PGT-A Testing in IVF

Abstract

Preimplantation Genetic Testing for Aneuploidy (PGT-A) is an elective add-on in the IVF process that screens embryos for aneuploidy before they are transferred. It is performed with the hope that reducing the use of aneuploid embryos will also reduce miscarriage risk. However, there is insufficient evidence to recommend its routine use to all infertile patients, as studies on its outcomes provide inconsistent results. This review of the literature will discuss the existing research and how addressing gaps in that research could provide meaningful information to guide provider and patient decisions.

Key words

In Vitro Fertilization, PGT-A, Mosaicism, Aneuploidy, Advanced Maternal Age, Recurrent Pregnancy Loss

Introduction

In Vitro Fertilization (IVF) is a type of assisted reproductive technology that combines egg and sperm outside of the body to create an embryo. The embryo is then transferred into the uterus which, if it implants in the uterine lining, can result in a pregnancy. Patients undergo the IVF process for many reasons, such as infertility or subfertility, including fertility that has been impacted by illness or chemotherapy, a history of miscarriage, age, to use frozen and/or donor

eggs or sperm, LGBTQ+ family building and to avoid passing genetic issues on to children. The IVF process and procedures differ between patients and can be tailored to their individual needs and challenges. Patients may be counseled on "add-on" options to include in their treatment that are recommended, but ultimately elective.

One such "add-on" is Preimplantation Genetic Testing for Aneuploidy, or PGT-A testing, which biopsies the newly formed embryo *before* it is transferred into the uterus to check for chromosomal abnormalities known as aneuploidy. Chromosomal abnormalities are considered to be the most common cause of miscarriage, accounting for an estimated 50-70% of pregnancy losses. These abnormalities can originate in a parent cell or randomly in the embryo itself, even if the parent cells are normal[1]. If an embryo does not have viable genetic material, it may not progress into a viable pregnancy, as few chromosomal abnormalities survive to birth[2]. Miscarriages are also fairly common - an estimated 10-15% of clinically recognized pregnancies end in miscarriage[2], and that number is likely closer to 26% when considering very early pregnancies that are lost before the person even knows they are pregnant[3]. Given these rates, it is

logical to wonder whether minimizing the use of aneuploid embryos through PGT-A testing would reduce an IVF patient's risk of miscarriage.

There are many metrics of interest to research while comparing euploid versus aneuploid embryos including rates of implantation, clinical pregnancy, miscarriage and pregnancy progression. However, the research is either lacking, inconclusive or contradictory when it comes to the ultimate success metric and desired patient outcome - a live birth.

History

Genetic screening of embryos during the IVF process has only been practiced for about thirty years, and has rapidly evolved over recent decades[2]. The technology used today has advanced quickly over time - it is less invasive, more comprehensive with the ability to examine all chromosomes,[4] and there are higher quality lab conditions to support embryo culture and cryopreservation[2]. We could even be approaching another shift forward right now. Scientists are developing technology to examine the genetic material of embryos using the exRNA they secrete into culture medium, potentially gleaning genetic information about embryos without ever biopsying them[5]. However, despite such significant strides in aneuploidy screening, there are still concerns about accuracy and impact on ultimate outcomes. The American College of Obstetricians and Gynecologists, which produces guidelines for providers, has stated there is insufficient evidence to recommend the test to all infertile patients[6].

Other Tools

PGT-A is not the only tool that analyzes embryo quality. Morphology analysis of embryos is routinely used in IVF to select the best quality embryo available to support single-embryo transfer, which carries fewer risks than a pregnancy of multiples[7]. However, high aneuploidy has been found even in good-morphology embryos,[2] underscoring a preference to supplement morphology results with PGT-A.

Randomized Clinical Trials

Earlier studies tended to show higher success rates in good-prognosis IVF patients who used PGT-A screening, or the equivalent chromosomal testing at the time, than those who did not [8, 9, 10]. More recently, however, a large randomized clinical trial study published in 2021 yielded different results that called previous assumptions and knowledge into question[13]. Table 1 shows the results of six studies that compared patients who transferred a PGT-A-tested embryo with those who transferred an embryo analyzed by morphology alone.

Study	**Year**	**# PGT-A**	**# Control**	**% Live Birth with PGT-A**	**% Live Birth Control**	**Results** (Higher, lower or equal birth rate in PGT-A group)
Yang et al[8]	2012	55	48	Not specified*	Not specified	Higher**
Scott et al[9]	2013	72	83	84.7	67.5	Higher
Rubio et al[10]	2017	100	105	44	24	Higher
Verpoest et al[11]	2018	205	191	24	24	Equal
Munné et al[12]	2019	274	313	50	46	Approx. equal (study did not consider this a significant difference)
Yan et al[13]	2021	606	606	72.2	81.8	Lower

Table 1. Results of outcomes using PGT-A tested embryos versus morphology only

* Study marked success as ongoing pregnancy reaching at least 20 weeks gestation. It did not specify whether all those who reached 20 weeks gestation also had a live birth

** 20 weeks gestation rates were higher in PGT-A group

The inconsistency in outcomes leaves the field with uncertainty about whether to recommend the test and to whom. Therefore, population characteristics are critical in study design. Table 2 shows the same studies' inclusion and exclusion criteria. IVF patients can have complex fertility histories and diagnoses, and the studies tend to include only good-prognosis patients. In fact, inclusion criteria can inherently select for good prognosis patients[12], excluding patients with some of the conditions for which PGT-A testing is currently offered, such as recurrent miscarriage.

