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Transfer of embryos with positive results following preimplantation genetic testing for monogenic disorders (PGT-M): experience of two high-volume fertility clinics

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Abstract

Purpose To assess the experiences of two large fertility clinics in which embryos with positive results following preimplantation genetic testing for monogenic disorders (PGT-M) were transferred upon patient request, in order to explore the nature of the conditions for which these requests have been made and review ethical considerations.

Methods Retrospective review of previous embryo transfers at the NYU Langone Fertility Center and ORM Fertility was performed. Embryo transfers prior to May 2019 in which embryo biopsy and PGT-M occurred were reviewed, and transferred embryos that were positive for a monogenic disorder (excluding autosomal recessive carriers) were identified.

Results Seventeen patients were identified who elected to transfer 23 embryos that tested positive for nine different monogenic disorders. Most of the embryos transferred were positive for disorders that are autosomal dominant (15/23), are adult-onset (14/23), are associated with reduced penetrance (16/23), and have available management to lessen symptom severity (22/23). Transfer of positive embryos most commonly occurred for hereditary cancer susceptibility syndromes (9/23 embryos), particularly hereditary breast and ovarian cancer syndrome.

Conclusions When unaffected embryos are not produced following in vitro fertilization with PGT-M, some patients request to transfer embryos with positive test results. The majority of transfers were for embryos positive for adult-onset, reduced penetrance diseases. As these requests will likely increase over time, it is essential to consider the practical and ethical implications.

Keywords Preimplantation genetic testing for monogenic disorders (PGT-M) · Embryo biopsy · Embryo transfer · Genetic counseling · Reproductive ethics

Introduction

Monogenic or Mendelian disorders are conditions in which the primary cause can be attributed to a single defined genetic variant. There are approximately 10,000 known monogenic disorders, and while many are individually rare, the collective global prevalence of all monogenic disorders at birth is approximately 1% [1] and they account for almost 20% of pediatric mortality [2]. These conditions generally follow three distinct inheritance patterns: autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL). Individuals or couples who are at increased risk to have a child with a monogenic condition, either due to one partner being affected with an AD disorder, due to both partners being carriers of an AR disorder, or due to a female being a carrier of an XL disorder, may choose to pursue certain reproductive options to mitigate this risk. Prenatal diagnosis can determine the genetic status of a developing pregnancy; however, patients who learn that the pregnancy is affected often face the difficult decision surrounding pregnancy termination. Therefore, those patients who wish to prevent the conception of a pregnancy with an inherited disease may opt for preimplantation genetic testing (PGT). PGT for monogenic disorders (PGT-M), which involves biopsies of embryos created through in vitro fertilization (IVF), is generally available for any monogenic condition in which the causative variant is known. The purpose of PGT-M is to select against embryos that inherit a monogenic

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disease for which an individual or couple is at increased reproductive risk, in order to reduce the chance of an affected pregnancy.

Over the past two decades, there has been rapid growth in uptake of PGT-M [3], exceeding the growth of prenatal diagnosis [4]. As genetic technologies continue to improve and costs continue to drop, genetic testing is becoming more commonplace in a variety of settings—particularly in the fertility clinic—leading to more patients being identified as candidates for PGT-M. Although its initial applications were largely intended to select against embryos with severe, life-threatening disorders that onset in childhood, use of the technology has now expanded to include milder and later onset conditions of greater clinical variability [5]. By 2006, one study found that 28% of PGT-M cycles in the USA were performed for an adult-onset disorder [6]. Given the increased use of PGT-M for this indication, the ASRM issued a statement in 2013 (updated in 2018) [7], in which the Practice Committee deemed PGT-M for adult-onset conditions to be "ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome." The Committee also determined that "for conditions that are less serious or of lower penetrance, PGT-M for adult onset conditions is ethically acceptable as a matter of reproductive liberty."

