The irrational attraction of elective single-embryo transfer (eSET)

Norbert Gleicher*

The Center for Human Reproduction (CHR), New York and the Foundation for Reproductive Medicine, New York, NY 10021, USA

*Correspondence address. E-mail: ngleicher@thechr.com

Submitted on September 24, 2012; resubmitted on September 24, 2012; accepted on October 22, 2012

ABSTRACT: In this issue of the journal, Niinimäki et al., colleagues from a pioneering Finnish center in the development of elective single-embryo transfer (eSET), propose the expansion of eSET to suitable women at ages of 40–44 years. This paper offers not only a critique of their proposal but also of eSET in general.

Key words: elective single-embryo transfer (eSET) / twins / multiple births / in vitro fertilization (IVF) / advanced female age

Introduction

When Templeton and Morris in their groundbreaking 1998 paper in The New England Journal of Medicine demonstrated that in good prognosis patients two-embryo transfers (2ET) resulted in similar pregnancy rates, but greatly reduced high-order multiples, in comparison with transfers of three (or more) embryos, they revolutionized in vitro fertilization (IVF) (Templeton and Morris, 1998). By that time, high-order multiple births had been widely identified as an adverse outcome of IVF (French National Registry, 1995; Society for Assisted Reproductive Technology, American Society for Reproductive Medicine, 1995; Human Fertilisation and Embryology Authority, 1997). The quick subsequent worldwide switch toward 2ET in good prognosis patients occurred because Templeton and Morris had achieved a goal researchers strive for in clinical medicine: they demonstrated improvements in outcomes (i.e. fewer high-order births), without adverse treatment effects (i.e. without reducing the patient’s pregnancy chances).

Elective single-embryo transfer

Approximately a year later, Finnish colleagues, in the pages of this journal, published a paper, which, in retrospect, likely achieved even greater notoriety (Vilska et al., 1999). Going beyond 2ET, these authors, for the first time, suggested that eSET in good prognosis patients may even be preferable over 2ET because eSET prevents not only high-order multiples but also most twin deliveries.

eSET has since gained wide popularity, initially more so in Scandinavian countries (Hamberger and Hardarson, 2003; Bergh, 2005; Karlström and Bergh, 2007) and the rest of Europe (Scotland et al., 2011; Rodriguez Barredo et al., 2012), but more recently also in Canada (Bissonnette et al., 2011), the USA (Kresowik et al., 2011; Practice Committee of the Society for Assisted Reproduction, Practice Committee of the American Society for Reproductive Medicine, 2012) and Asia (Kato et al., 2012). PubMed searches under the key word SET reveals not less than 2119 publications; a search under the more restricted term eSET offers 162 (both accessed 20 September 2012).

For many colleagues, eSET represented an apparently logical next step to Templeton and Morris’ work, with the Finnish investigators arguing in their 1999 paper that ‘the number of twin pregnancies after 2ET is still high, increasing health care costs for one IVF newborn ….’ (Vilska et al., 1999). Though we strongly disagree with this and other arguments, favoring widespread utilization of eSET in IVF (Gleicher and Barad 2008a,b,c, 2009; Gleicher, 2011), we have to acknowledge that the utilization of eSET to avoid twin pregnancies has almost become an established dogma. Indeed, increasingly, colleagues now consider twin pregnancies as much an adverse IVF outcome as high-order multiples (Olivienne, 2000; Land and Evers, 2003).

A principal reason why we disagree is that the suggested analogy between Templeton and Morris’ study and the one by Vilska et al., leading to the concept of eSET, is incorrect. The reason is rather simple: Templeton and Morris demonstrated in their study improved outcomes from 2ET without adverse effects on patients (Templeton and Morris, 1998); Vilska et al. (1999) and practically all subsequently published studies of eSET, however, have demonstrated, as reported in a Cochrane review, significantly reduced pregnancy chances in comparison with 2ET (Pandian et al., 2009) and, therefore, a very obvious, and important adverse effect of eSET on patients.

