

Virtual Mentor

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ETHICS CASE

Shared Decision Making about IVF for Savior Siblings

Commentary by Emily S. Jungheim, MD, MSCI

When Joe and Dana brought home their son Carl from the hospital, they were overjoyed. He quickly became their everything. Together, they lovingly captured Carl's "firsts"—his first bite of solid food, his first steps, the first time he put on his Thomas the Tank Engine backpack to head off to preschool. When Carl began to fall asleep earlier and earlier, they attributed it to all the activity of preschool. They thought his pallor was due to a wintertime lack of sun. They became concerned though, when they noticed swelling in his abdomen and face. Not long afterward, bruises began blooming over his skin, especially on his trunk and abdomen, and they knew that something was wrong.

They were devastated when, at just five years old, Carl was diagnosed with acute myeloid leukemia (AML). They vowed to do everything they could to save their son. And when it became clear that a stem cell transplant was the best option, and no one they knew was a match, they decided to have another child to supply stem cells for Carl. They went to see Dr. Preed, a reproductive endocrinologist, and began the process of in vitro fertilization (IVF) with preimplantation human leukocyte antigen (HLA) typing in earnest.

After a series of hormone injections, ova were taken from Dana and fertilized in vitro with Joe's sperm. Resulting embryos were biopsied and tested for aneuploidy and they were HLA-typed. Only euploid embryos that were HLA matches for Carl were transferred, but they were few, and, after three cycles and \$40,000 spent, Joe and Dana had not conceived. The hormones and appointments, on top of caring for a child who was quite sick, began to take a toll on the whole family. The course had also started to take its toll on Dr. Preed. Dana and Joe were impatient and frustrated. They called Dr. Preed many times each week, and he returned the calls, though he had nothing new to tell them. When Dana failed to conceive after a fourth cycle, Dr. Preed decided it was time to raise his concerns with the family.

When he started to do so, Joe stopped him. "We're not going to give up," he said, his eyes flashing, whether with anger or sadness Dr. Preed could not tell. Dana grasped her husband's hand and nodded her assent. "If Carl were your child, you'd do anything you could to save him too. If you won't continue to help us, we'll find someone else who will."

Commentary

Clinical application of preimplantation genetic diagnosis (PGD) was first announced in 1990 in a case series in which PGD was used to select female embryos to eliminate the risk of transmission of recessive X-linked diseases [1]. Today most IVF centers in the United States offer PGD for a variety of reasons, including embryonic screening for aneuploidy, elimination of single-gene disorders, medically indicated sex selection, and, despite much controversy, sex selection for nonmedical reasons.

Application of PGD for HLA matching was first reported in 2001 [2]. A couple in Colorado underwent four cycles of IVF-PGD before they conceived an HLA-matched sibling for their child who was affected with Fanconi anemia and needed a stem cell transplant. Similar cases have followed. To date, most data on PGD for HLA typing comes from Dr. Semra Kahraman and colleagues in Turkey [3]. Their 2011 report summarizes the results of 327 IVF-PGD cycles undergone by 171 couples—from one to nine cycles each—between 2003 and 2010. The rate of pregnancy was 34.9 percent, a total of 59 HLA-compatible children were born, and 21 siblings had undergone successful stem cell transplantation at the time of the report.

Such published experience on IVF-PGD for HLA matching demonstrates that it is indeed “not a quick fix,” as Willem Verpoest, medical co-director at the Centre for Reproductive Medicine at UZ Brussel, put it in a recent commentary on Dr. Kahraman’s report [4]. Dr. Verpoest cautions that couples with sick children may have unrealistic expectations of their chances of successful IVF-PGD. Thus, he proposes a multidisciplinary approach incorporating psychological counseling and support and emphasizes the need for open communication with the medical team caring for the sick child. Furthermore, he stresses the importance of considering the laboratory personnel’s IVF-PGD experience when deciding whether to pursue IVF with HLA matching, because that experience overwhelmingly determines the chance of a successful outcome.

Joe and Dana’s case illustrates the importance of Dr. Verpoest’s perspective and raises a number of issues, including the future of a child born as a savior sibling, the fate of extranumerary embryos created during the process, the mounting costs this couple is facing, the resources dedicated to their care that may be detracting from the care of other patients in Dr. Preed’s clinic, and more. Ultimately, Dr. Preed must determine whether he will offer additional IVF-PGD treatments to Joe and Dana. If he chooses to do so, he must also determine at what point the treatments will stop and when and if he should offer them an alternative, for example, a referral for another opinion. It is the path to making these decisions that is not clear.

