Ethical quandaries around expanded carrier screening in third-party reproduction

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Although current screening methods of gamete donors are capable of reducing the incidence of genetic anomalies in donor offspring below general population levels, targeted screening for a large number of conditions (expanded carrier screening or ECS) could be considered as part of the routine selection procedure for gamete donors. There are, however, important drawbacks to its practical implementation. Excluding all carriers of severe recessive monogenic pediatric disorders would disqualify virtually all donors, and other approaches negatively affect cost (and therefore access), present dilemmas in regard to disclosure of genetic findings, and/or overburden the intended parents. In all of the scenarios considered, adequate genetic counseling will be of central importance. Besides looking at benefits and drawbacks of possible ways of implementing ECS, we also examine whether a moral obligation exists to adopt ECS at all and on whose shoulders such an alleged obligation would rest: policymakers, medical staff at fertility clinics, sperm and egg banks, the intended parents? We argue that given the small risk reduction brought about by ECS, the possible negative effects of its implementation, and the absence of widespread preconception carrier screening in the general population, it is inconsistent to argue that there is a moral obligation to perform ECS in the context of donor conception. Finally, implications for the donors are discussed. (Fertil Steril® 2018;109:190–4. ©2017 by American Society for Reproductive Medicine.)

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Genetic testing for inherited conditions is becoming an important component of preconception planning, not only for those with an increased a priori risk due to the personal or family history of themselves or their partners, but also for the general population. Until recently, preconception carrier screening was limited to one or a handful of conditions that are relatively common (either in the general population or for someone's specific ethnic background) and that have a significant impact on quality of life and/or life expectancy. Recent technological advancements with high-throughput genotyping and sequencing approaches allow for simultaneous and efficient screening of a large number of autosomal or X-linked recessive conditions. This technique is referred to as expanded carrier screening (ECS). Expanded carrier screening has made it possible to identify a variety of genetic mutations that have significant variation in their presentation, including variable age of onset and phenotypes that are not always clearly defined. Expanded carrier screening can be done by means of genotyping (testing for a set of specific mutations of the genes) or sequencing (testing for all variations of the genes). Expanded carrier screening presents significant challenges in patient management, particularly in both sperm and egg donation, for which there has been a growing demand for more thorough genetic screening. This has been sparked by cases in which donors have transmitted genetic diseases to offspring (1–3), inciting concerns in recipients of donor gametes. This review explores some of the ethical quandaries that ECS creates in the context of third-party reproduction. We discuss the pros and cons of different ways of implementing ECS and address the underlying question of whether there is a moral obligation to perform ECS in gamete donors and whether this obligation rests with the intended parents, the clinic, the donor, or policy makers.

CURRENT RECOMMENDATIONS AND PRACTICE

The 2013 American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology recommendations for the genetic screening of gamete donors state that donors should be screened for heritable

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diseases through a family history and through genetic testing (4). Testing for cystic fibrosis (CF) carrier status should—according to the ASRM—be performed on all donors, and other genetic testing should be performed as indicated by the donor's ethnic background. Testing for fragile X on oocyte donors is to be considered but is not required. Furthermore, the ASRM specifies that genetic counseling for both donor and recipient is recommended when a prospective donor is identified as a carrier and that it is not appropriate to screen donors for adult-onset conditions without their full consent.

In practice a three-generation pedigree is taken, and additional screening is determined by self-declared ethnicity (5). Several companies and clinics offer additional testing and explicitly advertise their (more) thorough screening.

THE WAY FORWARD: DIFFERENT OPTIONS

There are several ways to respond to the challenge of ECS in third-party reproduction, each with its own advantages and drawbacks. One option that is no longer feasible when ECS is implemented is exclusion of all donors who test positive for carrying a harmful mutation for a recessive condition. Two separate studies, consisting of next-generation sequencing and variant analysis for more than 450 genes associated with severe monogenic pediatric disease, revealed that every candidate donor is a carrier of one or several harmful mutations for recessive conditions (6, 7). Excluding all carriers of severe recessive monogenic pediatric disorders would therefore stop the practice of gamete donation.

