CASE REPORT

Sibling and self ovum donation for sisters with an intermediate *FMR1* mutation: what's a program to do?

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Objective: To increase awareness of the unique clinical and ethical considerations invoked by the request of a patient with premature ovarian failure (POF) and her nulliparous sister, both with intermediate-size mutations in fragile X mental retardation 1 (*FMR1*), to pursue sibling ovum donation.
Design: Case report.
Setting: Academic medical center.
Patient(s): A 32-year-old woman with POF and her 26-year-old sister with occult diminished ovarian reserve, both of whom are carriers of an intermediate-size mutation in *FMR1*.
Intervention(s): Prospective donor ovarian function testing, genetic testing and consultation, and psychological evaluation; institutional assisted reproduction ethics committee consultation, and controlled ovarian hyperstimulation–IVF with cryopreservation of embryos for potential future self-use.
Main Outcome Measure(s): Successful cryopreservation of embryos for autologous use by the prospective donor (younger sister) before ovum donation.
Results(s): Three blastocysts were frozen.
Conclusion(s): Requests for sibling ovum donation, while understandable and ethically sanctioned under typical circumstances, prove particularly challenging in some patients with POF given uncertainties regarding the prognosis of the currently asymptomatic sister, risks of genetic transmission of POF, and fiduciary responsibilities to address the reproductive interests of the prospective donor. A multidisciplinary approach was highly beneficial in this case. (Fertil Steril® 2009;92:394.e9–e12. ©2009 by American Society for Reproductive Medicine.)

Key Words: Premature ovarian failure, FMR1 gene, fragile X, ovum donation, sibling ovum donation, cryopreservation, genetics, ethics, psychology

Premature ovarian failure (POF) generally is defined as hypergonadotropic amenorrhea in a woman under 40 years of age, entailing at least 4 months of primary or secondary amenorrhea associated with menopausal levels of serum FSH concentration detected on two separate occasions (1, 2). The prevalence of POF is approximately 1.1% (1). Treatment efforts focus on the hypoestrogenic sequelae, the psychologic impact, and the reproductive implications of POF. The clinical course and reproductive prognosis of women with POF are unpredictable: approximately 50% retain sporadic ovarian function for many years (3), and 5% to 10% of women with POF achieve treatment-independent pregnancies (4). Currently, the most effective means for achieving pregnancy among women in whom POF is diagnosed is IVF with use of donor oocytes.

Etiologies for POF are primarily genetic, autoimmune, and iatrogenic. When POF manifests as primary amenorrhea, 50% of patients have an abnormal karyotype (3). Most cases of POF, however, present as secondary amenorrhea associated with a normal karyotype and lack an attributable cause (2).

Among 46,XX women with nonfamilial POF, up to 7.5% manifest a premutation in the fragile X mental retardation 1 (*FMR1*) gene (5). The *FMR1* gene localizes to the X chromosome at Xq27.3 and normally comprises fewer than 40 cytosine-guanine-guanine (CGG) trinucleotide repeats. Chromosomal fragility at this site predisposes to various degrees of CGG expansion. Expansion beyond 200 CGG repeats causes hypermethylation and inactivation of the *FMR1* gene (5). This is the full mutation; individuals with inactivation of the *FMR1* gene have the characteristic

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phenotype of fragile X syndrome. Individuals with <200 but >60 CGG repeats have the *FMR1* premutation (6), which may manifest with the adult-onset neurologic disorder referred to as fragile X–associated tremor/ataxia syndrome. *FMR1* premutation alleles can expand to the full mutation in one generation. Individuals with <60 CGG repeats have not been known to transmit the full mutation in a single generation, but the lack of absolute knowledge of a "safe" lower limit of CGG repeats that precludes single-generation transmission has led to the definition of an intermediate or "gray zone," consisting of 41 to 60 CGG repeats (6). Individuals with these intermediate-size alleles do not manifest any characteristic phenotype, and, of practical significance, Nolin et al. (7) report that the smallest allele to expand to a full mutation in one generation contained 59 CGG repeats.

