Reducing the number of embryos transferred in Sweden—impact on delivery and multiple birth rates

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BACKGROUND: Reduction of the number of embryos transferred has been introduced to decrease the multiple birth rates (MBRs) after IVF and the associated risks for the children. The aim of this report is to present the effect of two steps in reduction of the number of embryos transferred, when applied in the majority of the patients, on national data for delivery and MBR after IVF in Sweden. METHODS: This observational study is based on annual reports from all IVF clinics in Sweden to the National Board of Health and Welfare for the time period 1991–2004. RESULTS: The main finding is that despite a successive reduction in the number of embryos transferred, delivery rates were maintained at around 26% while MBR decreased dramatically, from about 35% to around 5%. The same pattern was noticed, independent of age, for all women below 40. In comparison with the USA, lower delivery and MBR were noted for Sweden whereas a higher ‘birth per embryo transferred’ was found. CONCLUSIONS: Single embryo transfer (SET) results in satisfactory delivery rates and a dramatic decrease in the MBRs, also when applied on a broad scale. The experience from Sweden ought to encourage other countries to introduce SET more widely.

Keywords: single embryo transfer; multiple birth; IVF; delivery rate

Introduction

The main complication associated with IVF is the high risk of multiple births and the related adverse outcome for the children. In the beginning of the IVF era, the results were quite poor, with low delivery rates per cycle. The main goal for IVF treatment was therefore to maximize pregnancy rates. It became clear that the pregnancy rate was related to the number of embryos transferred (Edwards and Steptoe, 1983; Wramsby et al., 1987), and replacement of five to six embryos resulted in the highest pregnancy rates. Multiple birth rates (MBRs) were moderately increased at that time and were not regarded as a complication. Data from European and US registers (Nyboe-Andersen et al., 2006; Assisted Reproductively Technology in the United States, 2004) show that the pregnancy and delivery rates have improved continuously. However, simultaneously with the increased effectiveness of assisted reproductive technologies (ARTs), high multiple pregnancy rates were noted, not only consisting of twins but also of high-order multiple births. In Sweden, in the late 1980s, the first attempt to reduce multiple births, especially of higher order, was to restrict the number of embryos transferred to three. The high rate of multiple births was thus mainly regarded as a direct consequence of the number of embryos transferred.

In Sweden, owing to the increasing rate of multiple births despite the restriction of the number of embryos transferred, a voluntary shift from three to two embryos transferred began at the initiative of IVF clinics in 1993. This reduction resulted in an almost total elimination of triplets, whereas the twin rate still remained high, and the delivery rate was maintained. Large registry studies, particularly from Sweden, reported a less favourable outcome for IVF children than for children born from spontaneous conceptions, mainly related to multiple births (Bergh et al., 1999; Helmerhorst et al., 2004; Wennerholm and Bergh, 2004). The first study of elective single embryo transfer (eSET) (Vilska et al., 1999) was reported from Finland and showed that in selected cases a similar pregnancy rate could be obtained with one embryo as with two embryos. An intensive debate began in Sweden among obstetricians, neonatologists, IVF-doctors and politicians concerning the high MBR after IVF, and demands were made for limiting the number of embryos transferred to only one. In parallel, a randomized multicentre study in Scandinavia was initiated, aiming to investigate if a similar live birth rate could be obtained by replacement of one fresh embryo and, if no live birth occurred, another frozen/thawed embryo, as with two embryos (double embryo transfer (DET)) transferred at the same time (Thurin et al., 2004). That study showed that the cumulative live birth rate
after one fresh and one frozen SET was not substantially lower than for one fresh DET.

In 2003, before the results from this study were available, the Swedish law on IVF was revised, and in the guidelines from the National Board of Health and Welfare, the number of embryos to be replaced was regulated. SET was to be the normal routine, and only when the risk of multiple births is considered to be low, may two embryos be replaced. More detailed guidelines were worked out by IVF doctors themselves. Initially, eSET was recommended in the first two fresh treatment cycles for women below 36 years, if two good quality embryos were obtained. Later, these recommendations were revised and eSET was recommended for women up to 38 years in the first two treatment cycles, if one good quality embryo was obtained. An embryo was classified as a good quality embryo according to Steer et al., 1992; Gardner et al., 1998.

The aim of this article is to describe how the change in the number of fresh embryos transferred has affected the delivery and the MBR after IVF on a national level in Sweden. In particular, the effects of SET on delivery and MBR in different age groups are reported. We have also compared the effects of the two different transfer policies in Sweden and the USA on delivery and MBRs.

