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Ethical Considerations

Preimplantation Genetic Diagnosis for Elective Sex Selection, the IVF Market Economy, and the Child—Another Long Day's Journey Into Night?

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The promise of medical innovation has long evoked social commentary, particularly when personal reproductive autonomy may be involved. Development of the oral contraceptive, effective and safe surgical sterilization, and later IVF and ICSI are among the revolutionary developments where the initial reactions were dubious but were accorded mainstream status with sufficient clinical experience. In each instance, debate about the moral and social implications of these treatments accompanied their introduction into the medical marketplace. This pattern appears to be repeating itself in connection with the use of preimplantation genetic diagnosis (PGD) for elective sex selection of human embryos. As with prior challenges in reproductive medicine, the development of meaningful "guidelines" for this latest controversy has proven to be a contentious task. Indeed, the progression of ethics committee reports from the American Society for Reproductive Medicine seems to echo the ambivalence within society at large regarding this issue. In this report, we chronicle sex selection claims based on sperm sorting, and describe how flow cytometry and especially PGD have facilitated this selection at the gamete and embryo stage, respectively. In doing so, we also explore market forces and practitioner considerations associated with the application of PGD for this; related ethical issues with particular emphasis on the progeny derived from such treatment are also reviewed.

KEY WORDS: Ethics; IVF; PGD; sex selection.

INTRODUCTION

The technology of sex selection falls into two main categories, medical or elective. Thus far, the prevention of sex-linked genetic disease has been the chief goal of medically indicated sex selection, although compelling personal, social, cultural, or economic reasons for performing this, in the absence of any genetic abnormality, have also been described. Whatever the indication, all approaches to sex selection depend either on prefertilization, preimplantation, or postimplantation methodologies. Here we focus on flow cytometry (FCM) and preimplantation genetic diagnosis (PGD) as examples that relate to the first two approaches for sex selection.

ORIGINS OF SEX SELECTION

Cultural interest in finding ways to select the sex of the offspring was evident long before the arrival of the science required to accomplish it. The observation by Egyptians that castration led to decreased libido and sterility provided early insights into the role played by the testes in this context, and Anaxagoras (c.500–428 B.C.) hypothesized that the

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father was responsible for offspring gender and ascribed specific roles for each testicle. Semen derived from the right was thought to produce males, while females were considered to originate from the "seed" of the left testicle. Such beliefs persisted well into the eighteenth century, with some European noblemen undergoing surgical excision of the left testicle to assure a male heir. Many other equally unscientific approaches were tried throughout the ages, but none were successful and some were harmful (1).

The pioneering work of Gregor Mendel (1822–1884) introduced the gene concept and, while the basis for development as a male or a female remained unknown for many more years, the discovery of "accessory chromosomes" in mammals (2) foreshadowed an understanding of sex determination. The realization that genetic information was carried by DNA in the cell nucleus (3) suggested that this might contribute to the process at a fundamental level, but until the Y-chromosome was specifically identified by special staining with quinacrine mustard (4), birth outcomes were the only practical means to judge the effectiveness of any sex selection methods. For this reason, most early work in sex selection was based on sperm sorting in veterinary or livestock settings, where delivery patterns could be closely monitored.

Preconception methods were ostensibly based on supposedly characteristic (but mostly theoretical) features of X- and Y-chromosome bearing spermatozoa. For example, putative differences in surface charge(s) sparked an interest in electrophoretic sperm separation of X- and Y spermatozoa but this declined after the initial claims could not be independently reproduced (5). Claims that sperm H-Y antigen expression varies as a function of their X- and Y-chromosome status in some species (6,7), were not reproducible for human spermatozoa (8). Only with the advent of FCM did published reports on human sex selection find serious credibility.

Later refinements of the FCM techniques (9,10) have permitted exact measurement of DNA content in various cell systems, including human spermatozoa. The current method of computer-assisted FCM human sperm sex selection (Microsort®) is a derivative of this technology (11), the development and clinical applications of which are reviewed elsewhere (1).