Premature ovarian failure occurs in approximately 21% of *FMR1* premutation carriers (8). Conversely, premutation alleles are identified in up to 13% of women with familial POF. Preliminary evidence implicates intermediate-size alleles with an increased risk of POF as well (9). The ovarian insufficiency caused by CGG expansion stems from a hypothesized decreased initial pool of follicles or, alternatively, an accelerated rate of atresia. The following report describes the dilemmas raised by the request of a patient with POF and an intermediate-size *FMR1* mutation to use her younger, nulliparous sister as an ovum donor and how a multidisciplinary approach was used to optimize the reproductive interests of both prospective donor and recipient.

CASE REPORT

Our patient was a 29-year-old nulliparous white woman with a 2-year history of hypergonadotropic amenorrhea. Her serum FSH concentration was 130 mIU/mL, confirmed on repeated testing. Her endocrine profile was normal, and results of an autoimmune workup were negative. Her gynecologic, medical, and surgical history was noncontributory. Of note, the patient was conceived after 9 years of primary infertility; her younger sister was born after an additional 6 years of secondary infertility. As the patient wished to pursue sibling ovum donation, her workup was completed (fragile X premutation testing had not been performed previously), and she began screening tests for the procedure. In the meantime, the patient's 26-year-old, nulliparous sister—engaged to be married in the near future, but not interested in immediate childbearing—confirmed her desire to donate oocytes to her sibling.

The sisters underwent psychologic consultation to explore the impact that ovum donation would have on both the younger sister's impending marriage and her own timetable for childbearing. The nature and quality of the sisters' relationship was discussed. The nulliparity of the prospective donor was noted; parous donors are preferred in our program, particularly when known donors are used, given the risk of complication from controlled ovarian hyperstimulation (COH)–IVF that could compromise their own future fertility. Finally, the possibility—and repercussion—was explored that the younger sister might have POF after successfully donating oocytes to the older sister. In discussing the latter scenario, a suggestion was made to consider splitting the donor's cohort of oocytes from the IVF cycle: half would be donated, and half would be fertilized with sperm from the younger sister's fiancé and cryopreserved for potential future self-use, should it be necessary.

Fragile X genetic testing of our patient revealed that she carried an intermediate-size mutation, with 45 CGG repeats detected. The younger sister was subsequently tested, and she demonstrated the exact same intermediate-size mutation. At genetic counseling, three further points were emphasized to the sisters: First, there would be only a very minimal risk of transmitting a fully expanded mutation in one generation when a mutation of fewer than 59 CGG repeats was discovered in a prospective parent, as such an event has not yet been recorded. Second, the subsequent generation, should the *FMR1* gene be transmitted, would be at risk for the full mutation and thus the development of fragile X syndrome. Third, even intermediate-size mutations as in this case might confer an increased risk of POF.

The sisters maintained their desire to pursue sibling ovum donation. Ovarian function testing of the younger sister on cycle day 3 revealed a serum FSH concentration of 10.1 mIU/mL and E_2 of 35 pg/mL, despite her asymptomatic status and regular menses. Her FSH level, above the common, albeit arbitrary, cutoff value of 10 mIU/mL (10), nonetheless indicated potentially diminished ovarian reserve. Accordingly, under typical circumstances, she would have been rejected as an ovum donor. Repeated FSH testing revealed an FSH level of 8 mIU/mL, an E_2 of 49 pg/mL, and an adequate antral follicle count. The sisters requested that we proceed with treatment that would assist the donor (by freezing embryos) and the sister (by donating eggs to her). The unique circumstances in this case triggered a referral to our Assisted Reproductive Ethics Committee for review.

The Committee acknowledged that the younger sister's nulliparity and potentially diminished ovarian reserve ordinarily would preclude her from donating to her older sister. In this particular case, however, the younger sister confronts a heightened risk of POF and could benefit from undergoing a COH-IVF cycle at this point by harvesting and cryopreserving her own embryos. Difficulty was anticipated with splitting a cohort of oocytes: the donor's potentially diminished ovarian reserve might dampen the overall quantity and quality of the yield, and it might well prove to be challenging to decide how to apportion the available oocytes. An alternative was proffered: the younger sister would first undergo COH-IVF with fertilization of all of her eggs with her fiancé's sperm and cryopreservation of the resulting embryos for potential future self-use. After her own embryos were created, the younger sister would cycle as a sibling ovum donor.

The sisters agreed to this plan. The younger sister underwent pituitary down-regulation with leuprolide acetate (LA; TAP Pharmaceuticals, Deerfield, IL) 0.5 mg in the midluteal phase