Assessing the true incidence of mosaicism in preimplantation embryos

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Modern technologies applied to the field of preimplantation genetic diagnosis for aneuploidy screening (PGD-A) have improved the ability to identify the presence of mosaicism. Consequently, new questions can now be addressed regarding the potential impact of embryo mosaicism on diagnosis accuracy and the feasibility of considering mosaic embryos for transfer. The frequency of chromosomal mosaicism in products of conception (POCs) of early miscarriages has been reported to be low. Mosaic embryos with an aneuploid inner cell mass are typically lost during the first trimester owing to spontaneous miscarriages. Most of the mosaics in established pregnancies would derive from placental mosaicism or placental aneuploidy, and mosaic embryos with aneuploid inner cell mass should be lost mainly due to first-trimester spontaneous miscarriages. The well described clinical outcomes of live births from mosaic embryos suggest a wide spectrum of phenotypes, from healthy to severely impaired. Therefore, there is a need to balance the risks of discarding a possibly viable embryo with that of transferring an embryo that may ultimately have a lower implantation potential. (Fertil Steril® 2017;107: 1107–12. ©2017 by American Society for Reproductive Medicine.)

Key Words: Mosaicism, aneuploidy, blastocyst, embryo, preimplantation genetic diagnosis

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Preimplantation genetic diagnosis for aneuploidy screening (PGD-A) was introduced in the 2000s for the purpose of improving live birth rates and became popular at some large assisted reproduction centers. But after the publication of several randomized clinical trials (RCTs), controversies were raised regarding the usefulness of PGD-A, mainly owing to technologic limitations that allowed the analysis of only a small number of chromosomes. More recently, new diagnostic technologies, such as array comparative genomic hybridization (aCGH) and next-generation sequencing (NGS), which interrogate all 46 chromosomes, have become available. Three pilot RCTs that tested trophectoderm (TE) biopsy and aCGH on patients with a good prognosis for live birth showed significant improvements in ongoing pregnancy rates and have changed the view of the PGD-A field (1–3). However, owing to the ability of the new technologies to better discriminate the copy number for each chromosome, the possibility of identifying the presence of embryonic mosaicism has also increased. It is now possible to consider the potential impact of embryo mosaicism on diagnosis accuracy and whether mosaic embryos should be used for transfer.

DEFINING, TYPING, AND DETECTING MOSAICISM

Despite originating from the same zygote, not all embryonic cells share identical chromosomal complements. Mitotic errors during embryo development can result in chromosomally distinct cell populations; these are termed mosaic embryos. Mosaicism can occur as early as the 2-cell stage, although detection at the blastocyst stage is more common because more TE cells can be simultaneously analyzed.

At the blastocyst stage, four different types of mosaic embryos have been described depending on the cell lineage affected (4). A "total mosaic" embryo is observed when aneuploid and euploid cells are found indistinctly in the inner cell mass (ICM) and TE (Fig. 1). Alternatively, the mosaic population may be confined exclusively to one of these cell populations, thus generating "ICM mosaicism" or "TE mosaicism" (Fig. 1). Finally, having all cells in the ICM being aneuploid and those of the TE being euploid (or vice versa) confers "ICM/TE mosaicism" (Fig. 1).

Many factors contribute to the difficulty in diagnosing mosaicism. For example, ICM/TE and ICM mosaicism can not be detected with the use of a TE biopsy (Fig. 1). Even in embryos with TE mosaicism, detection will vary by biopsy location according to the tissue distribution of chromosomally distinct euploid and aneuploid cells (Fig. 1). Similarly, the percentage of mosaicism in the TE cells biopsied can not be extrapolated to the whole embryo. Therefore, the information from a biopsy should be considered to be

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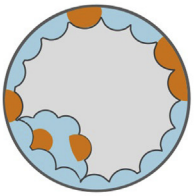
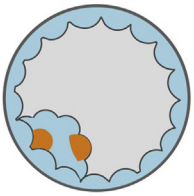
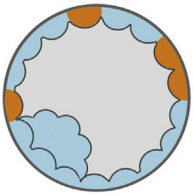
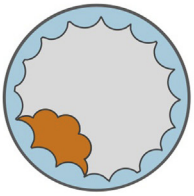
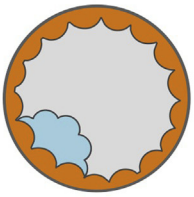
FIGURE 1

Mosaicism type	Possible TE biopsy	Diagnoses accuracy
Total Mosaic 	Euploid	Misdiagnosis
	Mosaic	Accurate
	Aneuploid	Misdiagnosis
ICM Mosaic 	Euploid	Misdiagnosis (Mosaicism never detectable)
TE Mosaic 	Euploid	Misdiagnosis
	Mosaic	Accurate
	Aneuploid	Misdiagnosis
ICM/TE Mosaic Type I 	Euploid	Misdiagnosis (Mosaicism never detectable)
ICM/TE Mosaic Type II 	Aneuploid	Misdiagnosis (Mosaicism never detectable)

Types of blastocyst mosaicism and options of trophectoderm (TE) biopsy. There are several types of blastocyst mosaicism according to the cell lineage affected. When the TE cell population includes aneuploid and euploid cells ("Total Mosaic" or "TE Mosaic"), the biopsy could include both cell lineages or just euploid or aneuploid cells. According to the biopsy location, the diagnoses will be more or less accurate. When the mosaicism is confined to the inner cell mass ("ICM Mosaic"), the TE biopsy will be always fully euploid, as the TE is, and will not represent the whole cell population in the embryo, giving a misdiagnosis. Similarly, when the ICM and TE are chromosomally distinct (ICM/TE Mosaic"), the trophectoderm biopsy will always show the contrary diagnoses, aneuploid versus euploid, to the one observed in the ICM.

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