Isn't it time to stop calling preimplantation embryos "mosaic"?

This August, the long-awaited Practice Committee opinion on the management of mosaic results from preimplantation genetic testing for aneuploidies (PGT-A) was published (1). It is an impressive body of work that will be helpful to clinicians and patients who are dealing with the difficult decision of which embryos to transfer. The opinion is overall very well balanced and carefully written. However, the authors stopped short of calling for the abandonment of the term, "mosaic" when referring to "intermediate copy number" of individual chromosomes. The latter term is more accurate, and we propose that it should be used in place of the inaccurate and, arguably, misleading term "mosaic."

According to the opinion, "Mosaicism is defined as the presence of more than one chromosomally distinct cell line in a single sample originating from one individual—for example, the peripheral blood karyotype in an individual who is mosaic for Turner syndrome, 45,X/46,XX. It is important to recognize that the diagnosis of chromosomal mosaicism in a trophectoderm biopsy is not made by direct witnessing of both euploid and aneuploid individual cells. Rather, the diagnosis is inferred from the presence of an intermediate chromosome copy number (between monosomy and disomy, or between disomy and trisomy) on a next-generation sequencing (NGS) profile. It is also important to recognize that, aside from mosaicism, other proposed explanations for intermediate copy number results include statistical variation (test artifact/'noise'), amplification bias, contamination, mitotic state, variation in embryo biopsy technique, and embryology laboratory conditions. It is unknown to what extent a mosaic trophectoderm biopsy reflects the true composition of the blastocyst and to what extent it predicts outcomes." This is well said. It is our thesis that the logical conclusion is to propose abandoning the misleading and inaccurate designation "mosaic."

When intermediate copy results were first encountered, it was not unreasonable to conclude that this was evidence of chromosomal mosaicism. Embryonic mosaicism had previously been described, and intermediate copy number observations were consistent with expectations in that setting. However, there are now many studies that have reported normal live births after the transfer of so-called mosaic embryos. For example, a series of 1,000 mosaic embryo transfers led to over 200 ongoing pregnancies (2). None of the pregnancies have been mosaic. The mosaic designation now seems not only inaccurate but potentially misleading. Should we be counseling patients about mosaic pregnancies resulting from the transfer of embryos with intermediate copy number results based on a single case report (3)?

Laboratories offering PGT are reporting mosaicism rates, which vary widely. It is possible that the measurements are real, and that mosaicism varies with embryo culture or ovarian stimulation. However, it is more likely that these differences reflect variations in laboratory techniques, biopsy methods, DNA amplification protocols, threshold settings, and/or data analysis approaches. In an ideal situation, laboratories would analyze individual cells obtained from the trophectoderm biopsy for their DNA content. The DNA from one or more chromosomes may be missing or duplicated in some cells, with normal results in other cells. This would provide stronger evidence of mosaicism within the biopsy but would arguably also introduce new artifacts associated with the decreased accuracy of single-cell analyses. Laboratories have already begun to predict the cell division origin of aneuploidy using genotyping data (4). This may provide a more rigorous method for predicting mosaicism within a biopsy. Observing an intermediate copy number with meiotic origin of aneuploidy may prevent false-positive predictions of mosaicism, while finding an intermediate copy number with mitotic origin of aneuploidy may improve the specificity of mosaicism predictions.

Even with these putative improvements in predicting mosaicism, it would still beg the question of its clinical significance. A study evaluating pregnancies after assisted reproductive technology found only 1.32% had evidence of mosaicism (5). This was not significantly different from the mosaicism rate observed after spontaneous conception (1.22%), providing early evidence that IVF is not a risk factor for mosaicism. If these data are substantiated by other studies, they may confirm that concerns about mosaicism in the preimplantation embryo are overstated.

The American Society for Reproductive Medicine has changed the terms "preimplantation genetic diagnosis (PGD)" and "preimplantation genetic screening (PGS)" to "preimplantation genetic testing (PGT)," because this designation is more accurate. We should also abandon the term "mosaic" and use a more accurate term, "intermediate copy number." Advances in any scientific field require precision, starting with precise terminology that leads us to accurate conclusions. Mosaicism is certainly one possible explanation for intermediate copy number, but there are many other possibilities. It is time to stop calling preimplantation embryos "mosaic."

Richard J. Paulson, M.D., M.S.[a,*]
Nathan R. Treff, Ph.D., H.C.L.D.[b,c]

[a] Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Keck School of Medicine, University of Southern California, Los Angeles, California; [b] Genomic Prediction, North Brunswick; and [c] Rutgers University-Robert Wood Johnson Medical School, Department of Obstetrics, Gynecology, and Reproductive Sciences, New Brunswick, New Jersey

*Reprint requests: Richard J. Paulson, M.D., M.S., Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Keck School of Medicine, University of Southern California, 2020 Zonal Ave, IRD Room 534, Los Angeles, CA 90033. (E-mail: rpaulson@med.usc.edu).

https://doi.org/10.1016/j.xfre.2020.10.009

R.J.P. has nothing to disclose. N.R.T. is a cofounder and shareholder of Genomic Prediction.

You can discuss this article with its authors and other readers at
https://www.fertstertdialog.com/posts/xfre-d-20-00235

REFERENCES

1. Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine. Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion. Fertil Steril 2020;114:246–54.
2. Viotti M, Victor A, Barne SF, Zouves C, Besser AG, Grifo JA, et al. New insights from one thousand mosaic embryo transfers: features of mosaicism dictating rates of implantation, spontaneous abortion, and neonate health. Fertil Steril 2020;114:e1–2.
3. Kahraman S, Cetinkaya M, Yuksel B, Yesil M, Pirkevi Cetinkaya C. The birth of a baby with mosaicism resulting from a known mosaic embryo transfer: a case report. Hum Reprod 2020;35:727–33.
4. Ottolini CS, Kitchen J, Xanthopoulou L, Gordon T, Summers MC, Handyside AH. Tripolar mitosis and partitioning of the genome arrests human preimplantation development in vitro. Sci Rep 2017;7:9744.
5. Huang A, Adusumalli J, Patel S, Liem J, Williams J 3rd, Pisarska MD. Prevalence of chromosomal mosaicism in pregnancies from couples with infertility. Fertil Steril 2009;91:2355–60.