Mosaic embryo transfer: a cautionary tale

Preimplantation genetic testing for aneuploidy (PGT-A) has evolved from fluorescence in situ hybridization for a limited number of chromosomes to platforms that are able to test comprehensively for all the 24 chromosomes. Its use has become increasingly prevalent as a method of embryo selection during in vitro fertilization cycles. With the advent of more sophisticated molecular technology, in particular array comparative genomic hybridization and next-generation sequencing, we are now faced with additional diagnostic findings of subchromosomal abnormalities, including duplications and deletions of individual chromosome segments along with mosaicism identified in the, ideally, 5–10 cell trophectoderm biopsy sample.

Originally, given the uncertainty of these findings, the safety of transferring these embryos was in question. Initial studies showed that the transfer of embryos deemed mosaic by PGT-A resulted in the birth of apparently genetically normal and healthy children (1), and subsequent studies reinforced this concept. This evolved into the thinking that, although transfer failures and miscarriage rates may be higher, the risk of abnormal births from a mosaic embryo transfer seems relatively low. It is important to note that mosaicism rates vary highly among clinics and the genetic testing platform used. This may be because of technical reasons, such as analysis platform, amplification variations, and analysis algorithms, or biologic reasons, such as localized embryonic mosaicism vs. uniform embryonic mosaicism.

There were attempts by societies to prioritize the transfer of embryos with these secondary findings based on the level of mosaicism, ploidy diagnosis, whether monosomy or trisomy, along with the chromosome in question and the chance of there being a live-born child with a concerning phenotype (2). Studies that looked at repeat biopsies of embryos deemed "high mosaic" were often found to be fully aneuploid (3). However, it does seem that embryos diagnosed as mosaic do not have an "all or nothing" outcome resulting in either a failed pregnancy or normal live birth. Indeed, there have been reports of children born with mosaic phenotypes after the transfer of a mosaic embryo.

In this edition, the case presented by Schlade-Bartusia et al. (4) reports the first known case of a live born diagnosed with a partial trisomy 15 and maternal uniparental disomy (UPD) 15 resulting from a mosaic embryo transfer. This was the result of a double embryo transfer; one embryo with high-level mosaicism for trisomy 15 with a deletion in chromosome 20, and the other embryo was a high-level mosaic for monosomy 21 and X. In this case, the genetic testing company reported the embryos as high-level mosaic, defined as 40%–80% of the cells tested being abnormal. The couple did receive genetic counseling, and UPD was discussed, given the involvement of chromosome 15. A singleton pregnancy resulted, and early pregnancy monitoring and second-trimester anatomy scan were normal, as was the noninvasive prenatal testing (NIPT). There was no invasive prenatal testing performed via amniocentesis, and a child was born at term. After developing feeding issues, a workup that culminated in a chromosomal microarray revealed a karyotype of 47,XY,+del(15)(q12q23)dn along with a 21.8 Mb region of homozygosity at 15q14q22.2 suggestive of UPD15. This was deemed to be the result of an incomplete trisomy rescue event.

This case report highlights the importance of a standardized approach to the transfer of embryos which have been diagnosed with secondary findings such as mosaicism and duplications and deletions. This should include thorough genetic counseling by a genetic counselor on the specific possible outcomes of a particular mosaic chromosome, paying particular attention to chromosomes that yield the possibility of UPD. The counseling should include a discussion that NIPT cannot provide reassurance of a normal ongoing pregnancy. This is particularly true of the standard NIPT, which analyzes only 5 chromosomes (21, 18, 13, X, and Y). Further, NIPT would only be able to detect placental mosaicism. To test the fetus, invasive testing is required. This should be performed by amniocentesis to avoid a potential false-positive or -negative result from placental mosaicism, which would be analyzed with chorionic villus sampling. As part of the prepregnancy counseling, consideration should be given to maternal-fetal medicine consultation to review the potential risks involved with amniocentesis. As noted by the investigators, communication by the fertility provider to the obstetric provider about the transfer of an embryo with secondary findings is paramount.

A point to highlight is the counseling that must be undertaken for all patients using PGT-A. The cells analyzed represent a small sample of the entire embryo. Nonselection studies have shown good predictive value for whole chromosome aneuploidy with the platform used (4). It should be noted that every nonselection study is PGT-A testing platform specific—the results cannot necessarily be extrapolated to all methods of PGT-A. Although some nonselection studies have included the transfer of mosaic embryos (5), there have not been robust nonselection studies that have included mosaic embryos and those with duplications and deletions. Several studies which have analyzed repeat trophectoderm biopsies from embryos deemed mosaic have found them to be uniformly aneuploid almost 1 out of 3 times (3), although there have now been several reports of live births with mosaic abnormalities.

With the increased use of PGT-A and the advent of new technologies, we are faced with new diagnoses of yet to be fully determined significance. Furthering our knowledge of these diagnoses can only truly be accomplished using carefully designed nonselection studies. If an embryo with secondary findings is to be transferred in clinical practice, careful physician counseling, a discussion with a genetic counselor, and a maternal-fetal medicine physician about invasive prenatal testing options should be considered. This report highlights the fact that, although many reports of mosaic embryo transfers have shown apparently healthy live births, the risk of live birth with a genetic abnormality remains.

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