

Virtual Mentor

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CLINICAL CASE

Evaluating Requests for Preimplantation Genetic Diagnosis

Commentary by Anam Pal and Lubna Pal, MBBS, MSc

Mr. and Mrs. Anderson were both in their mid-30s. Mr. Anderson was a carpenter and built wood furniture by hand for internationally renowned designers. Mrs. Anderson was a college field hockey player and now the head field hockey coach at a local college. They both wanted a child and, having tried without success to conceive for over a year, they made the decision to consult Dr. Wells, a reproductive endocrinologist.

After 6 months of standard testing and therapy, the Andersons still had not conceived; Dr. Wells suggested that the couple consider in vitro fertilization (IVF).

The Andersons were eager to start IVF and had also begun to investigate the possibility of preimplantation genetic testing of candidate embryos. The couple knew a family who had a child with congenital defects of both hands and an atrial septal defect (ASD). Mrs. Anderson was concerned that a child with a heart defect, even a relatively easily treated defect such as an ASD, would be at a disadvantage as an athlete. Mr. Anderson told Dr. Wells that he did not want to have a child who was unable to work with his or her hands because he would be unable to share his love for woodworking with such a child.

Dr. Wells was open to facilitating preimplantation genetic testing for the Andersons but had reservations about discarding embryos with mutations that would lead to disabilities he considered relatively minor.

Is Dr. Wells justified in offering testing only for conditions that significantly impact quality of life as he defines it? Should he communicate his own sense of what makes life valuable with the Andersons?

Commentary

This case describes a young and otherwise healthy infertile couple's consideration of proceeding with IVF, with an expressed interest in utilizing preimplantation genetic diagnosis (PGD) to minimize the risk of conceiving a child affected with Holt-Oram syndrome (HOS) [1-5]. The couple wishes to ensure against having a child who is affected by either cardiac defects or upper-limb anomalies, both integral to HOS—a rare genetic disorder that inflicts a risk of both aforementioned structural malformations [1].

HOS is a familial, heart-hand syndrome inherited in an autosomal dominant fashion with a high level of penetrance [2-5]. It is characterized by a combination of congenital cardiac anomalies and upper-limb malformations, with the type and severity of the specific deformities in a future generation being unpredictable [2-5]. ASD is the most common cardiac malformation seen in HOS; upper-limb abnormalities are fairly universal and of varying severity and nature.

Aspects of this dilemma worth perusing are: (1) the use of a sophisticated and expensive methodology (PGD) by a healthy couple with no discernable genetic risk beyond the age-comparable risk in the general population, leading to a tussle between the concept of patient autonomy and principles of nonmaleficence and justice reflected in Dr. Wells' reluctance to offer PGD to this couple; (2) the limitations of PGD that preclude ensuring against structural nongenetic anomalies; and, (3) while not explicitly stated, the suggestion that certain specific fetal anomalies (i.e., relatively minor variants of ASD or structural upper-limb deformities) might induce this couple to opt for an elective termination of a pregnancy because the fetus is afflicted by abnormalities that some people may consider minor [6]. (Given that a clear relationship between phenotypic expression of the genotype is lacking for HOS, however, Dr. Wells' conjecture that phenotypic expressions of the disorder may be minor is additionally simplistic.)

Although HOS is a rare genetic disease, it is the most common of heart-hand syndromes, with a frequency of approximately 1 in 100,000 live births [5]. Corrective surgical approaches are the mainstay in management of the respective structural anomalies. Genetic mutations in the TBX5 transcription factor are identified as the molecular mechanism underlying HOS, though a clear relationship between genotype and phenotype is far from apparent [7]. Prenatal diagnosis of HOS is feasible through chorionic villus sampling and amniocentesis; more recently, PGD has also been successfully employed in a patient with known HOS whose progeny have a 50 percent chance of being afflicted by this disorder [7].

Whilst the safety and efficacy of PGD in ensuring healthy progeny for genetically affected parents are well described, it remains an invasive and costly intervention that may have thus far unappreciated ramifications [1]. The potential for imprudent use of PGD cannot be ignored in the context of this scenario. The absence of HOS in the family and the cost of PGD for a rare monogenic syndrome such as HOS render the technique of no benefit to the couple. Therefore, though its use may satisfy patient autonomy, it falls short in fulfilling the physician's duty of beneficence. And, in the absence of a reasonable indication, the procedure may even carry potential for harm; hence PGD in this case may hold implications for slighting the principle of nonmaleficence, as reflected by anecdotal reports on PGD-related misdiagnoses and recent concerns regarding reduced success of IVF cycles following PGD in certain patient populations [8, 9].

Genetic screening for TBX5 in both partners may be reassuring, albeit unnecessary, given the high level of gene penetrance. More importantly, while heart-hand

anomalies are classically seen in HOS, individual structural defects may occur sporadically in the absence of any known genetic mutation; hence PGD for TBX5 cannot ensure against nongenetic structural anomaly, and this aspect must be discussed at length with the couple. Prenatal testing methods, including a first-trimester screen (ultrasound and biomarkers) and a second-trimester ultrasound, may be the optimal methodology for screening for heart and limb malformations in this couple [10].

Identifying the best screening methodology for the deformities of concern is the simpler of the issues at hand; the implications of detecting nonlethal and minor structural anomalies in an otherwise healthy fetus are more complex [10, 11]. While the logical sequence of events is to proceed with prenatal genetic testing to rule out fetal karyotype anomalies by amniocentesis, the couple, in light of their concerns, may decide to undergo elective termination of a fetus identified with structural anomalies with regardless of karyotype status. The onus remains upon the physician to communicate that, although any grade of abnormality may be devastating for the parents-to-be, they should bear in mind that many minor anomalies are not universally detrimental to the child's overall functionality and quality of life. Indeed, spontaneous closure of minor ASDs is well described without any long-term adverse sequelae for physical or athletic capabilities of an individual [12].

Elective termination of a structurally abnormal fetus, disregarding the severity of the anomaly, falls within the purview of respect for patient autonomy; the concept, however, remains highly debatable and well beyond the scope of this discussion. Suffice it to state that the likelihood of structural anomalies in a conceptus of an otherwise healthy infertile couple is quite small; recent data suggest that this risk may be higher, albeit slightly, in couples undergoing IVF with intracytoplasmic sperm injection [13, 14].

The concept that both genetic and nongenetic contributions to structural anomalies exist must be communicated to the couple and discussed at length. Prenatal testing utilizing first- and second-trimester ultrasound scans is the optimal screening methodology to identify a fetus afflicted by structural anomalies of the heart and upper limbs. The couple's decision to undergo an elective termination of a structurally malformed fetus, while medically reasonable, holds potential for ethical concerns that may not be dismissible easily.

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