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Preimplantation Genetic Testing for Rare Monogenic Disease: A Female Reproductive Medicine Perspective on the Clinical Pathway

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Preimplantation genetic testing for monogenic disorders (PGT-M) allows couples at high risk of transmitting a rare genetic disease to achieve an unaffected pregnancy while substantially reducing the likelihood of pregnancy termination after prenatal diagnosis. Although PGT-M is often presented as a molecular genetic technique, its clinical success also depends on reproductive variables: ovarian reserve, ovarian response to controlled stimulation, blastocyst yield, and obstetric management of the resulting pregnancy. This review follows the PGT-M pathway chronologically, from genetic diagnosis and pre-cycle workup through ovarian stimulation, embryo biopsy and genetic analysis, embryo transfer, and confirmatory prenatal diagnosis, and considers each step from the perspective of female reproductive medicine. Particular attention is given to the embryo attrition cascade that determines whether a transferable embryo will be available; the interpretation of outcomes per couple rather than per transfer; carrier states in which the pathogenic variant itself compromises ovarian function; and the counseling and regulatory framework applicable in Korea. PGT-M is best regarded not as a laboratory service but as a multidisciplinary program in which clinical genetics, the PGT laboratory, embryology, reproductive medicine, and obstetric care each contribute to the goal of a healthy live birth.

Key words: Preimplantation diagnosis, Genetic testing, Rare diseases, Genetic counseling, Fertilization in vitro

REVIEW ARTICLE

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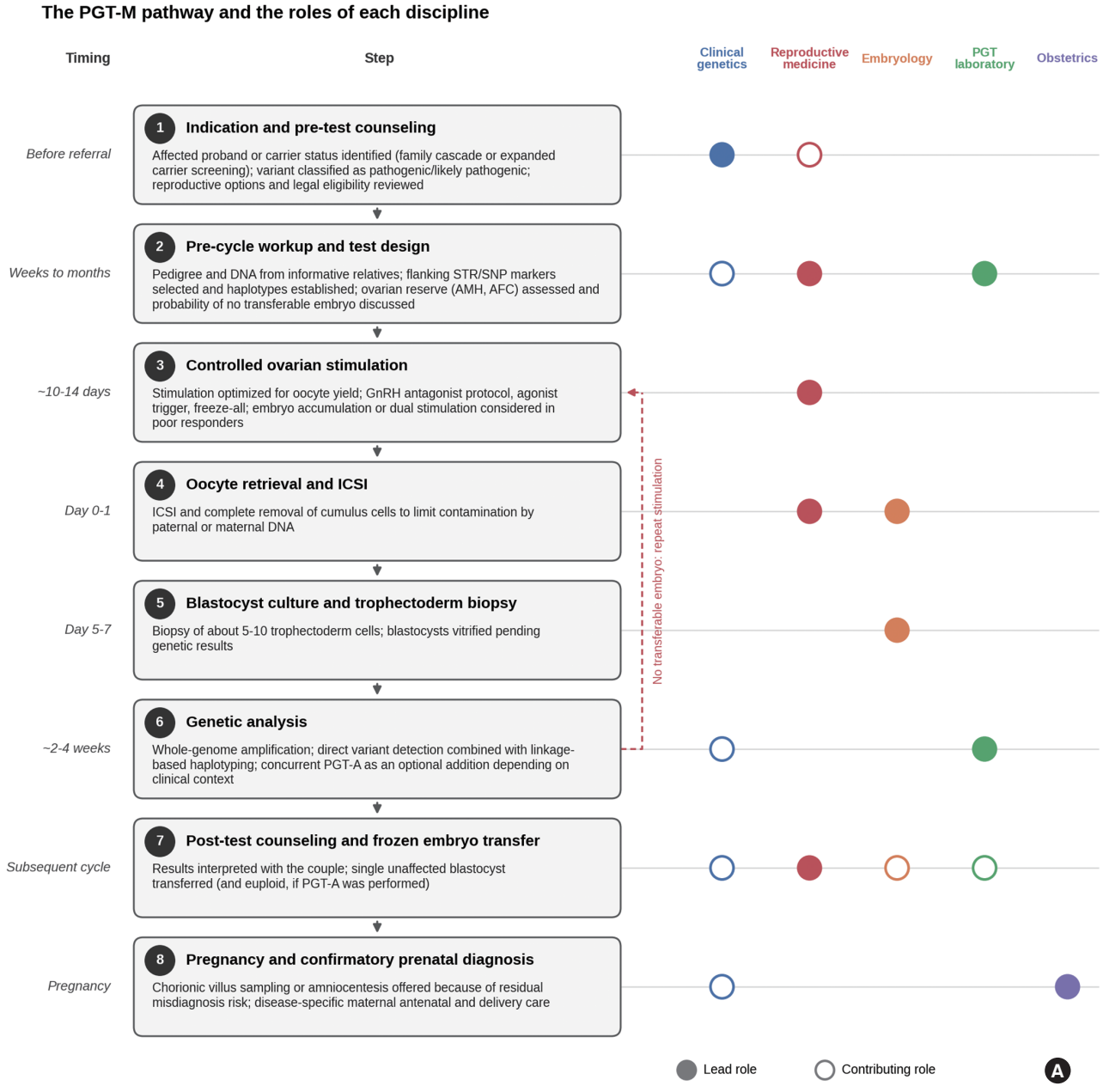
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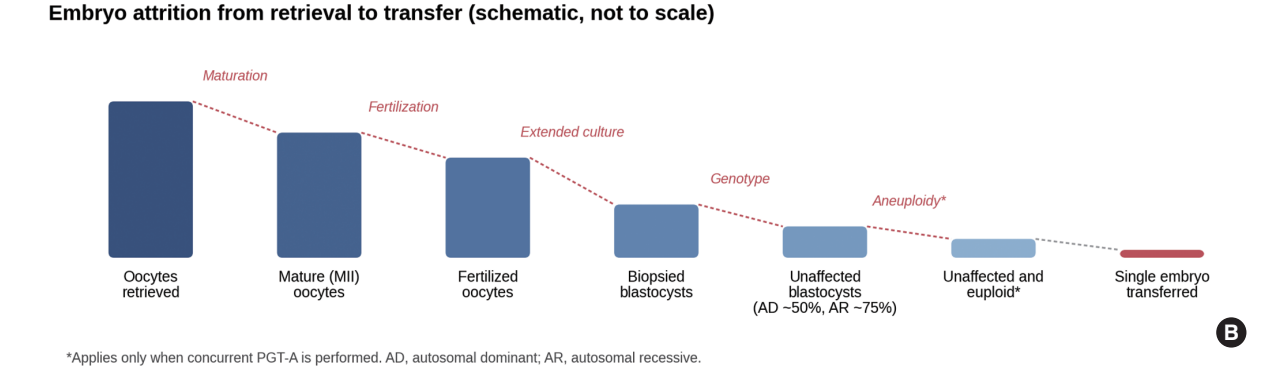
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INTRODUCTION