Material and Methods
The data presented here are based on the annual reports from all 16 IVF clinics in Sweden to the National Board of Health and Welfare for the time period 1991–2004. Consent was given by the National Board. For the years 1992 and 1993, additional data were collected from the reports sent to European Society of Human Reproduction and Embryology.

Each clinic reports a summary of the treatments and outcomes annually. Data collected include the number of oocyte retrievals, the number of fresh and frozen/thawed embryo transfers, the number of embryos replaced, the number of pregnancies, the number of deliveries and the number of twins and multiple births of higher orders. The number of women in different age groups and their corresponding outcomes in terms of pregnancies and deliveries are also reported. For the year 2000, a questionnaire was sent to the IVF clinics asking them to report the number of multiple births in the different age groups. From the registry for the year 2004, the number of SET cycles in different age groups can be identified as well as pregnancy, delivery and multiple births according to age. Another questionnaire was sent to the IVF clinics asking them to report how strictly SET was applied for the year 2004. Although many publications distinguish between eSET and SET, we have chosen to present national data as total SET, including all SETs, both elective and non-elective. Thus, eSET is only reported for all age groups together, whereas in the individual age groups, only the total number of SET was given. Data from the annual ASRM/ SART reports as well as from other literature were used (Assisted Reproductively Technology in the United States, Canada, 1996, 1998–2000, 2000a, b, 2004; Center for Disease Control and Prevention, 2001–2003 and Society for Assisted Reproductive Technology, 1993–1995; Jain et al., 2004) for comparison between Sweden and USA.

Statistics
Descriptive statistics are given, as numbers, means and percentages. The relationships between MBR and SET and between birth rate and SET were assessed using weighted linear regression, which takes into account the different numbers of treatments per clinic.

Results
During the period from 1991 to 2004, the number of oocyte retrievals increased from 2993 to 8982, the number of transfers with fresh embryos using IVF or ICSI from 2670 to 8137 and the number of deliveries from 454 to 2031 per year. The mean number of embryos replaced per transfer decreased from 2.7 (1992) to 1.3 (2004). The number of multiple deliveries increased from 156 to a maximum of 424 (2001) and then decreased rapidly to 115 for 2004.

The delivery rate per transfer with fresh embryos increased from 17% to about 26%. The MBR after fresh embryo transfer was 35% in 1991, after which it gradually decreased, subsequent to the shift from three to two embryos, to 25% in 1994, where it remained stable until 2002. Elective SET started as early as 1999 on a small scale (1.5% of all transfers), with a marked increase from 2002 and onwards with 21.2% eSET and 30.6% SET in 2002; 41.3% eSET and 54.3% SET in 2003; 51.0% eSET and 67.4% SET in 2004. Concomitantly, the multiple birth rates decreased dramatically: 19.4% (2002), 11.8% (2003), and 5.7% (2004) while the live birth rate per transfer was stable: 26.8% (2002), 26.4% (2003), 25.0% (2004) (Figure 1). Since the national guidelines did not advocate 100% SET, the use of SET was slightly different at the IVF clinics. The different SET rules used in 2004 are presented in the legend of Figure 2. One clinic used prediction model based on different patient variables and embryo scores for pregnancy chance and risk for twin pregnancy. It was applied, using a risk level for twin implantation of maximum 10% to determine for SET or DET (Holte et al., 2004, Holte et al., 2007).

The development of SET in different age groups is of particular interest (Table 1). The birth rates have remained stable for all age groups, whereas at the same time, a dramatic decrease in MBR has occurred for all age groups except ≥40 years (Table 1). Figure 2 shows the MBR rate in relation to the percentage of SET for women <40 years at different IVF units. According to the regression equation $\text{MBR} = 17.4 - 0.166 \times \%\text{SET}$, a SET rate of at least 75% is needed to achieve a MBR of maximum 5% for women under 40. We found no indication that delivery rates decreased with increasing SET rate at the different IVF units (Fig. 3).

![Figure 1: Birth rate and MBR in relation to the percentage of SET and triple embryo transfer (TET) in Sweden 1991–2004](image-url)
During the same period, 2000–2004, the delivery rate after DET decreased from 26.9% to 20.6% and the MBR from 24.6% to 18.1%. However, during 2004, there was still a wide variation (5–26%) in the MBR after DET among the units.

