NEW DEBATE

What about the remaining twins since single-embryo transfer? How far can (should) we go?

D.De Neubourg and J.Gerris

Centre for Reproductive Medicine, Middelheim Hospital, Antwerp, Belgium

1To whom correspondence should be addressed at: Centre for Reproductive Medicine, Middelheim Hospital, Lindendreef 1, 2020 Antwerp, Belgium. E-mail: diane.de.neubourg@skynet.be

Single-embryo transfer (SET) and more specifically elective SET (eSET) have taken their place in good clinical IVF/ICSI practice. After the initial cautious search for the characteristics of the twin-prone patient and of the selection of the embryo with the highest implantation potential many centres have embarked on the (progressive) implementation of SET, either by conviction or forced by legislation or both. It was only because the ongoing pregnancy rates remained largely unaffected that SET was accepted. Generally speaking, it can be said that the twinning rate after IVF/ICSI has dropped by at least 50% simply by transferring only one good-quality embryo in the first and second fresh IVF/ICSI cycles in young women, without decrease in the overall pregnancy rate. Preventing ‘the second half’ of IVF/ICSI twins constitutes another and probably tougher challenge because the target group is a heterogeneous mix consisting of patients in very different clinical situations. Can we expand our experience for further twin prevention to women of older age and to cycles of higher rank without a significant drop in pregnancy rates? Can we extend it to more cryopreservation cycles? To have an idea of future target groups for increased application of SET, we analysed the remaining twins after double-embryo transfer (DET), and from these data we suggest expanding the eSET policy to women <38 years of age until the third cycle and to cryopreservation cycles.

Key words: remaining twins/single-embryo transfer/twin prevention in ART

Introduction

Prevention of multiple pregnancies and of twin pregnancies in particular, has become a target of increasing importance for most European IVF centres. Data from the European IVF-monitoring programme (EIM, 2005), reporting on the European results of assisted reproduction technologies (ART) cycles from the year 2001, mention a total multiple delivery rate of 25.5% (24.0% twin pregnancy rate, 1.5% triplet pregnancies). This report also mentions that the total multiple delivery rate remained unchanged during the last 4 years. Numerous reports have since been published on diverse aspects of single-embryo transfer (SET) and have been reviewed by Bergh (2005) and Gerris (2005). The prospective randomized trials show the feasibility of SET with regard to pregnancy rate and evaluation of embryo selection criteria (Gerris et al., 1999; Martikainen et al., 2001; Gardner et al., 2004) as well as the equivalence of two transfer strategies: (i) transfer of one fresh embryo followed by one frozen-embryo transfer versus double-embryo transfer (DET) (Thurin et al., 2004); and (ii) two subsequent SET cycles versus one DET cycle (Lukassen et al., 2005). The observational studies show the acceptability and successful implementation of SET in daily practice and demonstrate an equivalence of eSET versus DET with regard to pregnancy outcome. In these studies, SET is applied in the twin-prone patient population comprising the young patient population (<36 or <38 years of age) in the first or second cycle with embryos of high implantation potential. Although the proportion of SET cycles is steadily growing, in the reported observational studies the percentage of SET cycles is only 25.4% (Table I), whereas the DET cycles (74.6%) still report 34.3% twin pregnancies (Bergh, 2005; Van Montfoort et al., 2005). We have previously described that introduction of SET halved the twinning rate (Gerris et al., 2002) while maintaining a high ongoing pregnancy rate. In countries and/or centres where a large proportion of transfers are SETs, this first half of twin prevention is now largely achieved and even surpassed. However, the second half or at least one-third of all IVF/ICSI pregnancies remains, with twinning rates that still hover around 10% of all ongoing pregnancies. Although this can only be considered a proof of improved quality of IVF/ICSI treatment, a further reduction of the twinning rate appears to be a more difficult task. This should not deter us from thinking about the problem. A linear implementation of SET has in the past not been and is at present not proposed for fear of unacceptable low pregnancy rates, particularly in the more difficult cases of patients with older age and cycles with higher rank. The problem should definitely be seen in a larger context, taking
cryopreservation as an integrating aspect of pregnancy rates. With a cryopreservation programme that guarantees 100% survival of all frozen embryos, SET could be the default transfer policy for all IVF/ICSI cycles. We have not reached that stage yet, but it is clear that because fewer embryos are transferred, the cryopreservation programme becomes increasingly more important (Figure 1). A retrospective analysis of 1647 frozen-embryo transfers shows that SET is also an option in cryocycles (Hydén-Granskog et al., 2005).

