EDITORIAL

The debate on single embryo transfer in IVF. How will today’s arguments be viewed from the perspective of 2020?

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Month by month the leading journals in reproductive medicine and science seek to publish innovative studies on cutting edge work relating to assisted reproduction. Many of these studies, whilst attracting scientific excitement and interest, do not directly feed into clinical care, and where there is clinical impact it is usually for a minority of IVF patients. An example of the latter might be the many innovations in pre-implantation genetic diagnosis. It is obvious that mainstream clinical IVF is built on foundations of extensive and ongoing scientific study which, over time, produces small adjustments to practice, but I would suggest that clinical IVF has been fundamentally influenced by a series of innovations that have become incorporated into core IVF practice and have become so basic to everyday work that they can seem almost ordinary to those who did not use them before their introduction.

Assisted reproduction is young enough that many of us have had direct experience of the whole history of the clinical subject and can remember practice before a number of these fundamentally important developments played their role in defining today’s standard clinical practice. I suggest as examples the introduction of reliable ovarian stimulation to yield a cohort of oocytes for fertilization; transvaginal ultrasound, which transformed oocyte retrieval by removing the need for laparoscopy or the relatively crude transvesical ultrasound retrieval procedures; GnRH agonist control of stimulation regimens, which brought about a significant increase in effectiveness; embryo cryopreservation which opened up the range of options over the available embryos; and ICSI, which changed male infertility management almost overnight. These innovations have changed mainstream IVF practice and have achieved almost universal application across the world. I speculate that when future generations look back to the development of this field in the early twenty-first century they would add to that list the move to the extensive use of single embryo transfer (SET) that started in the late 1990s with the limitation of embryo transfer to two embryos in some countries and which culminated in practical strategies that enable most women to receive embryos by SET.

This journal has recently published a substantial debate on methods of reporting IVF results in the wake of a proposal that the BESST (birth emphasizing a successful singleton at term) criteria would remove an incentive to promote multiple embryo transfer in the interest of maximizing success by focusing on singleton outcomes (Min et al., 2004). That debate attracted a lot of interest and many views were expressed. In this issue of Human Reproduction we publish contributions on the subject of SET from several authors (Saldeen and Sundström, 2005; Bergh, 2005) and invite further contributions. Templeton and Morris (1998) used the UK Human Fertilisation and Embryology Authority (HFEA) treatment register to highlight the potential equivalence of the results of two embryo transfer (2ET) and three embryo transfer (3ET) if there are several embryos from which to select the best for transfer. Subsequently 2ET has become established in a number of countries with the expected effective abolition of triplet pregnancy in those treatments but no reduction in twin rates.

From communication with colleagues around the world I can quote examples where 2ET is now the recommendation: Australia (Reproductive Technology Accreditation Committee requirement), Finland (by agreement between the clinics), Israel (for women ≤40 years of age in their first three cycles), The Netherlands (by agreement between the clinics), New Zealand and UK (for women aged <40 years). In the UK the pressure for 2ET came first in 2001 with an HFEA requirement that more than two embryos may only be transferred in exceptional circumstances. In 2004 the Code of Practice was revised to state that in women aged <40 years the maximum was to be 2ET whereas women aged ≥40 years could have a maximum of 3ET (HFEA, 2004). This change coincided with the publication of the National Institute for Clinical Excellence Clinical Guideline (NICE, 2004) which recommended a maximum of 2ET for state-funded IVF, and since the upper age limit recommended for NHS IVF was 39 years the two documents coincide in their recommendation.

The idea that there is a need to have a degree of flexibility over the number of embryos to transfer depending on the pregnancy prognosis is widely discussed and is reflected, to an extent, in the UK approach since it allows a higher number of embryos to be transferred in older women since the most clear prognostic variable is the female age. Some argue that the UK Code of Practice is too restrictive by not providing flexibility for those who have an especially poor prognosis aged <40 years, but the difficulty has been in designing recommendations that are clear in their effect and interpretation. The UK experience has been that it can be
especially difficult to reach agreement on what constitutes evidence of poorer than usual prognosis for pregnancy being achieved. For example, following implementation of the HFEA (2001) rules, a large number of clinics saw a major reduction in the proportion of cycles in which 3ET was performed, but a number of clinics maintained 3ET rates at ~80 or 90%, seemingly suggesting that they saw exceptional circumstances in most of their patients. What the HFEA seeks to achieve, through its Code of Practice, is effective regulation of the balance between the potentially competing interests of the pregnancy rate and the risk of the many problems associated with multiple pregnancy.

The landmark transition to SET has been initiated in Sweden and Belgium and we await shortly the outcome of these important developments. Swedish practice, influenced by a recognition of the paediatric consequences of multiple pregnancy, has tended to lead developments towards reducing the number of embryos transferred in IVF. Sweden was early to establish 2ET as the norm and in 2002 in Southern Sweden state-funded IVF was restricted to SET unless exceptional circumstances applied; then in 2003 the Swedish National Board of Health and Welfare declared that all IVF in Sweden would involve SET unless prognosis was poor (Saldeen and Sundström, 2005).

