In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial

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BACKGROUND: Elective single embryo transfer (eSET) in a selected group of patients (i.e. young patients with at least one good quality embryo) reduces the number of multiple pregnancies in an IVF programme. However, the reduced overall multiple pregnancy rate (PR) is still unacceptably high. Therefore, a randomized controlled trial (RCT) was conducted comparing eSET and double embryo transfer (DET) in an unselected group of patients (i.e. irrespective of the woman’s age or embryo quality). METHODS: Consenting unselected patients were randomized between eSET (RCT-eSET) (n = 154) or DET (RCT-DET) (n = 154). Randomization was performed just prior to the first embryo transfer, provided that at least two 2PN zygotes were available. Non-participants received our standard transfer policy [SP-eSET in a selected group of patients (n = 100), otherwise SP-DET (n = 122)]. RESULTS: The ongoing PR after RCT-eSET was significantly lower as compared with RCT-DET (21.4 versus 40.3%) and the twin PR was reduced from 21.0% after RCT-DET to 0% after RCT-eSET. The ongoing PRs after SP-eSET and SP-DET did not differ significantly (33.0 versus 30.3%), with an overall twin PR of 12.9%. CONCLUSION: To avoid twin pregnancies resulting from an IVF treatment, eSET should be applied in all patients. The consequence would be a halving of the ongoing PR as compared with applying a DET policy in all patients. The transfer of one embryo in a selected group of good prognosis patients leads to a less drastic reduction in PR but maintains a twin PR of 12.9%.

Key words: assisted reproductive technology/multiple pregnancy/randomized controlled trial/single embryo transfer

Introduction

A multiple pregnancy is a serious adverse outcome of an IVF treatment (Land and Evers, 2003). In many (European) IVF centres, the standard embryo transfer policy is to transfer two embryos (Nyboe Andersen et al., 2004). However, although higher order multiple pregnancies are reduced to 2% on average, the twin pregnancy rates (PRs) remain between 20 and 35% (Nyboe Andersen et al., 2004). Twin pregnancies should also be considered as a serious disadvantage, not only because of the increased risks of medical and perinatal complications (ESHRE Capri Workshop, 2000; Helmerhorst et al., 2004), but also because of the increased health care costs associated with enhanced pre- and postnatal care (De Sutter et al., 2002; Gerris et al., 2004; Lukassen et al., 2004). The only way to solve this problem is to reduce the number of embryos transferred to one.

Several studies have investigated elective single embryo transfer (eSET). At least five randomized controlled trials (RCTs) have been published (Gerris et al., 1999; Martikainen et al., 2001; Gardner et al., 2004; Thurin et al., 2004; Lukassen et al., 2005). In these studies, only patients at risk for a twin pregnancy were randomized between the transfer of one or two good quality embryos (double embryo transfer; DET). The selection criteria for patients at risk varied between the studies, but were based on female age (<34 years, Gerris et al., 1999; <35 years, Lukassen et al., 2005) and some of the patients in the study of Thurin et al. (2004); <36 years, Martikainen et al. (2001) and some of the patients in the study of Thurin et al. (2004), and the number of good quality embryos available (≥2 in the studies of Gerris et al., 1999, Thurin et al. (2004) and Lukassen et al. (2005); ≥3 in some of the patients in the study of Thurin et al. and ≥4 in one of the participating centres in the
study by Martikainen et al. (2001). Furthermore, no previous failed cycles were allowed in some of the studies (Gerris et al., 1999; Lukassen et al., 2005). These studies showed that the transfer of only one good quality embryo resulted in lower PRs as compared with the transfer of two good quality embryos, although the differences were not significant in all studies. However, as PRs after eSET were acceptable and twin pregnancies were avoided, it was concluded by the authors that eSET should be the transfer policy of choice in this subgroup of patients. Furthermore, in two RCTs, it was demonstrated that the difference in PRs between SET and DET can be overcome by performing one additional SET cycle (Lukassen et al., 2005) or a frozen embryo transfer cycle if frozen embryos from the fresh cycle were available (Thurin et al., 2004).