Given the often significant attrition from retrieved oocytes to testable embryos, combined with the reproductive risks associated with inherited disorders, some IVF/PGT-M cycles do not produce any embryos that are identified as unaffected (i.e., not at risk) for the condition tested. In particular, as PGT-A (aneuploidy screening) is more frequently incorporated into IVF cycles, the chance of finding an unaffected euploid embryo can be low, especially in women of advanced age and in couples with infertility diagnoses that may affect embryo yield [8]. In some cases, patients may find themselves in a situation where the only euploid embryos available are positive for the monogenic condition. If producing additional embryos is not possible (for example, due to exhausted financial or emotional resources or diminishing fertility potential), these euploid embryos may be their only opportunity for a genetically related child.

In 2017, the ASRM Ethics Committee issued a statement addressing the transfer of embryos detected to have "genetic anomalies" by PGT [9]. The Committee determined that it is ethically acceptable for an IVF provider to assist or decline to assist with transferring embryos that test positive for a genetic condition following PGT-M, and only discouraged this practice for circumstances in which a child is "highly likely to be born with a life-threatening condition that causes severe and early debility with no possibility of reasonable function."

As testing indications are expanding to include later onset, reduced penetrance, and milder conditions, transfer of embryos with positive genetic results has become a more commonly utilized option in the absence of unaffected embryos. The purpose of this study was to assess the experiences of two large fertility clinics in which patients have requested to transfer embryos that tested positive (i.e., affected or at significant risk for symptoms) following PGT-M, and to explore the nature of the conditions for which these requests have been made.

Materials and methods

Retrospective review of previous embryo transfers at the NYU Langone Fertility Center and ORM Fertility was performed. Fresh and frozen embryo transfers prior to May 2019 in which embryo biopsy (either blastomere or trophectoderm) and PGT-M occurred were reviewed, and transferred embryos that tested positive for a monogenic disorder were identified.

"Positive" PGT-M results included embryos that inherited an AD variant, two AR variants, or an XL genetic variant, including female embryos identified to carry an XL disorder in which carriers have a significant chance of developing symptoms. Embryos that were identified as carriers of AR disorders were excluded, as these carriers are typically asymptomatic.

In all cases, requests to transfer such embryos had been approved by the patient's physician and/or genetic counselor, and written consent was obtained.

Results

Seventeen patients who elected to transfer 23 embryos that tested positive for nine different monogenic disorders were identified (Table 1). All cases identified were frozen embryo transfer cycles; there were no fresh transfers of positive embryos performed. No cases were identified in which a patient requested the transfer of an embryo with a positive PGT-M result but was denied by the physician.

Inheritance

Five out of the nine conditions (15/23 embryos) identified are inherited in an AD manner, and in all of those cases, one parent was positive for the condition.

One condition, 21-hydroxylase-deficient congenital adrenal hyperplasia (21-OHD CAH; non-classic type) is inherited in an AR manner (2/23 embryos). In this case, the female partner was an unaffected carrier, while the male partner was affected (compound heterozygote).

The remaining three conditions (6/23 embryos) identified are inherited in an XL manner. One transfer involved a male embryo affected with Alport syndrome, while the others involved transfers of female carriers of Alport syndrome, Fragile X syndrome, and Danon storage disease, all of which are associated with a risk of symptoms among female carriers.

Table 1 Transfers performed of embryos with positive test results following preimplantation genetic testing for monogenic disorders (PGT-M)

