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Review Article

Gender preselection

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Abstract

This article reviews the different methods that are available in practice today for determining the sex of offspring and examines the efficacy of these methods based on scientific data from the literature. The largely unfounded claims of many popular methods are critically examined, and recent advances such as flow cytometry techniques and embryo biopsy methods are outlined. The legal, ethical and moral implications of such sex selection practices in modern society are also reviewed, and the position of the medical profession as regards such sex selection practices is discussed.

Keywords: Sex selection; Science; Ethics; Moral aspects

Introduction

The desire to control the sex of one's offspring is as old as recorded history. Most doctors dealing with pregnant or would-be pregnant women have been asked at one time or other whether there is a method which could determine the sex desired for a future child. Such methods have existed in folklore tales in many ancient cultures, such as Greek mythology, the Bible, the Talmud and indeed abundantly in historical Chinese scripts as well. Amongst humans and many other animal species, the average sex ratio at birth is about 105 males to 100 females. Females live longer than males, the former having an average life span of about five more years. Thus, towards the end of human lifespan, sex ratio shifts to a preponderance of females versus males. The assessment of the efficacy of methods of sex selection is difficult unless strict scientific verification techniques are applied, since, given nature's sex ratio, approximately half of the time, any method practiced will yield the desired results.

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Definitions

Sex selection is defined as the action of a medical practitioner intended to select the chromosomal sex of a baby.[1] Sex preselection is the attempt to influence the sex of a child before fertilization. Sex determination, i.e., the detection of a particular sex, should be distinguished from sex selection, where the process is designed to select a particular sex. Theoretically, sex selection could be attempted at any stage between the production of gametes and the birth of a child. In general, we can divide these methods into two broad categories: before fertilization and after fertilization. The former group can be further divided into in vivo and in vitro methods, depending on whether handling of sperm outside the body is required.

Before fertilization — in vivo methods

Abundant folklore methods have been advocated towards this end, such as timing coitus in relation to the age of the woman and the lunar calendar month, the position adopted during intercourse, dietary measures, or even tying off the left testicle to produce a male heir!

The relationship between diet and the sex of the offspring has stemmed from ancient Chinese yin-yang

philosophy. More recently, various animal studies have demonstrated a scientific basis to such beliefs. It has been shown that when tadpoles were raised in Ringer's solution, the male to female ratio was 1:1, but when the calcium or magnesium concentrations were increased, 70% were females. Similarly, a French study of calves showed that a balanced diet produced equal numbers of males and females, but with a diet enriched in alkaline earth elements, 70% were females.[2] Stolowski and Choukroun[3] proposed that in humans, a diet rich in sodium and potassium, i.e., sausage, meat, potatoes, beans, apricots, bananas, and excluding calcium rich foods such as diary products, eggs, greens, produced mostly boys. The opposite, i.e., a diet rich in calcium and vitamin D, produced mostly girls. In their study, dietary treatment was prescribed at the beginning of the menstrual cycle preceding fertilization and continued until pregnancy was confirmed. The success rate of conceiving a child of the preferred gender was 83% (39 out of 47). No further large scale studies exist in the literature to confirm these results.

Kleegman studied the effect of timing of coitus on the sex ratio in 150 births following a single exposure in the conception cycle.[4] Guided by basal body temperature (BBT) charting, he concluded that if insemination occurred at the time of ovulation, 80% of babies were male. When insemination occurred 48 hours prior to ovulation, 80% preponderance of females resulted. Unfortunately, there were no controls in this study, and the use of BBT alone without endocrinological assessment of ovulation time makes the reliability of the results dubious.

In 1960, Shettles first distinguished two morphological types of sperm, the large oval headed sperm correlating with the X chromosome, and the smaller round headed sperm correlating with the Y chromosome.[5] He proposed that Y-bearing sperm, being lighter, will move faster through cervical mucus, while X-bearing sperm will survive longer because of greater reserve. Coupled with the differential characteristics of cervical mucus in different parts of the menstrual cycle, he recommended that abstinence prior to ovulation with intercourse occurring at ovulation only, alkaline baking soda vaginal douching, female orgasm, deep penile penetration and preferably vaginal penetration from the rear, will assist the smaller faster Y-bearing sperm, while no prior abstinence, intercourse two to three days before ovulation, acid white vinegar vaginal douching, no female orgasm, shallow penetration in the missionary position will favour the larger X-bearing sperm. He reported 19 males from 22 attempts for male offspring, and 16 females from 19 attempts for female offspring. The confounding variables were numerous in his study, and further larger scale testing could not produce the same results.

