Embryo selection in IVF

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ABSTRACT: To optimize success rates of IVF, selection of the most viable embryo(s) for transfer has always been essential, as embryos that are cryopreserved are thought to have a reduced chance of implanting after thawing. Recent developments challenge this concept. Evidence is accumulating that all embryos can now be cryopreserved and transferred in subsequent cycles without impairing pregnancy rates or maybe even with an improvement in pregnancy rates. In such a scenario no selection method will ever lead to improved live birth rates, as, by definition, the live birth rate per stimulated IVF cycle can never be improved when all embryos are serially transferred. In fact, selection could then only lower the live birth rate after IVF. The only parameter that could possibly be improved by embryo selection would be time to pregnancy, if embryos with the highest implantation potential are transferred first.

Key words: assisted reproduction / embryo transfer / embryo quality / IVF / ICSI outcome

In the majority of human IVF cycles multiple embryos are created after ovarian hyperstimulation. The viability of these embryos, and as a consequence the chance for an embryo to successfully implant, is subject to biological variation. To achieve the best possible live birth rates after IVF while minimizing the risk for multiple pregnancy, one or two embryos that are considered to have the best chance of implanting are selected for transfer. Subsequently, supernumerary embryos with a good chance of implanting are selected for cryopreservation and possible transfer in the future while remaining embryos are discarded.

The best available method for embryo selection is morphological evaluation. On the basis of multiple morphological characteristics at one or several stages of preimplantation development, embryos are selected for transfer (Ebner et al., 2003; Gerris, 2005). However, with embryo selection based on morphological evaluation implantation rates in general do not exceed 35%, although varying results have been reported (Centers for Disease Control and Prevention et al., 2010). This has resulted in a strong drive for finding alternative selection methods.

The best studied alternative selection method is preimplantation genetic screening (PGS). The classical form of PGS involves the biopsy at Day 3 of embryo development of a single cell of each of the embryos available in an IVF cycle and analysis of this cell by fluorescence in-situ hybridization (FISH) for aneuploidies, for a limited number of chromosomes. Only embryos for which the analyzed blastomere is euploid for the chromosomes tested are transferred (Wilton, 2002). Although this method of PGS has been increasingly used in the last decade, recent trials show that it actually decreases ongoing pregnancy rates compared with standard IVF with morphological selection of embryos (Mastenbroek et al., 2008).

In an effort to overcome some of the drawbacks of PGS using cleavage stage biopsy and FISH, new methods to determine the ploidy status of a single cell are developed, such as comparative genomic hybridization arrays or single nucleotide polymorphism arrays (Wells et al., 2008). Furthermore, in an attempt to avoid the confounding effects of chromosomal mosaicism, embryos are now biopsied at either the zygote or blastocyst stage (Geraedts et al., 2009). In addition, increasing time and money are invested in the development of high-tech, non-invasive methods to select the best embryo for transfer in IVF. This includes metabolomic profiling, amino acid profiling, respiration-rate measurement and birefringence imaging (Nagy, 2008). In metabolomic profiling, spectrophotometric tests are used to measure metabolomic changes in the culture medium of embryos; in proteomic profiling, proteins produced by the embryo and released into the culture medium are identified; in amino acid profiling, amino acid depletion and production by the embryo is assessed using the culture medium; in respiration-rate measurement, the respiration rate of embryos is assessed; and in birefringence imaging, polarization light microscopy is used to assess the meiotic spindle or the zona pellucida (see for review Nagy, 2008).

All this research on alternative selection methods is driven by the concept that embryo selection is essential to optimize the success rates of IVF, since embryos that are cryopreserved have a reduced
chance of implanting after thawing. Better selection methods should thus result in higher live birth rates without an increase in multiple pregnancies.

Recent developments challenge this concept. Endometrial receptivity and synchronization between embryo and endometrial development have been suggested to be suboptimal in cycles with ovarian hyperstimulation (Paulson et al., 1990; Check et al., 1999; Shapiro et al., 2008). Therefore, cryopreservation of embryos and transfer later in a non-hyperstimulated cycle would not necessarily have to result in a lower chance of pregnancy, as the better endometrial receptivity could very well counterbalance the negative effect of cryopreservation on embryo viability. Reports on cycles where embryo transfer was disengaged from the cycle with ovarian hyperstimulation in case of embryo donation or in women at risk of ovarian hyperstimulation syndrome, indeed suggested comparable or even increased pregnancy rates (Check et al., 1995; Shaker et al., 1996; Ferraretti et al., 1999; Zhou et al., 2009).

The results described above were all obtained using slow freeze embryo cryopreservation protocols. With the use of vitrification even better results are to be expected (Zhang et al., 2010), since post-thaw survival rates and in vitro development after vitrification seem better than after slow freezing (Loutradi et al., 2008), and, more importantly, a recent meta-analysis showed a significantly improved ongoing pregnancy rate after vitrification in comparison with slow freezing (OR 1.82, 95% CI 1.04–3.20; Abdelhafez et al., 2010). Indeed, a recent well-designed and robust randomized controlled trial in women with a high response to ovarian hyperstimulation has shown that vitrification of all embryos followed by a transfer in a subsequent non-hyperstimulated cycle results in significantly improved ongoing pregnancy rates compared with a fresh transfer in a cycle with ovarian hyperstimulation (Aflatoonian et al., 2010).

If more well-designed and powered studies corroborate these findings, also for other groups of women, then the concept of embryo selection in IVF needs to be re-evaluated. In a scenario where all available embryos can be cryopreserved and transferred in subsequent cycles without impairment of pregnancy rates, or maybe even with improvement of pregnancy rates, no selection method will ever lead to improved live birth rates, as, by definition, the live birth rate per stimulated IVF cycle can never be improved when all embryos are serially transferred.

Embryo selection techniques will not only be unable to improve live birth rates but also they could even lower the success rate of IVF. In comparison to a situation where all embryos are transferred, the live birth rate per stimulated cycle will be lowered by any embryo selection method that identifies and discards non-viable embryos with an accuracy of <100%. Unfortunately, this holds for all selection methods currently available and a selection method that is able to identify non-viable embryos with 100% accuracy is not to be expected in the near future. The only parameter that can possibly be improved by embryo selection after optimal cryopreservation is time to pregnancy, if embryos with the highest implantation potential are transferred first.

In our opinion, the path of embryo selection is turning into a dead-end in the quest for optimal IVF success rates. Other routes should therefore be embarked upon, including optimization, evaluation and broad implementation of the best cryopreservation protocols. Decision models need to be developed to determine the most cost-effective transfer policies for cryopreserved embryos.

Such transfer policies could perhaps involve the transfer of multiple low-quality embryos at once after cryopreservation to obtain optimal pregnancy rates without increasing the multiple pregnancy risk, especially in aging women, as the time necessary to transfer all cryopreserved embryos in subsequent cycles might have an impact on the overall success rates. Cost-effectiveness analysis needs to confirm that the costs of extra transfer cycles after cryopreservation are counterbalanced by the savings related to the fewer hyperstimulation cycles, the avoidance of multiple pregnancies and the avoidance of selection methodologies.

Authors’ roles

S.M., F.V., S.R.: conceptualization of manuscript. S.M.: drafting the article. A.A., B.S., P.B.: refinement of the proposed concept. All authors: critical revision of manuscript and approval of final manuscript.

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