One method to continue our efforts to reduce the twins after IVF/ICSI constitutes that of analysing where we find the remaining twins after full implementation of the first set of transfer rules connected with reimbursement. The underlying idea is that, in the near future, all transfers are SETs except in a primary target, however, is the prevention of multiple and twin pregnancies. Although the incidence of monozygous twinning remains largely unknown, its prevention is probably not possible. The aetiology of monozygous twinning remains well known that the incidence of monozygous twins after ART is 1–3.4% (Derom et al., 1987; Bergh et al., 1999) and is increased when compared to 0.4% in the general population. Because the aetiology of monozygous twinning remains largely unknown, its prevention is probably not possible. The primary target, however, is the prevention of multiple and twin pregnancies from multiembryo transfers. We shall further analyse the 14 twins after DET.

### Table I. Frequency of eSET in observational studies comparing eSET versus DET

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cycles</th>
<th>eSET cycles [n (%)]</th>
<th>≥DET cycles [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vilska et al. (1999)</td>
<td>910</td>
<td>168 (18.5)</td>
<td>742 (81.5)</td>
</tr>
<tr>
<td>Tütünen et al. (2003)</td>
<td>1699</td>
<td>675 (39.7)</td>
<td>1024 (60.3)</td>
</tr>
<tr>
<td>Gerris et al. (2002)</td>
<td>1464</td>
<td>385 (26.3)</td>
<td>1079 (73.7)</td>
</tr>
<tr>
<td>De Sutter et al. (2003)</td>
<td>4845</td>
<td>790 (16.3)</td>
<td>4055 (83.7)</td>
</tr>
<tr>
<td>Catt et al. (2003)</td>
<td>385</td>
<td>111 (28.8)</td>
<td>274 (71.2)</td>
</tr>
<tr>
<td>Gerris et al. (2004)</td>
<td>367</td>
<td>206 (56.1)</td>
<td>161 (43.9)</td>
</tr>
<tr>
<td>Martikainen et al. (2004)</td>
<td>1271</td>
<td>468 (36.8)</td>
<td>803 (63.2)</td>
</tr>
<tr>
<td>Van Montfoort et al. (2005)</td>
<td>521</td>
<td>111 (19)</td>
<td>410 (81)</td>
</tr>
<tr>
<td>Total</td>
<td>11462</td>
<td>2914 (25.4)</td>
<td>8548 (74.6)</td>
</tr>
</tbody>
</table>

eSET, elective single-embryo transfer; DET, double-embryo transfer.

### Analysis of the remaining twins

We calculated the effect of the implementation of the Belgian law on the ongoing pregnancy and on the twin pregnancy rate since its introduction on 1 July 2003 in our centre. The number of SETs in our centre has been gradually increasing from 13% in 1998 to 63% in 2004. This has led to a decline in the mean number of embryos transferred from 2.26 in 1998 to 1.41 in 2004. The pregnancy rate for the whole programme remained stable with an ongoing pregnancy rate of 33.7% in 2004.