Risk/benefit considerations in medicine often accept adverse side effects if the treatment benefits outweigh them. This is what proponents have argued in support of eSET, pointing at higher risks and
costs from twin pregnancies in comparison with singleton deliveries. Proponents of eSET, therefore, argue that lower pregnancy rates are more than compensated for by lower maternal/neonatal risks and, consequently, lower health-care costs. They claim further support for their position from studies, such as the above-mentioned Cochrane review, demonstrating similar cumulative pregnancy chances from one fresh cycle eSET plus one thaw cycle eSET in comparison with one fresh 2ET (Pandian et al., 2009), and, therefore, consider a strategy switch from a 2ET approach to two consecutive eSETs an appropriate alternative.

**Are twins really an adverse IVF outcome?**

Whether twin pregnancies really are the villains they have been made to be by proponents of eSET, however, is at least questionable. Widely cited risk comparisons between IVF singletons and twins, indisputably, have used inappropriate statistical methodologies, utilizing data from retroactive obstetrical studies in a prospective infertility treatment paradigm. We have explained this point before in detail (Gleicher and Barad 2009; Gleicher, 2011). In short, nobody would argue with obstetrical outcome data, which demonstrate that maternal and neonatal risks of twin pregnancies are higher than those of singletons. These studies, however, compare, in a retroactive observational paradigm, the delivery of only one child in a singleton pregnancy to the delivery of two children in a twin pregnancy.

Infertility treatment paradigms are prospective. In patients desirous of more than one child, one has to consider how such patients can be best helped to have the desired two children. Two children, at least theoretically, can be the result of either one twin, or two consecutive singleton, pregnancies. The correct statistical comparison of risks and costs in such a prospective infertility paradigm is, therefore, not between a twin delivery and one singleton delivery (as in the obstetrical paradigm) but between a twin delivery and two singleton deliveries. When this is done, the excessive risks and costs of twin deliveries, reported in the retroactive obstetrical paradigm, not surprisingly, largely disappear (Gleicher and Barad, 2009).

At least in women who want two or more children and have no obstetrical contraindications to twin pregnancies, the statistically correct conclusion, therefore, is that the prevention of twin pregnancies with a broadly based eSET policy, likely, does not result in significant risk and cost reductions for IVF patients but does result in significant reductions in immediate pregnancy chances. Even the argument that one fresh eSET plus one thawed eSET, combined, result in similar pregnancy rates as one 2ET (Pandian et al., 2009) does not invalidate this point.

In other words, eSET offers exactly the kind of treatment outcome clinicians, typically, try to avoid: a very questionable treatment benefit (i.e. highly questionable reduction of risks) but an obvious negative treatment effect (i.e. reduction in immediate pregnancy chances). eSET, therefore, does not, as has been widely suggested, represent the logical next step to Templeton and Morris’ work, and should not be given the same deference.

**eSET in older women?**

In this issue of *Human Reproduction*, colleagues from the same Finnish center who gave birth to the concept of eSET now argue in favor of even further expansion of utilization of eSET from favorable prognosis patients to older women at ages of 40–44 years (Niinimäki et al., 2012). I find their argument nothing but astonishing yet reflective of the completely irrational eSET has assumed amongst some colleagues.

Arguments in favor of 2ET as well as eSET, up to this point, have always been restricted to good prognosis patients. Indeed, all studies addressing 2ET and eSET have usually emphasized this point, starting with Templeton and Morris (1998). Even proponents of eSET considered the procedure only suitable for patients with a favorable prognosis, a position also supported by recently published guidelines for eSET by the Practice Committees of the Society for Assisted Reproductive Technology and American Society for Reproductive Medicine (2012) (Table I).

One, therefore, has to wonder about the informed consent process women, between the ages of 40 and 44 years, were offered in the study by Niinimäki et al. to end up with eSET. Women of such advanced age under almost no circumstances can be considered to have favorable prognoses.

