Ethical Considerations on Indications for Gender Selection in Japan

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Gender selection is a matter of great concern to a cohort of parents. To what extent the methods available are ethically acceptable at present differs depending upon the society and times the couples live in. In the present communication, the current situation in Japan in use for gender selection by empirical methods without sperm separation, conventional methods with sperm separation and preimplantation genetic diagnosis of human embryos has been provided and considered in the light of human dignity as well as human right.

KEY WORDS: Ethical issue; family balancing; gender selection; gender variety; IVF; preimplantation genetic diagnosis; preimplantation genetic screening; sperm separation.

INTRODUCTION

In the long history of human reproduction, gender selection to seek a child of a preferred sex has persistently attracted parental interest. The desire for gender selection is a reflection of culture, tradition, religion, civilization, education, and medical technologies in a given society or community, all of which may influence morality and mentality of the people living there.

In Japan, like in many other countries, it has been the tradition that child-bearing is considered in "God's Hands" or "Nature's Providence." Human beings must obey without room to intervene following their own intention in, for example, to choose a child of preferred sex. Yet, it is also true that a small group of people have to take advantage of available modalities to select a particular sex for either medical or nonmedical reasons.

In this article, the authors intend to convey today's situation in Japan in respect to gender selection, and to describe options on how to manage this issue in a compatible way with moral perceptions in this country.

EMPIRICAL METHODS WITHOUT SPERM SEPARATION FOR GENDER SELECTION

A book by Rovik was translated into Japanese in 1970 introducing theory and practical approaches of sex selection, originally proposed by Shettles to this country (1). Two Japanese gynecologists then co-authored another book (2) after organizing a study group for sex selection and pointed out the practical effectiveness of the original method described. A Japanese reproductive biologist then followed up with a book for the general public (3). Their concept of sex selection was based on the physiological difference of sperm activation and motility, depending on the environmental pH between X- and Y-spermatozoa. Though acidic environments weaken the active movement of both kinds of spermatozoa, X-spermatozoa are more resistant than Y-spermatozoa against acidic conditions, leading to the dominant survival of X-spermatozoa over Y-spermatozoa in the acidic environment of the vagina. By contrast, alkaline environments strengthen the activity of both types of spermatozoa and Y-spermatozoa are apt to be more activated than X-spermatozoa. Consequently, it is believed that Y-spermatozoa will dominantly survive over X-spermatozoa in the alkaline environment of the cervical mucus.

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Based on these physiological differences between the two types of spermatozoa, these authors recommend three feasible ways for sex selection. The first is the timing of coitus. If a couple wants to conceive a child of female gender, they should have sexual intercourse on 2 days prior to ovulation, when the acidity of the vaginal secretion is expected to remain high, followed by refraining from the coital act for about 1 week thereafter. The reason for the abstention is that Y-sperm may still be able to migrate up into the cervical canal, because of the alkaline mucus and in spite of decreasing acidic conditions in the vagina, during the 2 days before ovulation. In contrast, if a couple wants a child of the male gender, they should have intercourse on the day of ovulation, when the vagina reaches the lowest acidic environment because of the cervical mucus containing strong alkaline fluids.

The second point of recommendation is a local application of acidic or alkaline jelly at time of coitus. These jellies, first suggested by the English gynecologist Pollard around 1978 (2), are said to be made of edible materials such as acetic acid, and, therefore, harmless to health. Acidic jelly (Pink Jelly) makes the vaginal environment acidic and alkaline jelly (Green Jelly) makes it alkaline. Instead of jelly, vaginal irrigation with 20 ml of 1–1.5% (v/v) acetic acid solution within 6–8 h before coitus for a female baby, and with 20 ml of 7% (v/v) sodium bicarbonate solution within 6 h before coitus for a male baby has been proposed as an alternative.

The third point of recommendation is the oral administration of tablets containing calcium phosphate and vitamins, with small amounts of iron, for at least 3 months. These preparations were originally developed to reduce the risk of anencephalus. It was then found by chance that more than 90% of newborn babies after the use of these tablets were boys. Though the method of action of this product is unclear, it may indirectly affect pH of vaginal secretions or of cervical mucus. Anecdotally, a birth rate of 81% male babies, among 6267 deliveries, using a combination method of timed intercourse plus calcium phosphate tablets, and 80% for female babies among 7129 deliveries, using a combination method of timed intercourse plus jelly, has been reported (no references available).

