Genetics inMedicine | CORRESPONDENCE

Lack of evidence to support recommendation for prenatal uniparental disomy (UPD) analysis following mosaic embryo transfer

A recent statement released by the American College of Medical Genetics and Genomics (ACMG) summarizes the clinical consequences of uniparental disomy (UPD) and provides guidance on indications for prenatal and postnatal UPD testing.[1]

In the context of preimplantation genetic testing for aneuploidy (PGT-A; previously known as preimplantation genetic screening or PGS), the ACMG states that transfer of embryos diagnosed as mosaic for certain chromosomes "should be followed by prenatal studies including UPD testing". Currently, however, there is a lack of evidence-based data to support this recommendation. While UPD discovered in the fetal or postnatal period may certainly have arisen via rescue mechanisms at the embryo stage,[1] mosaic PGT-A results are not presently known to be predictive of an increased risk for UPD in any given embryo.

It has been known for several decades that chromosomal mosaicism is prevalent in preimplantation embryos,[2] but its detection has become more common as embryo biopsy methods have shifted toward sampling the trophectoderm (TE) and next-generation sequencing (NGS) has become the primary testing platform.[3] As reports of apparently healthy newborns delivered following transfer of mosaic embryos continue to be published,[4] the analytical and clinical validity, as well as clinical utility of "mosaic" PGT-A results have come into question.[5] Embryonic mosaicism is presumed when NGS reveals an intermediate chromosomal copy number; however, other factors, including statistical variation, contamination, and artifactual "noise" can produce the same intermediate copy-number profile even in known euploid samples.[6,7] Consequently, the term "mosaic embryo" is not always an accurate representation of these results and the percentage of mosaic-result embryos that have true mosaicism in the sampled cells is currently unknown.

To date there have been no documented cases of prenatally or postnatally identified UPD involving chromosomes 6, 7, 11, 14, 15, or 20 following the transfer of an embryo diagnosed as mosaic. While UPD outcome data have undoubtedly been limited by the low number of mosaic embryo transfers involving these specific chromosomes and inconsistent pre- and postnatal follow-up (including UPD studies), it is irresponsible of the ACMG to issue a statement unequivocally recommending invasive diagnostic testing based on presumed rather than documented risk, particularly when it remains unknown whether the benefits of such testing outweigh the costs and risks.

The ACMG recommendation that transfer of embryos with mosaic aneuploidy of an imprinted chromosome be followed by prenatal UPD analysis cites Besser and Mounts.[8] As the authors of this paper, we wish to emphasize that prenatal (or postnatal) UPD testing in this context was not a recommendation set forth in this publication. Such follow-up analysis was presented as a consideration for providers and patients based on the theoretically increased risk presented by this clinical scenario. However, no recommendation regarding prenatal UPD testing was offered as there are currently no data upon which to base one.

The other two publications cited as supporting literature for this ACMG recommendation are Sachdev et al.[9] and Grati et al.[10] Similar to Besser and Mounts, the former paper simply acknowledges that an embryo reported as having a mosaic aneuploidy for an imprinted chromosome presumably carries a risk of UPD that should be addressed in counseling.

The Grati et al. study proposed a scoring system for prioritizing mosaic embryos based on prenatal data "due to the paucity of prospective studies on the actual transfer of mosaic aneuploid embryos". Retrospective cytogenetic results from products of conception and prenatal studies were analyzed to assess the risk for clinical impact (miscarriage, true fetal mosaicism, or UPD). Since the TE cells analyzed in PGT-A correspond embryologically to the cytotrophoblast that is analyzed in a chorionic villus sampling (CVS) direct preparation, the authors postulated that such data could be extrapolated to embryos. Based on their data they suggested deprioritizing for transfer embryos with a mosaic aneuploidy of an imprinted chromosome. While data from the prenatal period provide a valuable perspective, it may not necessarily be appropriate to apply to PGT-A results as it is unknown whether embryonic and fetoplacental mosaicism are intricately related or arise from distinct mechanisms.[4] Regardless, in their discussion of prenatal diagnosis recommendations following mosaic embryo transfer, the authors of this paper do not address UPD studies one way or the other.

In summary, none of the three studies cited by ACMG as supporting literature for the recommendation regarding prenatal UPD studies actually presented such a recommendation themselves, nor did they present any evidence of an increased risk for fetal UPD following transfer of an embryo diagnosed with mosaic aneuploidy of an imprinted chromosome.

We respectfully urge the ACMG to exercise caution in making clinical recommendations that are not evidence-

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based, particularly regarding procedures associated with clinical risks such as those posed by invasive prenatal diagnosis. As ACMG statements carry great weight in the medical community and have far-reaching effects on patient counseling and decision-making, we encourage the ACMG to reconsider this particular point of guidance.

DISCLOSURE

The authors declare no conflicts of interest.

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REFERENCES

1. Del Gaudio D, Shinawi M, Astbury C, et al. ACMG Laboratory Quality Assurance Committee. Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22:1133–1141.
2. Coonen E, Harper JC, Ramaekers FC, et al. Presence of chromosomal mosaicism in abnormal preimplantation embryos detected by fluorescence in situ hybridisation. Hum Genet. 1994;94:609–615.
3. Wells D. Next-generation sequencing: the dawn of a new era for preimplantation genetic diagnostics. Fertil Steril. 2014;101:1250–1251.
4. Practice Committee and Genetic Counselor 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. (in press).
5. Scott RT Jr, Galliano D. The challenge of embryonic mosaicism in preimplantation genetic screening. Fertil Steril. 2016;105:1150–1152.
6. Goodrich D, Tao X, Bohrer C, et al. A randomized and blinded comparison of qPCR and NGS-based detection of aneuploidy in a cell line mixture model of blastocyst biopsy mosaicism. J Assist Reprod Genet. 2016;33:1473–1480.
7. Capalbo A, Rienzi L. Mosaicism between trophectoderm and inner cell mass. Fertil Steril. 2017;107:1098–1106.
8. Besser AG, Mounts EL. Counselling considerations for chromosomal mosaicism detected by preimplantation genetic screening. Reprod Biomed Online. 2017;34:369–374.
9. Sachdev NM, Maxwell SM, Besser AG, Grifo JA. Diagnosis and clinical management of embryonic mosaicism. Fertil Steril. 2017;107:6–11.
10. Grati FR, Gallazzi G, Branca L, Maggi F, Simoni G, Yaron Y. An evidence-based scoring system for prioritizing mosaic aneuploid embryos following preimplantation genetic screening. Reprod Biomed Online. 2018;36:442–449.

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