Preimplantation genetic testing for aneuploidy: the conundrum with aneuploid embryo transfers

Aneuploidy is the principal genetic factor causing reproductive failure during both natural and in vitro fertilization (IVF) cycles. Meiotically derived chromosome malsegregation errors arising during gametogenesis are present in all of the cells of an embryo. Most meiotic abnormalities are lethal, but certain trisomies affecting smaller chromosomes, such as 13, 18, and 21, as well as sex chromosome abnormalities, such as monosomy X, XXY, or XYY, can become live births. Postfertilization chromosome malsegregation results in a phenomenon known as mosaicism. Mosaic chromosome abnormalities are present in only parts of the affected embryo, and their impact on its viability remains unclear. The identification and preferential transfer of euploid embryos has been hypothesized to lead to an improvement of clinical outcomes for couples undergoing IVF treatment. This hypothesis has evolved into the clinical test known as preimplantation genetic testing for aneuploidy (PGT-A). PGT-A has become increasingly popular in the past few years, with ~40% of all in vitro fertilization (IVF) cycles in the U.S. including it (1).

The main method that is currently used during PGT-A is next-generation sequencing (NGS). The high throughput capability of NGS has led to a reduction in the costs associated with PGT-A. Moreover, the nature of NGS makes it capable of identifying mitotic chromosome abnormalities causing mosaicism in a trophectoderm (TE) sample, in addition to the meiotic ones. The ability of NGS to detect mosaic aneuploidy in TE samples, combined with the fact that not much is known concerning the viability of mosaic embryos, has caused a great deal of uncertainty about how to best clinically manage such embryos when they are identified in an IVF PGT-A cycle.

McGowan et al. (1) sought to obtain a better understanding on the policies and opinions of a diverse group of IVF practitioners regarding the transfer of aneuploid embryos (aET). They prepared two different survey questionnaires that were sent out to laboratory directors belonging to the Society for Assisted Reproductive Technology (SART) and to other SART members. Laboratory directors were asked seven questions on the presence or absence of policies on their clinic's aETs, whereas other SART members were presented with a 32-question survey. This survey consisted of seven clinical scenarios of a couple with a single abnormal embryo after PGT-A, who were unable to have another cycle and were seeking guidance. There were several possible abnormalities scored in this embryo, including trisomy 21, trisomy 18, monosomy X, multiple complex aneuploidies, trisomy 2, trisomy 15, and monosomy 4. These abnormalities were selected based on guidelines published by the International Society of Preimplantation Genetic Diagnosis (PGDIS) in 2016.

McGowan et al.'s (1) effort in preparing and sending off these surveys is not only commendable, but also necessary, considering the controversy surrounding PGT-A owing to issues related to the detection of mosaicism and the aET. Unfortunately, of the 324 laboratory directors approached, only a very small minority (n = 48; 14.8%) responded. Similarly, 2,393 other SART members received the second questionnaire but very few (n = 212; 8.9%) completed it. This very low participation risks causing bias regarding this study's results and conclusions, which may therefore fail to provide an accurate insight in the clinical management of fully aneuploid or mosaic embryos. In addition, these surveys were only available to US clinics, meaning that the policies and opinions described by McGowan et al. (1) may not be representative of the situation in Europe nor the rest of the world.

Responses from both surveys demonstrated a lack of common policy and practice associated with aETs. Some of the participating clinics had written or verbal policies on aETs, whereas the opinion of SART members on how to manage aneuploid embryos was influenced by their role, namely, whether they were directly involved with patients. Unsurprisingly, the greatest lack of consensus observed in the answers to the 32-question survey was mostly associated with the identification of mosaic diploid aneuploid embryos in an IVF PGT-A cycle. Mosaic diploid aneuploid embryos consist of a combination of normal and aneuploid cells, and this can be determined during NGS analysis of TE samples biopsied from such embryos. Several investigations have been published recently, describing the viability and implantation ability of mosaic diploid aneuploid embryos (2–4). All those studies demonstrated that mosaic embryos, if selected for transfer, are associated with significantly lower implantation and pregnancy rates, as well as higher spontaneous miscarriage rates, compared with completely euploid embryos. However, ongoing pregnancies and live births have been reported after mosaic embryo transfers, and karyotyping of the resulting children has to date identified only one case with a mosaic chromosome constitution and with no apparent phenotypic impact (4). Despite these results and the fact that PGDIS has recently published more detailed guidelines (5) on how to clinically manage mosaic embryos, the responses to McGowan et al.'s questionnaires suggest that IVF practitioners generally hesitate to consider such embryos for transfer. Instead, some clinics advise their patients to freeze mosaic embryos until more data on their viability become available. Data from the answers regarding specific chromosome abnormalities demonstrated that >40% of the survey's respondents were willing to consider the transfer of an embryo with a trisomy 21 or monosomy X but not a trisomy 18. The questionnaire did not include any other sex chromosome abnormalities, such as XXY or XYY, to assess whether such an embryo would be deemed eligible for transfer. Thus, the attitudes toward aET were influenced also by the type of aneuploidy present in an embryo.

McGowan et al.'s (1) surveys and their responses emphasize the urgent need for evidence-based clear guidelines regarding aET policies following PGT-A. One way of establishing such guidelines would be through data obtained in prospective blinded nonselection studies and well designed and methodologically appropriate multicenter randomized

controlled trials. A genetic counselor trained specifically to advise patients during PGT-A should be an integral part of the process. The primary purpose of PGT-A is to identify and exclude from transfer those embryos that carry meiotically derived aneuploidies that have very low or no implantation potential. However, the detection of mosaic in addition to meiotic aneuploidies during PGT-A has created a major conundrum for IVF practitioners.

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