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Application of Combined PGT-A and PGT-M for Reproductive Management in a Couple Carrying GCDH Mutations with Prior Affected Offspring: A Rare Case Report

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Case Report
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Abstract

Case: A 31-year-old woman with secondary subfertility, four recurrent pregnancy losses, and one previous live-born child affected with glutaric acidemia type I (GA-I) was evaluated. Genetic testing confirmed that both partners were heterozygous carriers of pathogenic GCDH variants (c.769C>T in exon 8 and c.1204C>T in exon 11, NM_000159.4). Given the high recurrence risk, the couple underwent in vitro fertilization with intracytoplasmic sperm injection, blastocyst culture, trophectoderm biopsy, and combined preimplantation genetic testing for aneuploidy (PGT-A) and monogenic disease (PGT-M).

Outcome: Three blastocysts were biopsied. One embryo exhibited segmental aneuploidy of chromosome 16 and was excluded. A second embryo was euploid and wild-type for both GCDH variants, classified as genetically normal. The third was euploid but heterozygous for c.769C>T, consistent with carrier status. The genetically normal embryo was selected for frozen embryo transfer, resulting in a singleton intrauterine pregnancy. Non-invasive prenatal testing at 12 weeks showed a normal chromosomal profile. At the time of report, the pregnancy is ongoing at 20 weeks without complications.

Conclusion: This case demonstrates that combined PGT-A and PGT-M can effectively prevent recurrence of GA-I, improve reproductive outcomes, and provide a valuable option for couples with monogenic disorders and recurrent pregnancy loss.

Keywords: Aneuploidy; Glutaric Acidemia Type I; Preimplantation Genetic Testing (PGT); Recurrent Pregnancy Loss; Secondary Subfertility

Introduction

Couples who are carriers of pathogenic variants of the same autosomal recessive gene face an approximately 25% risk of conceiving an affected child with each pregnancy. Glutaric acidemia type I (GA-I), caused by biallelic pathogenic variants in the *GCDH* gene, is a potentially severe organic aciduria that can result in acute encephalopathic crises and permanent neurodevelopmental disability if not identified and managed early. Traditional strategies to avoid transmission include prenatal diagnosis with the option of termination of pregnancy for affected fetuses; however,

prenatal diagnosis occurs after conception and may carry significant emotional and physical burden to the couple. Preimplantation genetic testing for monogenic disorders (PGT-M) offers the potential to prevent transmission of single-gene disorders by testing embryos prior to embryo transfer, thereby avoiding affected pregnancies entirely. Simultaneous screening for chromosomal aneuploidy (PGT-A) can improve embryo selection by identifying euploid embryos with higher implantation potential and lower miscarriage risk. Here we present a case in which combined PGT-A and PGT-M guided embryo selection was done; in a couple where both partners were heterozygous for a *GCDH* variant, resulting in an ongoing pregnancy with normal NIPT and carrying the pregnancy at 20 weeks of gestation at the time of reporting this case [1-4].

Material and Method

A 31-year-old woman presented with nine-years of secondary infertility and four consecutive early pregnancy losses with a history of one live birth in 2014. Her obstetric history included a term caesarean delivery of a male infant in 2014 who was subsequently diagnosed with glutaric acidemia type I. After this birth, the couple experienced four spontaneous pregnancy losses. The patient's medical history was notable for type 2 diabetes mellitus (diagnosed three years earlier), for which she was taking metformin, and hypothyroidism managed with levothyroxine [5]. Her body mass index was 32.4 kg/m^2. Menstrual cycles were regular. Prior workup included a normal maternal karyotype, negative autoimmune and thrombophilia screening, and baseline hormonal studies that were within acceptable ranges for proceeding to assisted reproduction.

The partner's history was notable only for carrier status for β-thalassemia trait; semen analysis revealed normal volume, concentration and motility as per latest WHO standard of semen analysis. Genetic testing was undertaken in the context of the affected child and it was found that both partners were heterozygous carriers of a pathogenic variant in the *GCDH* gene. After genetic counselling that outlined options including prenatal diagnosis, use of donor gametes, and PGT, the couple elected to pursue IVF with combined PGT-A and PGT-M to both avoid transmission of GA-I and to maximize implantation potential by selecting euploid embryos [6,7].

