Implications of Hypertrophic Cardiomyopathy Transmitted by Sperm Donation

Barry J. Maron, MD
John R. Lesser, MD
Nelson B. Schiller, MD
Kevin M. Harris, MD
Colleen Brown, ScM
Heidi L. Rehm, PhD

Context Sperm donation is an increasingly common practice for achieving pregnancy in the absence of a male partner or when fertility is problematic. The unintended consequence in which genetic diseases are unwittingly transmitted to offspring is an underrecognized public health issue not previously prioritized by US Food and Drug Administration guidelines.

Objective To report the clinical circumstances and implication of hypertrophic cardiomyopathy (HCM) transmitted by sperm donation to recipients.

Setting Voluntary sperm donation through a US Food and Drug Administration–approved tissue bank.

Main Outcome Measure Incidence of genetically affected offspring and clinical outcomes to date.

Results An asymptomatic 23-year-old man who had no personal knowledge of underlying heart disease and who underwent standard testing that was negative for infectious diseases, repeatedly donated sperm over a 2-year period (1990-1991). The donor was later shown to be affected (in 2005) by a novel β-myosin heavy-chain mutation that caused HCM, after an offspring was clinically diagnosed with this disease. Of the 24 children known to be offspring of the donor, including 22 who were products of fertilization via sperm donation and 2 conceived by the donor's wife, a total of 9 genetically affected offspring, 2 to 16 years of age and 6 males, have been identified with HCM (2005-2009). Three of the 9 gene-positive children have currently expressed phenotypic evidence of HCM, including one who died at age 2 years due to progressive and unrelenting heart failure with marked hypertrophy, and also 2 survivors with extreme left ventricular hypertrophy at age 15 years. The latter 2 children and the donor are judged likely to be at increased risk for sudden death.

Conclusions This case series underscores the potential risk for transmission of inherited cardiovascular diseases through voluntary sperm donation, a problem largely unappreciated by the medical community and agencies regulating tissue donation. Recommendations include improved screening guidelines for donors to exclude cardiovascular diseases (eg, HCM) such as consideration for 12-lead electrocardiograms.

JAMA. 2009;302(15):1681-1684 www.jama.com

DONATION OF SPERM TO achieve pregnancy, either in the absence of a male partner or when a fertility problem exists, is practiced with considerable frequency.[1,2] Sperm banks, Internet-based agencies, or private agreements have evolved over the past 25 years as mechanisms for interfacing potential recipient women with suitable donors. The donor thereby becomes the genetic and biological father of each child produced with his sperm. While the US Food and Drug Administration (FDA) inspects the operation of the banks and screening procedures for donors,[1] this process has been directed primarily toward the prevention of infectious diseases, with little attention to the potential transmission of genetic diseases.[1,2]

We report a novel circumstance in which sperm donated by a man with unrecognized hypertrophic cardiomyopathy (HCM)[3] produced several affected children including some at increased risk for premature cardiac death.

CASE REPORT

Donor

A 23-year-old white man (III-3, FIGURE 1) in good health, and asymptomatic, with no history of cardiac disease, donated his sperm on multiple occasions (n=95) over a 2-year period in 1990-1991 under a contractual agreement with one of the 110 US sperm banks. He was screened by a comprehensive personal and family history, physical examination, and by laboratory testing for infectious and transmittable diseases: human immunodeficiency virus 1 and human immunodeficiency virus 2, human T-lymphotropic virus 1 and human T-lymphotropic virus 2, syphilis, cytomegalovirus, hepatitis B and C, gonorrhea and chlamydia, as well as Tay-Sachs disease.

See also p 1702 and Patient Page.

Several years later an offspring was diagnosed with HCM, which triggered the notification to all known recipients of this donor's sperm that

Author Affiliations: Hypertrophic Cardiomyopathy Center, Minneapolis Heart Institute Foundation and Abbott Northwestern Hospital, Minneapolis, Minnesota (Drs Maron, Lesser, and Harris); Partners Healthcare Center for Personalized Genetic Medicine, Department of Pathology, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts (Dr Rehm); and Divisions of Cardiology and Medical Genetics, University of California at San Francisco, San Francisco (Dr Schiller and Ms Brown).
Corresponding Author: Barry J. Maron, MD, Minneapolis Heart Institute Foundation, 920 E 28th St, Ste 620, Minneapolis, MN 55407 (hcm.maron@mhif.org).

an inherited form of heart disease could have been transmitted to their children. Genetic testing was offered[4] first to the donor and later to the offspring.

