
The results showed there were significantly more live pregnancies with DET than with SET, although the rate of obstetric and paediatric complications were significantly lower in the SET group.

Measure of benefits used in the economic analysis
The measure of benefits used was the rate of pregnancies resulting in at least one live-born child. This was directly obtained from the clinical study.

Direct costs
The direct costs to the health care system were included in the analysis. These comprised the costs of IVF treatment, drugs, complications resulting from IVF treatment, and pregnancy losses. For hospital services the authors used NordDRG (diagnosis-related groups). All hospital services (which included GnRH agonist treatment, ovarian stimulation with FSH, ovulation induction with HCG, and luteal support with progesterone) were estimated on the basis of DRG points for one particular hospital in Sweden. Swedish sales prices for drugs were used to cost the treatments. The cost for antenatal care was calculated based on its organisation in Goteborg, Sweden, and included laboratory tests.
appointments with a midwife, and one appointment with a physician. Discounting was not necessary, as the costs were incurred during a 6-month period, and was therefore not performed. The study reported the average costs. The price year was 2004.

**Statistical analysis of costs**
The costs were compared using Student's t-test.

**Indirect Costs**
The costs of productivity losses were included in the analysis. Absence from work during pregnancy was divided into sick leave, maternity leave and parental insurance leave. Working status and the number of days absent from work were assessed using questionnaires and medical records. In order to calculate productivity losses, the authors added 50% for the employer's contribution to national social insurance systems to the mean daily income in 2004 for all Swedish women of relevant ages. There were no productivity losses for women who were unemployed. The price year was 2004.

**Currency**
Euros (EUR).

**Sensitivity analysis**
A series of one-way sensitivity analyses were performed in which the mean actual treatment cost for IVF or intracytoplasmic sperm injection was doubled, and the neonatal intensive care unit (NICU) costs were increased by 50%.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The mean cost for maternal and paediatric health care was EUR 9,303 (standard deviation, SD=8,944) in the SET group and EUR 12,318 (SD=15,678) in the DET group, (95% CI for the difference: -4,964 to 1,065; p=0.003).

The mean cost for health care and productivity loss was EUR 10,905 (SD=10,891) in the SET group and EUR 14,676 (SD=18,331) in the DET group, (95% CI for the difference: -6,074 to -1,468; p=0.001).

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-effectiveness ratio (i.e. the additional cost per extra birth gained with DET when compared with SET). The additional cost per birth gained with DET was EUR 73,307 when including only health care costs and EUR 91,702 when productivity losses were also included.

The results of the sensitivity analysis showed that doubling the costs of IVF did not alter the incremental cost-effectiveness ratio. When doubling the NICU costs, the incremental cost-effectiveness ratio rose to EUR 98,361 per extra delivery when only health care costs were included.

**Authors' conclusions**
The single embryo transfer (SET) strategy was perceived as superior to double embryo transfer (DET) because, although SET resulted in fewer deliveries, there was a reduction in maternal and paediatric complications at lower total costs.
CRD COMMENTARY - Selection of comparators

Although the authors did not report explicitly the reasons for choosing the comparator, it would appear that both DET and SET strategies are common practice in IVF. You should decide if these strategies are commonly used in your own setting.

Validity of estimate of measure of effectiveness

The methods used in the effectiveness study were not reported in as they had already been published (Thurin et al 2004). Consequently, it was not possible to determine the internal validity of the authors' results. However, it would appear that the clinical study was well conducted as a randomised controlled study was used, the sample size was large and based on patients from three different countries and 11 different clinics, and appropriate statistical analyses were used to compare the outcomes.

Validity of estimate of measure of benefit

The estimation of benefits was obtained directly from the effectiveness analysis. The authors reported that quality of life was not included as a measure of benefit in the economic analysis because there were no differences between the two groups.

Validity of estimate of costs

Most of the cost categories relevant to the societal perspective adopted were included in the analysis, together with all major relevant costs. The authors reported that several costs were omitted from the analysis, such as the costs of absence from work for complications and pregnancy loss for patients not achieving a live birth, and transportation costs. The authors reported that these costs probably affected both groups equally. The authors also omitted the productivity losses of unemployed mothers, who might have to forego housework or leisure time due to sickness. The costs and the quantities were not reported separately, which will hamper reflation exercises in other settings. The costs were derived from the authors' settings. Appropriate statistical analyses of the costs were undertaken to determine whether group differences were statistically significant. Further, a limited sensitivity analysis of the costs was performed. Since all the costs were incurred during a 6-month period, discounting was unnecessary and was therefore not performed.

Other issues

The authors reported that no health economic analysis had yet been published with costs based on a large population randomised between SET and DET. They also reported that the study had a high degree of generalisability since the patients were recruited from 11 IVF units in three Scandinavian countries. The authors do not appear to have presented their results selectively. They reported that DET was not cost-effective in comparison with SET under a situation of budget restriction. However, in order to validate this conclusion, the authors should have reported a cost-effectiveness threshold to show the monetary value at which an extra birth is not good value for money. The authors did not report any further limitations to their study.

Implications of the study

The authors reported that their findings did not support continuing transfers of two embryos. However, they recommended that, before a final conclusion on policy recommendations is drawn, the expected lifetime costs of two alternatives should be modelled. The authors highlighted difficulties in interpreting the study findings, given that DET resulted in a few more deliveries but at a high incremental cost and with higher complications.

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Other publications of related interest


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