The difference in pregnancy rates between elective single embryo transfer (SET) compared to double embryo transfer is dependent on the implantation rates of embryos being transferred. Using mathematical modeling to determine when SET becomes a viable option

Sir,

The article by van Montfoort *et al*. (2006) concludes that undertaking single-embryo transfer in unselected patients will halve the pregnancy rate compared with double-embryo transfer. Their conclusion was derived following a randomized controlled trial (RCT) of single-embryo transfer versus double-embryo transfer. They also concluded that only in selected patient groups, which have a good prognosis of pregnancy establishment following IVF, would a less drastic effect of single-embryo transfer on pregnancy rate be observed compared with double-embryo transfer. Although we congratulate van Montfoort and colleagues on undertaking an RCT on this subject, we believe that the conclusion is inaccurate, because of their lack of consideration of the impact of the implantation rate of embryos on both the pregnancy rate and the proportion of twin pregnancies.

There is a dramatic relationship between pregnancy rate and twinning rate with embryonic implantation rate. Using the concept of 'e' for embryo contribution to pregnancy and 'r' for contribution of patient at transfer to pregnancy, as outlined in McMillan (1998), and based on binomial independence of embryo survival, improving the quality of the embryos being transferred and/or the management of patients undergoing embryo transfer, an exponentially increased risk of twin pregnancies occurs with an exponentially decreased advantage to improving the pregnancy rate under double-embryo transfer. From such modelling, we would predict a 10% twinning rate when single-embryo transfer and double-embryo transfer pregnancy rates are 21 and 40%, respectively, in the same population, as described by the van Montfoort *et al*. (2006) study. This is lower than the observed 21% twinning rate in their study. We would further predict that by increasing the quality of embryo and patient management to where the pregnancy rate for single-embryo transfer is ~35% (which has been achieved in many units), the equivalent double-embryo transfer pregnancy rate would be ~50% (i.e. a 40% increase) and the twinning rate doubled to a theoretical 21%. This demonstrates that the twinning rate increases more dramatically than pregnancy rate when improvements are made to the implantation potential within an IVF unit that continues to perform double-embryo transfer.

Other modelling suggests that survival of human embryos in double-embryo transfer is not independent, such that the transfer of two embryos enhances the survival of each other (Matorras *et al*., 2005). If this is true, then transfer of two embryos will only further exacerbate the twinning rate. This could explain why our expected twinning rate underestimated the observed value in the van Montfoort *et al*. (2006) study.

Rather than declaring that single-embryo transfer will halve pregnancy rates compared with double-embryo transfer and that single-embryo transfer is appropriate only in good-prognosis patient groups, we recommend that single-embryo transfer be adopted when in either any or all patient groups the overall implantation rate of embryos is such that there is a rapidly declining advantage to the pregnancy rate and a rapidly increasing twinning rate when double-embryo transfer is applied. Mathematical models can help predict such shifts and can be utilized in assisted reproduction treatment (ART) units to make decisions about which patient groups should be treated with single-embryo transfer or double-embryo transfer. Furthermore, ART units should seek to continually increase the implantation rate of embryos across all patient groups, by improving laboratory systems and patient management, in an effort to decrease the requirement for double-embryo transfer.

References

Matorras R, Matorras F, Mendoza R, Rodriguez M, Remohi J, Rodriguez-Escudero FJ and Simon C (2005) The implantation of every embryo facilitates the chances of the remaining embryos to implant in an IVF programme: a mathematical model to predict pregnancy and multiple pregnancy rates. Hum Reprod 20,2923–2931.

McMillan WH (1998) Statistical models predicting embryo survival to term in cattle after embryo transfer. Theriogenology 50,1053–1070.

van Montfoort APA, Fiddelers AAA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman AJ, Land JA, Geraedts JPM, Evers JLH and Dumoulin JCM (2006) 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. Hum Reprod 21,338–343.

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Reply: In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared to double embryo transfer

Sir,

Prof. J. Thompson and Dr M. Lane suggest that we should rephrase our conclusion—'our study shows that applying elective single embryo transfer (eSET) in the first cycle of an unselected group of patients will lead to a twin pregnancy rate of 0%. The price to be paid is a reduction of the ongoing pregnancy rate to approximately half of that obtained after double embryo transfer (DET). The transfer of only one embryo in a selected group of good prognosis patients leads to a less drastic reduction in pregnancy rate but maintains a twin pregnancy rate of 12.9%' (van Montfoort *et al*., 2006)—to a recommendation that eSET should be adopted only when in the target patient group (either all patients or a specific patient group with a good pregnancy prognosis) the overall implantation rate of embryos is so high that performing DET will lead to only a small increase in pregnancy rate but in a dramatically, and therefore unacceptable, high twin pregnancy rate.