IRB approval and protocols for this study were provided through Brigham and Women's Hospital, Boston, Massachusetts, and Abbott-Northwestern Hospital.

Genetic Studies

At the Laboratory for Molecular Medicine, Partners Healthcare Center for Personalized Genetic Medicine, DNA from the donor was tested for mutations in 5 genes (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, and *TPM1*). A novel β-myosin heavy-chain (*MYH7*) missense mutation, Arg169Gly (505A>G), was located at a highly conserved residue in the myosin motor domain.

Twenty-two children (among at least 13 families) are known to have been products of fertilization via sperm donation. Of these, 16 have been tested for the Arg169Gly mutation, and 8 were positive (Figure 1). Eight other offspring have tested negative, aged 9 to 15 years (mean age, 12.5 years; 4 males).

The donor (III-3, Figure 1) also had 2 children conceived with his wife; one of these children tested positive.

Several factors support a pathogenic role for the Arg169Gly mutation including the absence of the variant in more than 3000 chromosomes tested, the high conservation of the Arg169 residue, the location within the motor domain of the β-myosin heavy-chain protein, and consistent segregation of the mutation with the affected offspring.

Clinical Findings

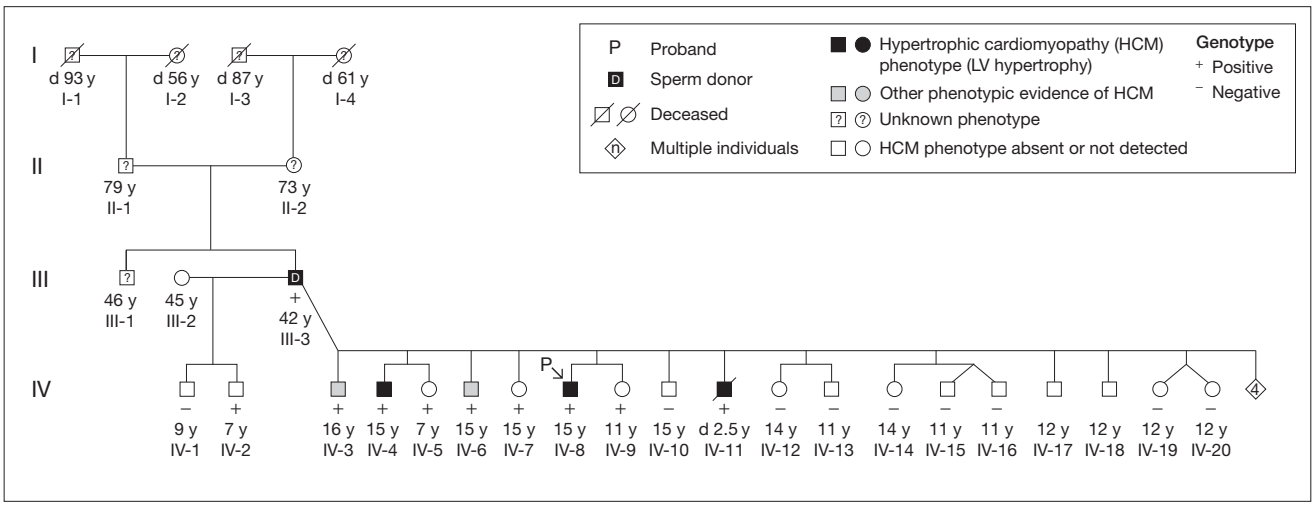
Of the 9 children who were mutation-positive (aged 2-16 years; 6 males), one has functional limitation with exertional chest pain and fatigue (IV-4), one experienced presyncope and palpitations (IV-8), and the other 7 remain asymptomatic. Two of the living offspring (IV-4 and IV-8; both with symptoms) have phenotypic evidence of HCM with left ventricular (LV) hypertrophy in the absence of obstruction to LV outflow at rest (Figure 1), are 15 years old, and show extreme LV wall thickness involving the ventricular septum[5] of 30 mm and 34 mm (FIGURE 2).

One of these children (IV-8) has received a prophylactically implanted cardioverter-defibrillator for prevention of sudden death.[6] Another genetically affected offspring, (IV-11, Figure 1) died at 2.5 years of age of obstructive HCM (ventricular septal thickness, 22 mm) and progressive heart failure[7] while awaiting transplant.

Six of the 9 genetically affected children do not currently show LV hypertrophy as assessed by 2-dimensional echocardiography at ages 7, 7, 11, 15, 15, and 16 years (mean age, 12 years), although other findings were consistent with phenotypic expression, including mild systolic motion of the mitral valve in one (IV-6) and an abnormal electrocardiogram in the other (IV-3).

