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CLINICAL CASE

Sex Selection for Nonhealth-Related Reasons

Commentary by Lusine Aghajanova, MD, PhD, and Cecilia T. Valdes, MD

Mr. and Mrs. Carter had been married for 6 years when they visited Dr. Jones, a well-known infertility specialist, to ask for help creating their family. Mrs. Carter had given birth to a beautiful, healthy baby girl 3 years earlier. She was the light of their lives, and they loved her dearly. Now that their daughter was in preschool, they had decided it was time for them to complete their family by having another child—a son.

They sat down in the plush chairs in Dr. Jones's office. Mr. Carter spoke first, "We've done a lot of research, Dr. Jones, and we think you can help us. A couple that we are friends with came to you to make sure they had a girl, since they have a disease in their family that runs in boys. We're here to see if you can help us conceive a son for our family."

Dr. Jones was confused about what they were asking for, and why. "Have you been having trouble getting pregnant?" he asked Mrs. Carter.

"Oh, no," she responded. "We haven't been trying. We wanted to wait to see you, so that we could make sure we had a boy. We love our daughter, and we always thought it would be perfect to have one of each. A balanced family."

"Hmm," Dr. Jones said. "We have done sex selection for patients in the past, but only based on medical conditions that occur in certain families, like what we did for your friends—"

"No, it's nothing like that," said Mr. Carter. "I just think we should have a boy and a girl. All my life I've envisioned having a kid I can take fishing and play ball with."

"So, what do you think?" Mrs. Carter pressed. "Does this sound like something you can help us with?"

Commentary

Use of assisted reproductive technologies (ART) for nonmedical reasons presents several ethical dilemmas. Issues that should be considered include: (i) indications for medical, as well as for elective, sex selection, (ii) methods for sex selection, (iii) relevant policies in different countries, (iv) arguments for and against sex selection for nonmedical reasons, and (v) risks associated with the procedures. This discussion

should help us to work out the moral dilemma that Dr. Jones is facing with his patients in this case.

The desire to have a child of a particular sex tracks back through centuries. Kings were desperate to have a male heir to the throne, peasants desired sons to help with the work, while some families with many boys were longing for girls. However, until now, there were no effective means of sex selection, except for highly speculative and unproven methods relating to the timing of intercourse and positions of the partners during intercourse. The definitive method during the past few decades with the ultrasound era has been prenatal diagnosis and elective abortion of a fetus of undesired sex, which raises many ethical issues as well as risks to maternal health. Advances in assisted reproduction technologies allow many dreams to come true: infertile couples are able to experience parenthood, and parents affected by chromosomal mutation or carriers of an abnormal gene can select healthy embryos for implantation. With the implementation of new technologies, sex selection has become more precise and achieves the goal of avoiding a sex-linked genetic disorder.

Reasons for sex selection can be divided into two categories: medically indicated and elective (nonmedical) reasons [1]. What does that mean? In the former category, sex selection is used to avoid so-called sex-linked diseases, which male children inherit from their mothers, such as hemophilia A and B, Duchenne muscular dystrophy, Lesch-Nyhan syndrome and others. In some cases, conditions are more severely expressed in one gender (e.g., fragile X syndrome in males) than the other. Elective sex selection is not done for medical reasons, but to accord with a desire for “family balancing,” as in the present case, or a strong preference for a child of a particular sex [2]. A situation in which parents who have lost a child desire another child of the same sex may be considered another nonmedical indication for sex selection.

There are two primary methods now available for sex selection: (1) the sperm-sorting technique, which is selection of sperm with the preferred sex chromosome (X or Y), followed by intrauterine insemination (IUI) or in vitro fertilization (IVF), and (2) pre-implantation genetic diagnosis (PGD) followed by IVF [3, 4].

Because the male gamete determines the gender of the offspring, sperm is an obvious target for selection. Sperm selection allows for prefertilization sex selection and is based on the flow cytometry technique. Prior to flow cytometric sorting, sperm are labeled with a fluorescent dye, Hoechst 33342, which binds to the DNA of each spermatozoon. Every man has one X and one Y chromosome. Because the X (female) chromosome is 2.8 percent larger (i.e., has more DNA) than the Y (male) chromosome, the spermatozoa bearing X chromosomes will absorb a greater amount of dye than those bearing Y chromosomes. Consequently, when they are exposed to UV light during flow cytometry, X-bearing spermatozoa fluoresce brighter than Y-bearing spermatozoa. As they pass through the flow cytometer in single file, they are separated by means of electrostatic deflection and collected in separate tubes for processing. This sperm-sorting technique has a success rate of 91 percent for selecting girls and 76 percent for selecting boys [5]. Once the sample is processed,

there is often only sufficient quality and quantity of sperm for laboratory-controlled IVF rather than the less costly and less invasive IUI.

Pre-implantation genetic diagnosis sex selection is the most reliable method, with almost 100 percent accuracy. This procedure is performed in the context of IVF, when embryos are created from eggs obtained from the female partner (after overstimulating her ovaries) and sperm collected from the male partner in the laboratory. When embryos are 3 days old and have about 8 cells, one of the cells is taken from each embryo for chromosomal analysis. Then, only the embryos of the preferred sex are transferred back to the mother or frozen for future use, and the rest are discarded. This procedure, however, is not risk-free and is associated with significant cost. Of note, the sperm-sorting method still requires subsequent IVF and possibly even PGD for 100 percent accuracy. Sperm sorting is associated with the minimum number of discarded embryos, less than the 50 percent resulting from the IVF-PGD-only method, since sperm sorting should produce a high percentage of embryos of the desired sex.