Before fertilization — in vitro methods

Studies in the 1930s reported that when rabbit spermatozoa were placed under a cathode and anode field, X sperm migrated to the anode and Y sperm migrated to the cathode. Insemination of rabbits in this manner led to 80% of the offspring belonging to the expected sex. Further more sophisticated studies, however, failed to find any electrophoretic surface differences between X and Y spermatozoa. This was, nevertheless, one of the first attempts aimed at the separation of X and Y sperm for insemination to produce the desired sex. Diasio and Glass studied the effect of pH on sperm motility by allowing sperm migration through capillaries containing media of different pH, but showed motility of Y-bearing sperm were not affected by the pH of the media.[6] Scanning electron microscopy studies also failed to identify a bimodel distribution of sperm sizes.

In 1973, Ericsson *et al.* reported on a technique of separation of X and Y spermatozoa based on a differential centrifugation technique and migration of the sperm through progressively denser solutions of liquid bovine serum albumin.[7] Samples containing up to 85% Y spermatozoa were recovered from 20% bovine albumin fraction. The technique was again based on the theory that Y sperm swim faster than X sperm. The method was patented by Ericsson, and franchised by Gametrics Limited, USA. Modifications of the technique in recent years include utilizing human serum albumin instead of the bovine product.

Based on the same theory, Steeno *et al.* studied the effects of filtration of sperm suspended in Leck's solution and filtrated on a Sephadex G50 column, and reported that X spermatozoa were increased to 74% in the final fraction.[8] The method was thus proposed for female offspring enhancement in contrast to Ericsson's method of male enhancement.

In a more recently published series by Beernink *et al.*[9] with a total of 1,034 births occurring after insemination with sperm processed for sex preselection by Ericsson's technique, attempts at enhancing male sex offspring produced from 71 to 76% depending on the centre. The same article also described a derivative technique that combines sperm separation processing with prescription of clomiphene citrate to the woman to enhance female offspring. While 69% female births was reported, the authors themselves offered no explanation as to how clomiphene citrate could radically alter the effects of albumin gradient filtration from male enhancement to female enhancement. Despite the large numbers, the study was essentially a retrospective analysis without any pretence of a comparative controlled trial. The study has been criticized for its lack of control for confounding variables, such as the sex of previous offspring, and follow-up of these clients was not rigorous enough to offer confi-

dence that cases were not lost to subsequent analysis. The authors involved in the study were either license holders of the patent or paying royalties for the use of the patent. One of the original centres in the study had already ceased to use the procedure by the time the article was published because of the inconsistent success rate.

Another recent report by Vidal *et al.* using fluorescent in-situ hybridization of decondensed sperm nuclei to evaluate enrichment efficiency of human sperm separation using Sephadex filtration and human serum albumin gradients, also did not support the claims of enhancement of either X or Y sperm with these methods.[10] Sephadex filtration yielded 52.5% Y-bearing sperm, while human serum albumin gradients yielded 49.4% Y-bearing sperm. The control sample yielded 49.3% Y-bearing sperm. The differences were not statistically significant. A similar study designed to validate the albumin column procedure by chromosomal analysis of penetrated hamster eggs also failed to confirm the claims made for the clinical data.[11]

In another study by Cellsoft, New York, USA,[12] computerized image analysis failed to show a bimodal distribution of sperm velocities, therefore strongly questioning the basic assumption of Ericsson's method.

Lobel *et al.* studied 98 unmanipulated semen samples and 37 samples before and after either swim-up or Sephadex filtration, analyzing them for sex chromosome content using a quantitative polymerase chain reaction.[13] The chromosome compositions of semen samples ranged from 41.9 to 56.7% Y-bearing sperm, with a mean average of 50.3%. There was again no significant change in sex chromosome composition after either swim-up or column filtration.