The donor (III-3) demonstrated segmental LV hypertrophy (thickness, 18 mm) confined to the posterior (inferior) LV, a region not reliably detected by echocardiography and

Figure 1. Pedigree Showing Offspring of the Sperm Donor



In the 2 genetically affected offspring without left ventricular (LV) hypertrophy, other clinical evidence of the hypertrophic cardiomyopathy (HCM) phenotype was present, including abnormal electrocardiogram with T-wave inversion in leads II and III, aVF, and Q waves in leads V_4 to V_6 (IV-3), or mild systolic anterior motion of the mitral valve (IV-6). One offspring (IV-11) died of progressive heart failure due to obstructive HCM and was tested retrospectively on a stored DNA sample extracted from peripheral blood obtained prior to death. Although cardiac evaluation was not available in any of the donor's parents, grandparents, or siblings, the donor reported that he was unaware of any evidence of HCM in these family members. The cause of death in the paternal grandmother (I-2) was reported to be a "heart attack" at age 56 years. Both of the donor's parents underwent prosthetic valve replacement. All offspring with unshaded pedigree symbols had reportedly normal cardiac evaluations. Diamond represents 4 additional offspring who did not participate directly in the study but have not pursued genetic testing and have had ongoing cardiac evaluations that were reportedly normal.

recognized in this patient only by cardiovascular magnetic resonance imaging[8] (Figure 2). Also, the electrocardiogram was abnormal with T-wave inversion (most prominent in V_4-V_6), and left atrial enlargement. Following gadolinium contrast, extensive delayed enhancement consistent with myocardial fibrosis was largely confined to the hypertrophied region of LV. Hypertrophy was absent by echocardiography in each of the 9 offspring with negative genetic testing.

COMMENT

This case study underscores several important principles regarding the relation of sperm donation with inherited heart diseases such as HCM, by illustrating the possibility that genetic conditions can be transmitted unwittingly to offspring by this practice. We are aware of only 1 other documented instance in which a genetic disease was transmitted to an offspring by sperm donation.[9]

In the present scenario, the donor was young, healthy, had no personal knowledge of underlying heart disease, and the medical history, physical examination, and standard testing prior to sperm donation showed negative results. Indeed, his diagnosis of HCM was made only after phenotypically expressed disease was identified in an offspring.

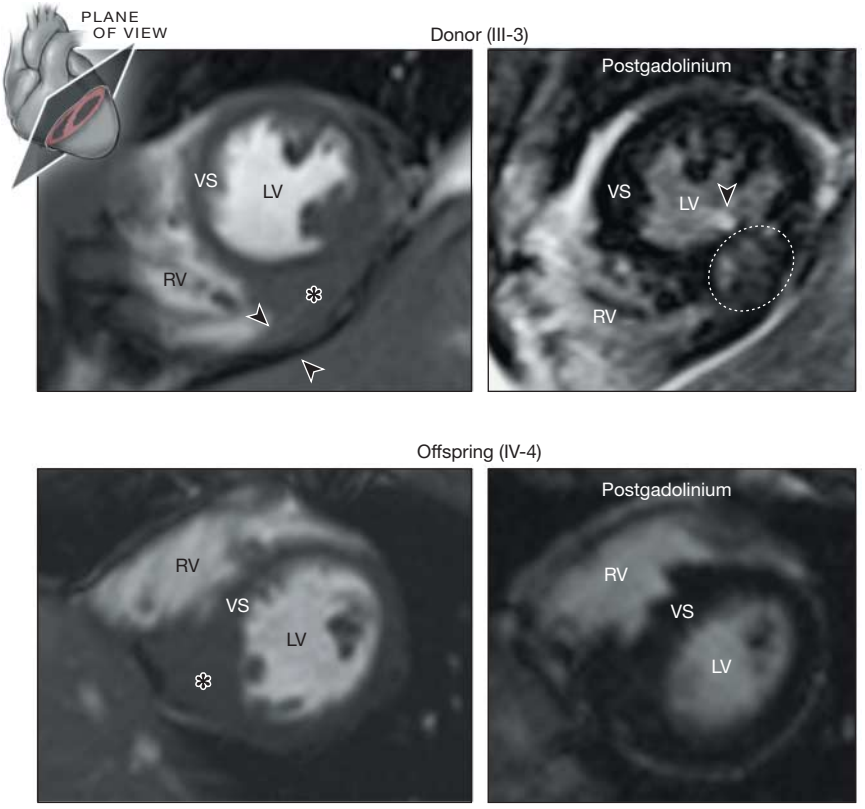
Since May 2005, the FDA[1] has regulated donor eligibility and sperm banks for compliance with guidelines also offered by the American Society of Reproductive Medicine,[2] the American Association of Tissue Banks, and many states. Although the FDA is mandated to ensure the good health status of donors and prevent transmission of disease, its regulations for sperm banks have focused disproportionately on communicable diseases such as human immunodeficiency virus, human T-lymphotropic virus, cytomegalovirus, hepatitis B and C, gonorrhea, syphilis, and chlamydia (tested every 3 months during the donation period).