While we thank Prof. J. Thompson and Dr. M. Lane for their suggestion, we think that it is not up to us to make such a general recommendation because this was not the subject of our study. The aim of our study was to analyse what the

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pregnancy rate would be when the transfer policy is either eSET for all patients or eSET in a selected group of patients and DET in the remaining population. It is up to every infertility centre to decide what their transfer policy will be and what price (in reduction of pregnancy rate) is acceptable for reducing the twin pregnancy rate. As we discussed in our article, whether eSET or DET is preferable depends not only on ongoing pregnancy rates and twin pregnancy rates but also on several other factors such as the health care system (reimbursement of costs) in a particular country and patient preferences.

We think, however, that the reduction in pregnancy rate after eSET in an unselected group of patients does not balance the reduction in twin pregnancy rate. In our clinic, therefore, eSET is applied in a selected group of patients. Our selection is in complete agreement with those suggested by Prof. J. Thompson and Dr M. Lane: eSET will be performed only when our criteria for a good prognosis patient are met, which consist of a patient factor (= 'r') contributing to the pregnancy chance (age 37 years or younger) and an embryo quality factor (= 'e'), i.e. at least one good-quality embryo available. In all eSET studies, selection criteria based on 'e' and 'r' are used (e.g. Tiitinen *et al*., 2003; Gerris *et al*., 2004; Thurin *et al*., 2004). And as the pregnancy rate after applying DET is always higher as compared with that achieved using eSET, every study group has made an appraisal between the reduction in pregnancy rate and the reduction in twin pregnancy rate after applying eSET instead of DET. We accept Prof. J. Thompson and Dr M. Lane's suggestion that mathematical models on the relationship between pregnancy and twinning rates with embryonic implantation rate can help to make decisions about which patient group should be treated with eSET or DET. But we think that empirical information on the implantation rate in different patient groups with different embryo qualities is even more important.

When applying our selection criteria, the implantation rate according to the definition of Matorras *et al*. (2005) ($IR = n_{\text{gestational sacs}}/n_{\text{transferred embryos}}$, where $n_{\text{gestational sacs}}$ is the number of gestational sacs observed at vaginal ultrasound 3–5 weeks after transfer and $n_{\text{transferred embryos}}$ the number of transferred embryos) was 45.0% (Table III), with an ongoing pregnancy rate of 33.0% (van Montfoort *et al*., 2006). This is comparable with the pregnancy rates that have been described for similar selected good-prognosis groups of patients in many other IVF centres, as indicated by Prof. J. Thompson and Dr M. Lane (Gerris *et al*., 2002; Tiitinen *et al*., 2003; Martikainen *et al*., 2004). Besides the data on eSET in a selected group, which are comparable to those of other clinics, we also reported on eSET in an unselected group. In the latter group, we found an implantation rate of 33.1% (Table II) and an ongoing pregnancy rate of 21.4% per embryo transfer. As far as we know, our study is the first to report on pregnancy and implantation rates after eSET in such an unselected group of patients (van Montfoort *et al*., 2006).

References

Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Vercruyssen M, Barudy-Vasquez J, Valkenburg M and Ryckaert G (2002) Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme. Hum Reprod 17,2626–2631.

Gerris J, de Sutter P, de Neubourg D, Van Royen E, Vander Elst J, Mangelschots K, Vercruyssen M, Kok P, Elseviers M, Annemans L *et al*. (2004) A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Hum Reprod 19, 917–923.

Martikainen H, Orava M, Lakkakorpi J and Tuomivaara L (2004) Day 2 elective single embryo transfer in clinical practice: better outcome in ICSI cycles. Hum Reprod 19,1364–1366.

Matorras R, Matorras F, Mendoza R, Rodriguez M, Remohi J, Rodriguez-Escudero FJ and Simon C (2005) The implantation of every embryo facilitates the chances of the remaining embryos to implant in an IVF programme: a mathematical model to predict pregnancy and multiple pregnancy rates. Hum Reprod 20,2923–2931.

van Montfoort AP, Fiddelers AA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman GA, Land JA, Geraedts JP, Evers JL and Dumoulin JC (2006) 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. Hum Reprod 21,338–343.

Thurin A, Hausken J, Hillensjo T, Jablonowska B, Pinborg A, Strandell A and Bergh C (2004) Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. N Engl J Med 351,2392–2402.

Tiitinen A, Unkila-Kallio L, Halttunen M and Hyden-Granskog C (2003) Impact of elective single embryo transfer on the twin pregnancy rate. Hum Reprod 18,1449–1453.

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