Rare genetic diseases are individually uncommon but collectively affect a substantial proportion of the population, and most are monogenic. For couples who have already had an affected child or who have been identified as carriers through expanded carrier screening or family cascade testing, the reproductive options are limited: accepting the recurrence risk, gamete donation, adoption, prenatal diagnosis with the possibility of termination, or preimplantation genetic testing for monogenic disorders (PGT-M) [1]. Among these options, PGT-M is the only approach that offers the possibility of a genetically related, unaffected child while largely avoiding the physical and psychological burden of pregnancy termination after an affected prenatal diagnosis.

Following the 2017 terminology revision, preimplantation genetic diagnosis was subdivided into PGT-M for monogenic conditions, PGT for structural rearrangements (PGT-SR), and PGT for aneuploidy (PGT-A) [2]. The PGT-M literature has been dominated by molecular genetics. From a reproductive endocrinology perspective, however, the number of blastocysts available for testing can be as decisive as the assay itself, although assay development and the establishment of informative haplotypes may also be limiting in individual families [3]. Accordingly, this review follows the PGT-M pathway chronologically (Fig. 1A) and examines each step through an explicit female reproductive medicine lens rather than attempting a comprehensive review of the molecular methods.





*Applies only when concurrent PGT-A is performed. AD, autosomal dominant; AR, autosomal recessive.

Fig. 1. Continued to the next page.