Beyond ethical considerations, one, however, has to wonder even more about the scientific hypothesis behind such an approach. What would be the rationale for eSET in women at this age? Considering the relative rarity of twin pregnancies at these advanced ages even if multiple embryos are transferred, is the risk of twin pregnancies really serious enough to warrant a potential delay in pregnancy at such advanced ages?

If the authors, indeed, considered twins a realistic risk in these patients, their study proved them wrong. Not only did eSET not reduce twining risks to a statistically significant degree, but, cumulatively, twin pregnancy rates were uniformly quite low at 6.7% in eSET and 8.3% in 2ET patients.

The failure to reduce twin rates is, however, not even the major argument against eSET in unfavorable patients. What mars the whole discussion of eSET in the medical literature, amply again demonstrated by the paper of Niinimäki et al., is that patient preferences have been widely ignored by proponents of eSET. The medical literature quite unequivocally demonstrates the urgent infertility women perceive in achieving motherhood. We pointed this out in as early as 1995, when reporting that, despite well-understood risks, well-educated infertility patients in a large majority favored twin over singleton deliveries (Gleicher et al., 1995). Similar results have been obtained in studies all over the world, with one of the best recently reported in the UK (Scotland et al., 2007).

**Table I** Best-suited patients/IVF cycles for eSET according to SART/ASRM.

<table>
<thead>
<tr>
<th>Age &lt;35 years</th>
<th>More than one top-quality embryo</th>
</tr>
</thead>
<tbody>
<tr>
<td>First or second IVF cycle only</td>
<td>Previous successful IVF cycle</td>
</tr>
<tr>
<td>Oocyte donor recipient cycles</td>
<td>Blastocyst-stage embryos</td>
</tr>
</tbody>
</table>

SART/ASRM, Practice Committee of the Society of Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine 2012.
Conclusions

Is it really ethically acceptable to urge 40- to 44-year-old women to reduce their immediate pregnancy chances? Is it ethically acceptable to do this to even younger women? After all, even in best cryopreservation programs, not all frozen embryos survive thawing. No patient can, therefore, be guaranteed that she will be given a second chance to conceive, once she decides to split the initial 2ET chance into two consecutive eSET cycles.

In their paper, Niinimäki et al. correctly point at the aging of infertile patient populations in most developed countries. At our center, the mean age of new patients in 2011 for the first time exceeded 40 years. Such older women have different needs, and require not only special medical but also social considerations when receiving infertility treatments. Our specialty has not yet fully confronted many of these newly arising issues. It, however, appears quite obvious to us that eSET does not make this list. Indeed, we see nothing in the paper by Niinimäki et al. that would suggest benefits from eSET in older women, unless, of course, the patients at these ages only desire one child or have medical contraindications to carrying two (both not infrequent circumstances in older women).

We recently calculated that a government-sponsored eSET program in a Canadian province reduced the total number of IVF offsprings born by approximately one-third (Gleicher, 2011). Our Canadian colleagues, who reported the experience, considered the program a success because twin rates dropped significantly (Bissonnette et al., 2011). Considering the loss of one-third of newborn children from lower pregnancy chances and missing twins, we would argue that, especially in a country like Canada, which is striving for population growth, this program is a good example of unintended negative consequences.

This Canadian province is not alone; eSET has in many countries become government-driven or -incentivized, even though a large majority of multiple pregnancies created through infertility treatments are actually the consequence of non-IVF ovulation induction cycles (Jones, 2007; McClamrock et al., 2012), and have remained untouched by such interventions. We fail to understand the logic of such an approach, and it therefore appears to us that the time has come to reconsider eSET policies in association with IVF, not only for older women.

Author’s role

N.G. is solely responsible for this manuscript.

Funding

No external funding was either sought or obtained for this study.

Conflict of interest

None declared.

References


cost-utility of elective single versus double embryo transfer over a 20-year time horizon. BJOG 2011;118:1073–1083.