Inheritance	Condition	Gene (embryo sex if applicable)	Type of disorder	Age of onset	Penetrance	Disease management	Patients electing embryo transfer (n)	Embryos transferred (n)
AD	Hereditary breast and ovarian cancer syndrome	*BRCA1* (male)	Cancer susceptibility	Adulthood	Reduced	Risk-reducing surgical intervention, medication, screening	4	6
		BRCA2 (male)					1	2
	Lynch syndrome	*MSH2* (female)	Cancer susceptibility	Adulthood	Reduced	Risk-reducing surgical intervention, screening	1	1
	Hereditary multiple osteochondromas	*EXT2* (2 male, 1 female)	Skeletal	Childhood	Full	Surgical intervention	3	4
	Huntington's disease	*HTT*	Neurologic	Adulthood	Full	Supportive	1	1
	Autosomal dominant polycystic kidney disease	*PKD2*	Renal	Adulthood	Full	Screening, medication, surgical intervention	1	1
AR	21-Hydroxylase deficient congenital adrenal hyperplasia	*CYP21A2* NC/NC variants (female)	Endocrine	Variable	Reduced	Medication	1[a]	1
		CYP21A2 NC/C variants (male)						1
XL	Alport syndrome	*COL4A5* affected (male)	Renal, audiological	Childhood	Full	Screening, medication, surgical intervention	1	1
		COL4A5 carrier (female)		Adulthood[b]	Reduced[b]		1	1
	Fragile X	*FMR1* carrier (female)	Endocrine, neurologic[b]	Adulthood[b]	Reduced[b]	Reproductive alternatives, medication	2[c]	2
	Danon storage disease	*LAMP2* carrier (female)	Cardiovascular, muscular	Variable[b]	Reduced[b]	Screening, medication	1	1
							Total = 17	Total = 23

[a] Double embryo transfer. The female embryo had two non-classic (NC) variants, which is expected to result in a NC congenital adrenal hyperplasia (CAH) phenotype. The male embryo had one NC variant and one classic (C) variant, which is expected to result in a NC-CAH phenotype > 97% of the time, and a C-CAH phenotype < 3% of the time [10].

[b] These characteristics apply to female carriers of the condition only

[c] One embryo had a premutation size of 62 repeats, and the other had a premutation size of 95 repeats

Types of disorders

Six disease categories (based on primary manifestations) are represented among positive embryos transferred: hereditary cancer susceptibility, renal (with or without audiological involvement), skeletal, neurologic, endocrine, and cardiovascular/muscular. The most common disease category in which positive embryo transfer occurred was hereditary cancer susceptibility (9/23 embryos), the majority of which (8/9 embryos) was hereditary breast and ovarian cancer (HBOC) syndrome. All of the transferred embryos with HBOC in this cohort were male.

Age of onset

Six monogenic disorders represented (14/23 embryos) are adult-onset and two disorders (5/23 embryos) are associated with the onset of symptoms in childhood (note that XL Alport syndrome is included in both categories, as it is adult-onset in carrier females and childhood-onset in affected males). Two disorders are associated with variable onset.

Penetrance

Six conditions (16/23 embryos) are associated with reduced penetrance (including XL Alport syndrome in carrier females), while four conditions (7/23 embryos) are generally believed to have full penetrance (including XL Alport syndrome in males).

Disease management

Eight out of nine conditions (22/23 embryos) have available management or treatment to lessen the burden or severity of symptoms, while management for one condition (Huntington's disease) is currently only supportive.

Other factors

In two cases, embryos that tested negative for the condition (HBOC and Fragile X syndromes) were available; however, the patients elected to transfer embryos that tested positive, for purposes of non-medical sex selection.

In another case, a patient elected to transfer a male embryo that was affected with XL Alport syndrome despite having unaffected embryos available, as the affected embryo was created with an autologous oocyte while the unaffected embryos were created with donor oocytes.

One patient who underwent PGT-M for paternally inherited HBOC had also tested the embryos for maternally inherited osteogenesis imperfecta (OI) type 1. The patient transferred a male embryo that was negative for OI but positive for a *BRCA1* variant.

Discussion

The majority of PGT-M patients enter into treatment with the explicit goal of avoiding transmission of a genetic condition to their child, and most patients in this series likely did not anticipate transferring embryos with positive results. However, after undergoing IVF with PGT-M, selection and stratification of embryos may reveal that some patients only have embryos with positive results available for transfer. In some cases, there is a lack of unaffected embryos available from the time that PGT results are reported, while in other cases, unaffected embryos are transferred initially and only positive embryos remain for subsequent transfers. Additionally, patients may change perspectives about transferring positive embryos over time; for example, in the situation of a later diagnosis of infertility in PGT-M patients who were fertile at the time of initial treatment, or lack of success in alternative family-building options. If a patient is unable to undergo another IVF cycle, embryos with positive results may provide the only opportunity for genetic parenthood. To date, however, no studies systematically exploring the use of this option have been published.

