NEWS AND VIEWS

CONTROVERSIES IN ASSISTED REPRODUCTION

Preimplantation Genetic Diagnosis: Considerations for Use in Elective Human Embryo Sex Selection

Few contemporary issues stir the public consciousness as dramatically as the new reproductive technologies. Innovative infertility treatments have resulted from advances in reproductive medicine in recent years, and public controversies and debates about the moral and social implications of these treatments have often accompanied their introduction into mainstream clinical use. Although it is infrequently advertised, sex selection of human embryos (i.e., the ability to choose the sex of one's progeny) is currently being offered by some infertility centers. While ethical concerns regarding human embryo research continue to receive extensive analysis, scant public discussion has preceded the use of techniques to achieve elective human embryo sex selection. How was this important and necessary debate overlooked?

For nearly a decade, sex selection of human embryos has been an urgent matter for infertile couples at high risk for transmission of a sex-linked genetic disease. In preimplantation genetic diagnosis (PGD), a four- to eight-cell embryo is biopsied and subjected to DNA analysis; the viability of the tested embryo is not usually affected (1). For patients undergoing in vitro fertilization (IVF), this technique permits highly reliable sex selection and avoids the transfer of affected embryos to the uterus after IVF (2). First successfully used in humans in 1990, the number of infants born world-

wide after PGD used for genetic indications is believed to be approximately 100 (3).

If used just for sex-chromosome identification, PGD can prevent the birth of males or females in the same way it prevents implantation of genetically abnormal embryos and the birth of infants with debilitating heritable defects. It was perhaps inevitable that some couples without any known genetic indication would seek to use PGD specifically to choose the sex of their offspring. Some practitioners have shown a willingness to satisfy this request, possibly in response to couples' growing expectations for greater control over their reproductive choice. Similarities between elective embryo sex selection and abortion (both manifestations of reproductive freedom) could explain the avoidance of the former topic.

How often is PGD being used to pick the sex of IVF babies? Prevalence data describing how frequently PGD is used specifically for human embryo sex selection has yet to be systematically collected, but an elementary internet search or a few phone calls to fertility centers is all that is needed for patients to engage a willing provider. The introduction of human sperm sex selection via flow cytometry (FCM) has enabled yet another reliable method of influencing offspring sex (4), but thus far such technology works best only if female babies are desired. The fact that sperm sorting offers sex selection at a stage before conception will no doubt be welcomed by patients and clinicians alike, although PGD will remain the standard against which results from FCM will be validated.

The opinions presented in this column are those of its authors and do not necessarily reflect those of the journal and its editors, publisher, and advertisers.

Physicians should be familiar with elective sex selection and be prepared for important questions from patients about the use of new reproductive technologies like PGD. Can *a priori* embryo sex selection, in the absence of a sex-linked genetic disorder, justify the use of this medical test? What are the ethical and social implications of elective human embryo sex selection, and how should doctors respond to those who request it?

The notion of PGD being used specifically for elective sex selection is relatively new, but the general aim of human sex selection is not. Indeed, indications for amniocentesis, chorionic villus sampling and ultrasound have been rightly criticized when these procedures permit identification of a "wrong-sex" conceptus for termination. Such practices, occurring mainly outside the United States, have been condemned by the American College of Obstetricians and Gynecologists, American Society of Reproductive Medicine, and National Advisory Board for Ethics in Reproduction. In this country, however, PGD has emerged as a novel embryo testing method to yield similar results. As the demand for such testing is unlikely to diminish, a focused study of this issue is needed.

At our centers we do not offer elective sex selection, but encounters with referred patients who have found this service elsewhere inform some preliminary observations. Couples who want to select the sex of their child generally feel that if a mechanism is available, then why not use it? (5,6) From this viewpoint, sex selection is merely the latest extension of a individuals' right to control their own procreation. Conversely, opponents question the soundness of sex-ratio tampering and cite the practice as an offense to basic principles of equality (7). Importantly, elective human embryo sex selection reinforces the devaluation of one sex in favor of another and would enable gender discrimination at the very earliest stage of development.

Elective sex selection, whether by pre- or post-conception techniques, is no longer theoretical, but the long-term sequelae remain entirely speculative. Since elective sex selection is unlikely to become used by the overall population, its impact on global or regional sex ratios will probably be minimal (8). Disturbances of sex ratios following elective sex selection among smaller ethnic or national subgroups (9) may be harder to dismiss, however, and could persist for many generations.

The uncertain psychological impact their choice might have on their offspring has not been consid-

ered by most couples interested in sex selection, yet such factors must be central to any informed dialogue on this topic. Advocates of "family balancing" generally base their arguments on parental needs and group dynamics (10), instead of asking what is best for the child as a person. For example, exclusive parental determination of a child's sex might adversely influence the child's interpersonal development, socialization processes, and core identity. It is too soon to know if most couples will keep their decision to sex-select embryos a secret or to share this with their children at an appropriate time.