We performed 447 cycles in 2004 (Table II). One hundred and five ongoing pregnancies occurred in 268 SET transfers (39.2%) and 39/137 (28.5%) pregnancies occurred from DET transfers [relative risk (RR): 1.39; 95% confidence interval (CI): 1.01–1.86]. There were 102 pregnancies reaching beyond 25 weeks of gestation in the SET group and 37 in the DET group (RR: 1.40; 95% CI: 1.02–1.93). The mean age of the patients was 33.43 (±4.61 SD) years. This was 32.33 (±4.15 SD) years for the SET patients and 34.59 (±4.74 SD) years for the DET patients (P = 0.0001; 95% CI: 1.36–3.15).

We wanted to obtain a picture of the patients who still conceived of a twin pregnancy since the introduction of reimbursement of IVF/ICSI laboratory costs. Therefore, we analysed the twin pregnancies obtained in 2004 (Table II). There were 20 twin pregnancies in 202 conception cycles (9.9%) of which six were monozygotic twin pregnancies (3.0%) after SET. It is well known that the incidence of monozygous twinning after ART is 1–3.4% (Derom et al., 1987; Bergh et al., 1999) and is increased when compared to 0.4% in the general population. Because the aetiology of monozygous twinning remains largely unknown, its prevention is probably not possible. The primary target, however, is the prevention of multiple and twin pregnancies from multiembryo transfers. We shall further analyse the 14 twins after DET.

### Table II. Analysis of cycles performed in 2004

<table>
<thead>
<tr>
<th>Cycles (n = 447)</th>
<th>Ongoing pregnancy (&gt;12 weeks)</th>
<th>Pregnancy &gt;25 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfers [n = 424 (94.8%)]</td>
<td>144</td>
<td>139</td>
</tr>
<tr>
<td>SET cycles [n = 268 (63.2%)]</td>
<td>105 (39.2)</td>
<td>102 (38.0)</td>
</tr>
<tr>
<td>Twin pregnancy [n = 6]</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>DET cycles [n = 137 (32.3%)]</td>
<td>39 (28.5)</td>
<td>37 (27.0)</td>
</tr>
<tr>
<td>Twin pregnancy [n = 14]</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>3ET cycles [n = 19 (1.5%)]</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

DET, double-embryo transfer.
Twelve of 14 twins (85.7%) occurred in the first three cycles, 9/14 transfers (64.3%) did not contain embryos with an a priori high implantation potential and were thus considered as ‘not at risk’ for twin pregnancy. Seven of 14 twins (50%) occurred in patients older than 36 years of age, who are allowed two embryos for transfer as of the first cycle; no twin pregnancies occurred in patients older than 36 years of age, who are 'not at risk' for twin pregnancy. Seven of 14 twins (50%) a priori cycles in which a top-quality embryo had been transferred cycles, 9/14 transfers (64.3%) did not contain embryos with an 

**Considerations for further twin prevention**

If we want to extend the prevention of twin pregnancy further we have to consider the expansion of the definition of the 'twin-prone patient' by the implementation of SET in the first three treatment cycles as suggested by Van Montfoort et al. (2005).

Furthermore, we can formulate the suggestion from our data that SET can be proposed to patients up to 38 years of age. We have previously shown that implantation rate of embryos with high implantation potential is unaffected until the age of 38 years (De Neubourg et al., 2004). It is clear from the above data that the patient group between 38 and 40 years in their first cycle is also at risk and can be offered eSET.

eSET implies a validated system of embryo selection for the ‘first half’ of twins to prevent after IVF/ICSI treatment. However, once it is decided to tackle the ‘second half’ of the twins, one should probably consider SET regardless of embryo selection and just transfer the best available embryo.

However, some reflections need to be kept in mind when further implementation of eSET is considered. It is unknown whether eSET would truly not compromise the overall chances for pregnancy in these couples. The patients’ initial dislike towards twin pregnancy at the start of IVF/ICSI treatment may change to desire along the treatment period. When fewer embryos are transferred, more embryos remain for cryopreservation, and this will bring extra work and costs and may lead to waiting lists in some countries.

**References**


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