Avoiding multiple pregnancies in ART

A plea for single embryo transfer

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It has been generally accepted that triplets after IVF/ intracytoplasmic sperm injection (ICSI) can and should be avoided by adopting a standard strategy of replacing no more than two embryos. However, this approach has been hampered by our relative inability to identify embryos with a very high implantation potential. To identify such embryos, a number of strategies are being considered, both at the two pronuclear (2PN), early cleavage and the blastocyst stages. At the 2PN stage, the polarity characteristics of the nucleoli have been shown to be correlated with a high implantation rate. Similarly, the morphological characteristics at day 2 and 3 have been used to describe top quality embryos in ~75% of all IVF/ICSI cycles. Blastocyst culture has resulted in very high implantation rates in the hands of some authors. No approach has shown its superiority at present, but initial experience with single embryo transfer (SET) at the early cleavage stage by Scandinavian and Belgian groups shows that an ongoing pregnancy rate of 35% and more can be achieved. Proper identification of patients at risk of a twin pregnancy after double embryo transfer is equally important. It is clear that mainly young patients (aged <34 years) during their first, perhaps first two, IVF/ICSI cycles constitute the main population at risk (responsible for >80% of all twins) and are the main target group for twin prevention by SET of a top quality embryo at whatever stage. Therefore, in our opinion, although a further fine-tuning of both embryo and patient characteristics relating to a high risk for (twin) pregnancy is desirable, SET should be introduced carefully and progressively in each IVF/ICSI programme from now on. Correct counselling is very important and both public and private insurers will have to join in the discussion.

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An illuminating insight into the causal relationship between embryo transfer policy and multiple gestation can be found in two debates in this journal (Bavister and Boatman, 1997; Bronson, 1997; Faber, 1997; Van Blerkom, 1997; Coetsier and Dhont, 1998; Liebermann, 1998; Murdoch, 1998), including the recommendations of the British Fertility Society and the American Society of Reproductive Medicine. Health economists, obstetricians and neonatologists have deplored the epidemic of multiple births after assisted reproductive techniques (ART) (Hidlebaugh et al., 1997; Bergh et al., 1999; Fisk and Trew, 1999). The medical outcome of both singleton and twin children after IVF/ICSI treatment (ICSI) is worse than in spontaneous pregnancies (Dhont et al., 1997, 1999; Bergh et al., 1999; Koudstaal, 1999). The opening article of the present debate (Hazenkamp et al., 2000) focuses on the risks of multiple pregnancy and strategies to avoid them.

Today, irrespective of the day of transfer, transferring two or three embryos yields similar results, reducing only the incidence of triplets but not of twins (Staessen et al., 1999). The medical outcome of both singleton and twin pregnancies after IVF/ICSI treatment (ICSI) is worse than in spontaneous pregnancies (Dhont et al., 1997, 1999; Bergh et al., 1999; Koudstaal, 1999). With twins and higher multiples totalling up to 30% of all ongoing pregnancies, more than half of all IVF/ICSI children nowadays belong to a set of multiples. Among patients themselves, there is a growing awareness of the risks involved in a twin pregnancy, especially with those requesting IVF/ICSI treatment for second or third pregnancies. Many no longer consider the high incidence of iatrogenic twins as an unavoidable price to be paid in order to achieve an ‘acceptable’ ongoing pregnancy rate.

The time is ripe for IVF/ICSI to be what it ought to be: a treatment of childlessness offering patients an ongoing pregnancy rate equal to or even slightly higher than the natural ongoing pregnancy rate in normally fertile people, i.e. 30–35% per cycle, while keeping twins within reasonable (5–10%) limits. Achieving this goal, although in principle quick and easy by employing single embryo transfer (SET), is hampered by a number of opposing forces. The major obstacle is the persistent difficulty of easily identifying the embryo(s) with a very high implantation potential. Efforts have focused on embryo characteristics at the 2-cell stage (polarity characteristics) (Scott and Smith, 1998; Edwards and Beard, 1999; Tesarik and Greco, 1999), at the early cleavage stage (Ziebe et al., 1998; Van Royen et al., 1999) and on culturing embryos to the blastocyst stage (Gardner and Lane, 1997; Alves da Motta et al., 1998; Behr, 1999). The major obstacle outside the medical arena is the high direct and indirect cost of IVF/ICSI treatment, leading to an expectant pressure for quick success that weighs on doctors and patients alike. This problem is linked to differences in the way...
IVF/ICSI is financed. At the one end of the spectrum, there are countries where the public sector covers the majority of costs, while at the other end there are those countries where patients themselves have to pay directly or indirectly through expensive private insurance systems for their treatment. In the former (e.g. Scandinavian countries), physicians tend to agree on a more careful approach, whereas in the latter (e.g. USA), patients agree to assume heavier risks.