However, there has been little specific attention directed toward detection of inherited cardiovascular diseases. Available screening guidelines rely largely on obtaining a family history,[1,2] a strategy not likely to be particularly effective for the clinical identification of most HCM patients.[3] Although not required by FDA, some sperm banks test for cystic fibrosis, thalassemia anemia, sickle cell trait, Tay-Sachs, and other genetic diseases that have increased frequency in Ashkenazi Jews; all of these conditions are much less common than HCM in the general population.[10]

In the present case, the donor transmitted an HCM-causing mutant gene to at least 9 children, with the oldest being 16 years of age at the time of this publication. Furthermore, in 3 of these children this mutation was associated with evidence of a high-risk clinical profile, including a 2.5-year-old offspring who died of HCM with intractable heart failure, 2 offspring with massive LV hypertrophy, as well as the donor with extensive myocardial fibrosis.[11] Recognition that this β-myosin heavy-chain HCM mutation appears to have conveyed increased risk underscores the importance of assembling and sharing clinical data for all individuals in such a pedigree (who were otherwise largely unaware of each other).

Although no accepted guidelines presently exist for the process of noti-

Figure 2. Phenotypes of Hypertrophic Cardiomyopathy



Cross-sectional short axis magnetic resonance images. Top left, In the donor, segmental hypertrophy involving the posterior (inferior) free wall of the left ventricle (LV) and small contiguous portion of ventricular septum (VS) in the mid-LV cavity at papillary muscle level (black asterisk, 18-mm thickness) and also extending into the adjacent right ventricular (RV) wall (black arrowheads). Top right, Confluent midmyocardial (and transmural) delayed enhancement in the region of hypertrophy (dotted ellipse) and posterior papillary muscle (black arrowhead).
Bottom left, In a 14-year-old male offspring, the distribution of LV cavity hypertrophy is almost identical to that in the donor (see top left), with marked segmental hypertrophy involving posterior (inferior) septum and contiguous posterior free wall at papillary muscle level (black asterisk, 30-mm thickness). Bottom right, Absence of delayed enhancement.

fication, counseling, and offspring evaluation after a genetic disease is identified due to gamete donation,[12] a unique process transpired in this case due to collaboration between the sperm bank, the donor, and the genetic testing facility. In this regard, sperm recipients were notified that transmittable heart disease had been identified in the proband, of the availability of molecular diagnosis, as well as the advisability for cardiovascular assessments in the offspring. The success of this strategy underscores the need for guidelines to notify gamete donors, recipients, and other affected parties once genetic disease arises.

This scenario has important medical implications given the possibility of multigenerational transmission of a mendelian autosomal dominant disease such as HCM.[4] Also, the required long-term donor-compensated contracts (of 1-2 years), and the absence of restrictions to the number of pregnancies permitted for each donor potentially promotes large numbers of affected offspring. Even in retrospect, it is difficult to envision a practical screening protocol that could reliably target the entire multitude of genetically transmitted diseases that could arise in such clinical circumstances. Nevertheless, our observations raise considerations for effective screening strategies to prevent donors from propagating mutant genes that cause relatively common genetic diseases such as HCM.

In this regard, it would be impractical to require routine echocardiography as part of noninvasive cardiovascular evaluations, nor is HCM-specific genotyping likely due to its current expense and limited clinical sensitivity.[13] However, given the observations in the donor (12-lead ECG was strikingly abnormal but the echocardiogram was nondiagnostic),[8] as well as recognition that ECGs are abnormal in 80% to 95% of affected HCM adults with LV hypertrophy,[14] it is suggested that the ECG may represent an efficacious strategy for excluding sperm donors with this disease. This approach is reminiscent of that used to detect HCM in large Italian populations of competitive athletes,[15,16] and also could potentially serve to identify other familial diseases associated with sudden death, such as ion channelopathies (including long QT syndrome).[17]

In conclusion, the novel medical situation reported in this case series raises a largely ignored but potentially significant public health issue, namely the risk for transmission of genetic disease by voluntary gamete donation. There is considerable value in providing the public with information about this issue and raising the possibility of screening strategies for donors to prevent future undesirable propagation of genetic cardiovascular diseases such as HCM.