The Ethics Committee of the American Society for Reproductive Medicine (ASRM) offers some guidance on cases like this [5]. The committee states that “clinicians may refuse to initiate a treatment they regard as futile or having a very poor prognosis” [5]. In Joe and Dana’s case however, Dr. Preed has already initiated treatment, and, while they haven’t conceived, they have had HLA-matched, euploid

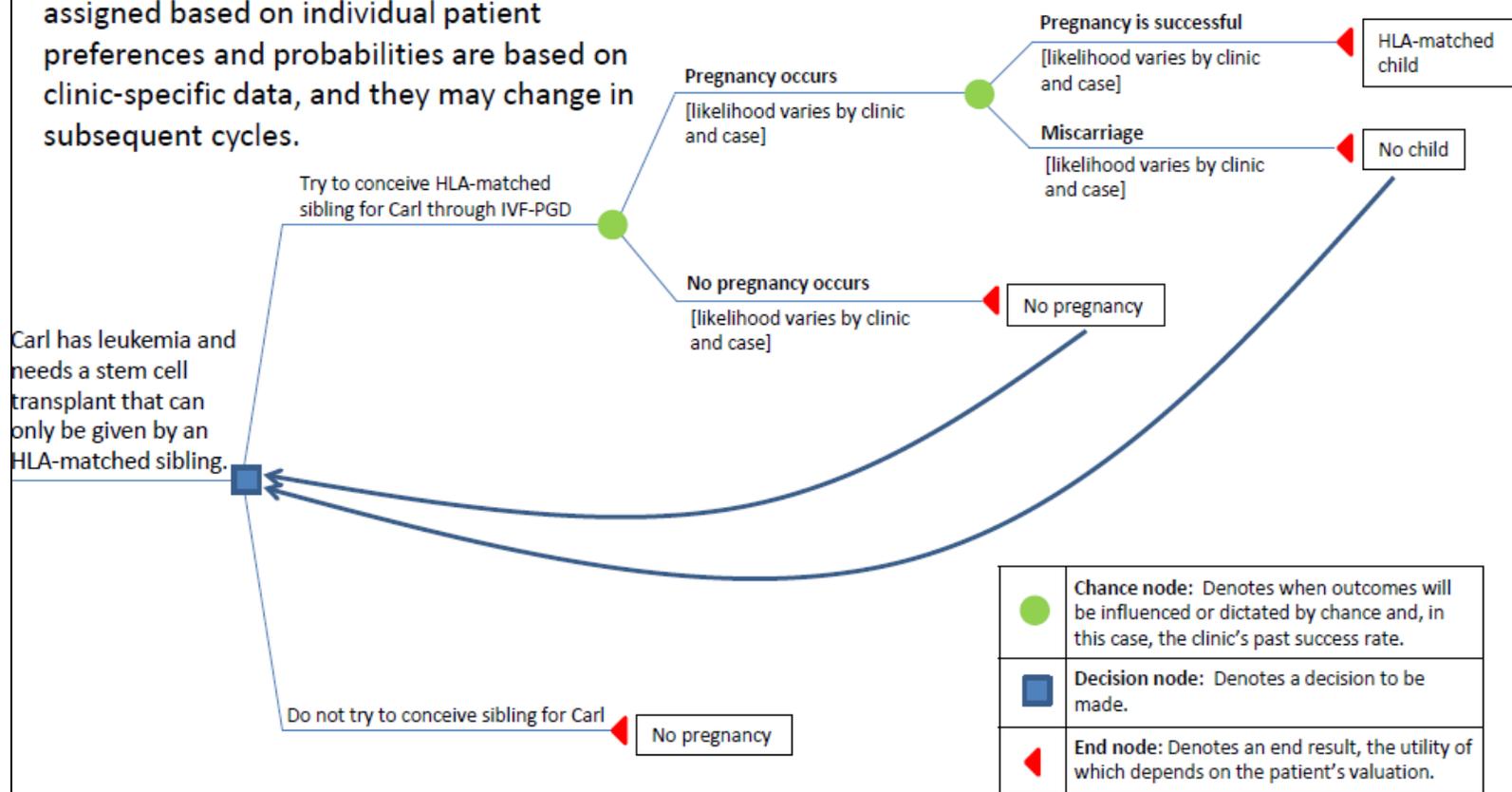
embryos available for transfer in their previous cycles. Given this, the published experience on PGD for HLA matching and data regarding cumulative success from IVF suggests the couple still has a chance of a successful outcome [3, 6]. On the other hand there is no guarantee [6]. Further, the committee states that “decisions about treating or refusing to treat couples and/or individuals always should be patient-centered” and they “should be made in cooperation with couples” [5]. They advise clinicians to revisit the treatment plan with couples. This is an ideal time for Dr. Preed to do so.

