MOSAICISM IN PREIMPLANTATION EMBRYOS

Dwindling fertility is one of the major health concerns of our (Western) societies. Not surprisingly, approaches to increase fertility rates are long sought for. With the development of techniques to map aneuploidies in single blastomeres and blastocysts of human preimplantation embryos came the discovery of high numbers of chromosomal mosaic aneuploidy. It was hypothesized that the selection against aneuploid embryos could increase the in vitro fertilization (IVF) success rate. Hence, preimplantation genetic testing for aneuploidy (PGT-A) was swiftly evaluated and implemented in IVF centres.

The high rate of mosaicism in blastocyst biopsies puzzled the IVF field. Most IVF centres offering PGT-A do not transfer mosaic embryos. While different lines of evidence suggested that some mosaic embryos could develop into healthy fetuses and babies, convincing evidence was lacking. In a study led by Capalbo et al. (in press in Am J Hum Genet[1]), this evidence is convincingly provided. By dissecting blastocysts and analyzing five different samples of each embryo, the authors provide a glimpse of the incidence of mosaicism in embryos and also demonstrate that for low grade mosaicism the aneuploidies are often confined to a single biopsy. When mosaicism impacts fewer than 50% of cells in one Trophectoderm (TE) biopsy (low-medium mosaicism), only 1% of aneuploidies affect other portions of the embryo. More importantly, the study presents the results of a double blinded prospective randomized trial demonstrating that the transfer of low and medium grade mosaic embryos does not affect the IVF outcomes at all. The pregnancy rate, miscarriage rate and baby-take-home rates are equal to those for euploid embryos. This study is a landmark paper for the IVF field as it demonstrates that the main-stream practice in IVF centres performing PGT-A destroys embryos and has the potential to reduce rather than enhance pregnancy rates.

Interestingly, another landmark study suggests that PGT-A does not improve cumulative baby-take-home rate. Whereas embryo selection with PGT-A has been shown to improve pregnancy outcome per embryo transferred, it has remained uncertain whether PGT-A improves the cumulative live-birth rate as compared with conventional in vitro fertilization. Yan et al. (New England Journal of Medicine2 (N Engl J Med[2]) addressed this question by performing a multicenter, randomized, controlled trial which randomly assigned subfertile women to undergo either PGT-A or conventional IVF. Interestingly, the cumulative live-birth rate after up to three embryo-transfers within 1 year following randomization did not show any significant difference. This study undermines the clinical rationale for PGT-A.

One gets a feeling of déja vu: The hypothesis that selection against aneuploid embryos could increase the IVF success rate was first launched at the beginning of this century and led to a first wave of FISH based PGT-A screening of cleavage stage embryos. However, several randomized trials showed no benefit. This was probably because the chromosome constitution of a single blastomere is, as was later shown, not representative for the rest of the embryo, due to the chromosomal instability at the cleavage stage. Since the degree of chromosomal instability is much lower at the blastocyst stage, aneuploidy screening of blastocyst biopsies was shown to be more reliable. Randomized control trials did show an increased IVF success rate per embryo transferred. But now, the question remains whether this also benefits the (subfertile) women. Clearly, both studies, which will require follow-up studies, raise new questions. Is too strong a selection against mosaic embryos resulting in a reduced baby-take-home rate and does it jeopardize overall fertility rates? Would transferring low grade mosaic embryos result in an improved baby-take-home rate? Can we develop better approaches to select viable embryos? Hopefully we can provide the answers… and increase the IVF success rates. That is what society expects.

[1] https://linkinghub.elsevier.com/retrieve/pii/S0002-9297(21)00412-2

[2] https://www.nejm.org/doi/full/10.1056/NEJMoa2103613