The development of IVF in Sweden and USA is described in Figs 4 and 5. A continuous increase in delivery rate per transfer is observed in USA, whereas the delivery rate in Sweden increased until 1993 thereafter to stabilize at ~25%. A two-step reduction in MBR can be seen in Sweden, where the second step is huge during the last two years. In the USA, the MBR continuously increased until the middle of the 1990s, where after a slight reduction can be observed. Simultaneously, the mean number of embryos transferred has been more than halved in Sweden, whereas the reduction in the USA is less pronounced (30%). In Fig. 5, live births per embryo transferred are presented. This figure shows that both countries have had continuous improvements in their live birth rates per embryo transferred, but the rate is generally higher in Sweden than in the USA.

Discussion

The main finding in this Swedish national report is that a stable live birth rate has been maintained, despite a successive reduction in the number of embryos replaced resulting in a dramatic decrease in the MBR. Similar patterns are observed for all age groups, except for women ≥40. This has been achieved by introduction of SET to the vast majority of all IVF patients, with a total SET level of 67.4% for 2004. The present report covers 100% of all IVF cycles performed in Sweden between 1991 and 2004, and no cycles were lost for follow-up or not reported.

Two steps in altering the number of embryos transferred in order to reduce the high rates of multiple births could be identified. The first step was a shift from three to two embryos, which began voluntarily at the IVF clinics in 1993. The second, more dramatic, step induced a shift from two embryos to one. This step also began voluntarily (in 2000) after recommendations from IVF doctors and demands from obstetricians and neonatologists. Later, it was accelerated by the change in the Swedish guidelines for IVF in 2003.

In contrast to this report, several randomized controlled trials (RCTs) have shown superiority for DET versus SET. A summary of the results from all RCT on SET versus DET published so far on cleaved embryos (Gerris et al., 1999; Martikainen et al., 2001; Thurin et al., 2004; Lukassen et al., 2005; van Montfoort et al., 2006) indicate that DET gives both a statistically and clinically significant higher ongoing pregnancy/live birth rate but at the price of high MBR. The SET approach gives satisfactory delivery rates and minimizes the MBR. These results are quite consistent between studies using different inclusion criteria and performed in different settings. When frozen/thawed SETs are included, as in the Scandinavian trial (Thurin et al., 2004), the live birth rate does not differ substantially from what was achieved in the DET group. Clearly, a well functioning freezing program is a prerequisite for a more general SET policy (Tiitinen et al., 2001, 2004; Lundin and Bergh, 2007).

The results from the present report are in agreement with national data from Finland (Tiitinen and Gissler, 2004) and several observational studies from different clinics in Finland, Sweden, Belgium and the Netherlands for cleaved embryos (Vilska et al., 1999; Gerris et al., 2002, 2004; De Sutter et al., 2003; Tiitinen et al., 2003; Martikainen et al., 2004; Saldeen and Sundström, 2005; van Montfoort et al., 2005; Veleva et al., 2006) and from the USA and Australia for blastocyst transfers comparing SET and DET (Critini et al., 2005; Henman et al., 2005), where similar birth rates have consistently been observed after SET and DET, with a huge decrease in MBR in the SET groups. In another European country, Belgium, the government decided to reimburse IVF

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of ET</th>
<th>SET (%)</th>
<th>Delivery rate (%)</th>
<th>MBR (%)</th>
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<tbody>
<tr>
<td>&lt;30</td>
<td>965</td>
<td>1211</td>
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<td>32.3</td>
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<tr>
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<td>2937</td>
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<td>2005</td>
<td>69.8</td>
<td>22.8</td>
</tr>
<tr>
<td>38–39</td>
<td>771</td>
<td>1032</td>
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<td>38.3</td>
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</tr>
<tr>
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<td>6586</td>
<td>8136</td>
<td>12.6</td>
<td>67.4</td>
</tr>
</tbody>
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treatments after introduction of a new legislation in 2003, if a new transfer policy was incorporated, aiming to reduce the number of multiple births after ART. Depending on the woman’s age and previous treatment cycles, the number of embryos for transfer is restricted. After the implementation of SET, several IVF centres in Belgium (Gordts et al., 2005; Ombelet et al., 2005; Van Landuyt et al., 2006) have reported a dramatic decrease in MBR, whereas clinical pregnancy rates have not been compromised. However, in all these studies, the SET and DET groups are not strictly comparable. Good prognosis women received SET whereas less good prognosis women received DET. The same confounders certainly also exist in the present national report comparing historical DET with present SET results, in spite of the fact that the women receiving SET in the Swedish national SET cohort were chosen much less selectively. If Sweden had continued to transfer two embryos, an increase in the live birth rate might well have been observed, similar to the observation in the USA (Jain et al., 2004). However, from the patient’s point of view, as well as the points of view of doctors and society, a maintained live birth rate is probably quite acceptable if it is possible at the same time to decrease the MBR considerably and thereby decrease the risks for the IVF children.