In European countries, efforts have aimed at reducing the incidence of both multiple pregnancy (i.e. over two fetuses) and of twin pregnancy by reducing the number of transferred embryos from an original ‘maximum’ of three (given legal status in the Human Fertilisation and Embryology Authority) to a ‘maximum’ of two (Staessen et al., 1993; Devreker et al., 1999) and by recently introducing the concept of SET. In these studies, the authors used embryo selection criteria at the 2-cell stage or at the early cleavage stage. In Europe nowadays, not only higher-order multiple pregnancies, but also twin pregnancies are considered serious iatrogenic complications, although the figures do not yet show a substantial decline in the incidence of twins. Early European reports on ‘compulsory’ SET in cycles where only one embryo was available and no form of embryo selection was possible (Giorgietti et al., 1995) and therefore yielding poor results, did little to stimulate SET. Nevertheless, the idea of SET using day 2 or 3 embryos in combination with clinical ‘high risk’ criteria was seriously reconsidered by a Belgian group (Coetsier and Dhont, 1998) and then introduced clinically, first in patients with a medical indication for SET (e.g. diabetes mellitus, congenital uterine anomalies, insufficientity of the cervical isthmus, previous loss of a twin) (Vilska et al., 1998) and later electively in clinically normal patients aged <38 years (Gerris et al., 1999; Vilska et al., 1999). The cost-effectiveness of IVF after the transfer of one or two embryos has been estimated theoretically (Wolmer-Hanssen and Rydstrom, 1998).

In contrast, in the USA, fertility specialists were thoroughly impressed with the unacceptable complications linked to high-order multiple pregnancy but much less so by the quantitatively much larger problem of twin pregnancies, which still seem to be considered an acceptable price for ‘reasonable’ IVF/ICSI results. In addition, in the USA, clinical efforts to reduce the multiple pregnancy rate have been confounded by the hypothesis that prolonged culture of embryos to the blastocyst stage would automatically result in selection of ‘the best’ embryos. This approach is heralded as ‘natural evolution’ (Meldrum, 1999), although a critical appraisal and hopefully a constructive integration of all three levels of selection, i.e. two pronuclear (2PN) stage, early cleavage embryo, blastocyst, has yet to be formulated.

In the early 1990s, a retrospective analysis (Staessen et al., 1992) of 1915 consecutive transfers after IVF in Belgium, clearly documented the relationship between the number of embryos transferred and the pregnancy rate: 11.9% of the single, 19.0% of the double, and 34.1% of the triple embryo transfers were successful. Of all triple transfers 31% resulted in a twin or a higher multiple pregnancy. They transferred at day 2 after fertilization and found an implantation rate of 23% per transferred embryo if the embryo had at least two mitotic divisions versus 12.3% if the embryo was still at the 2-cell stage. In 1993, the same authors (Staessen et al., 1993) conducted a prospective cohort study where 183 good-prognosis patients were given the choice to receive either two or three embryos: 80 agreed to have double embryo transfer and obtained a pregnancy rate of 42.5% with 23.5% twins; 103 received three embryos and obtained a pregnancy rate of 48.5% (not significant) with 24% of twins and 18% of triplets. Their conclusion was that triplets can be avoided by elective transfer of two good quality embryos. Ever since, double embryo transfer has been the official standard of good medical practice in Belgium and in other European countries, e.g. in France (Nicollet, 1996) in this patient group. The percentage of triple transfers, although still high, has been on the steady decline over the past few years. It first equalled the percentage of double transfers (41.7%) in 1997 and has dropped below it for the first time in 1998 (unpublished data from the Belgian Register of Artificial Reproduction, BELRAP).

In contrast, in an American retrospective analysis (Svendsen et al., 1996), 1836 women aged <34 years are presented who received either two, three or four embryos. Patients receiving four embryos obtained just 17.2% singletons, 7.4% twins and 2.4% triplets (total 27% pregnancy), whereas patients receiving three embryos showed 15.8% singletons, 4.2% twins and 0.3% triplets (total 20.3% pregnancy) and patients receiving two embryos obtained no more than 12.8% of singletons and 1.3% of twins (total 14.1% pregnancy). The authors therefore advocated transfer of ‘only’ three embryos to avoid drastically low pregnancy rates.

