ORIGINAL ARTICLE: GENETICS

Management of the risks for inherited disease in donor-conceived offspring

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Objective: To illustrate the burden of inherited disease on donor-conceived offspring based on mode of inheritance and to provide guidance on methods of risk reduction.
Design: An 8.5-year retrospective review of outcome reports and donor management to summarize medical risks to donor-conceived offspring that presented after the sperm donors were qualified for participation in the donor program.
Setting: Not applicable.
Patient(s): None.
Intervention(s): None.
Main Outcome Measure(s): Description of our experience with newly identified medical risks in donor-conceived offspring as well as how this information was ascertained and managed.
Result(s): More than half of the indications to restrict donor specimen distribution were due to multifactorial disorders. Approximately one third of the restrictions involved autosomal recessive disorders. The remainder of the restrictions were due to the other indications, including autosomal dominant disorders.
Conclusion(s): The risks for multifactorial disorders or undiagnosed autosomal dominant disease cannot be significantly reduced or eliminated with routine donor screening procedures. Ongoing risk assessment is essential to identify new genetic risks for autosomal dominant and multifactorial disorders. These assessments require an investment of resources and genetics professionals in the long-term management of changing health information as well as collaboration among gamete facilities, recipients, donors, and their health care providers. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Gamete donor, sperm donor, autosomal recessive, autosomal dominant, multifactorial

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Current eligibility guidelines for gamete donors state that potential donors should not have autosomal dominant (AD) disorders or significant familial disease with a genetic component (1). Gamete providers typically perform personal and family history risk assessments (2) to screen for these risks, but they cannot always be detected at the time of a donor's eligibility assessment owing to reduced penetrance, variable expressivity, or temporal factors.

The number of offspring conceived from a single gamete donor in the United States is determined by individual gamete providers. The American Society of Reproductive Medicine recommends a maximum of 25 births from one donor in a population of 800,000 individuals (1). In practice, this means that there may be many more births from an individual donor particularly if a donor's specimens are distributed globally. At our facility, we aim for 20–30 family units per donor globally, each of which may include one or more children. Owing to these large potential birth rates, when genetic mutations or susceptibility factors are undetected in gamete donors they may be transmitted to a large number of donor-conceived individuals, leading to a significant disease burden in subsequent generations compared with what would typically occur from an average affected individual.

While significant attention has been directed to carrier screening for autosomal recessive (AR) disease through application of expanded carrier screening platforms (3–5), to identify and reduce the incidence of disease in donor-conceived individuals, it is important that the reduction in overall disease risk is not overstated to recipients of donated gametes. The risks of transmission of other inherited conditions to donor-conceived individuals remains substantial, and the best practices to identify these risks have been infrequently discussed. Here we provide evidence from our sperm donor program that significant risks to donor-conceived individuals include inherited

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susceptibility for multifactorial disease and undiagnosed AD disorders. We examine the disease burden on donor-conceived individuals and recommend strategies for managing these risks in the gamete donor setting.

MATERIALS AND METHODS

Genetic risk assessments are performed on sperm donors at our facility on an ongoing basis as new genetic tests are performed on qualified donors or new medical issues are reported in offspring, donors, or their family members through our Special Testing, Adverse Outcome Report, and Donor Update services, respectively. If new information from these programs suggests a significant risk for previously unidentified medical issues in offspring of a donor, distribution of vials from that donor is restricted and relevant client populations are notified, depending upon the specific concern. Records from these operations for the 8.5-year period from January 2007 through June 2015 were reviewed to extract the following data and summarize the medical risks to donor-conceived offspring that were identified after applicants qualified for participation in our anonymous sperm donor program:

- New diagnoses reported in the sperm donors and their family members.
- New diagnoses reported in donor-conceived individuals. This data set is limited to the reporting period and independent of the year of birth, age of onset of symptoms, or age at diagnoses in offspring.
- Supplemental genetic testing performed on donors.
- Restricted distribution of donors' specimens due to increased inherited risks.

This time frame was selected because data were captured from standardized procedures and through consistent reporting methods.

All recurrence risk calculations and estimates were derived from general population risks figures. The incidences and carrier frequencies of some disorders are elevated in some specific populations; however, the general population risk estimates were used because they are representative of the diverse population of gamete-donor recipients. In our experience, it is not unusual for recipients to select donors from ethnic and racial groups different from their own.

Institutional Review Board approval was not obtained because this research involved review of existing internal data that had been voluntarily reported to our facility and the information compiled did not identify any individuals.

RESULTS

Distribution of vials from 108 donors was restricted from January 2007 through June 2015 based on 114 confirmed or suspected diagnoses in the sperm donor, his family members, or donor-conceived offspring. Six donors had two separate restrictions due to different, unrelated indications.

Approximately one third of the restrictions (35/114) involved risks for 21 different AR conditions (Table 1). The majority of donors who were restricted owing to AR carrier status were identified because of a report of an affected child (20/35). This includes three cases of cystic fibrosis (CF) in which the sperm donors were identified as carriers of rare, previously untested mutations, despite routine carrier screening for CF as part of the qualification process. Six cases were identified because carrier screening was requested by a client who was previously identified as a carrier for a specific recessive condition herself, and one case occurred when a donor had additional screening for his personal reproductive purposes. Six donors were identified as carriers when additional carrier screening was performed on previously qualified donors owing to new donor program requirements (15). In one case, a donor was identified as a carrier when a genetic testing laboratory incorrectly interpreted a test order and performed an expanded carrier screening panel on the donor in error. Two other cases involved offspring who had abnormal newborn screening results but who were not affected with the diseases.

Eleven restrictions were implemented owing to identification of AD disease risks (Table 2), including BRCA1/2-

TABLE 1

Newly identified risks for AR disorders in donor-conceived offspring (6–14).

Condition	No. of donors	General population risk (%)	Average risk to donors' offspring (%)
Achromatopsia	1	1/38,000 (0.003)	1/390 (0.26)
Congenital adrenal hyperplasia (due to 21-hydroxylase deficiency)	3	1/15,000 (0.006)	1/248 (0.40)
CF	3	1/3,136 (0.03)	1/112 (0.9)
DFNB1 (nonsyndromic hearing loss)	1	1/7,259 (0.014)	1/170 (0.59)
Galactosemia	3	1/40,000 (0.0025)	1/100 (1)
Glycogen storage disorder type 1a (GSD1a)	1	1/100,000 (0.001)	1/632 (0.16)
Joubert syndrome	1	1/80,000 (0.001)	1/564 (0.18)
Medium-chain acyl-CoA dehydrogenase deficiency	1	1/14,600 (0.007)	1/242 (0.41)
Phenylalanine hydroxylase deficiency	2	1/10,000 (0.01)	1/200 (0.5)
Pompe disease	1	1/40,000 (0.0025)	1/100 (1)
Smith Lemli Opitz syndrome	1	1/18,604 (0.005)	1/273 (0.37)
Spinal muscular atrophy	8	1/12,996 (0.008)	1/228 (0.44)
Very-long-chain acyl-CoA dehydrogenase deficiency	1	1/31,500 (0.003)	1/374 (0.27)
Other disorders	8	1/40,000 (0.0025)	1/100 (1)

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