Mosaicism in preimplantation embryos: Are we overinterpreting the results?

In this edition, a retrospective analysis of 17,366 patients who underwent preimplantation genetic testing for aneuploidy (PGT-A) during 21,345 assisted reproductive therapy (ART) cycles where 86,208 embryos (mean 4 embryos per cycle) were tested (1) provides insight into the nature and complexities of interpreting the results of aneuploidy testing for early preimplantation embryos. It should be straightforward, right? A few cells are removed from an early preimplantation embryo for testing, and the embryo is either genetically healthy and potentially viable or not. However, the more we uncover about the processes of human preimplantation embryo development, the more we realize that the biology of embryos at this stage of development does not allow for such dichotomous thinking. The results of this study and other previous studies (2) show quite clearly how common abnormal divisions occur in developing human preimplantation embryos undergoing mitotic growth. Extrapolating the results from a few cells, randomly selected from a region of trophectoderm distant from the inner cell mass, to determine the viability of the embryo as a whole is bound to result in errors, both overinterpretation of aneuploid lethality and missing errors due to lack of sufficient sampling. Although sampling errors that fail to identify lethal abnormalities may not be identified because of lack of a subsequent pregnancy, those that identify abnormal cells or overinterpret those results may lead to discarding potentially viable embryos and will reduce the probability of pregnancy. This may be the reason for the lower cumulative live birth rate with PGT-A testing. In this study, 1,212 patients with good prognosis, with ≥ 3 blastocysts on day 5 of culture, were randomly assigned to biopsy with cryopreservation and cryopreservation without biopsy groups (3). Up to 3 embryo transfers were included in the final analysis. Mosaic embryos (11.7%) were considered abnormal and excluded. Cumulative ongoing/live birth rates were significantly lower in the PGT-A group (79%) compared to the no PGT-A group (84.8%).

This particular study highlights how common the occurrence of mitotic abnormalities is in human preimplantation embryos, resulting in the enigma of "mosaicism." Whether the results of testing are accurate or merely an artifact of the ultrasensitive nature of the analysis is, as yet, unknown. What is also not known is the implications of trophectoderm cell abnormalities on the chromosomal complement of the inner cell mass or embryo viability as a whole. Additionally, what arbitrary threshold of aneuploid cells in a sample should be considered reportable or clinically relevant cannot be agreed upon.

This retrospective study was not designed to answer those questions. It merely provides another insight into the importance of getting answers to these questions because mosaicism is common and will result in a significant number of patients ending up without embryos considered "suitable" for transfer. In fact, including mosaic embryos for transfer would have increased the number of transferrable embryos by 52% among patients older than 42 years of age, where 36.7% of patients had no euploid embryos for transfer. Even in younger patients, with 7.4% having no euploid embryos for transfer, an additional 33% would have had an embryo for transfer. Although high-level mosaic embryos may have a lower implantation rate, the rate is not 0, and many healthy infants have now been born as a result of the transfer of known mosaic embryos (4).

When mosaic results are replaced by aneuploid results as women get older, many older patients have no "healthy" embryos for transfer. Physiologically, that makes sense if each cell division is considered to be a separate event as cells divide clonally. There is an increased likelihood of abnormal divisions in each and every cell in the embryo from older eggs; therefore, the likelihood of more cells in a sample being abnormal and the embryo being diagnosed as aneuploid rather than mosaic would increase with advancing maternal age. What is also interesting to note is that mosaicism was neither related to the individual patient (a mosaic result did not correlate with an increased risk of a mosaic result in a subsequent cycle) nor to the specific clinic performing the stimulation or embryo biopsy.

The take-home point from this study is that we should be careful when making clinical decisions on the basis of biologic phenomena that are not fully understood. Making embryo transfer decisions on the basis of PGT-A results would lead to the following: more patients will undergo stimulation with no embryos deemed suitable for transfer; there will be a lower cumulative probability of pregnancy from a given ART cycle; and more stimulation cycles per patient will be required with the associated increased cost, inconvenience, and risk. Therefore, judicious use of PGT-A will help minimize this downside.

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