Besides the RCTs mentioned, several observational studies have been published (Tiitinen et al., 2001; Gerris et al., 2002; Van Montfoort et al., 2005) in which the results of eSET applied in a selected group of good prognosis patients (20–30% of the IVF population) were compared with the results of DET applied in the remaining group of patients. These studies concluded that eSET and DET resulted in comparable PRs and that the overall twin PR in an IVF programme could be reduced considerably. In the most recent studies, 55–60% of all patients were offered eSET, while DET was offered to the remaining patients (Tiitinen et al., 2003; Gerris et al., 2004). This resulted in an overall twin PR of ~10%. Although this rate is significantly lower than the rate obtained with a transfer policy consisting of only SET (20–35%), it is still substantially higher than the rate in spontaneous pregnancies. From the studies published so far, it can be concluded that eSET offers an acceptable PR with a low twin PR in a selected group of patients. It is unknown whether PRs remain acceptable if eSET is applied in an unselected group of patients, thereby reducing the twin PR to a value comparable with the spontaneous twin PR. Therefore, a prospective RCT was conducted where patients were assigned to either eSET or DET irrespective of their age (within the age limits applied in our IVF programme) and irrespective of whether or not a good quality embryo was available.

The primary aim of this study was to compare the PRs in both study groups. The RCT was limited to the first cycle of patients and to the transfer of fresh embryos only. A secondary aim of this study was to evaluate PRs after eSET and DET when the decision of whether to transfer one or two embryos was based on female age (<38 years) and the presence of at least one good quality embryo.

Materials and methods

Patients and study design

From January 2002 until December 2004, patients who started their first IVF cycle in the academic hospital of Maastricht, The Netherlands, were assessed for eligibility to participate in the study. Patients applying for PGD, patients requiring the transfer of only one embryo (in most cases because of medical reasons) and patients who could not be informed adequately because of a language barrier were excluded. All other patients were informed about the study, including the possibility of a lower PR after eSET and the pre- and postnatal risks of twins. Eligible patients choosing not to participate in the RCT were offered our standard transfer policy (see below).

Consenting patients had to have normal fertilization of at least two oocytes (i.e. 2PN embryos) in order to be randomized between eSET (referred to as the RCT-eSET group) and DET (referred to as the RCT-DET group). Randomization was performed immediately prior to embryo transfer. To ensure comparability between eSET and DET with respect to female age (<38 years or ≥38 years) and fertilization technique (IVF or ICSI), the patient population was stratified with respect to these four characteristics. Furthermore, to avoid confounding by fluctuations of success rates over time, the groups were subdivided into smaller groups to ensure an equal distribution of eSET and DET over a time period (an average of 3 months). By varying the size of these subgroups (ranging from eight to 14) and by using a non-transparent box containing the sealed opaque envelopes, the randomization procedure was blinded. The laboratory personnel performing the randomization were unaware of the size of the subgroups.

After transfer, patients were informed about the number of embryos transferred. Any subsequent IVF or ICSI cycle and all transfer cycles of cryopreserved embryos were not a part of the RCT. In these cycles, our standard transfer policy was applied. The standard transfer policy in our clinic consisted of the transfer of a single embryo when female age was <38 years and at least one good quality embryo (see below) was available. Otherwise, two embryos were transferred. In order to compensate for any possible disadvantage due to a lower PR in the RCT-eSET group of the study, these patients were offered a fourth IVF or ICSI cycle free of charge if pregnancy was not achieved in the first three cycles which, as a rule, are covered by the national health system or by private insurance companies in The Netherlands.

To address the secondary aim of our study, data from patients who received the standard transfer policy in their first treatment cycle were used. This group was composed of all patients eligible for the study, but not willing to participate and the patients not eligible for the study because of a language barrier (non-participants group). Furthermore, in order to compare eSET (referred to as the standard policy eSET group; SP-eSET) with DET (SP-DET group), at least two normally fertilized oocytes (2PN zygotes) had to be present. The study was approved by the Institutional Ethical Board of the academic hospital of Maastricht and all participating patients in the RCT signed an informed consent. The non-participating patients signed an informed consent for the use of their data.

Sample size calculation

To calculate sample size for the RCT part of the study, data from a previous period in our IVF clinic, in which DET was our standard policy, were used. An ongoing PR of 29% was achieved after DET. Assuming a similar ongoing PR for the DET group in the study and considering an ongoing PR in the eSET group of <15% as clinically unacceptable, the required sample size was 150 cycles in both the eSET and DET study group with a power of 80% and an α of 0.05.