Fig. 1. Continued. Schematic overview of preimplantation genetic testing for monogenic disorders (PGT-M). (A) The PGT-M pathway from indication to confirmatory prenatal diagnosis, with approximate timing and the lead (filled circles) and contributing (open circles) roles of clinical genetics, reproductive medicine, embryology, the PGT laboratory, and obstetrics at each step. The dashed arrow indicates return to ovarian stimulation when no transferable embryo is obtained. (B) Schematic representation of embryo attrition from oocyte retrieval to transfer (not to scale). The expected unaffected fraction is approximately 50% for autosomal dominant (AD) and 75% for autosomal recessive (AR) conditions; the aneuploidy step applies only when concurrent preimplantation genetic testing for aneuploidy (PGT-A) is performed. ICSI, intracytoplasmic sperm injection; STR, short tandem repeat; SNP, single-nucleotide polymorphism; AMH, anti-Müllerian hormone; AFC, antral follicle count.

THE PGT-M PATHWAY

Genetic diagnosis and pre-test counseling

PGT-M cannot begin until the causative variant has been confirmed and classified as pathogenic or likely pathogenic in the affected proband [3]. Pre-test counseling, ideally provided jointly by a clinical geneticist or genetic counselor and the reproductive physician, reviews the reproductive options, the inheritance pattern and expected proportion of unaffected embryos, the legal eligibility of the condition in Korea (Section 4), and the probability that treatment will not yield a transferable embryo. Indications have broadened beyond classic severe childhood-onset recessive diseases to include autosomal dominant late-onset conditions, inherited cancer predisposition, X-linked disorders, *de novo* variants, mitochondrial DNA disease assessed using heteroplasmy thresholds, and human leukocyte antigen (HLA) matching for an affected sibling [1].

Pre-cycle workup and test design

A detailed pedigree and DNA samples from as many informative relatives as possible are required because contemporary protocols do not rely on direct mutation detection alone. Informative polymorphic markers, either short tandem repeats (STRs) or single-nucleotide polymorphisms (SNPs), that flank the locus are selected so that the high- and low-risk haplotypes can be traced [3]. This step can itself be demanding: *de novo* variants, the absence of informative relatives, or limited marker informativeness may require additional family samples, alternative phasing strategies, or custom assay development and may delay or occasionally preclude testing [3]. This preparatory phase takes several weeks to a few months and should be initiated before, rather than during, ovarian stimulation. In parallel, the reproductive assessment should include ovarian reserve evaluation using anti-Müllerian hormone (AMH) and antral follicle count, semen analysis, and uterine evaluation so that the likely number of stimulation cycles can be estimated at the outset.

Controlled ovarian stimulation

Because the number of blastocysts is a principal determinant of whether a transferable embryo will be obtained (Section 3), ovarian stimulation for PGT-M should be optimized for oocyte yield rather than a conventional fresh-transfer endpoint. AMH and antral follicle count guide gonadotropin dosing; antagonist protocols with a dual trigger and a freeze-all strategy are standard because all embryos are cryopreserved pending genetic results. In poor responders, embryo accumulation over consecutive cycles and, in selected cases, dual stimulation within a single ovarian cycle have been proposed to increase the cumulative probability of obtaining at least one transferable blastocyst [4]. Evidence for the latter strategy is mixed: a randomized comparison of dual stimulation with two conventional stimulations found no significant difference in the number of euploid blastocysts obtained. Thus, the strategy is best presented as a means of shortening the time to a transferable embryo rather than increasing yield [5].

Carrier states that compromise the ovary

Several monogenic conditions relevant to PGT-M directly affect female reproductive potential, making reproductive medicine input into the pathway particularly important. *FMR1* premutation carriers are at risk of fragile X-associated primary ovarian insufficiency [6]. Women with pathogenic *BRCA1* variants have been reported to have reduced ovarian reserve; however, a systematic review found no consistent difference in AMH or response to stimulation, so this possibility should be discussed during counseling without being overstated [7]. Myotonic dystrophy type 1 is characterized by both anticipation, which makes the severity of recurrence unpredictable, and well-described obstetric risks, including polyhydramnios, preterm labor, disordered labor, and an increased operative delivery rate [8]. In these families, PGT-M must be planned early and considered alongside fertility preservation because delay may render treatment impossible.

Oocyte retrieval, fertilization, and embryo biopsy

Intracytoplasmic sperm injection (ICSI) is used to avoid contamination by extraneous sperm, and cumulus cells are carefully removed [3]. Trophectoderm biopsy of five to ten cells at the blastocyst stage has replaced cleavage-stage blastomere biopsy, providing more template DNA, a lower relative impact on the embryo, and better implantation outcomes [9]. Biopsied blastocysts are vitrified while genetic analysis is completed.