Progressive efforts were made both in the USA and in Europe to identify embryos with a high implantation potential at different stages of embryo development. Some authors aimed at identifying very early embryos with a high implantation potential (Scott and Smith, 1998). In a retrospective analysis of 114 IVF cycles, they described a method to identify embryos with an implantation rate of as high as 28% by looking at pronuclear stage morphology. Others have used a similar approach to eliminate embryos with a very low implantation potential with a single observation at the 2PN stage (Tesarak and Greco, 1999). A German group, constrained by the German embryo protection law, allowing embryo selection only at the pronuclear stage, has conducted a prospective trial using the approach employed by Scott and Smith. They showed that zygotes with a score of >13 had an implantation rate of 22%, whereas zygotes with a score <13 had an implantation rate of only 4% (Ludwig et al., 2000). A Danish group studied single, double and triple embryo transfers and found differences in implantation rates to be linked more with timely cleavage than with the presence of small amounts of fragments, reporting similar findings after thawing (Ziebe et al., 1997, 1998). Our own group has described a method to identify day 3 embryos with an ongoing implantation rate of >40% in clinically selected patients (Van Royen et al., 1999; Gerris et al., 1999) and of 35% in unselected patients (unpublished data). Similar results have been published by Finnish authors (Vilska et al., 1999). It is of importance to identify embryos with multinucleated blastomeres that often carry chromosomal abnormalities (Kligman et al., 1996) and
are shown to have a decreased implantation potential (Pickering et al., 1995; Jackson et al., 1998; Pelinck et al., 1998).

Although fundamental work was already being carried out on blastocyst culture during the early 1990s (Gardner and Lane, 1997), the first clinical application of blastocyst transfer was reported by a Dutch group (Scholtes and Zeilmaker, 1996), who performed a prospective randomized study of embryo transfer after 3 or 5 days of embryo culture in IVF. The overall embryo transfer results after 3 and 5 days were comparable. They concluded that with an average implantation rate of >23% per day 5 embryo, replacement of one or two embryos would minimize the incidence of triplets. In a prospective study, the same authors (Scholtes and Zeilmaker, 1998) found that blastocyst implantation decreased after two cycles: from 23% in cycle 1 and 23% in cycle 2 to 14% in cycle 3 and 12% in cycle 4. They related this finding to the lower number of oocytes and not to age. In their work, use was made of conventional culture media and not of specific media used for prolonged embryo culture (Gardner and Lane, 1997; Jones et al., 1998). An American group reported retrospective data suggesting that blastocyst culture and transfer might allow reduction of the number of embryos from three to two (Gardner et al., 1998a). The same group reported a subsequent prospective randomized trial comparing day 3 with day 5 embryo transfer, in which specific culture media used for prolonged embryo culture were used (Gardner et al., 1998b). Randomization took place using a computer-generated randomization table. The conclusion of this study was a superior implantation rate (30.1 versus 50.5%) and a similar pregnancy rate (66 versus 71%) in day 5 transfer cycles. However, no explanation is given for the fact that the group with day 3 transfer received on average 3.7 embryos, while the group with day 5 transfer received on average 2.2 embryos. This suggests that the authors did not know how to select optimally day 3 embryos, therefore transferring a mixture of high and low implantation embryos, possibly withholding high implantation embryos. Another American retrospective cohort study showed better results with day 5 transfer than with day 3 transfer (Milki et al., 2000). Day 3 criteria were conventional and, again, there was a bias in favour of patients receiving a mean of 2.4 blastocysts versus those receiving a mean of 4.6 day 3 embryos. The conclusions therefore remain hypothetical.

In another prospective study (Huisman et al., 2000), overall implantation and pregnancy rates in 1787 couples were not statistically different with different culture periods (3, 4 or 5 days). Blastocysts were formed in 62% of patients and gave an implantation rate of 26 versus 18% for traditionally selected 8-cell embryos.

Blastocyst culture has been applied in two clinically distinct situations: as a method to prevent (higher) multiple pregnancy and in patients with repeated failure of implantation. In a retrospective cohort study it was shown that in patients with three or more unsuccessful IVF cycles, the group that was subsequently treated with day 3 embryo transfer showed a clinical pregnancy rate of 9.1% and an implantation rate of 3.4%, whereas the group treated with blastocyst transfer had a clinical pregnancy rate of 40% and an implantation rate of 11.3% (Cruz et al., 1999). Some authors jumped to the hasty conclusion that blastocyst culture and transfer should be the rule for all patients in an IVF programme (Del Marek et al., 1999) while others have propagated a more fine-tuned integration of extended embryo culture in an IVF programme (Patton et al., 1999). Although publications on blastocyst culture show the highest implantation rates in the literature, data on single blastocyst transfer have to date not been published. Nevertheless, in the USA as well as in some European centres, the opinion is gaining ground that before embarking on SET, one should introduce blastocyst culture as a necessary first step. On the other hand, in Europe, many centres have already embarked on SET as a possibility or even a standard of care in good-prognosis patients in their first IVF/ICSI cycle, in patients who already have (IVF/ICSI or other) children, and in patients with medical indications for SET. In these centres, embryo selection at the 2PN stage or at the early cleavage embryo stage is presently given preference over systematic blastocyst culture.

