Newsletter 2025 – June

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PGT-M to eliminate pathogenic mutations. Is PGT-A beneficial?

There is little controversy that eliminating the transmission of deleterious genetic mutations to future generations is not only ethical but also highly desirable. Nonetheless, potential parents who harbor cancer associated mutations are often hesitant to start a family for fear of passing on these mutations. Additionally, some patients are also concerned about undergoing IVF and subjecting an embryo to the stress and risk of biopsy and cryopreservation. However, when informed about the benefits of the procedure and testing, they soon appreciate that these minimal risks pale in comparison to the physical toll and psychological trauma associated with harboring one of these mutations.

Testing embryos for a dominant, disease-causing mutation carried by one of the parents is very different from testing for random aneuploidies that may occur in an embryo. Aneuploidy, a consequence of abnormal chromosome segregation can occur during meiotic maturation of the oocyte or sperm or post-fertilization from a mitotic error. Meiotic errors are uniformly present in all cells of the developing embryo while abnormal chromosome segregation after fertilization results in mosaicism characterized by a mixture of both normal and abnormal cells. Since PGT-A testing relies on analysis of a small sample of trophectoderm cells of the developing blastocyst, biopsied cells may not be representative of the whole embryo resulting in inaccurate interpretations of embryo viability.

Selecting an embryo for transfer has traditionally relied on morphologic assessments of embryo development to identify the embryo most likely to implant. Recent advances in embryo culture and continuous photographic evaluation of embryo developmental hallmarks have led to only modest gains in determining embryo viability and improving implantation rates. Although Pre-implantation Genetic Testing for Aneuploidy (PGT-A) has been proposed as another embryo assessment technique reflecting embryo viability, the utility of PGT-A has engendered much controversy, and the results of several trials have not been conclusive. In a large randomized controlled trial, PGT-A for younger patients (less than 35 years of age) did not improve implantation rates per embryo transferred nor lower the rate of miscarriages when comparing outcomes in women where untested morphologically similar embryos were transferred. (Munne et al., 2019)

In the above-mentioned study, 984 good prognosis patients (up to age 40) were randomized and only included if they had at least 2 good quality blastocysts. This left only 661 patients in the final analysis as 13.7% (70/510) patients <35 years of age and 20.5% (97/474) of patients 35–40 years of age did not have at least 2 good-quality blastocysts. Additionally, 67 patients

in the PGT-A arm were excluded because they did not have normal embryos available for transfer whereas, in another 6 patients the embryo did not survive the thaw. Mosaicism was present in about 16.5% of all embryos irrespective of patient age and in this study, mosaic embryos were not considered for transfer.

The conclusion of this study was that younger patients were potentially harmed by having their embryos tested. The ongoing pregnancy rate was lower in the PGT-A group (42.5%) compared with the control group (50.3%). In the older group (35-40 years old) the ongoing pregnancy rates were not statistically different between the 2 groups when all patients who started a cycle were included: 41.1% and 35.7% for the PGT-A and control groups, respectively. Additionally, miscarriage rates were similar between the 2 groups, even in this older population at 8.2% and 11% for tested and untested embryos respectively. It is important to note that these “rates” only include outcomes from the first “best” embryo transfer and do not include any remaining embryos.

When we account for the number of zygotes lost because they fail to reach the blastocyst stage (Orvietto et al., 2025) or are discarded because of presumed aneuploidy, the cumulative pregnancy rate from a single batch of non-renewable oocytes or embryos is not improved when compared to transfer of untested embryos. This is exactly what was shown in a trial by Yan et al., 2021 where 1,212 patients ages 20–37 were randomized if they had at least 3 blastocysts. Cumulative live birth rates within the first year or until no embryos remained were analyzed between patients who underwent preimplantation genetic screening (606 patients; 468 total live births; 77.2% per patient) and those who did not have their embryos biopsied (606 patients; 496 total live births; 81.8% per patient). As expected from the prior study, the number of babies born was greater in the untested group without a clinically significant increase in the miscarriage rate: 12.6% for untested embryos versus 8.7% for tested embryos. While older patients may experience some benefit in terms of lower miscarriage rates, it potentially comes at the cost of reducing the chances of having a child with their own gametes.

While many of our patients seek our assistance prior to receiving gonadotoxic treatments following a diagnosis of cancer, others may have frozen their oocytes or embryos previously. Patients post gonadotoxic treatments will have diminished ovarian reserve and their cryopreserved gametes represent a non-renewable resource that should be utilized judiciously. Based on the above data regarding the potential pitfalls of PGT-A, counseling patients to avoid PGT-A analysis when undergoing PGT-M, especially in patients who froze their gametes under 35 years of age is critical. While available data has demonstrated increased implantation rates for PGT-A tested embryos in patients older than 35 years of age, cumulative live birth rates are similar. As attested by the above-mentioned studies, PGT-A due to the limited sampling of the trophectoderm cells may in fact result in discarding

embryos that have some possibility to be viable. (Scott et al., 2012) In other words, the true test of embryo viability is implantation and development of the transferred embryo. Discarding an embryo based on the results of a small sample of trophectoderm cells carries with it the risk of not using potentially viable embryos.

PGT-A also adds significant cost to the cycle in 2 ways. The laboratory charges for the additional analysis and additional stimulation cycles to create more embryos if a potentially viable embryo were discarded. All cryopreserved gametes should be treated according to the age of the patient when they were cryopreserved. Embryo biopsy for PGT-M is beneficial and should be performed to remove the deleterious mutation from future generations. For patients who cryopreserved oocytes prior to age 35, the addition of aneuploidy screening may not be beneficial and the limitations of this testing as well as any potential benefits should be discussed. In patients who cryopreserved oocytes older than 35 years of age, PGT-A in addition to PGT-M improves the implantation rate for each transferred embryo but may come at the cost of lower cumulative live birth rate from a given cohort of warmed oocytes. This potential risk of PGT-A is minimized if the patient is able to undergo additional cycles of stimulation to create more embryos in the future.

Conclusion

Available evidence does not support the use of PGT-A to increase the probability of a live birth. And common sense predicts this result and the only absolute guarantee we can tell our patients is this: A discarded embryo will never result in a pregnancy.

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