The proportion of unaffected embryos expected to be available in a given cycle depends on the inheritance pattern of the condition being tested, specifically 75% of embryos in AR cases, 50% of embryos in AD cases, and 50–75% of embryos in XL cases (depending on the likelihood for female carriers of a given XL disorder to be phenotypically affected). However, the actual proportion of unaffected embryos available can be limited by several factors. First, it has become increasingly common to perform PGT-A in conjunction with PGT-M, in which case, unaffected embryos may be excluded due to aneuploid chromosomal status. Similarly, cases in which more than one monogenic condition is tested, such as the aforementioned case in which both HBOC and OI were tested, reduce the availability of embryos unaffected with both conditions. Additionally, when one parent is affected with (rather than a carrier of) an AR disorder, such as in the 21-OHD CAH case presented, the chance of an embryo testing negative is reduced from 75 to 50%.

Factors that may influence a patient's decision to transfer embryos with positive PGT-M results include the nature of the monogenic condition (age of onset, penetrance, phenotype, availability of management, or promise of new therapies), tolerance of uncertainty (i.e., for conditions with reduced penetrance or variable expressivity), personal experience with the condition, views on illness and disability, moral and religious views, and availability of alternative reproductive options [9].

AD conditions accounted for the majority of positive embryo transfers in our study. While this study did not assess patient reasoning behind their decisions, it is possible that these transfers were more common than those involving AR or XL conditions because in each case, one member of the

couple had a personal history of the condition. Patients may have felt that their own familiarity with the condition could provide some perspective on the condition for their child, help to anticipate issues, and possibly improve clinical outcomes. Conversely, being an asymptomatic carrier of an AR disorder does not provide the same direct experience with the phenotype and management of the condition. It is, however, necessary to recognize that variable phenotypic expression of a monogenic disorder may exist among members of the same family. Therefore, a patient who is familiar with their own diagnosis and management should be made aware that an embryo with the same genetic variant may develop into a child with a more severe phenotype. For this reason, consultation with a disease specialist should be encouraged prior to transfer regardless of the patient/couple's personal experience with the condition, to ensure that both partners (when applicable) are adequately informed about the nature and scope of the condition, including any updated information that may not have been available at the time of the patient's diagnosis, and current management recommendations.

The majority of embryo transfers in our cohort had positive results for adult-onset diseases. Current guidelines by several professional societies recommend against testing minors (including prenatally) for adult-onset conditions, in order to maintain the autonomy of the child to make his or her own decisions about pursuing predictive genetic testing in adulthood [11–15]. It is important, therefore, to consider that for a patient who transfers an embryo diagnosed with an adult-onset condition, the genetic status of that potential child will be known pre-symptomatically. Presuming that the parents eventually disclose the child's genetic status to them, it should be recognized that carrying out such transfers violates the child's right to an open future and ability to consent to independent testing decisions.

The 2017 ASRM Ethics Committee Opinion strongly discourages the transfer of embryos with severe, life-limiting childhood conditions. There were no requests among our patients to transfer embryos with monogenic disorders that fit this description. Among our cohort, the most severe early-onset disorder was represented by a male embryo affected with XL Alport syndrome, which causes progressive renal insufficiency and sensorineural hearing loss. The patient (a female Alport carrier) had undergone multiple cycles with both autologous and donor eggs before choosing to transfer an affected autologous male embryo. Prior to transfer, the patient received extensive counseling regarding the phenotypic risks to this embryo. A gestational carrier was used (due to the patient's own medical complications resulting from her genetic status), and the gestational carrier also received counseling regarding the implications of the embryonic diagnosis.