Observational data have shown that similar birth rates could be achieved by transferring two instead of three embryos, while at the same time reducing the MBR (Templeton and Morris, 1998). This particular set of data had an enormous influence on IVF practices worldwide and encouraged the shift to transferring fewer embryos. The arguments used then to change practice hold true today and can be used to encourage more people to move voluntarily to SET.

In a recent debate in Human Reproduction (Gleicher and Barad, 2006; Gleicher et al., 2006) Gleicher and co-workers compared a large dataset from UK (Templeton and Morris, 1998) with published RCTs on SET versus DET and claimed that although the UK data showed maintained live birth rates with two compared with three embryo transfers, the studies on SET showed inferiority for SET versus DET. However, it then seems that the authors mixed evidence from RCTs with evidence from observational studies. In fact, the observational data from UK showed an almost identical pattern as observational data from SET versus DET, as presented in this paper and elsewhere (Vilska et al., 1999; Gerris et al., 2002, 2004; De Sutter et al., 2003; Tiitinen et al., 2003; Martikainen et al., 2004; Saldeen et al., 2005; van Montfoort et al., 2005; Veleva et al., 2006). It is only in randomized settings that DET has been found to be superior to SET (Gerris et al., 1999; Martikainen et al., 2001; Thurin et al., 2004; Lukassen et al., 2005; van Montfoort et al., 2006). To our knowledge, no RCT has been published comparing two versus three embryos.

The most confusing part in the Gleicher argument is that these ‘differences’ (which are not differences but instead are similarities) in outcome of observational studies are taken as a reason not to introduce SET in the USA.

Results from USA show generally higher delivery rates compared with Europe (Gleicher et al., 2006). The difference is, at least partly, due to a higher number of embryos transferred but also other factors are probably of importance. It is of interest, however, when comparing ‘birth per embryo transferred’ as in Fig. 5, that despite the USA showing a higher delivery rate per ET compared with Sweden, an opposite pattern is found when comparing ‘birth per embryo transferred’, a variable reflecting treatment quality in a positive way.

However, despite good results and a favourable approach in countries such as Finland, Sweden, the Netherlands and
Belgium, eSET is still being debated and has not been widely accepted. It might be considered a greater step to reduce from two embryos to one than from three to two. Fear of lowering pregnancy and delivery rates is probably the main reason. Another is the financial system in different countries. In countries, where IVF is covered by public funding, it seems to be easier to introduce SET than in countries relying on private care and/or insurance systems. However, it should be remembered that in Sweden only 50% of IVF is publically funded whereas the other 50% is privately funded, and there is no insurance system for infertility treatment in Sweden. Still, SET has been well and equally accepted among both private and public IVF clinics. It has recently been shown in a Scandinavian study that attitudes among doctors to SET and multiple births are also of high importance (Bergh et al., 2005).

It is still an open debate if the presented SET and DET levels in Sweden are optimal. The MBR after DET were still high, around 18%, and are not in accordance with the Swedish law on IVF, which provides that two embryos should only be transferred when the risk of multiple births is low. According to the regression analysis, a SET rate of 75% would result in a MBR of 5% or less for women under 40. A recent observational study from Finland (Veleva et al., 2006) reported similar results for SET and DET for women 36–39 years of age, indicating that SET may also be applied in this age group. A newly developed prediction model resulted in the lowest MBR and seems to be a promising instrument for achieving optimal results (Holte et al., 2004, 2007). Since the delivery rate seemed not to decrease with increasing SET levels, other limits for eSET may be used to further decrease MBR.

In conclusion, this study is the first report of the effects of SET, when introduced for the majority of patients, on national delivery and MBR. The main finding is that delivery rates are maintained while MBR decrease dramatically. This seems to occur independently of the women’s ages. The results obtained ought to encourage other countries to introduce SET as the main transfer policy in women up to 40 years, with the overall aim of decreasing the obstetric and neonatal risks for children born after IVF.

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