Ovarian stimulation protocol

Patients were downregulated with 0.1 mg of triptorelin daily s.c. (Decapeptyl; Ferring BV, Hoofddorp, The Netherlands) according to the long protocol. To stimulate multiple follicular development, recombinant FSH (Puregon; Organon, Oss, The Netherlands) was used. Follicle growth was monitored by ultrasound, and 5000 IU of HCG (Pregnyl; Organon) was administered as soon as at least three follicles were ≥18mm. Ultrasound-guided oocyte retrieval was performed 36 h after HCG administration. The luteal phase was supported by progesterone (Progestan; Organon) 200 mg three times daily intravaginally, starting at the day of ovum pick-up and continued for 14–16 days. In the case of a pregnancy, progesterone was continued for another 3 weeks.
Culture procedure, embryo quality assessment and transfer policy

IVF, ICSI and embryo culture procedures have been described in detail earlier (Dumoulin et al., 2000). For each embryo originating from a normally fertilized oocyte, an embryo score was calculated on the basis of morphological grade (1–4, with grade 4 being the best grade), number of blastomeres and presence or absence of multinucleated blastomeres (MNBs) (Van Montfoort et al., 2005). Embryos that had reached the 4- or 5-cell stage on day 2, or the 8-cell stage on day 3, in combination with having the best morphological grade (regular, even sized blastomeres with <20% fragmentation) and an absence of MNBs were classified as good quality embryos (Van Montfoort et al., 2005). Embryos were transferred on day 2 after ovum pick-up or, in a minority of cases, for reasons of convenience, on day 3. In all cases, including those in the RCT study, embryos with the highest embryo score were transferred.

Cryopreservation of supernumerary embryos was performed on the morning of the third day after ovum pick-up if one or more embryos had reached the 8-cell stage, and if they were of good morphological quality.

Outcome variables

Primary outcome variables were ongoing PR and twin PR at 10 weeks after ovum pick-up (12 weeks gestational age). An HCG pregnancy test with a detection limit of 50 IU/l in urine was performed 14–16 days after embryo transfer, and patients with a positive test had an ultrasound examination 3 weeks later. An ongoing pregnancy was defined as the presence of at least one intrauterine gestational sac with fetal heart beat on ultrasound at 7 weeks gestation, and no report of pregnancy loss when patients were contacted at 12 weeks gestation.

Statistics

Analysis of variance (ANOVA) with Tukey’s multiple test procedure was used to compare the continuous variables, and the χ² test with Bonferroni correction was used for binary variables. A P-value <0.05 was considered significant.

Results

Of the 807 patients who visited the clinic for their first IVF or IVF/ICSI cycle in the period from January 2002 until December 2004, 133 (16.5%) patients did not meet the inclusion criteria [PGD (n=72), eSET for medical reasons (n=42) or language barrier (n=19)]. Furthermore, 53 (6.6%) patients refrained from IVF treatment or achieved a spontaneous pregnancy while waiting for the start of their first IVF cycle. Of the 621 eligible patients, 348 (56%) agreed to participate in the RCT part of the study. Of these, 40 patients (11%) could not be randomized because of fertilization failure or because only one embryo was available. The remaining 308 patients were randomized immediately prior to embryo transfer: 154 patients received one embryo and 154 received two (Figure 1). In 123

Figure 1. Flowchart of patient selection for the RCT part of the study.
(80%) patients in the SET group and 116 patients (75%) in the DET group, the transfer was performed on day 2. The remaining patients received their embryos on day 3.

Patient and cycle characteristics were comparable between the two study groups of the RCT (Table I). When the clinical outcomes of the eSET and DET groups of the RCT were compared, the percentage of positive pregnancy tests after transfer of fresh embryos differed significantly between eSET and DET (33.1 versus 47.4%, respectively) (Table II). In addition, the abortion rate was significantly higher after eSET as compared with DET (35.3 versus 15.1%), resulting in a doubling of the ongoing PR after DET as compared with eSET (40.3 versus 21.4%). The twin PR after eSET was reduced to 0%, whereas 21.0% of the ongoing pregnancies after DET were twin pregnancies (Table II).

In the non-participants group (n=292, composed of 273 patients who declined to participate in the RCT and 19 otherwise eligible patients with a language barrier), in 70 patients the standard transfer policy could not be applied for the following reasons: (i) cancellation of the cycle before ovum pick-up (n=28); (ii) no fresh embryo transfer and cryopreservation of all embryos was performed because of ovarian hyperstimulation syndrome (OHSS) (n=3); (iii) total fertilization failure was found (n=11); or (iv) only one embryo was obtained and transferred (compulsory SET) (n=28). The remaining 222 patients had at least two fertilized embryos and were suitable for a comparison between eSET and DET according to our standard transfer policy (SP-eSET and SP-DET). SP-eSET was applied in 45% of the patients (Table III). Patient characteristics from the non-participants group were similar to those of the participants in the RCT study except for the mean age (Table I). The ongoing PRs in the SP-eSET and SP-DET groups were 33.0 and 30.3%, respectively (Table III).