Author Contributions: Dr Maron had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Maron, Lesser, Rehm.
Acquisition of data: Maron, Lesser, Schiller, Brown, Rehm.
Analysis and interpretation of data: Maron, Lesser, Schiller, Harris, Brown, Rehm.
Drafting of the manuscript: Maron, Lesser, Schiller, Harris, Brown.
Critical revision of the manuscript for important intellectual content: Maron, Lesser, Harris, Brown, Rehm.
Statistical analysis: Lesser, Rehm.
Obtained funding: Lesser, Brown.
Administrative, technical, or material support: Maron, Lesser, Schiller, Harris, Rehm.
Study supervision: Lesser, Rehm.
Financial Disclosures: Dr Maron reports having a consultant relationship with GeneDx, a subsidiary of Bio-Reference Laboratories (a company that performs genetic testing for hypertrophic cardiomyopathy and other diseases), but reports that he did not have contact with or a relationship to the genetic testing reported in this study. The other authors report no relevant disclosures or associations with industry.
Funding/Support: This study was supported in part with a grant from The Hearst Foundations.
Role of the Sponsor: The Hearst Foundations did not participate in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the presentation, review, or approval of the manuscript.
Additional Contribution: We thank the donor and the families of the affected offspring for providing permission to publish this information about their cases.

REFERENCES

1. US Department of Health and Human Services; US Food and Drug Administration; Center for Biologics Evaluation and Research. Guidelance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 27, 2007. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm. Accessed September 2, 2009.
2. Practice Committee of American Society for Reproductive Medicine; Practice Committee of Society for Assisted Reproductive Technology. 2008 Guidelines for gamete and embryo donation: a Practice Committee report. *Fertil Steril*. 2008;90(5)(5 suppl):S30-S44.
3. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42(9):1687-1713.
4. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. *J Cardiovasc Electrophysiol*. 2008;19(1):104-110.
5. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342(24):1778-1785.
6. Maron BJ, Spirito P, Shen W-K, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;298(4):405-412.
7. Maron BJ, Tajik AJ, Ruttenberg HD, et al. Hypertrophic cardiomyopathy in infants: clinical features and natural history. *Circulation*. 1982;65(1):7-17.
8. Rickers C, Wilke NM, Jerosch-Herold M, et al. Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. *Circulation*. 2005;112(6):855-861.
9. Wirojanan J, Angkustsiri K, Tassone F, Gane LW, Hagerman RJ. A girl with fragile X premutation from sperm donation. *Am J Med Genet A*. 2008;146(7):888-892.
10. Maron BJ, Gardin JM, Flack JM, Gidding SS, Bild D. Assessment of the prevalence of hypertrophic cardiomyopathy in a general population of young adults: Echocardiographic analysis of 4111 subjects in the CARDIA Study: Coronary Artery Risk Development In (young) Adults. *Circulation*. 1995;92(4):785-789.
11. Maron MS, Appelbaum E, Harrigan CJ, et al. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy [published online ahead of print June 23, 2008]. *Circ Heart Fail*. 2008;1:184-191. doi:10.1161/circheartfailure.108.768119.
12. Gazvani R, Hamilton MPR, Simpson SA, Templeton A. New challenges for gamete donation programmes: changes in guidelines are needed. *Hum Fertil*. 2002;5(4):183-184.
13. Van Driest SL, Ommen SR, Tajik J, Gersh BJ, Ackerman MJ. Yield of genetic testing in hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2005;80(6):739-744.
14. Maron BJ, Niimura H, Casey SA, et al. Development of left ventricular hypertrophy in adults with hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C mutations. *J Am Coll Cardiol*. 2001;38(2):315-321.
15. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med*. 1998;339(6):364-369.
16. Myerburg RJ, Vetter VL. Electrocardiograms should be included in preparticipation screening of athletes. *Circulation*. 2007;116(22):2616-2626.
17. Miller MD, Porter CB, Ackerman MJ. Diagnostic accuracy of screening electrocardiograms in long QT syndrome. *Pediatrics*. 2001;108(1):8-12.

