Understanding the risks associated with the transfer of embryos diagnosed as mosaic following PGT-A: one perspective, there are others—a commentary on Viotti et al.

The stated objective of the manuscript by Viotti et al. (1), "to understand the clinical risks associated with the transfer of embryos classified as mosaic by preimplantation genetic testing for aneuploidy," is a very concise objective; however, when tasked with writing a commentary for this article, it was a bit more difficult to remain concise. I consider this work to be ground-breaking and very important for the health of the reproductive genetics field. I will use this commentary to point out some very important aspects of the data, but I will also bring up a few topics that were not covered, either on purpose, because of the editorial review process, or both. Lastly, I hope to convince the reader that this is the beginning of the data that can be collected toward our shared goal of better in vitro fertilization (IVF) care globally.

It is important to note that the information contained in this manuscript is truly ground-breaking and should, for the first time, give clinicians interested in this topic some very useful and important data that can be used to better inform decisions about preimplantation genetic testing for aneuploidy (PGT-A), mosaic embryos, and the transfer and follow-up of all patients. Here, the investigators had two main outcome measures: spontaneous loss rate compared with euploid embryo transfer and obstetric outcome comparisons. The investigators showed that implanted euploid embryos have a significantly lower risk of spontaneous abortion compared with mosaic embryos. They also showed no difference in obstetric outcomes between the two embryo diagnosis classes. Out of 488 babies from mosaic embryo transfers, one had overt gross abnormalities as defined by the Centers of Disease Controls and Prevention, and from 250 prenatal diagnostic tests on mosaic embryo transfers, three pregnancies exhibited PGT-A mosaicism during prenatal testing (1.2%). Overall, embryos classified as mosaic in this study have poorer outcomes when compared with embryos classified as euploid; however, most mosaic embryo transfers performed during this study seem to have been largely benign overall. This is not to diminish the difficulties of achieving pregnancy, getting to transfer during an IVF cycle, miscarriage, and others; however, this article details the clinical outcomes that clinicians should be aware of when ordering or counseling patients on tests.

Detailing what happens to mosaic embryos when transferred seems a perfectly reasonable, perhaps necessary, task associated with the clinical service of IVF cycles. However, when one digs into the topic so simply stated above, it becomes quite clear that this topic could not be covered by one manuscript or by one group of investigators who see mosaic embryo diagnosis and transfer during preimplantation genetic testing (PGT) in a concise manner. That is, at the base of the question, this group believes that a diagnosis of "mosaic" during PGT should not preclude or hinder the transfer of this embryo during some future attempt at pregnancy. In addition, this group from multiple IVF centers globally has all agreed on one set of "rules" for diagnosing, reporting, and transferring embryos diagnosed as mosaic during PGT.

Viotti et al. (1) have made some very large assumptions to arrive at the stated objective above; however, I would suggest that not all readers here would agree on all the assumptions. To start, the investigators assume, without any bias or much commentary, that testing embryos for aneuploidy during assisted reproduction (PGT-A) is a positive test for patients and is considered fairly routine; others disagree (2). This question has been debated for the last 30 years and does not need repeating here. Second, the investigators assume that aneuploidy determination should be considered a gradient across the various ploidy states. In addition, there should be "ploidy cut-offs" tied to specific percentages of mosaic vs. normal calls across any one part of the genome. In other words, these laboratories have designated three ploidy states for reporting embryos clinically: euploid (<20% of mosaic calls tolerated); mosaic (20%–80% of mosaic calls tolerated); and aneuploid (>80% of mosaic calls tolerated).

The manuscript then details a very large set of data using one way to view this question; however, other ways of viewing this topic exist across the industry, with commercial reference PGT laboratories utilizing their own "brand" of calling algorithms, masking technologies, artificial intelligence-based systems for assessing data, and others. Again, this commentary is not meant to be a review of this topic in any way, so I will not delve too much deeper here other than to suggest that the publication of data such as the Viotti et al. (1) article should open the dialog between reference PGT laboratories and their IVF laboratory customers (patients) that can help improve patient care.

There is an inherent bias in this data set, as it only really stands for this set of clinics that faithfully added their data using a predetermined set of rules governing this task. To fully understand the true nature of the clinical use of embryos diagnosed as mosaic during PGT-A testing, more laboratories and clinicians need to band together, or join this group, and collect data like this. Ideally, this would include other commercial (and noncommercial) PGT platforms, along with as much follow-up data as possible, to deepen our understanding of this hazy topic.

Here, we are to say that there is no perfect study; however, this one is quite elegant in its simplicity and the limits the investigators set ahead of time, and really should be the blueprint for how collaborative science should work today. This manuscript is a triumph of putting aside clinical, geographic, scientific, and perhaps commercial interests in the name of

data collection and education. Here, I have noted several topics that could have been covered or mentioned in the manuscript but were not; however, that does not diminish the work. My hope is that this commentary and the manuscript that follows elucidate a clear path to data collection and collaboration for the greater good of patient education and satisfaction. A note of praise should be sent to the European Society for Human Reproduction and Embryology PGT Consortium and the decades of articles published in the name of true scientific collaboration (3).

At this moment, a small group of interested souls are working with these clinicians and scientists to try and find a path to creating a shared, collaborative database detailing the clinical use of embryos diagnosed as mosaics during IVF. Please, come collaborate!

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https://doi.org/10.1016/j.fertnstert.2023.09.011

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