The Belgian approach appears to recognize the need for a degree of flexibility in the model of practice that will be attractive to many since it is stratified by age and also by cycle number, so that lack of success enables an increase in the number of embryos to be transferred. The policy on state-funded IVF in Belgium in 2004 involves an age stratification with three groups. For those aged <36 years the first two cycles must be SET, but, if these fail, cycles 3 to 6 can be 2ET. For those aged 36–39 years the first two cycles can be up to 2ET and cycles 3 to 6 can be up to 3ET. For those aged >39 years there can be up to 3ET from cycle 1. The state allows funding for six cycles in a lifetime. This appears to be a model which is flexible but makes the landmark transition to SET for a large proportion of the IVF population. Obviously the additional embryos will be cryopreserved for later SET (Ombelet et al., 2005).

The articles from Sweden (Bergh, 2005; Saldeen and Sundström, 2005) and Belgium (Ombelet et al., 2005) indicate that the approaches to IVF being adopted appear to be having a major impact on reducing multiple pregnancy rates without significant changes in pregnancy rates. For example, Saldeen and Sundström (2005) report pregnancy and twinning rates through the three phases of the Swedish policy changes on SET, in which the SET rate has risen from 25.1 to 55.5% and now 72.7%. The accompanying clinical pregnancy rates have been sustained at 33.3, 32.8 and 37.4% respectively and the twinning rate has fallen progressively from 22.6 to 16.3% and now 6.2%.

If the Swedish and Belgian data are confirmed in ongoing work, especially work which incorporates the cumulative effect of the subsequent frozen–thawed SET, then it should be increasingly difficult to accept the rates of multiple pregnancy seen in IVF around the world. The emergence of these straightforward treatment models is in marked contrast to the approach of transferring more than three embryos, with fetal reduction as the backstop procedure, as is preferred by some North American IVF clinics who claim that their approach is justified by higher pregnancy rates. I suggest that the historical tide runs in favour of the SET approaches rather than approaches which need to rely on fetal reduction.

If SET is to be employed then it might be argued that unstimulated treatment will become standard. I remain unconvinced at present that this will be the case. The Belgian practice appears to be based around optimizing the assessment of the early embryos in order to select the best embryo for SET, with cryopreservation of the other good quality embryos. In order to have a number of embryos from which to make a selection, the woman would undergo a stimulation cycle, thus generating embryos for the fresh SET and usually several frozen–thawed SET from the single oocyte retrieval procedure. I judge that maximizing the choice of embryos and minimizing the number of invasive oocyte retrieval procedures is sufficiently important that avoiding the risk of OHSS by not stimulating should not outweigh this. Of course, the risk of OHSS should be minimized by responsible use of stimulation and monitoring. Indeed in the Belgian model, where the woman aged <36 years will have 2ET in cycle 3, it can be argued that it is of some value that cycles 1 and 2 involved stimulation so that there is experience of the woman’s responsiveness for optimal stimulation in cycle 3. Those currently developing in vitro maturation (IVM) of oocytes might argue that when this is optimized it will change the model. This might be the case for women affected by polycystic ovarian syndrome, in particular, but we await the evidence from widespread clinical practice so I have not included IVM in my speculation here.

A goal should be to disentangle success in fertility treatments from the burden of multiple pregnancy associated with ovarian stimulation. This is more difficult to deliver in relation to IUI and donor insemination (DI). From my experience, entirely valid DI programmes can be based on unstimulated DI and the systematic review data suggest that for male infertility IUI the use of stimulation does not add to the success of unstimulated IUI (Ford et al., 1997; Cohlen et al., 2000). In the recent NICE Guidelines, where we had a defined remit to consider strategies that would minimize multiple pregnancy (NICE, 2004), we suggested that, based on the best trial evidence (Guzick et al., 1999; Goverde et al., 2000), unexplained infertility IUI should also be unstimulated. We argued that this would be more effective than intercourse but admitted that it would be less successful than stimulated IUI in this indication. This decision was based on the principle of removing the multiple pregnancy risk with the sacrifice of some success in a state-funded programme offering six treatment cycles. This proposal has possibly been the most controversial in the Guideline and it is criticized by many UK clinicians who simply do not believe that unstimulated IUI is valid and that multiple pregnancy is a necessary price of stimulated IUI. I believe that the best approach to IUI will remain controversial on present evidence but the SET story in IVF has a growing momentum to which this issue of Human Reproduction adds.
I suggest that a policy along the Belgian lines, if it is validated by the results in terms of live birth rates and multiple pregnancy rates, will bring together the practice of the major components of IVF, each used optimally, to achieve a safer but successful model. It will require optimal stimulation and oocyte retrieval, the ability to select from a group of embryos with reasonably valid assessment tools and effective cryopreservation programmes so that women will receive SET followed by repeated frozen–thawed SET procedures. The idea that this would be the standard approach for all but those above an age threshold is sensible, with reversion to 2ET if the first two fresh treatments, and their associated frozen–thawed cycles, fail. I believe that the issue of what is best for those women aged > 40 years remains open and it is possible that 3ET will remain common for this group.

With these elements in place I believe we have the possibility of an IVF treatment scheme emerging which could be the model for the future. Once established successfully, our successors in 2020 might wonder how it could ever have been different. Time will tell.

References
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