Study	PGT-A Outcome	Age	Inclusion Criteria	Exclusion Criteria
Yang et al[8]	Higher	< 35	Good prognosis	**Prior miscarriage**, abnormal karyotype
Scott et al[9]	Higher	21 - 42	Normal endometrial cavity, FSH equal less than 15 iu/L, basal follicle count 8	No more than 1 previous failed IVF cycle
Rubio et al[10]	Higher	38 - 41	AMA* only	Endocrine/systemic pathologies, previous PGD, **previous miscarriage due to chromosomal abnormality**
Verpoest et al[11]	Equal	36 - 40	AMA only	3 or more previous unsuccessful IVF or ICSI cycles, **3 or more clinical miscarriages,** poor response, low ovarian reserve
Munné et al[12]	Equal	25 - 40	Good prognosis	Diminished ovarian reserve, **one or more previous miscarriage**, more than 2 previous IVF failures
Yan et al[13]	Lower	20 - 37	Good prognosis	Known uterine abnormality, the presence of a contraindication to pregnancy, a plan to undergo other preimplantation genetic testing

Table 2. Patient characteristics in studies

* Advanced maternal age, defined as ≥ 35

Two compelling criteria featured in Table 2 are age and miscarriage history. In women, fertility declines with age, and rates of aneuploidy in maternal oocytes rise with age[2]. In the two studies that included only women of advanced maternal age (Rubio et al and Verpoest et al), the PGT-A group had more or equal live births compared to the control (Table 2). And even though the Munné et al study showed approximately equal births in the PGT-A group, the only women who *did* have live births after PGT-A were 35-40. This difference among the patient results has led to the postulation that perhaps PGT-A is not suitable or necessary for the general population, but for

only certain patients, namely those with AMA.

Another diagnosis to examine more closely is recurrent pregnancy loss, or RPL, which is defined by ACOG as two or more miscarriages[14]. While there are *some* documented and treatable causes of RPL, 50-75% of cases go "unexplained" as idiopathic, and are attributed to randomness or the common incidence of aneuploidy[15]. Since those unexplained RPL cases are most likely due to aneuploidy, using PGT-A could logically lead to better outcomes in those patients, or at least provide more information about their fertility. However, RPL patients were excluded from most of the studies mentioned (Table 2).

While most of the described studies provide valuable information about the good prognosis patients in a general population, we are unable to glean information about the fate of a screened versus unscreened embryo in other, targeted subsets of the IVF population, like RPL patients, and whether they would result in a live birth[16].

What is the Risk?

Though PGT-A is an elective IVF add-on, it is not without risk. As seen in the Tables above, evidence is unclear on whether it improves outcomes, and there is concern that it could harm outcomes in certain cases. PGT-A cannot be discussed without considering embryo mosaicism. The purpose of PGT-A is to eliminate aneuploid embryos and use the remaining euploid embryos. However, the test is not a *perfect* predictor of embryo viability. Some embryos are

mosaic, meaning at the time of biopsy they have a combination of normal and abnormal cells. There is a small risk (1.5%) of misdiagnosis, where the cells biopsied do not reflect the overall health of the embryo, giving a false positive or false negative result. Even if abnormal cells are present, they may self-correct during blastocyst development, and an estimated 30-47% of mosaic embryos do go on to result in normal live births [13]. In fact, mosaic embryos are sometimes chosen for transfer when no euploid embryos are available even though they are less likely to implant and progress to viability than euploid embryos. But when prioritizing euploid embryos after PGT-A screening, mosaic embryos could be discarded along with aneuploid embryos, possibly lowering a patient's number of available embryos and chances of pregnancy, even if those chances are considered small. So, more research is needed not only for PGT-A testing, but for its results. It is uncertain whether the binary results provided by PGT-A (normal or abnormal, euploid or aneuploid) are sufficient for categorizing embryos for transfer use, and whether it is limiting patient outcomes by discarding viable embryos.

Another major reason why PGT-A testing should be recommended as accurately as possible is financial cost. The screening costs can range from $1,800 to $6,000, and are usually not covered by insurance. Most states do not require insurance companies to cover the IVF process at all, either, and the average cost of a cycle is $15,000-$30,000[17]. There can be significant financial burden associated with IVF, so patients should be counseled in making the best decisions for their particular case. This is simply hard to do without strong evidence, especially when patients may be willing to try anything, add anything, and pay anything for a chance at a better outcome.

Summary

PGT-A testing is a technology used to optimize embryo selection in an IVF cycle under the assumption that transferring chromosomally euploid embryos will lead to better birth outcomes than aneuploid embryos. However, there is not currently sufficient evidence to determine who the technology benefits and who it does not. There is concern about recommending the test to the general population due to risks of mosaicism and financial cost. More information is needed about IVF population subsets to target patients who can benefit from PGT-A testing.

Conclusion

It is currently unclear to whom PGT-A testing should be recommended as an IVF treatment add-on. There is still a need to develop appropriate studies that prioritize including more types of patients. This is particularly true for RPL patients who, according to current knowledge, may be impacted by aneuploidy at very significant rates. The exclusion of RPL patients from most trials leaves a gap in information that, if studied, could provide meaningful insight into the subset. And finally, especially when evidence is still in progress, patient counseling and education is critical, especially if their unique needs, diagnoses and fertility histories are not yet represented in available literature.

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