An alternative option, aimed at maximal avoidance of affected offspring, is offering ECS to both donors and recipients, and matching them. In this way, heterozygous gametes for the same condition have no chance of combining. An example of this strategy is a program of oocyte donor screening with next-generation sequencing, which analyzes 200 genes associated with 368 conditions (of which 277 are autosomal recessive and 37 are X-linked conditions) (8). In 3% of assigned donor–recipient pairs the selected donor had to be replaced because of high reproductive risk. Advantages of this approach are minimizing genetic conditions in donor offspring without losing a great number of candidate donors. The disadvantages are the cost of sequencing for both donor and recipient, plus genetic counseling for both. In this scenario, choices need to be made about what information will be shared with donors and recipients: [1] no information about their carrier status (except when they carry a mutation from the American College of Medical Genetics and Genomics incidental finding panel) (9), [2] carrier status for "common" recessive conditions, such as CF, spinal muscular atrophy, and conditions prevalent in the individual's ethnic population, [3] carrier status for other disease-causing mutations (that will have no effect on their own health), or [4] all findings, including variants of unknown significance. In all cases the need for thorough genetic counseling can hardly be overstated. Besides explaining the basic inheritance pattern of autosomal recessive disorders, it is important to point out to recipients that many congenital abnormalities remain unexplained, that there is always a residual risk even after a negative screen, that the child can be born with a de novo mutation, and that the child can have a multifactorial condition that could not be predicted before conception.

A second approach could be to limit screening to a narrow panel of specific variants and conditions, followed by exclusion of all affected donors without screening recipients. Although it is unlikely that sperm/egg banks and fertility clinics would agree upon a set panel, professional organizations might propose a recommended panel and educate the public that screening beyond this panel will not have a substantial added benefit. That being said, there will always be commercial companies that are willing to cater to those who request more-extensive screening. Nevertheless, it may also be in private companies' interests to agree on a set panel. At present, different commercial carrier screens lead to different results (7). Settling on one set panel would avoid confusion and would avoid future parents feeling pressured into opting for the most elaborate screening even at a marginal added benefit. Other advantages of this approach are the more limited costs and less complicated genetic counseling for both donor and recipient. Disadvantages are the possibility of an occasional case of matching a donor and a recipient who carry the same recessive disorder (that was not screened for). Also in this scenario, pretest genetic counseling is important, to ensure that both donor and recipient have realistic expectations and understand the limitations of screening.

A third strategy is to provide more options to the recipients by making a distinction between required testing of the donor (e.g. family history, CF), recommended testing (e.g., fragile X, screening based on ethnic background), and optional testing (additional testing above the two previous categories), so that recipients can weigh the benefits and disadvantages of each additional layer of screening. As illustrated in a study by Baker et al. (10), not all fertility patients desire the same level of genetic screening of their donor. Financial restrictions may play a role in this decision. Additionally, in other contexts, an increase in the number of conditions screened for has been linked to an increase in negative feelings and a decrease in knowledge about the conditions screened for (11). In practice, especially for sperm donors, this system would require the sperm/egg bank or fertility clinic to set up different categories of donors with more or less screening because one donor oftentimes donates to several recipients. Such a system also allows more respect for the donor's own wishes regarding the level of genetic screening he/she is willing to undergo. Advantages of this approach are that recipients are not forced to take on an extra cost that is not imposed on the general population, and it offers some legal protection for sperm banks and fertility clinics against wrongful life or wrongful birth claims. Disadvantages are a more elaborate process that requires extra effort with regard to genetic counseling and a transfer of the responsibility for genetic screening to the intentional parents. They are put in a difficult position and may be overwhelmed with guilt if their child turns out to have a genetic disorder for which they declined screening.

A related strategy is to perform ECS on all donors, excluding only those who test positive for dominant or X-linked conditions and handing the information about