The penetrance and phenotypic expression of some monogenic conditions differ depending on the sex of the affected individual. For example, the lifetime cancer risks associated with HBOC and Lynch syndromes are significantly higher in females compared with males. Similarly, females with 21-OHD CAH (both classic and non-classic forms) are more likely to be clinically recognized, while penetrance of hereditary multiple osteochondromas is slightly higher in males. For most XL disorders, males who test positive for a genetic variant are categorized as "affected," while females who test positive are categorized as "carriers"; however, female carriers of XL conditions may be symptomatic (the likelihood of which depends on the condition itself as well as X-inactivation patterns, which can be unpredictable). In our study, we only included XL carrier embryos for conditions in which symptoms are common among female carriers, specifically fragile X syndrome, in which female premutation carriers are at increased risk for fragile X tremor ataxia syndrome and premature ovarian insufficiency; Alport syndrome, in which female carriers are at increased risk to develop renal disease; and Danon storage disease, in which female carriers frequently develop cardiomyopathy and are also at risk for skeletal and visual symptoms. Therefore, it is important to be aware of these nuances when counseling patients about PGT-M results for XL disorders, given that a diagnosis of "carrier" may have vastly different meanings depending on the specific condition tested.

Symptom management (to varying degrees) is available for most of the conditions in our study for which positive embryos were transferred. The majority of embryos transferred in this series were positive for cancer susceptibility disorders, for which surveillance practices can assist with early detection and treatment, and risk-reducing procedures can minimize the chance of developing a cancer altogether. There was only one condition among our patient cohort for which effective treatment or management is not currently available (Huntington's disease). The patient underwent multiple IVF cycles that eventually yielded one unaffected euploid embryo and a failed embryo transfer. The couple elected to proceed with transfer of their remaining euploid embryo despite positive genetic status for Huntington's, as they were optimistic that effective treatments would be available by the time the potential child reached the later age at which symptoms onset. It is common for patients to express the hope that medical technologies and therapies will improve in the near future, and to retain optimism that their potential child's genetic status will not have a significant impact on their quality of life and lifespan.

The most common condition overall for which positive embryos were transferred in this cohort was HBOC, which is caused by pathogenic variants in the *BRCA1* and *BRCA2* genes. Providers who agree to transfer these embryos should be cognizant of the link between HBOC and a different condition—Fanconi anemia (FA), which is an autosomal recessive, childhood-onset disorder caused by homozygous or compound heterozygous pathogenic variants in the *BRCA2* (and less often *BRCA1*) gene. FA is characterized by progressive bone marrow

failure, high risks of malignancy in both childhood and adulthood, and congenital anomalies. If an embryo is positive for a *BRCA2* variant, it is necessary to counsel the patient about the risk for FA in the event that the other partner is also *BRCA2*-positive, and genetic testing should be offered to the partner whenever possible. As there are other conditions with these same properties (i.e., both AD and AR risks), referral to a genetics professional may be warranted to ensure that all current information is considered prior to embryo transfer.

Few studies have examined provider opinions regarding transfer of embryos with positive PGT-M results. In one study [16], many PGT professionals felt that transferring a positive embryo was "an understandable choice" in the absence of unaffected embryos, although opinions differed depending on the severity of the condition. Some participants raised concerns about how to determine an acceptable threshold of disease severity, whether such transfers are a financial burden on society, and whether parents may feel differently about a child whose positive genetic status is known from birth.