It has been proposed that couples using sex selection technologies be required to make their "deselected" embryos available for adoption by another couple (11). Alternatively, some have argued for allowing a couple committed to eventual transfer of all embryos to choose the sex of the embryos that are to be transferred initially (the remaining embryos would be cryopreserved for later use). Though these strategies do allow all generated embryos to attain their potential, encouraging a couple's agreement to such schemes in exchange for elective sex selection may be coercive and the serious objection of gender bias is not truly remedied.

As with cloning, elective sex selection is an early step toward the programming of specific, fundamental characteristics of an individual before birth (12). While avoidance of genetic disease is clearly a desirable goal, it remains uncertain if controlling for male or female sex confers any similar benefit. Viewing elective sex selection in this context can help recognize the issues attendant to any molecular biology technique that is used as a modifier of our genetic makeup.

The philosophical, social, and ethical issues of elective sex selection are profound and deserve the attention appropriate for such a complex subject. Public reaction to elective human embryo sex selection is critical for progress in our field. PGD, when used to target genetic conditions, offers couples at high risk the chance to begin their pregnancy knowing their baby will not have a lethal or crippling heritable disease. Selecting against disease, rather than sex alone, should be the preferred role of PGD in reproductive medicine. To allow the powerful therapeutic benefits of PGD to be obscured by the sensationalism of sex selection would be regrettable.

Political leaders have shown that public concerns about controversial medical advances, even if only theoretically applicable to humans, can trigger regulatory interest when leadership from physicians is late or poorly organized. The medical community's recognition of the sex selection issue, and what role it should have in standard medical practice (if any), is a worthwhile and timely goal. A well-informed public discussion to develop a consensus opinion for clinical practice has not yet occurred; it would be prudent for physicians to take part in this effort. In Europe, where related but no less difficult issues prompted popular ballot initiatives, such a strategy has worked well (13,14). Alternatively, others who are less informed may succeed in regulating yet another facet of medical practice.

REFERENCES

1. Soussis I, Harper JC, Handyside AH, Winston RML: Obstetric outcome of pregnancies resulting from embryos biopsied for pre-implantation diagnosis of inherited disease. *Br J Obstet Gynaecol* 1996;103:784-788
2. Handyside AH, Kontogianni E, Hardy K, Winston RML: Pregnancies from human preimplantation embryos sexed by Y-specific DNA amplification. *Nature* 1990;344:768-770
3. Handyside AH, Delhanty JDA: Preimplantation genetic diagnosis: strategies and surprises. *Trends Genet* 1997;13:270-275
4. Fugger EF, Black SH, Keyvanfar K, Schulman JD: Births of normal daughters after MicroSort sperm separation and intrauterine insemination, in-vitro fertilization, or intracytoplasmic sperm injection. *Hum Reprod* 1998; 13:2367-2370
5. Pennings G: Family balancing as a morally acceptable application of sex selection. *Hum Reprod* 1996; 11:2339-2345
6. Liu P, Rose GA: Sex selection: The right way forward. *Hum Reprod* 1996;11:2343-2345
7. Dawson K, Trounson A: Ethics of sex selection for family balancing—Why balance families? *Hum Reprod* 1996;12:2577-2578
8. Glover J: Comments on some ethical issues in sex selection. *In Ethical Aspects of Human Reproduction*, C Sureau, F Shenfeld (eds). Paris, John Libbey Eurotext, 1995, pp 305-313
9. Liu P, Rose GA: Social aspects of >800 couples coming forward for gender selection of their children. *Hum Reprod* 1995;10:968-971
10. Egozcue J: Sex selection: Why not? *Hum Reprod* 1993; 8:1777
11. Siebel MM, Glazier S, Zilberstein M: Gender distribution—not sex selection. *Hum Reprod* 1994;9:569-570
12. Weiss R: Human cloning research will be regulated: FDA decides it has statutory authority. *Washington Post* 1998, Jan 20:A1
13. McGregor A: Swiss go to polls over genetic manipulation. *Lancet* 1998;351:1713
14. Zinkernagel RM: Gene technology and democracy. *Science* 1997;278:1207

E. Scott Sills¹
Dan Goldschlag
Delphine P. Levy²
Owen K. Davis
Zev Rosenwaks

Center for Reproductive Medicine and Infertility
 Weill Medical College of Cornell University
 New York, New York

¹ To whom correspondence should be addressed at Atlanta Reproductive Health Centre, 285 Boulevard N.E., Suite 320, Atlanta, Georgia 30312.

² Also Population Council/The Rockefeller University, New York, New York.