CONVENTIONAL METHODS WITH SPERM SEPARATION FOR GENDER SELECTION

Although Percoll had been used originally for the purpose of preparing motile, sperm-enriched

fractions of semen and eliminating immotile sperm and impurities from ejaculated semen samples, a method of separating X- and Y-spermatozoa with discontinuous Percoll density gradient procedures has been used for medical as well as for nonmedical reasons of sperm sorting at a small number of clinics (4). In place of Percoll, a similar product of sterile colloidal suspension of silica particles, called ISolate (Irvine Scientific) (5), is recently becoming more widely used.

The Japan Society of Obstetrics and Gynecology (JSOG) publicized guidelines on clinical application of sperm separation, using Percoll density gradients in 1986. These guidelines stated the procedure was permitted exclusively for medical indications to avoid conceptions of fetuses with severe sex-linked recessive genetic diseases (6). In 1994, these guidelines were withdrawn and it was stated that Percoll should not be used for X, Y-sperm separation at all based on information from the manufacturer, which raised questions about the safety of the product (7).

Since then, the compound was not supposed to be used in Japan for any medical indications. Yet, it still has been used in a large but unidentifiable number of clinics, not only in enhancing the selection of motile spermatozoa for inseminations, but also in sperm separation procedures for gender selection by density gradient for nonmedical indications. It has been anecdotally reported that 80% of patients were able to select for female offspring successfully using the Percoll density gradient (personal communication), though the efficacy of the procedures has been strongly questioned by published investigations (8,9).

Other methods of sperm separation, particularly by flow cytometry sorting, based on a 2.8% difference in total DNA content between the two kinds of spermatozoa (10), have so far not been introduced into this country up until now. Successful births of daughters with the use of MicroSort sperm separation, in conjunction with intrauterine inseminations have been reported at a rate of as high as 92.9% (11).

GENDER SELECTION BY PREIMPLANTATION GENETIC DIAGNOSIS AND PREIMPLANTATION GENETIC SCREENING

The parallel developments in assisted reproductive technologies and human molecular genetics opened the door to the new discipline of developmental genetic medicine, as best symbolized by the success of sex diagnosis of embryos by Y-specific DNA

amplification in 1990 (12). Preimplantation genetic diagnosis (PGD) provides a scientifically reliable, technically feasible tool for gender determination of preimplantation embryos. The method is of extreme clinical significance, distinct from postconception or prenatal genetic diagnosis, such as chorionic villi sampling and amniocentesis, and allows to circumvent gender-driven infanticide.

It is anticipated that PGD will be proven to be an accurate and safe modality for the diagnosis of gene disorders as well as numeric chromosomal abnormalities, including chromosomes X and Y, which is reported to occur at rates of 23–61% (13). Expanding and improved technologies, such as cell recycling (14), whole genome amplification (15), comparative genomic hybridization (16), and other technologies such as primer extension preamplification, single strand conformation polymorphism, nested PCR, and DNA tip technology will allow for significant progress (17).

The European Society of Human Reproduction and Embryology (ESHRE) organized a PGD Consortium in 1997 with commitments from all PGD-performing centers. Collected data was compiled under two categories (18): One is the use of PGD for diagnosis of inherited disorders, including single gene defects, X-linked diseases, and chromosomal translocations. The other is preimplantation genetic screening (PGS) for the diagnosis of aneuploidies that are shown to arise in almost half of the embryos in poor-prognosis IVF patients (19,20) and at astonishingly high rates of 75% even among normal-looking embryos (21). Thus, PGD and PGS can serve as apparently safe and effective tools to avoid genetic disorders and to eliminate embryos not eligible for transfer. This should improve implantation rates, the currently still rate-limiting step of implantation in ART, particularly in patients of advanced age (22).