Development of blastomere biopsy protocols (PGD in tandem with IVF) provided another even more precise means of determining gender, whereby human embryos could be evaluated in this regard prior to transfer (12). In PGD, a blastomere from a four- to eight-cell embryo is biopsied and subjected to DNA analysis (either fluorescent in-situ hybridization for chromosome labeling, or fluorochrome PCR-based assay for specific gene identification). This does not compromise the viability of that embryo, which is later transferred in a standard IVF procedure (13). Worldwide, the total number of infants born after PGD (either for elective or medical indications) is currently believed to be <300. Although initially developed to identify genetically abnormal embryos, it was perhaps inevitable that some couples would seek to use PGD simply as a way of choosing the sex of their offspring electively; it is apparent that this technique has since emerged as the "gold standard" for sex selection.

ETHICAL CONSIDERATIONS

Attention to social, legal, and ethical consequences of "reproductive choice" has only intensified with the technological advances that permit ever broader therapeutic options for a desired outcome. Regarding PGD and elective human embryo sex selection, many voices from multiple disciplines have contributed to the debate on how such technology should be used—if at all. Within the medical and scientific community, some have expressed the view that sex selection is intuitively acceptable to society (14–16) and some patients may feel that if such an avenue is available to achieve this goal, then why not use it (14,15)? From this perspective, elective embryo sex selection with PGD becomes but a simple extension of the individual right to control reproductive choice (16,17).

Another philosophy is embraced by those who regard the use of PGD solely for elective sex selection as an irresponsible application of reproductive resources (18), this group includes both the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (19), and the Programme of Action endorsed by the United Nations International Conference on Population and Development (20), who oppose sex selection for any nonmedical indication. Although some intermediate positions have also been proposed, a definitive conclusion is lacking and the place of "consumer-driven" PGD in the context of IVF remains an awkward one (21).

WHAT HATH MOM WROUGHT?

The uncertain psychological impact a patient's choice could have on their offspring has received

comparatively little attention when prospective parents express interest in sex selection, yet such issues must be central to any informed consent for elective sex selection based on PGD. Some patients firmly believe that a blend of both girls and boys will produce a happier family. By extension, this view implies that families with children of only one sex are in some way intrinsically "unbalanced," and implies the existence of an even more severe asymmetry for the child with no siblings at all.

An early study of this issue found "similarity and complementarity were morally acceptable reasons for wanting a child of a certain sex" (22). It is notable that such parental desire to govern offspring sex is traditionally accorded primacy over any future identity issues the child might one day encounter as a result of this kind of parental control. Given the complex psychosocial milieu present in natural family systems, the insertion of PGD and elective sex selection into the equation seems likely to at least complicate this relationship.

It has been proposed that couples using PGD for sex selection should be required to make their 'deselected" embryos available for adoption (23). Alternatively, some have argued for allowing a couple to choose the sex of the embryos that are to be transferred initially, where the remaining embryos would be cryopreserved for later use. While these strategies are well intentioned, a couple's agreement to such schemes could be regarded as coercive, and nor is the serious objection of gender bias truly remedied. Should embryos cryopreserved specifically for "wrong sex" reasons be viewed differently than embryos stored for any other reason, given the very different parental motivations involved? Further, would IVF patients plan to keep secret their decision to sex-select embryos or to share this information with their children at an appropriate time?

Unlike traditional infant adoption where the baby is legally embraced by a family without precondition, with elective embryo sex selection it is genetic sex itself that represents the sole basis of admission to personhood. Such parental determination of offspring sex might reasonably be viewed as a potentially adverse influence on the child's interpersonal development, socialization, and core identity. Patients contemplating PGD for this purpose would be wise to prepare for the eventual question from their offspring—"Why did you make me this way?" Since other difficult questions regarding identity and self are likely to arise as the sex-selected child grows up, we should maintain an adequate anticipation of these issues for our patients during IVF patient counseling.

