Strategies for Embryo Utilization in Assisted Reproduction—How Do We Assess Their Relative Effectiveness?

The application of assisted reproductive techniques, specifically in vitro fertilization and embryo transfer (IVF/ET), will normally consist of a series of strategic and often highly subjective decisions which may be influenced by clinical, scientific, and even economic considerations. It is important to assess the impact on pregnancy rate of any proposed changes in IVF practice. The availability of techniques for extended embryo culture and blastocyst transfer (BT) is a topical example.

In considering the effectiveness of various approaches to embryo utilization, Gardner and Lane (1) have suggested that blastocyst transfer may be a feasible option in human IVF. Adoption of this approach has been reported by Menezo *et al.* (2) using a coculture system containing heterologous somatic cells, a technique which may not be generally acceptable (the Reproductive Technology Accreditation Committee in Australia has not authorized its use and it is unlawful in the state of Victoria). More recently Jones *et al.* (3) have reported pregnancies from blastocyst transfer following culture using a cell-free system. The rationale for extended culture consists mainly of selection of the "best" embryos on a more objective basis than early cleavage-stage morphology and, consequently, elimination of those embryos which arrest or undergo aberrant development. The principal anticipated advantage of blastocyst transfer would be an increase in the implantation rate (IR) [fetal heart (FH) detected] relative to the rate for routine transfer on day 2, with a concomitant decrease in the embryo utilization rate (EUR) due to the elimination of arrested embryos over the extended culture period. However, it is not yet clear how many of these discarded embryos might have produced babies had they been cryopreserved rather than subjected to extended culture.

Under optimal cell-free culture conditions, Jones *et al.* (3) report a blastocyst development rate of 51.9% and an IR of 22.6% from the transfer of 93 embryos in 34 ET procedures (2.74 embryos/ET), resulting in 21 detected fetal hearts in 13 pregnan-

cies from 35 cycles (37%) subjected to this protocol—a series of cycles with a mean of 12.1 dipronucleate zygotes per cycle.

With what group of conventional IVF patients should these results be compared? We most commonly transfer two embryos 2 days after egg retrieval and freeze the remaining suitable embryos. Analysis of the results from this approach when 8 or more embryos are available on day 2 (mean, 12.3) would seem broadly appropriate. Our overall EUR is 90.5% and we transfer 81% of our thawed embryos. Our current IR is 9.4% for fresh embryos and 8.9% for thawed embryos. As a consequence of our relatively high EUR, however, 55% of our oocyte collections which result in eight or more embryos being available also result in at least one confirmed implantation (FH detected), with over 80 fetal hearts being detected per 100 oocyte collections. To match this cumulative pregnancy rate, implantations would be required from frozen/thawed blastocysts in a further six or seven of the extended culture cycles described above. Although good rates of survival and implantation have been reported for cocultured blastocysts following freezing and thawing (4), the results of Hartshorne *et al.* (5) using blastocysts cultured under cell-free conditions showed that only 11 deliveries were obtained from 341 frozen–thawed blastocysts (3.2%), while Nakayama *et al.* (6) reported an IR of 1.7% from frozen–thawed blastocysts obtained in the absence of coculture.

It appears to us that a strategy of extended culture with ET at the blastocyst stage (in vitro selection) cannot guarantee a better return from the available zygotes than a policy of replacement of a small number of embryos (usually two) on day 2 together with the extensive use of cryopreservation to permit similar subsequent replacements (in vivo selection). This case has in fact been argued by Trounson and Jones (7), who concluded that a substantial increase in the efficiency of blastocyst freezing would be required before extended culture could be considered the strategy of choice for IVF/ET. This would be particularly true if we were to consider the eventual aim of

moving to a policy of transferring only one blastocyst per ET procedure.

Similar arguments may apply to the approach reported by Gianaroli *et al.* (8), who observed an increase in IR when embryos were selected for ET on the basis of chromosomal analysis of biopsied blastomeres from day 3 embryos. This would, however, seem to be an unrealistic proposition for general application at present purely on the basis of laboratory logistics.

We believe that progress toward a system that will allow the transfer of single embryos of high viability is desirable. However, until the efficiency of extended culture in vitro and freezing noncultured blastocysts has been shown to allow cumulative pregnancy rates equivalent to those achievable by a more conventional approach (preferably in a controlled clinical trial), the adoption of extended culture should be considered with caution. Reporting success rates of subgroups of patients who have blastocysts for transfer as if they represent the average IVF couple is sure to deceive the lay press and scientifically unsophisticated public to the potential detriment of infertile couples (9).

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