Genetic analysis

Following biopsy, DNA is amplified by whole-genome amplification or, in targeted protocols, direct multiplex polymerase chain reaction (PCR). These amplification procedures introduce the principal analytical risks: allele dropout, preferential amplification, and contamination by cumulus or sperm DNA [3]. Robust PGT-M combines direct detection of the variant with indirect linkage-based haplotyping so that each result is internally corroborated and allele dropout is recognized rather than misread [3]. Several analytical strategies are in use. Targeted approaches based on multiplex PCR of flanking STR or SNP markers, with or without direct variant detection, remain widely used and do not assess chromosomal copy number. In the most recent ESHRE PGT Consortium data, targeted PCR-based testing still predominated for PGT-M, whereas comprehensive whole-genome methods were applied mainly to PGT-A and concurrent testing [10]. Genome-wide SNP array approaches such as karyomapping [11] and, more recently, next-generation sequencing with haplotype reconstruction allow the disease locus to be analyzed without the need for fully family-specific assay design and can also report chromosomal copy number from the same biopsy. Concurrent PGT-A is therefore an optional addition rather than an inherent component of PGT-M. It may be considered depending on maternal age, reproductive history, and local practice, but its benefit is not universal. In a randomized trial of 1,212 women aged 20–37 years with a good prognosis and at least three good-quality blastocysts, the cumulative live birth rate within 1 year was 77.2% (468/606) with PGT-A and 81.8% (496/606) with conventional IVF (absolute difference, −4.6 percentage points; 95% confidence interval [CI], −9.2 to −0.0), and conventional IVF was noninferior to PGT-A [12]. When concurrent PGT-A is performed, the requirement that an embryo be both unaffected and euploid further reduces the transferable fraction, particularly in women of advanced age.

Post-test counseling and embryo transfer

The genetic and reproductive teams jointly review the results with the couple, including the handling of carrier embryos in recessive conditions, inconclusive results, and, when PGT-A has been performed, mosaic findings. Transfer of a single unaffected blastocyst, which is also euploid when concurrent PGT-A has been performed, should be the default to avoid multiple pregnancy in couples who have already accepted substantial reproductive risk.

Pregnancy and confirmatory prenatal diagnosis

Because PGT-M carries a small residual risk of misdiagnosis arising from allele dropout, undetected recombination, contamination, or embryo mosaicism, it does not replace confirmatory prenatal diagnosis. Chorionic villus sampling or amniocentesis should therefore be offered and discussed at the outset [3]. Disease-specific antenatal and delivery planning, such as cardiovascular surveillance in Marfan syndrome, renal and blood pressure monitoring in autosomal dominant polycystic kidney disease, and anesthetic precautions in neuromuscular disease, follows from the same maternal diagnosis that prompted PGT-M and requires early communication between the reproductive and obstetric teams.

EMBRYO ATTRITION AND CLINICAL UTILITY

The attrition cascade

The number of oocytes retrieved is not equivalent to the number of embryos ultimately tested. Attrition occurs during maturation, fertilization, and extended culture to the biopsiable blastocyst stage, and only a proportion of the blastocysts that are eventually tested are suitable for transfer (Fig. 1B). In a review of PGT-M cycles, the probability that a given embryo would be classified as appropriate for transfer differed by inheritance pattern and decreased further when aneuploidy testing was performed concurrently [13]. Before any aneuploidy testing is considered, the expected unaffected fraction is 50% for an autosomal dominant condition and 75% for an autosomal recessive condition. A woman with diminished ovarian reserve who carries an autosomal dominant variant may therefore complete a full cycle without a transferable embryo. Counseling before the first cycle should explicitly address the probability of a “no-transfer” outcome, and treatment planning should anticipate the possibility of more than one retrieval.

Diagnostic performance

Diagnostic efficiency in experienced centers is high, with the large majority of biopsied embryos yielding a conclusive result. Trophectoderm biopsy combined with comprehensive testing strategies is associated with higher diagnostic efficiency and better clinical outcomes per transfer than earlier approaches, and misdiagnosis is rare when direct and indirect analyses are used together [10,14].