### Table I. Patients’ and cycle characteristics of the study subjects (RCT-eSET and RCT-DET) and the non-participants in the first cycle

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RCT-eSET (n=154)</th>
<th>RCT-DET (n=154)</th>
<th>Non-participants (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Mean female age ±SD</td>
<td>32.7 ± 3.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32.4 ± 3.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>34.0 ± 3.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>No. of patients ≥28 years (%)</td>
<td>8 (5.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (3.8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47 (21.2)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration of subfertility ±SD</td>
<td>3.3 ± 1.8</td>
<td>3.3 ± 2.1</td>
<td>3.5 ± 2.8</td>
</tr>
<tr>
<td>Cause of subfertility (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubal factor</td>
<td>24 (15.6)</td>
<td>28 (18.2)</td>
<td>38 (17.1)</td>
</tr>
<tr>
<td>Male factor</td>
<td>85 (55.2)</td>
<td>87 (56.5)</td>
<td>124 (55.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>34 (22.1)</td>
<td>37 (24.0)</td>
<td>45 (20.2)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (7.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (1.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15 (6.8)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cycle characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of ICSI cycles (%)</td>
<td>88 (57.1)</td>
<td>89 (57.8)</td>
<td>126 (56.8)</td>
</tr>
<tr>
<td>No. of IVF cycles (%)</td>
<td>66 (42.9)</td>
<td>65 (42.2)</td>
<td>96 (43.2)</td>
</tr>
<tr>
<td>Mean no. of oocytes per retrieval ±SD</td>
<td>8.9 ± 4.3</td>
<td>9.6 ± 4.7</td>
<td>9.2 ± 4.6</td>
</tr>
<tr>
<td>Fertilization rate ±SD</td>
<td>72.5 ± 22.2</td>
<td>68.4 ± 21.2</td>
<td>73.2 ± 20.1</td>
</tr>
<tr>
<td>Rate of embryos with ≥4 blastomeres on day 2 per retrieval ±SD</td>
<td>72.9 ± 28.7</td>
<td>71.3 ± 29.5</td>
<td>66.6 ± 29.6</td>
</tr>
<tr>
<td>Mean embryo score on day 2 ±SD</td>
<td>8.4 ± 2.4</td>
<td>8.6 ± 2.4</td>
<td>8.2 ± 2.6</td>
</tr>
<tr>
<td>No. of cycles with at least one good quality embryo (%)</td>
<td>63 (40.9)</td>
<td>66 (42.9)</td>
<td>100 (45.0)</td>
</tr>
</tbody>
</table>

<sup>a,b</sup>Numbers with different superscripts within one row are significantly different (ANOVA with Tukey’s multiple test procedure for continuous variables and χ² test with Bonferroni correction for binary variables, P < 0.05).

### Discussion

During the last few years eSET has become more and more accepted as the solution for the high multiple PR after IVF and IVF/ICSI. Until now, eSET was only applied in a selected group of patients. In this study, an RCT was performed in the first cycle of an unselected group of patients, i.e. irrespective of female age (within the age limits applied in our IVF programme) and irrespective of the availability of a good quality embryo. The transfer of one embryo in this unselected group resulted in a significantly lower PR (21.4%) than the transfer of two embryos (40.3%). This tendency is also seen in previously performed RCTs, which were conducted in a subset of good prognosis patients. In these studies, the ongoing PRs after eSET and DET were 38.5 versus 74.0% (Gerris et al., 1999) and 28.5 versus 44.1% (Thurin et al., 2004), and the live birth rates after eSET and DET were 29.7 versus 40.0% (Martikainen et al., 1999). Overall, the ongoing PR with the standard transfer policy was 31.5% and the overall twin PR was 12.9%.
et al., 2001) and 26 versus 36% (Lukassen et al., 2005), respectively. In all the aforementioned studies, in selected, good prognosis patients as well as in non-selected patients (present study), the transfer of two embryos leads to higher PRs than the transfer of one embryo.

In contrast to the markedly reduced ongoing PR found in our study after eSET compared with DET in an unselected group of patients, the ongoing PR between eSET applied in a subset of good prognosis patients and DET applied in the remaining patients (33.0% after SP-eSET versus 30.3% after SP-DET) was comparable. This is in agreement with the observational studies described in the literature, obtaining PRs of 34 versus 37% (Tiitinen et al., 2003) and 40.3 versus 40.4% (Gerris et al., 2004), respectively, after applying eSET in a subgroup of good prognosis patients and DET in the remaining patients. The twin PR in the overall IVF programme when applying our standard embryo transfer policy was 12.9% in our study, which is comparable with the findings of other studies [7.5% (Tiitinen et al., 2003) and 13.5% (Gerris et al., 2004)].

