Is preimplantation genetic testing for aneuploidy (PGT-A) getting better? How can we know and how do we counsel our patients?

Preimplantation genetic testing for aneuploidy (PGT-A) is increasingly used in the United States as part of the practice of in vitro fertilization. Because human reproduction is associated with a high incidence of chromosomally abnormal embryos, eliminating those embryos from the cohort of blastocysts obtained during in vitro fertilization avoids the futility of transferring embryos that have no chance of implanting. Thus, acquiring the knowledge of the chromosomal content of the embryo is intuitively very appealing to patients as well as health care professionals. The problem in the past has been that the process of PGT-A (trophectoderm biopsy and subsequent DNA amplification and analysis) was exceedingly inefficient, with high loss rates of potential embryo implantations (1). The largest randomized controlled trial of PGT-A (2) was associated with an approximately 50% loss of potential implantations. (For example, a patient with 10 blastocysts underwent PGT-A, 50% of the embryos were discarded because of "aneuploidy," and the patient was left with 5 "euploid" embryos, which implanted at the same rate as untested embryos, thus giving up 50% of potential implantations.) With a 50% rate of loss of potential implantations, unless the patient had many eggs retrieved, using PGT-A necessarily translated into additional egg retrievals needed to achieve the desired number of live births. (For example, a 40-year-old patient may need, on average, to undergo 3 egg retrievals to achieve a live birth, using fresh embryo transfer of day 3 embryos. With PGT-A and a 50% loss of implantations, the same patient would have to undergo 6 retrievals to have the same chance of live birth, albeit with fewer embryo transfer procedures and a lower risk of multiple gestations.) The question is, with ongoing advances, has the efficiency of PGT-A improved?

Despite arguments to the contrary, utilization of PGT-A is unlikely to ever achieve a 0% loss rate of potential implantations. By its nature, PGT-A is a purification process that seeks to maximize the implantation rate in a cohort of mixed euploid and aneuploid blastocysts. Like all purification processes, PGT-A causes some losses of the desired implantations. No test is perfect, and false-positive results cause potentially viable embryos to be discarded. There are also losses of potential implantations, which result from the trauma of the trophectoderm biopsy, so that viable embryos that are accurately judged to be euploid, nevertheless, implant at a lower rate than they would have in the absence of having undergone the biopsy. In spite of data to the contrary (2), many believed that these losses were small and insignificant. These beliefs led to disagreements and controversy. Fortunately, it now appears that these losses are, in fact, getting smaller.

One way to estimate losses associated with PGT-A is to examine the reported aneuploidy rate associated with blastocysts derived from donor oocytes because the implantation rate of tested and untested embryos derived from donor eggs is approximately the same. This observation is mathematically convenient because it means that any benefit derived from discarding aneuploid embryos is balanced by the decrease in implantation rates caused by the PGT-A process. Therefore, the percentage of lost potential implantations should be equal to the percentage of embryos discarded because of a diagnosis of aneuploidy. (For example, a recipient may obtain 10 blastocysts from a cohort of donor eggs. If those are transferred one at a time, approximately 5 babies will be born. If PGT-A is performed and 6 of the 10 blastocysts are found to be euploid, the transfer of those euploid blastocysts will produce approximately 3 babies, representing a 40% loss of potential implantations, which is equal to the 40% aneuploidy rate.) In the past, aneuploidy rates for embryos derived from donor oocytes were reported to be as high as 40%–50%, a number consistent with the observation of high loss rates in early studies. However, more recently, donor egg aneuploidy rates appear to be lower, perhaps closer to 25% (3). Other laboratories report rates closer to 20% (Progenesis, personal communication). These numbers suggest that the loss of potential implantations caused by the PGT-A process is now reaching a new low rate of 20%–25%. The caveat is that embryos derived from donor eggs may be particularly resistant to damage from the trophectoderm biopsy. Therefore, extrapolation of these rates to the embryos of patients of advanced reproductive age with infertility may not be valid. Nevertheless, the numbers are reassuring and imply that PGT-A is, indeed, getting better.

It is interesting to note that the infertility insurance company, Progyny, includes PGT-A as part of their fertility plan (4). Because cost-effectiveness is a key element of insurance coverage, this decision on the part of Progyny would seem to imply that PGT-A should be cost effective. The caveat is that this does not mean that the attainment of a successful pregnancy after PGT-A is associated with a lower cost of fertility treatment. The cost of the PGT-A process is not insignificant, and if additional egg retrievals are needed, those will also add to the overall cost. However, the cost of fertility treatment does not represent the big picture. In many cases, the most expensive part of the attainment of a live birth is not the fertility care but, rather, the cost of the subsequent obstetric care, especially in the case of multiple gestations. The latter cost is almost always borne by medical insurance. If PGT-A leads to a higher utilization of single embryo transfer, the resulting reduction in multiple gestations greatly reduces the overall cost of achieving a live birth, thus saving the overall cost to the healthcare system. In contrast, patients whose insurance pays for obstetric care but not for fertility care may well conclude that the least expensive method of achieving an ongoing pregnancy is the fresh transfer of multiple day 3 embryos. The problem with that strategy is that it results in high rates of twins and risks higher-order multiple gestations.

The other element in deciphering losses associated with PGT-A is the rate of so-called "mosaicism," which represents intermediate copy numbers of individual chromosomes, and which confounds the interpretation of euploidy during

PGT-A. Previous reports suggested that intermediate copy number rates were as high as 30% with average rates of approximately 15% (5). Furthermore, when PGT-A was first implemented, embryos with intermediate copy numbers were not transferred because of concerns about mosaicism in the conceptus. These concerns have been greatly mitigated by clinical experience. More importantly, rates of "mosaicism" are now reported to be <5% (Progenesis, personal communication). This drastic change has been attributed to changes in PGT platforms as well as adjustments in bioinformatics in the PGT laboratory. "Mosaicism" may perhaps best be considered "noise" in the analysis of the DNA content of the trophectoderm biopsy. Nevertheless, the decrease in reported rates has been very clinically significant to our patients and to the clinicians who struggle to explain how "mosaic" embryos produce healthy infants, even if, in the past, they were considered abnormal.

What is the bottom line? It seems reasonable to conclude that PGT-A is getting better. It also seems prudent to monitor two parameters resulting from PGT-A: the egg donor aneuploidy rate, which estimates the loss rate of potential implantations, and the reported rate of intermediate copy number ("mosaicism"), which is a measure of the "noise" in PGT-A. It seems likely that the PGT-A process will continue to improve and that loss rates will decrease further. In the meantime, it is reasonable to tell patients that our best estimate is that PGT-A is associated with a loss of potential implantations of approximately 20%–25%. This number needs to be balanced against the potential benefits of PGT-A: higher implantation rates in older patients; psychological benefits of knowing the chromosomal complement of the embryo; and greater efficiency of single embryo transfer. Because each clinical case is different, we owe our patients the best possible information to allow them to decide whether the information obtained from PGT-A is, or is not, worth the cost in their individual situation.

Richard J. Paulson, M.D., M.S.
USC-HRC Fertility, Keck School of Medicine, University of Southern California, Los Angeles, California

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