Clearly the situation is painful, and the couple’s need for psychological counseling has likely exceeded Dr. Preed’s skills in this arena. If he hasn’t already done so, Dr. Preed should insist that Joe and Dana seek the services of a mental health professional (MHP). Many fertility treatment centers have MHPs on staff or refer to licensed MHPs with expertise in reproductive counseling and the issues raised by infertility [7]. Although the Mental Health Professional Group of the ASRM recommends counselors have training in medical and psychological aspects of infertility, this is not required, and indeed Joe and Dana are not using these treatments for infertility.

The ASRM Ethics Committee also states that “fertility centers should develop evidence-based policies to guide decisions about treating couples and/or individuals” [5]. But, outside of the experience published by the group in Turkey described above, there is little evidence on which to base policy for decision making; reports of these cases are sporadic and hard to generalize from. The question at hand is really what to do when the outcome is uncertain and patient desire is of great importance. Thus, this is a case in which medical decision making (MDM) techniques may help reduce conflict and lead to a mutually agreeable decision.

In 1983, in a medical news piece for *JAMA*, medical writer Terra Ziporyn reported on a session entitled “Ethical Issues in Medical Decision Making” at the fourth annual meeting of the Society for Medical Decision Making. Ziporyn discusses how an uncertain case such as the one presented here could be approached systematically using techniques such as decision analysis. Decision analysis would allow Dr. Preed to incorporate each of the issues at hand into one “decision tree” factoring individual likelihoods and utilities or patient preferences into the ultimate decision [8, 9]. Decision trees are constructed as follows: squares represent “decision nodes” outlining the choices; circles represent “chance nodes” breaking down the possible outcomes of those decisions [10]. The probabilities of and utility scores for each outcome can be entered into software programs like TreeAge to help assign a value to each of the choices [11, 12]. Figure 1 represents a simple decision tree.

Figure 1. Simple example of a decision tree that may aid in making patient-centered decisions. The utility values of end results are assigned based on individual patient preferences and probabilities are based on clinic-specific data, and they may change in subsequent cycles.



In the example outlined in Figure 1, the choices include moving forward with another IVF-PGD cycle and ceasing treatment. Other choices that could be considered and expanded upon include pursuing treatment at another clinic or trying to conceive spontaneously. Those choices would make for a more detailed tree with additional decision nodes and chance nodes. Probabilities can come from historical clinic data, published data, or from Dr. Preed's expert knowledge [11]. Utility scores would be informed by Dana and Joe [11]. If nothing else, constructing a decision tree would allow Dr. Preed to work with Joe and Dana to weigh all options in light of the facts, the available evidence, and their preferences [9].

Dr. Preed needs to consider whether there are other clinics that may be able to offer Joe and Dana a better chance of a successful outcome. The ASRM Ethics Committee recommends that, when the prognosis is very poor or futile, "individuals should be fully informed and offered information about referrals, especially if other clinics have had greater success with similar medical indications" [5]. Another opinion may be of great benefit for this couple and for Dr. Preed alike. Dr. Preed most likely has a number of resources for identifying a clinic to which to refer this couple and for arranging for timely consultation through his professional relationships with

individual clinicians, through professional organizations like the American Society for Reproductive Medicine, the Society for Assisted Reproductive Technology, and international organizations like the European Society for Human Reproduction and Embryology.

The undeniable facts of the case are as follows: IVF success plateaus after four to six cycles, and optimal results from IVF-PGD cases are obtained “by a dedicated teams and by highly skilled laboratory technicians and embryologists” [13]. While the majority of clinics in the United States offer PGD, individual clinic success rates with procedures used in ART including PGD are often variable [14]. Decision analysis could be used in a shared decision-making process to include these facts along with individual preferences —Joe’s, Dana’s, and Dr. Preed’s—to help the stakeholders come to a mutually agreeable conclusion regarding what steps to take next [15].

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