The JSOG has restricted the clinical application of PGD exclusively to medical indications to avoid the birth of children with severe incurable genetic disorders devoid of treatment modalities (23). This guideline was a compromise after debates between the Ethics Committee of the JSOG and social bodies supporting handicapped patients suffering from inherited diseases. The preconditions imposed upon the potential patients by this guideline are (1) the patient herself has to suffer from the disease to be diagnosed or has to be a carrier of the gene responsible for the disease, (2) the patient has a history of having conceived a disease-affected fetus or has delivered an affected baby, (3) consent for PGD must be obtained not only from the couple but also from the

respective families, and (4) the couple has to consult genetic counselors and/or physicians specializing in human genetics and to submit their written consent. Presumably because of these severe preconditions, no single case of PGD has been performed in Japan up to the end of 2001 in spite of the rapidly rising number of PGD cycles worldwide, by now exceeding 2500 with a 98.2% rate of diagnostic accuracy (24).

PGS is regrettably not allowed in Japan to pre-select aneuploidy-free embryos for transfer in poor-prognosis IVF patients and/or repeated aborters.

SOCIAL BACKGROUNDS INFLUENCING GENDER SELECTION

Population Dynamics

After World War II, Japan experienced two waves of a baby boom; the first one occurred during the years from 1947 to 1949 and the second during 1971 through 1974 (25). Thereafter, the number of live births kept decreasing year by year to reach a minimum of 1.18 million in 1999. The decrease in number of born children tempted couples to attempt to select a child of a wanted gender. Another aspect of population dynamics is the increasing number of elderly people. The proportion of people over 65 years old increased from 7.1% of the total population in 1970 to 16.7% in 1999. This is in sharp contrast to the gradual but continual decrease in the proportion of young people below the age of 14 years, which decreased from 23.9% to 14.8% during the same span of years. Though the Ministry of Health, Labor and Welfare of the Japanese Government has attempted actions since 1971 to incensitize child bearing, these political activities could not stop the decreasing trend in number of children for most families. The increasing average longevities of men and women in Japan affected their preference for female offspring suspecting that they would be better taken care of by daughters rather than sons later in life.

Economical Development

The marvelous economic growth that was achieved in Japan during the 1970s resulted in previously unknown financial stability and improved living standards for a majority of families. With improving life standard, people were apt to minimize their number of children to be able to offer them a satisfactory education, the expenditure of which is a considerably

heavy burden on family finances. Though it is difficult to estimate how much the idea of limiting the number of children is causally related to gender selection, it could be an issue supporting the concept of gender variety as has been mentioned in the Ethics Committee Report of American Society of Reproductive Medicine (ASRM) (26).

Movements for Women's Rights

The concept of equal rights and social status for women has nowadays become popular among people in Japan. Being initiated by the statement of the International Union on International Women's Year for the year of 1975, a series of domestic movements have arisen with the aim of realizing equal rights for women and men and of abolishing gender bias and segregation toward women.

Expanded employment of women resulted in marriages at more advanced ages, with conceptions at advanced ages being the consequence. As reproductive rights, the concept of liberty and the right to reproductive health have become fundamental rights of women. Gender selection of children has become an increasingly important matter for couples attempting pregnancy.

Alteration in Traditional Style of Family Life

In the past, sex discrimination of women was customarily accepted in Japan. The head of a family was always the man. He governed everything in the family, and the first son held the right to succeed almost all the family property under legal protection. In such a traditional situation, with severe gender segregation, the wife was often merely an attribute to her husband. This structure mandated a boy as at least one of their children.

In those times, two or more families of successive generations lived together under one roof, thereby establishing a big family, which provided a better environment for the raising of many children. This traditional style of family life has, however, now been replaced. With many a family now capable of having their own house, a large majority of families live separately as a small family unit in a style called "Kakukazoku," meaning a core family.

Morality

In Japan, a majority of people are likely to be conservative and to reject the artificial manipulation of

nature. This naturalism, rooted at least in part in Buddhism, sometimes affects negatively on the introduction of new medical technologies. Japanese people also used to obey mass opinion rather than pursue their own individual opinions. This rejection of individualism produces at times an artificial indifference on particular ethical issues in question in order to avoid unnecessary friction within a community. The pursuit of individualistic goals, however, is becoming more and more popular among younger generations in both sexes of the Japanese.

Finally, emotional rather than logical responses, though not necessarily peculiar to the Japanese people, often result in irrational fear in regards to the safety of new medical technologies. We encountered such a response, for example, with the introduction of IVF.