There is no country that explicitly permits sex selection. Five countries prohibit it for any reason, while 31 countries prohibit it for social or nonmedical reasons. Other countries either do not have any laws or policies regarding sex selection, or such policies are unknown [6]. There is no official policy in the United States of America. Israel allows nonmedical sex selection only if a family has 4 children of one sex and desires a child of the opposite sex [7].

As is clearly outlined in the latest statement of the ethics committee of the American Society for Reproductive Medicine (ASRM), PGD for sex selection to prevent the transmission of serious sex-linked genetic disease is acceptable and recommended [8]. There is no argument against medically indicated sex selection: the ASRM's position is that all families have a genuine right to healthy offspring, and they can implement all available technologies to avoid a known genetic disorder. Moreover, in such cases, no preference of one sex to another is expressed based on its supposed *value*. The ASRM committee advocates that use of PGD for nonmedical sex selection should not be encouraged but does not favor its legal prohibition [8]. The nonmedical reasons are the area of continuing debate.

Proponents of elective sex selection argue about one's right to reproductive choice—including sex selection—in terms of constitutional rights. Family balance is considered to be another valid reason for sex selection. Interestingly, Judaism and Islam largely allow sex preselection, while it is forbidden by the Catholic Church even for medical use [9]. The strongest argument for pre-implantation sex selection is that it may be considered a lesser evil than prenatal diagnosis (ultrasound or amniocentesis) and abortion solely for unwanted sex. The latter carries more significant risks for the mother's health, not to mention stronger ethical concerns.

One of the concerns of elective sex selection is sex discrimination that results in an imbalance in the sex ratio within a given society. This already exists in China and India, where male children are particularly favored [10, 11], but is less likely to

happen in the Western world [12, 13], where “family balancing” is the usual reason for nonmedical sex selection [3]. Because of unavailability of sex selection in a majority of countries around the world, patients from China and India undertake “sex-selection traveling” to the clinics that provide such services in the U.S. The risk of population sex imbalance in the U.S. is not great, largely due to its ethnically mixed population, in which different preferences in sex selection balance each other. Asian and Middle Eastern couples often prefer sons, while Caucasian and Hispanic couples prefer daughters [14]. Nonetheless, nonmedical sex selection risks indulging or reinforcing sex discrimination and may even contribute to sex-based stereotyping [8].

Another argument against sex selection for nonmedical reasons is exposure to unnecessary medical risks. As mentioned above, IVF carries certain risks, such as ovarian hyperstimulation syndrome. The risks associated with sperm sorting are still unclear due to the lack of relevant research, though some studies have found that Hoechst dye can have a mutagenic effect on sperm [15]. These findings suggest caution when using sperm sorting as an elective procedure [15], as does the unknown risk associated with repeatedly freezing and thawing sperm. Further studies are warranted before recommending sperm sorting.

In the meantime, do providers and proponents of sperm sorting have an ethical obligation to fully disclose the unknown risks of the DNA labeling of sperm on the health of offspring?

These procedures also carry a large financial burden in countries where patients are usually responsible for treatment costs. Another issue in countries where patients pay treatments costs is the fairness of access to medical resources [8, 16].

Detailed informed consent before initiating ART for sex selection, including scenarios specific to this treatment modality, are of particular importance. Patients need to be informed of the small possibility of having a child of the unwanted sex despite the procedure or of having produced embryos only of the “unwanted” sex. It is better to agree beforehand if the couple will still choose to transfer healthy embryos even if they are of the “wrong” sex, or if they will donate those embryos if there are none of the desired sex. A significant ethical dilemma arising from IVF-PGD for the purpose of sex selection is subsequent discarding of the embryos of unwanted sex. In that case, couples are to be offered alternatives, such as donating their embryos to infertile couples or for research.

One multicenter study reported that some couples pursuing IVF-PGD for sex selection for nonmedical reasons view this procedure as an ethically complex decision and express considerable uncertainty about its ethical acceptability [17]. Discussions regarding the couple’s wishes in these difficult situations should occur prior to beginning the IVF-PGD cycle to avoid presenting these dilemmas on the day of embryo transfer, when there is insufficient time for the couple to consider their decision carefully. Thus, detailed informed consent should be obtained prior to initiation of the whole process, because many couples seeking help with nonmedical

sex selection are usually not aware of the seriousness and full complexity of either IVF and PGD or flow cytometry sperm sorting procedures. This however, is not the case with the Carters, who are aware of IVF, but need to be informed about the specific risks and side effects of PGD for sex selection.

Due to patient demand and financial pressures, reproductive endocrinology and infertility physicians may consider providing ethically controversial services. However, it is important to know that practitioners who offer assisted reproductive services are under no legal or ethical obligations to provide nonmedically indicated preconception methods of sex selection [8]. Applying this to the current scenario, Dr. Jones should not feel any legal or ethical obligations to provide reproductive services to the Carters, if doing so conflicts with his own clinical judgment, values, or beliefs.

Thus, we can summarize the above discussion in a few points:

- Sex selection for sex-linked disease prevention is well established and not controversial.
- Sex selection for nonmedical reasons is not encouraged, but neither is it prohibited in the U.S., according to the latest guidelines.
- Based on available research data, we believe that sperm sorting should not be used until more safety data are available.

Dr. Mark Hughes, one of the pioneers of PGD in the U.S., expressed a clear opinion on the topic: “Your gender is not a disease, last time I checked. There’s no pathology. There’s no suffering. There’s no illness. And I don’t think doctors have any business being there” [18].

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