Preimplantation Genetic Diagnosis (PGD) for Genetic Prion Disorder Due to F198S Mutation in the PRNP Gene

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IMPORTANCE To describe the first case of preimplantation genetic diagnosis (PGD) and in vitro fertilization (IVF) performed for the prevention of genetic prion disease in the children of a 27-year-old asymptomatic woman with a family history of Gerstmann-Sträussler-Scheinker syndrome (GSS).

OBSERVATIONS PGD and fertilization cycles resulted in detection of 6 F198S mutation-free embryos. Of these, 2 were selected for embryo transfer to the patient’s uterus, yielding a clinical twin pregnancy and birth of healthy but slightly premature offspring with normal development at age 27 months.

CONCLUSION AND RELEVANCE IVF with PGD is a viable option for couples who wish to avoid passing the disease to their offspring. Neurologists should be aware of PGD to be able to better consult at-risk families on their reproductive choices.

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Preimplantation genetic diagnosis (PGD) with in vitro fertilization (IVF) has emerged as an important option for at-risk couples wishing to conceive a healthy child without a fatal or severely debilitating inherited disorder.1,2 PGD allows for transferring only embryos without the disease-causing mutation into the uterus.1,2

Prion diseases, also termed transmissible spongiform encephalopathies, are a group of fatal neurodegenerative disorders linked to abnormal folding of the prion protein. Genetic prion diseases (gPrDs) are divided into 3 forms based on clinicopathologic features: familial Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia. There is currently no cure, and the illness is uniformly fatal. One genetic mutation linked to GSS is a phenylalanine to serine change at codon 198 (F198S) in the prion protein gene (PRNP), which has known high penetrance.3 We describe the first application to our knowledge of PGD for a patient carrying the F198S mutation, identified with an F198S mutation into the uterus.1,2 allows for transferring only embryos without the disease-causing mutation to our knowledge of PGD for a patient carrying the F198S mutation for the gPrD GSS.

Twelve of 14 mature retrieved oocytes were fertilized by intracytoplasmic sperm injection and were available for testing (Figure). PGD by sequential polar body 1 (PB1) and polar body 2 (PB2) mutation analysis, followed by additional blastomere analysis of day-3 embryos and confirmation, identified 6 mutation-free embryos (Nos. 1, 2, 3, 7, 10, and 14) (Figure). Elective single embryo transfer to prevent multiple pregnancy was discussed, and the patient elected to transfer 2 embryos. Based on PGD analysis, 2 mutation-free embryos (Nos. 1 and 3) (Figure) were chosen for fresh embryo transfer, with 3 remaining viable embryos designated for cryopreservation.

The 2 embryos implanted successfully, and the patient conceived twins. Healthy infants were delivered by a Cesarean section at 33 weeks and 5 days of gestation, each weighing more than 4 pounds. As expected, due to their prematurity, the infants were slightly below the curve for weight for age and for head circumference, both of which normalized by age 3 months. By age 27 months, the infants had consistently completed communicative, social, and emotional developmental milestones on schedule.

Report of a Case

This case report was deemed exempt research by the Duke University School of Medicine institutional review board, and the patient gave written permission for this report.

A 27-year-old asymptomatic woman with a known family history of GSS chose to undergo predictive testing after genetic counseling and was identified with an F198S PRNP mutation with codon 129 VM (V cis) polymorphism. The patient opted to be informed of the results of her genetic test. During prior genetic counseling, PGD had been presented as an option, and she and her husband chose to have PGD at a private experienced IVF and PGD center.

After providing written informed consent, the patient underwent IVF-PGD cycles, using methods reviewed elsewhere.7-4 Twelve of 14 mature retrieved oocytes were fertilized by intracytoplasmic sperm injection and were available for testing (Figure). PGD by sequential polar body 1 (PB1) and polar body 2 (PB2) mutation analysis, followed by additional blastomere analysis of day-3 embryos and confirmation, identified 6 mutation-free embryos (Nos. 1, 2, 3, 7, 10, and 14) (Figure).
Discussion

To our knowledge this is the first published report of IVF with PGD for a genetic prion disease with 27-month normal follow-up of the offspring. Although the patient in our case chose to learn her genetic status, because of emotional risks associated with learning one’s carrier status of a PRNP gene mutation, nondisclosure PGD (a specialized protocol in which the subject remains unaware of his/her genotype) was discussed as an option.²

![Image of a pedigree showing the maternal partner is a 27-year-old asymptomatic woman with an F198S mutation in the prion protein gene (PRNP))

Figure. Preimplantation Genetic Diagnosis (PGD) for Gertmann-Sträussler-Scheinker Syndrome (GSS) Determined by an Autosomal Dominant Mutation in the Prion Protein Gene (PRNP)

A.

MG29F SNP
D20S883
D20S889
PRNP

PGD

PGD

Marker order:
D20S887
D20S889
PRNP

120
171
155
N
N
220
177
144
N
N

200
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Other forms of genetic prion disease and other inherited neurologic disorders are also candidates for PGD.6,9 For example, guidelines from professional reproductive societies have been created for PGD in Huntington disease,9 and similar guidelines for other neurologic conditions may be forthcoming.

In summary, PGD can serve as a viable reproductive option for patients faced with genetic prion disorders, such as GSS, and may affect their inclinations for predictive testing and consideration of nondisclosure PGD. Clinicians should discuss PGD as an option with patients genetically predisposed to prion disease.

Conflict of Interest Disclosures: Dr Doraiswamy has received research grants (through Duke University) from Elan, Avid, Lilly, Novartis, Neuroneutrix, Medivation, Wyeth, Janssen, Pfizer, and National Institutes of Health (NIH) over the past 3 years. He has received advisory or speaking fees in the past from Accera, Avid, AstraZeneca, Abbvie, Baxter, Cognoptix, Lundbeck, Takeda, Piramal, Genomind, Sonexa, Shire, Targacept, Grifols, Neuroneutrix, TauRx, Medivation, Danone, Neurocog Trials, Alzheimer's Association, Alzheimer's Foundation, University of California, National University of Singapore, and University of Copenhagen. He owns shares in Maxwell Health, Sonexa, Clarimedix, and Adverse Events Inc, whose products are not discussed here. Dr Rechitsky is employed by the Reproductive Genetic Institute, where the PGD procedure was performed. Dr Tur-Kaspa is employed by the Institute for Human Reproduction, where the IVF was performed. No other disclosures were reported.

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REFERENCES