ETHICAL CONSIDERATIONS ON INDICATIONS FOR GENDER SELECTION

To my understanding, ethics can be defined as a practical philosophy to realize goodness in human beings that creates dignity and happiness. In any field of clinical medicine, except for reproductive medicine, one can behave "ethical" if one protects the "sanctity-of-life." Reproductive medicine, which basically serves the procreation of *new* life, often, however, confronts ethical conflicts as the consequence of new medical technologies (27). The use of technologies developed in reproductive medicine for gender selection purposes is one such example. A practical compromise overcoming conflicting view points on this issue has been suggested by the Ethics Committee of ASRM (26). Careful attention has to be paid to three cardinal issues: gender discrimination, welfare of the child, and human dignity.

Gender selection of a preferred sex is not likely to impact profoundly or cause gender discrimination in current day Japan. Arguments that differences in physical and psychological nature exist between males and females should not affect fundamental human rights, since concepts of gender equality and protection of fundamental human rights have prevailed among a vast majority of the general public.

The welfare and happiness of any child born, regardless of his or her gender, has to be protected. Counseling of the parents, especially whenever a child of an unwanted gender is born should be always made available as stated in the Committee report of ASRM (26).

The authors believe that gender selection at the prefertilization stage through X- or Y-sperm separation, exclusively for nonmedical indications, can be ethically justified, because the gamete is not deemed to represent "life" with identifiable integrity, dignity, and personhood. By contrast, postfertilization gender selection should be limited to medical indications to prevent the births of offspring with inherited genetic diseases.

It is recommended that empirical methods of sex selection, without sperm separation, undergo clinical trials under appropriately designed protocols and to encourage the scientific evaluation of such techniques before a final conclusion can be reached on their validity. Until this is done, the empirical methods should not be used for genetic indications, because gender selection for such indications must be as accurate as possible.

Sperm separation by flow cytometric sorting or by density gradient involves more "artificial" procedures than the empiric methods. However, since the procedures involve prefertilization gender selections, they appear ethically permissible for social indications only after one child, based on the concept of gender balancing (26). An improvement in the accuracy of conventional methods, for the use in medical indications, would obviously be desirable.

In the authors' opinion, since PGD is based on embryo selection, and represents a postfertilization procedure its utilization would interfere with human dignity. In spite of its superior accuracy and proven safety, clinical application of PGD should, therefore, be restricted to single gene type disorders. Where applicable, user-linked diseases, to avoid misdiagnosis, the combined use of sexing with single gene diagnosis is recommended.

An increasing demand for aneuploidy-free embryos for transfer by PGS has been pointed out by the ESHRE Consortium data (16). The potential merits of PGS outweigh the ethical detriments for patients of advanced maternal age in women with repeated IVF failures, as well as for patients with recurrent abortions (18,19,24). Therefore, it is strongly recommended that PGS be permissible for such infertility patients in Japan.

The authors reemphasize the opinion that to apply PGD for nonmedical reasons despite its guaranteed diagnostic capability is ethically not acceptable. The use of PGD should, therefore, be limited to medical indications and be banned for nonmedical reasons. Although we favor the protection of reproductive freedom in terms of gender balancing within a

family, postfertilization sex selection for social indications favors the parents' happiness at the potential expense of their children's dignity as human beings. The unlimited extension of social indications in the name of reproductive liberty could also accelerate the use of gender-driven pregnancy terminations through the misuse of such noninvasive methods of gender determination as Y-chromosome specific sequences in maternal plasma (28). The authors, therefore, concur with previously published ASRM Ethics Committee guidelines that the application of PGD for such social indications for gender selection should be prohibited (29).

CONCLUSION

It is hardly possible to construct criteria for universally acceptable standards for gender selection. Advancements in medical science and technologies should be incorporated into medical practice in such a way as to uphold human dignity. In principle, empirical methods should be limited for nonmedical indications, while postfertilization methods should be restricted exclusively to medical reasons for gender selection. There is no absolute principle at present in evaluating ethical acceptability of prefertilization gender selection for nonmedical indications. Any community has to formulate their own standards for gender selection to meet their own cultural and social backgrounds and scientific capabilities, which may greatly differ depending on locations and times.

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