IVF Cycle and Embryo Biopsy

Controlled ovarian stimulation was performed using a standard antagonist protocol. Oocyte retrieval yielded a sufficient number of metaphase II oocytes, and intracytoplasmic sperm injection (ICSI) was performed. Embryos were cultured to blastocyst stage and three high-quality blastocysts underwent trophectoderm biopsy on day 5–6; biopsies were sent for combined PGT-A (next-generation sequencing based copy-number analysis) and PGT-M (Sanger sequencing / targeted NGS of *GCDH* exons with linked polymorphic markers as appropriate to rule out allele dropout). All biopsies were processed in a reference molecular genetics laboratory accredited for PGT [8].

Genetic Test Results and Embryo Selection

Of the three biopsied embryos, one exhibited segmental aneuploidy of chromosome 16 and was reported as abnormal on PGT-A. Second embryo demonstrated a cytogenetically normal complement on PGT-A and no detectable pathogenic *GCDH* variant on PGT-M; this embryo was classified as euploid and genetically unaffected. Third embryo was euploid on PGT-A but heterozygous for the *GCDH* variant on PGT-M and therefore classified as a carrier [9]. Following counselling and informed consent that reiterated the residual limitations of PGT (notably mosaicism and the possibility of allele dropout), the couple elected to get embryo transfer with second embryo in a subsequent frozen embryo transfer cycle.

Procedural and Laboratory Details

The patient underwent ovarian stimulation with a flexible antagonist protocol. Recombinant gonadotropins were administered; GnRH antagonist was introduced when leading follicles reached 14mm as per the standard protocols. Triggering of final maturation was performed with hCG and GnRH agonist (Dual trigger) as per clinic protocol, and transvaginal oocyte retrieval was carried out 36 hours later. ICSI was utilized to minimize the risk of DNA contamination for downstream genetic analysis.

Embryos were cultured in sequential media to the expanded blastocyst stage. Trophectoderm biopsy was performed on day 5–6 by laser-assisted removal of several TE cells, which were collected into PCR tubes and cryopreserved at −20°C before being shipped to an accredited molecular genetics laboratory. PGT-A was performed using low-pass whole-genome next-generation sequencing for copy-number analysis (resolution adequate to detect whole-chromosome aneuploidies and clinically relevant segmental aneuploidies); PGT-M for the *GCDH* gene was performed using targeted sequencing of exons 8 and 11 (the loci of the family-specific variants) alongside linked polymorphic markers to mitigate allele dropout. Results were interpreted by clinical molecular geneticists with expertise in PGT, and reports were reviewed in a multidisciplinary meeting including the referring clinical team and the genetic counsellors.

Prenatal follow-up after a positive pregnancy test followed standard obstetric protocols. NIPT was performed

using a validated cell-free DNA assay at a commercial laboratory; results were used as an adjunct to, not a replacement for, diagnostic prenatal testing. The couple was counselled that confirmatory invasive testing (amniocentesis or chorionic villus sampling) remained the gold standard if definitive prenatal diagnosis was required.

Results

A positive beta HCG test was obtained after frozen embryo transfer, and serial ultrasounds demonstrated a viable singleton intrauterine pregnancy. First-trimester screening was unremarkable. Given the couple's history and despite negative PGT-M on the transferred embryo, non-invasive prenatal testing (NIPT) using cell-free fetal DNA was performed at the recommended gestational age; the test results were well within the normal range for common trisomies. The patient continued routine antenatal care and, at the time of compilation of this report, the pregnancy has progressed to 20 weeks' gestation without major complications.

In this couple where both partners were heterozygous for a pathogenic *GCDH* variant, combined PGT-A and PGT-M allowed selection and transfer of an embryo that was both chromosomally normal and free from the pathogenic mutation; this resulted in a viable ongoing pregnancy with normal NIPT at 20 weeks' gestation. This case underscores the potential of integrated reproductive genetic strategies to prevent transmission of severe monogenic disease while optimizing the likelihood of implantation and pregnancy continuation. Comprehensive preconception counselling, careful laboratory technique, and continued prenatal follow-up remain indispensable components of care.

