Genetics inMedicine | CORRESPONDENCE

Response to Mounts and Besser

We thank Mounts and Besser[1] for their careful reading of our paper and for sharing their concerns. In "Diagnostic Testing for Uniparental Disomy: A Points to Consider Statement from the American College of Medical Genetics and Genomics (ACMG)"[2] we described a scenario in which preimplantation genetic screening/testing (PGS/PGT) detects mosaic embryos with trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20. If such embryos are transferred, the points to consider document states that this "should be followed by prenatal studies including UPD testing".

In their letter, Mounts and Besser[1] point out that to date there have been no documented cases of prenatally or postnatally identified uniparental disomy (UPD) involving chromosomes 6, 7, 11, 14, 15, or 20, following the transfer of an embryo diagnosed with mosaicism for these chromosomes. The a1uthors state that "it is irresponsible of the ACMG to issue a statement unequivocally recommending invasive diagnostic testing based on presumed rather than documented risk".

The workgroup members carefully considered the concerns of Mounts and Besser.[1] In response, we would like to make the following points:

1. This paper represents a points to consider statement, rather than a practice guideline. The main purpose of points to consider papers is to educate providers and provide assessment of emerging issues and new technologies. Points to consider documents may bring attention to important issues related to clinical practice, but do not represent guidance for practitioners on how to render clinical services.
2. The statement in the paper that "transfer of embryos with trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 should be followed by prenatal studies including UPD testing" does not "unequivocally recommend invasive diagnostic testing". Although UPD testing would require an invasive procedure, we state that such testing *may be* included. We do not state that invasive testing for UPD is mandated. However, we do believe that thorough genetic counseling and performing clinically appropriate prenatal studies (chosen on a case-by-case basis) should be conducted if a decision is made to transfer an embryo with mosaic trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20, considering the theoretically increased risk for UPD.
3. The authors highlight that 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. The authors conclude that the risk of UPD is presumed rather than documented, although they acknowledge that the UPD outcome data are limited by the low number of mosaic embryo transfers involving "de-prioritized" chromosomes. While there are at present no documented UPD cases confirming the increased risk, there is also no evidence that the risk is not increased, which justifies exercising caution and implementing close monitoring of pregnancies resulting from transfer of embryos diagnosed as mosaic for the abovementioned chromosomes.
4. The workgroup feels that the points to consider statement in the paper is aligned with the following opinions, recommendations, and guidelines in published peer-reviewed articles[3,4] and opinion[5] and position[6] statements describing PGS/PGT recommended practices:

- Besser and Mounts.[3]

"However, mosaic aneuploidies of virtually every chromosome have been documented in liveborn with a range of phenotypic effects. While known phenotypes—particularly Down syndrome, trisomies 13 and 18, syndromes involving sex chromosomes, IUGR and **UPD syndromes—must be factored into embryo transfer decisions**, it is essential to recognize that any aneuploidy can theoretically be viable in the presence of a euploid cell line".

"There are a small number of apparently healthy live births following conception with embryos diagnosed as mosaic. There is, however, a risk of live birth with persisting aneuploidy (in the full or mosaic state) or **UPD, which could result in congenital anomalies to varying degrees**. When the identified aneuploidy is associated with a known syndrome or phenotype (with particular emphasis on those involving chromosomes 13, 18, 21, X, Y), **patients should be made aware of any corresponding clinical information**, with the understanding that a mosaic full or partial aneuploidy involving any chromosome could have a poor outcome".

"If indicated, prenatal FISH, microarray and/or UPD studies may also be offered".

"Prenatal UPD studies may additionally be considered, particularly in cases involving chromosomes associated with known UPD syndromes or when one parent is a known carrier of a recessive disorder for which the gene is located on the chromosome of interest".

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- Sachdev, Maxwell, Besser, and Grifo.[4]

"When mosaicism is the result of a trisomy or monosomy rescue event, **UPD may occur**…. **It is therefore important to consider whether UPD may be a potential risk factor when contemplating transfer of a mosaic embryo".**
"Prenatal Testing after Transfer of Mosaic Embryos: **In some cases, FISH or microarrays may be indicated to detect segmental aneuploidies, and UPD studies may be considered for chromosomes that carry a known risk of UPD-related phenotypes".**

- The American College of Obstetricians and Gynecologists Committee on Genetics Opinion Statement.[5]

"Several studies have shown term delivery of euploid fetuses after mosaic embryo transfer, albeit with lower pregnancy rates. Proposed etiologies for this success include self-correction of the mosaicism or inaccuracy of the initial embryo biopsy. Given this data, some patients may choose to implant select embryos with mosaicism detected on preimplantation genetic testing-aneuploidy, after detailed consent and counseling. Referral to a specialist with genetic training and expertise should be considered, **and prenatal diagnosis with CVS or amniocentesis should be strongly encouraged".**

- PGDIS Newsletter.[6]

"In the event of considering the transfer of a mosaic blastocyst, the following options should be discussed with the patient: (i) Initiation of a further PGT-A cycle to increase the chance of identifying a euploid blastocyst for transfer; (ii) Transfer of a blastocyst with lower-level mosaicism, after appropriate counselling. **Prenatal diagnosis of the fetus and placenta of any established pregnancy after PGT is highly recommended—this especially applies after any mosaic embryo transfer".**
"The following is a guide only to assist the clinician (or a genetic counselor if available) when a mosaic embryo is being considered for transfer:…. If a decision is made to transfer embryos mosaic for a single chromosome, one can prioritize selection primarily based on the level of mosaicism and then the specific chromosome involved…. If there is a choice between the transfer of two mosaic embryos with similar levels of mosaicism, **embryos mosaic for chromosomes that are associated with potential for uniparental disomy, severe intrauterine growth retardation or liveborn syndromes may be given lower priority**".

5. The workgroup consulted prenatal genetic counselors to evaluate how our statement matched their clinical practice. Our genetic counseling colleagues described their practice as follows (personal communication):

   Patients are counseled that the magnitude of the risk for adverse outcomes with mosaic embryo transfer is currently unknown. They are strongly advised to consider prenatal genetic testing if the embryo transfer results in a pregnancy (amniocentesis preferred over CVS). Aside from a routine karyotype, additional tests should be considered depending on the embryo's specific results, including chromosome microarray (CMA) if a partial aneuploidy was present on PGT, UPD studies (especially if chromosomes 6, 7, 11, 14, or 15 are involved), and additional cell counts in an effort to detect lower-level mosaicism.

After careful consideration and based on the points discussed above, the workgroup decided not to modify the original statement published in the paper, and not to publish a correction or commentary. However, we deeply appreciate bringing this point to our attention, and fully agree with the need to exercise the highest level of caution and responsibility in writing ACMG documents.

DISCLOSURE

D.d.G. and G.R. serve as directors in clinical laboratories that perform a breadth of genetic and genomic analyses on a fee for service basis. M.S. declares no conflicts of interest.

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