Transfers of embryos positive for monogenic disorders weave a delicate relationship with the principles of medical ethics. Patients have a right to autonomy and reproductive choice concerning disposition of their gametes [17]. Arguably, patients undergoing transfer of an embryo positive for a monogenic disorder after PGT-M may be the most prepared and well informed of such prospective parents. Thus, patient reproductive autonomy may tip the scales toward acknowledging the right for such transfer. The principle of beneficence demands that there be intent of "doing good." Exclusion of positive embryos that would otherwise leave patients incapable of their ideal family building, as well as the potential associated psychological and emotional risks, argues also in favor of transfer of positive embryos. However, non-maleficence contends that there be no harm to either the patient or society. Considerations of the psychological and potential medical burden for the child, as well as burdens on other relatives and the healthcare system at large, must be measured and may be in direct opposition to the principles of autonomy and beneficence [17]. Lastly, the tenet of justice demands that there be consideration of the fairness of resources and the balance between competing needs, rights, and obligations for all patients and scenarios. It may be unjust to deny transfer of a positive embryo while other patients may be undergoing transfer of embryos with the same disease risks, though not known. The potential liabilities on patients, physicians, genetic counselors, embryologists, and clinics are additional factors that must be considered and highlight the need for informed consent and decision-making protocols for clinics that transfer positive embryos as well as pathways for referral or other options for clinics that do not. The ethical considerations surrounding transfer of embryos positive for monogenic disorders will continue to transform as technologies and policies simultaneously advance.

Currently, there are no laws in the USA regulating or restricting embryo transfer. In contrast, the Human Fertilisation and Embryology Authority (HFEA) in the UK explicitly permits transfer of embryos that are known to have a significant risk for a serious physical or mental disability as long as they are not transferred preferentially to unaffected embryos [18]. Such decisions in the USA, however, are negotiated by individual clinics, providers, and patients, resulting in a wide range of policies and case-by-case decisions. The ASRM encourages clinics to "draft and make available to all patients written policies on whether or not the program agrees to the transfer of embryos with known health-affecting genetic anomalies" [9]. Given the transfer requests made by the patients in this study, it would be wise for such policies to note whether positive embryo transfers are restricted for (A) any particular categories of genetic conditions (e.g., based on age of onset, severity); (B) situations in which unaffected embryos still remain (including those involving a sex preference); and (C) cycles utilizing a gestational carrier. Clinics should also consider whether pre-transfer consultation with a genetic counselor, mental health provider, and/or disease specialist is required prior to transfer.

It is likely that the use of PGT-M will continue to increase as awareness of the option grows, genetic testing costs fall, and a greater number of PGT-M candidates are identified. The availability of new and more robust technologies may enable PGT-M for those who previously were not candidates due to technical limitations. With a greater volume of PGT-M patients and test indications rapidly expanding into more variable disease territory, some patients may pursue testing without the intent to exclude positive embryos entirely, but instead may use PGT-M to rank or prioritize embryos for transfer in order of lowest to highest disease risk. Therefore, requests to transfer embryos with positive results will almost certainly become more common, and IVF providers will be faced with challenging clinical and policy decisions.

Our study is limited by the small sample size, owing to the fact that most patients who undergo IVF/PGT-M do not transfer positive embryos. A larger survey of clinic practices could better establish how often embryos with positive results are transferred and determine which resources are needed to support providers and patients through these decisions. Patients in our cohort were not surveyed to determine the factors considered in deciding to proceed with transfer. Additionally, several patients who considered transferring embryos with positive results but first elected to pursue a new IVF/PGT-M cycle were not included, and data on how these options are compared would provide a deeper understanding of contributory factors and patient goals. Further research is needed to determine how well patients who pursue IVF with PGT-M grasp the possible outcome of having only positive embryos available, whether this prompts them to reconsider their goals, and how frequently patients are using PGT from the outset to rank, rather than eliminate, embryos for transfer. Longitudinal surveys of patients who have transferred positive embryos could provide insight into their experience and adjustment in

pregnancy, the immediate postnatal period, and into childhood. As these children enter adolescence and adulthood, it will become essential to understand their experiences as well.

Conclusions

As IVF with PGT-M may not always produce unaffected embryos, some patients may request to transfer embryos that are positive for the monogenic condition for which they were tested. The majority of requests among our patient cohort were to transfer embryos positive for adult-onset, reduced penetrance conditions. As PGT indications continue to expand, these requests will likely increase, and it is essential to consider relevant practical and ethical implications.

Compliance with ethical standards Approval for this study was obtained by the Institutional Review Board (IRB) of the New York University (NYU) School of Medicine (No. 13-00389) and the ORM Fertility Ethics Committee.

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