Mosaic embryos present a challenging clinical decision

Biologic mosaicism is defined as two or more genotypes within the same embryo and typically results from mitotic error in the postzygotic state of development. Mosaicism can also be identified as a result of technical limitations of the testing platform, in which an intermediate result is generated that resembles a mosaic profile. Embryonic mosaicism was initially detected in the 1990s but was not routinely reportable owing to limitations in technique. Now with the use of high-throughput methods and detailed resolution, the detection of mosaicism is routinely reported. The current use of next-generation sequencing (NGS) has the capability of detecting mosaicism levels as low as 20%. However, depending on the platform used and the technical processing of results, the incidence of mosaicism is widely heterogeneous, ranging from 3% to 83% in the literature, but with most studies quoting an average of 15% (1). This leads to a challenging clinical question, for both clinicians and patients, when trying to determine the ultimate disposition for embryos labeled as mosaic and warrants further review of the literature.

Clinical outcomes of mosaic-embryo transfer (MET) include implantation failure, early pregnancy loss, and live birth. Both diploid-aneuploid and aneuploid-aneuploid mosaicism exists, with clinical outcomes of the former being reported in the past several years. Diploid-aneuploid transfers are associated with inferior pregnancy outcomes compared with euploid blastocyst transfers, with ongoing pregnancy rates averaging 15%–20% and miscarriage rates up to 55.6% (2). There is insufficient evidence currently and additional risk is presumed in the transfer of aneuploid-aneuploid embryos. The potential for a healthy live birth after mosaic embryo transfer must be weighed against the risk of implantation failure, pregnancy loss, and ongoing aneuploid gestation. The disposition of mosaic embryos becomes more complex in situations where there are financial or age-related treatment constraints. Often, these are the last embryos available and patients are faced with the difficult decision of transferring mosaic embryos or proceeding with alternate treatment strategies, such as oocyte donation. As of April 2018, nearly 110 pregnancies had been reported from mosaic embryo transfer (3), 80 of which were ongoing at the time of publication. This underestimates the true incidence of pregnancies that have resulted from MET, which is likely underreported worldwide.

In the current issue of *Fertility and Sterility,* Besser et al. (4) present a retrospective review of 98 patients who underwent at least one cycle of in vitro fertilization (IVF) with preimplantation genetic testing for aneuploidy (PGT-A) yielding mosaic embryos in their cohort and no euploid embryos. The primary objective was to analyze all patients with mosaic embryos and among this cohort compare patients that proceeded with transfer with patients that underwent additional IVF or intrauterine insemination (IUI) cycles. Mosaicism was reported for embryo biopsies with aneuploidy ranging from 20% to 80%. Patients underwent genetic counseling regarding reproductive potential, pregnancy outcomes, and antenatal genetic testing in the event that a pregnancy occurred after MET. The authors emphasize the critical role that genetic counseling plays in the informed decision to either discard, transfer, or retain mosaic embryos in cryopreservation until more is understood regarding long-term outcomes of children resulting from MET.

The rate of mosaicism per embryo biopsied was reported as 28.4%, with 19.1% having only mosaic aneuploidies. Thirty-two patients elected to proceed with MET throughout the course of 35 total cycles, and 41 patients chose to proceed with additional IVF or IUI cycles. Six patients elected to discard their mosaic embryos and not pursue further treatment at the center where the study was conducted. Seventeen patients elected not to proceed with MET, and their embryos remained in cryopreservation. The patients who chose MET were more likely to be older and to have had pursued more oocyte retrievals compared with those who elected not to transfer mosaic embryos. The ongoing pregnancy rate for MET was 27.6%, which was significantly different than the pregnancy rate of 51.2% for patients pursuing additional treatment cycles.

A clear strength of this study was the importance placed on genetic counseling for couples proceeding with MET. During these consultations, prenatal genetic testing was emphasized, including the risk and benefits of amniocentesis compared with chorionic villous sampling (CVS). More than one-half of the patients ($n = 6$) with an ongoing pregnancy after MET elected to pursue amniocentesis, with one-third opting for chromosomal microarray along with traditional karyotyping. The number of patients who chose MET was relatively steady throughout the course of the 2-year study period and potentially confounded by both counseling and transfer occurring at a single center. Long-term outcomes for patients who did not choose to pursue MET but retained embryos in cryopreservation are unknown, as are long-term clinical outcomes of the children born from these pregnancies. Unfortunately, information regarding correlation of the biopsy genotype with the pregnancy outcome was not included.

This study highlights the importance of genetic counseling before the MET and provides clinical data resulting from the transfer of these embryos compared with the continuation of additional treatment cycles. Despite this information, it still remains challenging to offer clear guidelines to patients and clinicians regarding the ultimate fate of these mosaic or potentially aneuploid embryos of undetermined significance. The Preimplantation Genetic Diagnosis International Society (PGDIS) has published a set of guidelines to help guide clinicians on this topic by stratifying mosaic abnormalities in relation to known reproductive outcomes. In one example, the PGDIS prioritizes monosomy MET over trisomic MET, although further studies have shown no difference in outcome after the transfer of these mosaic embryos (5). Subsequent attempts at a risk stratification system for MET have been developed from retrospective data of CVS samples but have not been clinically validated. Caution should always be exercised when a mosaic aneuploidy is associated with a known phenotype, and patients should be

counseled on the clinical manifestations of such aneuploidies and the potential for antenatal or postnatal mortality. Further research in this area should focus on antenatal screening results, pregnancy outcomes, and early development data after the transfer of mosaic embryos. Until long-term clinical outcomes of children conceived as a result of MET are known, priority should be placed on transfer of euploid embryos when available. In situations where mosaic embryos are to be transferred, patients should be counseled on the clear diminution in pregnancy outcomes, including lower implantation rate, and potentially higher risk of pregnancy loss, including the risk of ongoing aneuploid gestation, with a strong recommendation for invasive prenatal testing to confirm PGT-A results.

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https://doi.org/10.1016/j.fertnstert.2018.10.032

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