Discussions

This case illustrates several important and contemporary principles in reproductive genetics and assisted reproduction. First, it demonstrates how combined application of PGT-M and PGT-A can be utilized to both prevent transmission of a severe autosomal recessive disorder and to reduce the risk of early pregnancy loss associated with embryonic aneuploidy. Selection of an embryo that was both euploid and free from the family-specific *GCDH* variant permitted transfer of an embryo with the highest anticipated chance of achieving a healthy live birth while simultaneously preventing recurrence of GA-I.

GA-I is a metabolic disorder with a potentially severe neurological phenotype. Early diagnosis and metabolic management can mitigate morbidity; nevertheless, preventing birth of an affected child remains a primary goal for carrier couples where feasible. PGT-M allows couples to avoid the difficult choice of pregnancy termination by ensuring that only embryos without the bi-allelic pathogenic combination are transferred. In practice, PGT-M involves establishing the family-specific mutation(s) and often constructing haplotypes using polymorphic markers to address technical issues such as allele dropout and contamination. Coupling PGT-M with PGT-A addresses another major cause of early pregnancy failure and miscarriage—aneuploidy—thereby improving the chances of implantation and sustained pregnancy.

The couple in this report experienced multiple early pregnancy losses following a previously affected live birth, underscoring that recurrent pregnancy loss may be multifactorial; in this case, both genetic transmission risk and sporadic embryonic aneuploidy likely contributed to reproductive failure. The woman's comorbidities, including diabetes and hypothyroidism, are additional recognized risk factors for adverse pregnancy outcomes and may also have influenced prior losses. The partner's thalassemia trait did not affect embryo selection in this case but highlights the importance of comprehensive genetic screening and counselling tailored to local population genetics.

While PGT is a powerful tool, limitations must be emphasized. Mosaicism—where different cells within an embryo have different chromosomal complements—can complicate interpretation of TE biopsy results. TE biopsy samples only a subset of outer cells destined to become placenta and may not always represent the inner cell mass that becomes the fetus. Allele dropout, technical artifacts, and diagnostic errors are additional caveats; therefore, confirmatory prenatal diagnostic testing remains recommended when an affected or carrier status has significant implications. In the present case, NIPT was performed and was normal; NIPT is highly sensitive and specific for common trisomies but is a screening test and cannot definitively exclude all chromosomal or single-gene abnormalities—hence the recommendation for invasive testing when clinically indicated.

A growing body of literature supports the clinical effectiveness of PGT-M to prevent transmission of monogenic disorders and of PGT-A to reduce miscarriage rates in selected populations, though the impact of routine PGT-A on live birth rates in unselected populations remains debated. Combining the two tests in couples at high genetic risk is increasingly used in tertiary centres and has been associated with favourable outcomes in published case series and cohort studies. This case adds to the clinical experience demonstrating that combined testing can yield a favourable pregnancy outcome even in couples with prior affected offspring and recurrent losses.

From an ethical standpoint, use of PGT raises questions regarding access, equity, and reproductive autonomy. Informed consent and pre- and post-test genetic counselling are critical elements of care to ensure that couples understand the benefits, limitations, and potential psychological impacts of testing decisions. Informed counselling should also address alternative reproductive options (e.g., use of donor gametes) for couples who prefer not to use PGT.

Limitations of our Report

As with any single case report, generalizability is limited. The specific laboratory methods (exact PGT-M assay design, sequencing platform, and sensitivity thresholds) and the variant details are institution-dependent and should be reported in detail for reproducibility in formal submissions. We have described the clinical course to 20 weeks' gestation; long-term neonatal outcome is pending and will be important to report when available. Finally, although NIPT was normal, definitive prenatal diagnostic testing would provide confirmatory evidence of fetal genotype and should be discussed and offered to the couple.

Declarations

Ethics and Consent to Participate: This study was conducted in accordance with the ethical standards of the Review board. Approval was obtained from the Institutional Ethics Committee of WINGS Academy (Approval No: 2025/WA/CR0024). Written informed consent was obtained from participant included in the study.

Consent for Publication: Participants have provided consent for publication of anonymized data. No identifying information of individual participants is disclosed in this manuscript.

Competing Interests: The authors declare that they have no competing interests.

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Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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