The ongoing PR obtained with our standard transfer policy (eSET in selected patients) is higher than with a policy of transferring one embryo in all patients (31.5 versus 21.4%). This is, at least for patients <36 years, confirmed by the data from Debrock and co-workers, who compared PRs before and after implementation of the new legislation on embryo transfer in Belgium (Debrock et al., 2005). Before implementation, one embryo was transferred just in case it was a good quality embryo. After implementation, in patients <36 years, no selection based on embryo quality was made for eSET, which means that all patients <36 years received one embryo. The clinical PR decreased non-significantly from 41.0% before implementation to 35.1% after implementation.

Of all eligible patients in our study, 46% were randomized in the RCT part of the study, comparing favourably with the participation rate in other studies [11% (Martikainen et al., 2001); 25% (Thurin et al., 2004); 33% (Lukassen et al., 2005); and 39% (Gerris et al., 1999)]. The higher participation rate in our study might explain the slightly lower PRs compared with the other RCTs described in the literature. A high rate of participation will diminish selection bias. To evaluate selection bias in our study, the characteristics of the study population and the non-participants were compared. It was shown that the study population reflected the total IVF population with the exception of the percentage of patients ≥38 years, which was 4.5% in the study population and 21.2% in the non-participants. This can be explained by the fact that patients ≥38 years often considered their chance for pregnancy to be low and requested the standard embryo transfer policy, in which they would receive two embryos.

As our study shows, after the transfer of only a single embryo, more good quality embryos are left for cryopreservation. If the transfer of cryopreserved embryos (for practical reasons not a part of this RCT and therefore performed according to the standard transfer policy) was included in the results, the probability of a pregnancy after the first ovum pick-up increased. The overall PR was nevertheless still significantly lower in the eSET group as compared with the DET group (29.9 versus 42.2%, respectively). As from 17 eSET and 10 DET cycles a transfer of frozen/thawed embryos has not yet been performed, cumulative ongoing PRs will increase. The importance of cryopreserved embryos in eSET has already been stressed by other authors (Tiitinen et al., 2001; Thurin et al., 2004).

A remarkable finding in our study is the high abortion rate after eSET (35% in the RCT-eSET group and 27% in the SP-eSET group). It is known that in the first weeks after implantation, 15–20% of all pregnancies are lost, both in spontaneous pregnancies and in pregnancies conceived after assisted reproduction (Tummers et al., 2003; De Neubourg et al., 2004). Theoretically, the difference in the abortion rate found between eSET and DET might be explained by vanishing twins in the DET group, which are continuing as a singleton pregnancy and therefore not recorded as an abortion. Since it has been shown that in pregnancies with two gestational sacs ~30% result in a singleton pregnancy, only part of the difference in abortion rate between eSET and DET can be explained by vanishing twins (Landy and Keith, 1998). Winter et al. (2002) found that pregnancy loss before 6–7 weeks of gestation was related to poor embryo quality. However, in our study, the high abortion rate after eSET was found not only in the eSET group of the RCT part (in which 31% of the pregnancies developed after transfer of poor quality embryos) but also in the eSET group of our standard transfer policy group (in which eSET was performed with good quality embryos only).

In addition, in the RCT-eSET group, 33% of the pregnancies achieved after the transfer of a poor quality embryo and 38% of the pregnancies achieved after the transfer of a good quality embryo resulted in an abortion. This indicates that the abortion rate in our study was not related to poor embryo quality.

Whether eSET or DET is preferable depends not only on ongoing PRs and twin PRs, but also on several other factors, such as patients’ preferences and the health care system in a particular country. Patients should be counselled thoroughly about PRs in the different transfer policies and about the risks associated with multiple pregnancies. Patients’ attitudes towards eSET were shown to be positively adjusted in countries where new legislation regarding embryo transfer was implemented, stating that eSET should be the routine procedure in at least the first cycle of young patients (Ombrelet, 2004; Thurin et al., 2004). Finally, the extent of reimbursement of costs will influence the acceptance of eSET. Therefore, as an integral part of the present study, the cost-effectiveness of eSET compared with DET was analysed (Fiddelers et al., 2005).

In conclusion, our study shows that applying eSET in the first cycle of an unselected group of patients will lead to a twin PR of 0%. The price to be paid is a reduction of the ongoing PR to approximately half of that obtained after DET. The transfer of one embryo in a selected group of good prognosis patients leads to a less drastic reduction in PR but maintains a twin PR of 12.9%.

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eSET in an RCT with unselected patients