Live birth outcomes and the choice of denominator

Reported outcomes depend strongly on the denominator used. A single-center retrospective cohort from Australia analyzed 572 PGT-M cycles performed in 299 patients between 2015 and 2022; only cycles in which at least one embryo was biopsied were included, and all embryos underwent karyomapping with concurrent aneuploidy screening [15]. With these 572 biopsy cycles as the denominator, 392 (68.5%) yielded at least one embryo suitable for transfer and 355 (62.1%) resulted in at least one embryo transfer. With embryos transferred as the denominator, the 513 embryos transferred in 490 transfer procedures resulted in 263 clinical pregnancies and 230 live births, corresponding to a clinical pregnancy rate of 51.3% (95% CI, 47.0%–55.6%) and a live birth rate of 44.8% (95% CI, 40.6%–49.2%) per embryo transferred [15]. Within the cohort, a recorded subfertility factor was associated with a lower likelihood of clinical pregnancy per embryo transferred ($\beta = -0.48$, $p = 0.026$), whereas its association with live birth did not reach statistical significance ($\beta = -0.42$, $P = 0.052$) [15]. Cycles that were canceled before oocyte retrieval or that produced no biopsiable blastocyst were not included in any of these denominators; the proportion of all initiated cycles reaching transfer would therefore be lower than 62.1% [15]. Per-transfer figures therefore describe the prognosis of couples who reach transfer rather than that of all couples who begin treatment. Cumulative live birth rates per couple or per intention to treat, which would account for canceled cycles, cycles without a transferable embryo, and repeated stimulation, are rarely reported for PGT-M and represent an important gap in the evidence. Until such data are available, counseling should present per-transfer outcomes together with the realistic probability of reaching transfer in a given cycle, which depends on maternal age, ovarian reserve, and inheritance pattern [13,15]. Clinical utility is best expressed as a cumulative outcome per couple, specifically the probability of an unaffected live birth per intention to treat, and as the avoidance of successive terminations after prenatal diagnosis.

LIMITATIONS, COUNSELING, AND REGULATION

The principal limitations are often biological: insufficient oocytes, absence of transferable embryos, mosaic results of uncertain significance, and variants of uncertain significance that cannot be used for embryo selection. Technical limitations, including failure to establish informative haplotypes and inconclusive embryo results, can also occur. Cost and incomplete reimbursement remain barriers. Non-directive genetic counseling, ideally provided jointly by the reproductive physician and a clinical geneticist, must address the possibility of cycle failure, the disposition of affected embryos, and the ethical questions raised by selection for variable-penetrance or adult-onset conditions.

In Korea, genetic testing of embryos is governed by the Bioethics and Safety Act, which restricts PGT-M to designated conditions [16]. The list has expanded well beyond the original small set, and a 2024 amendment to the Enforcement Decree changed the designation procedure from ministerial notification to public announcement, with the aim of allowing new conditions to be added more rapidly at the request of treating institutions or academic societies. Clinicians managing families affected by rare diseases should confirm the current status of a given condition before counseling and should be aware that an unlisted condition may be submitted for addition rather than simply declined.

CONCLUSION

PGT-M has become a reliable means of preventing the transmission of rare monogenic disease. Its outcomes, however, depend on ovarian reserve, stimulation strategy, blastocyst yield, and obstetric management as much as on molecular technique. Framing PGT-M as a multidisciplinary reproductive program, in which clinical genetics, the PGT laboratory, embryology, reproductive medicine, and obstetric care each contribute across a single coordinated pathway and outcomes are counseled per couple rather than per transfer, offers the most realistic path to the outcome that matters to families: an unaffected child delivered safely.

NOTES

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Ethical statement

This article is a narrative review based entirely on previously published literature and publicly available regulatory documents. It does not report any study involving human participants, human-derived material, or animals; therefore, institutional review board approval and informed consent were not required.

Author contributions

Conceptualization: Park D. Literature review and acquisition of data: Choi H. Drafting of the manuscript: Park D., Choi H. Critical revision of the manuscript for important intellectual content: Park D. Final approval of the version to be published: Park D., Choi H. Both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Use of artificial intelligence

The authors used Claude (Anthropic, PBC; Claude Opus 5) in the preparation of this manuscript. The tool was used for three purposes: (1) drafting of the manuscript text based on an outline and content framework specified by the authors, (2) assistance in searching for and identifying candidate published references, and (3) drafting of the layout of Fig. 1 based on content specified by the authors. In accordance with the JIG Artificial Intelligence Use Policy, the authors verified the accuracy, validity, and appropriateness of all artificial intelligence–generated content, and independently confirmed every cited reference against the original publication. The content of Fig. 1 was defined, reviewed, and approved by the authors; no photographic or realistic image-generation tool was used. No identifiable patient information, genomic data, or confidential research data were uploaded to any artificial intelligence platform. Artificial intelligence does not qualify for authorship, and the authors take full responsibility for all content of this manuscript.

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