It is our view that we must avoid an empty discussion on for or against blastocyst culture. The fundamental question of this debate is whether we are in favour of single embryo transfer or not, and in which clinical circumstances. Once this prime moral-ethical question has been answered, the subsequent medical-technical question can be addressed, i.e. how do we successfully select the one embryo with a very high implantation potential which we shall replace in the uterus?

We hold the opinion that the answer to the first question, are we in favour of SET or not?, must be answered with an emphatic ‘yes’. Clearly, a distinction must be made between two partly overlapping populations of patients. On the one hand there is the large group of young and clinically normal patients who enter a successful IVF/ICSI programme for the first time. On the other hand there are the older patients and patients with concomitant pathology, e.g. a myomatous uterus, known poor responders, heavy smokers, patients requiring difficult procedures, e.g. micro-epididymal sperm aspiration (MESA)/testicular sperm extraction (TESE) + ICSI, or patients who have had several IVF/ICSI cycles with good embryos without implantation. Generally speaking, the first group is the a priori good prognosis group, the second one is the a priori poor prognosis group. Twins and multiples are most likely to occur in the first group and, therefore, efforts to prevent these complications should be oriented towards these patients. Embryo selection is of the greatest importance, but patient selection should also be emphasized in order to end up with an acceptable pregnancy rate after SET. Commenges-Ducos et al. in an effort to identify factors influencing the probability of success after IVF/ICSI found previous livebirth a favourable factor. A large number of ampoules for adequate ovarian stimulation and age above 38 years were unfavourable (Commenges-Ducos et al., 1998). If we can offer an ongoing pregnancy rate per started cycle in the range of the natural ongoing pregnancy rate (30%) to good-prognosis patients, an iatrogenic twin pregnancy rate of 25% is unacceptable. Therefore, SET should be considered in good prognosis patients whenever a top quality embryo is available, in whatever way it has been selected.
The answer to the secondary question (whether one has or has not to achieve that goal by systematically transferring 2-cell embryos or early cleavage stage embryos or blastocysts in good prognosis patients) can only be given by prospectively randomized studies comparing single embryo transfer of 2-cell embryos, day 3 embryos or blastocysts. Randomization must be performed before the cycle is started, so that all results are expressed as ongoing implantation rates per started cycle.

Two issues will guide the further debate. One is the fact that when SET becomes the standard, centres will have to focus on ongoing implantation rates instead of ‘pregnancy rates’. This will be the ultimate test for centre quality. Therefore, the suggestion of an individualized embryo transfer strategy (Hazekamp et al., 2000) seems to be a useful one. Their proposal to use ‘birth per embryo transferred’ as the criterion of ART excellence goes in that direction. However, this criterion does not by itself discriminate the centre that transfers one embryo whenever possible from the centre that systemically transfers two or three embryos if both centres obtain the same implantation rate. It offers a figure that is related to the excellence of embryo culture and transfer technique, but is at the same time totally unrelated to the embryo transfer policy applied. Therefore, results must also be expressed as ongoing implantations per started cycle. The specific importance of the technique of embryo transfer should also not be underestimated (Naaktgeboren et al., 1997).

The other consideration is purely financial. Why does IVF cost US$10 000 in New York, US$3000 in London and US$2000 in Antwerp (for similar results)? Differences in insurance coverage, however understandable in the light of differences in history and politics, should, from an ethical point of view, not dictate patients’ ‘willingness’ to ‘accept’ risks. Even if huge differences exist between the absolute cost of IVF/ICSI in different countries, the huge expense generated in each country through twins and multiples pregnancies (curative medicine) can and should be diverted towards a substantial refund of the cost of treatment itself (preventive medicine), thereby making SET in the right clinical circumstances more acceptable to patients. There is need for health-economic studies to examine the difference in cost between successful SET versus successful double embryo transfer cycles, and then to assess whether the expense gained by SET suffices to bridge the gap between the ongoing pregnancy rate obtained by SET versus that obtained by double embryo transfer, given the fact that more SET cycles will be necessary to obtain the same cumulative ongoing pregnancy rate as when performing double embryo transfer. The slightly positive effect of obtaining more pregnancies after thawing when applying SET will have to be taken into account as well. It is necessary to underline again that there is a huge difference between first ever IVF/ICSI patients and those patients who have failed to conceive after three or four cycles, where other factors may be responsible and where a completely different embryo transfer policy may be warranted, e.g. applying blastocyst culture and transfer.

In conclusion, common sense dictates that all approaches aiming at identifying embryos with a high implantation potential are welcome. Common sense also dictates that of several methods with proven equal efficacy, the quickest and cheapest is likely to become the standard. At present, it is pure speculation to guess whether identification of high implantation embryos at the 2PN stage, the day-3 stage or the blastocyst stage have a mutually overlapping or a complementary value. The best course to embark upon seems to aim at an integration of different approaches, and then determining which singular or combined approach best fits which particular patient.

References
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