PGD AND THE IVF MARKET ECONOMY

Although the technology enabling elective embryo sex selection via PGD first appeared more than a decade ago, awareness of its potential in this regard has remained marginal among most patients until only recently. Furthermore, overall public opinion on the appropriateness of elective human embryo sex selection has been inadequately measured and considerable regional variation is likely. Particularly when nonurgent or elective medical services are studied, meaningful assessments of consumer preference remain imprecise so long as limited general awareness of the service prevails.

This economic principle may be especially applicable to elective sex selection by PGD, since increased consumer awareness could drive the "demand" for this medical procedure. At present, however, the proportion of general IVF patients who might be interested in elective sex selection of embryos is not clear. Unpublished data from our two urban IVF facilities (in different regions and with separate referral populations) suggest that those seeking PGD for elective sex selection actually represent a minority of IVF patients, and that the expectation of most is anchored primarily on obtaining a healthy baby.

The fact that PGD represents several additional steps during IVF (24) also appears underappreciated by some patients we have interviewed. Indeed, many patients interested in elective sex selection at the embryo level do not know that this type of micromanipulation is impossible without a high level of basic expertise. It is unlikely that any center reporting below-average success with standard IVF would attract more patients because elective sex selection is offered. As additional data become available, consumers will probably find that those best suited to perform PGD (whether for medical or elective indications) are the centers already reporting the better routine pregnancy/embryo transfer rates. Centers offering PGD may provide separate outcomes data for patients based on their prior PGD experience. This would afford a key opportunity to explain why the numbers are so low, and give proper caution as the data are interpreted during counseling.

How does a facility decide to offer elective human embryo sex selection? This represents another undocumented but fascinating interior facet of the new IVF market economy, which is likely to be just as complex

as the overarching PGD debate itself. Indeed, the parallels of this issue with prior controversies (i.e., oral contraceptives, anonymous donor insemination, abortion, IVF, gestational surrogacy, etc.) are especially striking. For example, an institutional policy could be established with the reasonable expectation that those IVF couples desiring PGD especially for sex selection would engage a particular treatment center, primarily drawn by this service. Yet given the controversy surrounding this selection, a practice philosophy embracing the use of PGD for such a nonmedical indication would risk the antipathy of other IVF patients (and other social commentators) who may disagree strongly with this aim. To perform this type of sex selection in couples who are not infertile and so would not otherwise be candidates for IVF, is improper and unjustified.

We believe those who contemplate offering PGD for elective sex selection should first clarify their own personal moral position, and then evaluate each clinical circumstance on a case-by-case basis. This approach is consistent with the policy that IVF patients should have free access to PGD for elective sex selection, but that physicians should first use "moral suasion" to promote offspring sex by chance, even when the assisted reproductive technologies could be used to influence the outcome (25).

Guidelines may be helpful to provide ethical boundaries within which this essential doctor–patient dialogue can occur. However, where human reproduction and public policy have intersected previously, the resulting guidelines were often cumbersome and, for some, difficult to understand (26). Therefore, it behooves reproductive endocrinologists to maintain the high public confidence in our subspecialty, rather than defer to a statutory remedy legislated by outside agencies.

CONCLUSION

Increased physician familiarity with PGD is a welcome trend, and clinicians should prepare for important questions from patients about the risks and benefits of this technology. While the advances of PGD are relatively new, the desire for sex selection is not. The issue of PGD for elective sex selection seems likely to occupy the stage of public discourse for some time. Meanwhile, the innovation of PGD which has made human embryo sex selection possible has, at the same time, provided an opportunity to explore the increasingly complex terrain of clinical reproductive medicine.

Given the lack of consensus in regard to PGD and elective embryo sex selection, and recognizing that such disagreement is not itself a sufficient basis to prohibit it, we concur with the Ethics Committee of the American Society for Reproductive Medicine (ASRM) that it would be unwise to adopt rigid clinical guidelines that condemn this practice. While we ourselves would not promote the use of PGD for this, regulatory measures that mandate its elimination would be even more worrisome and objectionable. Since a resolution satisfactory to all interested parties is unlikely to be achieved now on this issue, continued multidisciplinary study as proposed by ASRM is clearly appropriate (21).

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