Based on the principle that X sperm have 4% more DNA content than Y sperm, Johnson *et al.* reported separation of X and Y chromosome bearing sperm based on DNA content differences and thus fluorescent properties when exposed to flow cytometry separation.[14] The sperm was stained by adding a vital fluorochrome bisbenzimide, and then sorted using a flow cytometer/cell sorter modified specifically for the analysis of spermatozoa DNA content and for their flow sorting. In the X enriched sorted pool, an average of 82% of sperm showed a hybridization signal with the X probe; in the Y enriched sorted pool, 75% gave signal with the Y probe. The scientific basis of this method was further tested out in various animal models, with significant modifications of natural sex ratios observed. Nevertheless, human insemination had not yet been undertaken.

Post-fertilization methods

Post-fertilization methods mainly involve the determination of the sex of the foetus at various stages of its development after fertilization, and termination of the pregnancy if the conceptus is of the undesired sex. Established methods of sex determination in modern obstetric practice include chorionic villus biopsy or amniocentesis for karyotyping, or by ultrasound examination of the morphological appearance of the external genitalia starting from late second trimester. Terminations of the pregnancy, when necessary, will obviously have to be in the late first trimester or beyond. A novel method of coelocentesis,[15] with the use of transvaginal ultrasound guided needle aspiration of coelomic cavity of the foetuses from a gestation of six weeks onwards, has recently been reported. The removed coelomic fluid cells could predict foetal sex successfully in all cases in which tapping was successful. The method may offer an advantage of 2 to 3 weeks compared to chorionic villus sampling, but further study is obviously needed.

An isolated report on the use of endocervical smear cells for X chromatin analysis at six to eight weeks gestation with a 93% accuracy appeared in the Chinese medical literature in the 1970s, but no further studies in this area have yet appeared.[16] The isolation of foetal cells from maternal circulation to determine the karyotype and sex of the foetus have all along been a very attractive idea, but has encountered numerous technical difficulties and is not a pragmatic method at present.[17]

It is of interest to note that apart from the report of Beernink *et al.*[9] on the use of clomiphene to manipulate the sex of offspring, there is no evidence that ovulation induction agents will influence the sex ratio.[18] Moreover, most laboratories report no difference in the numbers of male and female embryos formed following either in vivo or in vitro fertilization, implying that the use of artificial insemination or assisted reproductive procedures are unlikely to alter the sex ratio of offspring produced.[19]

Within the realms of assisted reproduction techniques, the employment of embryo biopsy to determine the sex of the embryo after fertilization in vitro but before intrauterine transferal have been successfully reported in cases where sex-linked genetic diseases is the primary concern.[20] Unfortunately, the assisted reproduction procedure is highly expensive, and the method is further limited by the relatively low successful pregnancy rate per cycle.

With the absence of an ideal method for early determination of the sex of embryo/foetus to effect a very early termination of pregnancy if necessary, it is not astonishing that pre-fertilization techniques remain the more popular of the group.

Legal considerations

At present, there is little, if any, law which can be brought to bear either to prevent or to permit the

selection by potential parents of the sex of their child. Disapproval of particular techniques such as that of Ericsson's, appears to arise because of their unreliability, and the suggestion that they would be presented in a commercial setting.[1] In the United Kingdom, the only legislation which could affect or limit pre-fertilization techniques is where the provisions, or some of the provisions, in the Human Fertilization and Embryology (HFE) Act 1990 could be applied. The HFE Act requires a license for assisted conception and embryo donation, where gametes, either male or female, are used. Such procedures as in vitro fertilization and donor insemination involving egg donation and embryo donation are therefore only performed under license. Natural or donor sperm can be used for fertilization according to the appropriate circumstances. Any sex selection procedures, either pre- or post-fertilization contemplated in these circumstances would then come under the regulations of the HFE Act. However, when pre-fertilization techniques do not require storage of gametes, they will not be 'caught' by the HFE Act. Nevertheless, no similar legislation exists at present in the law of Hong Kong.

In the United Kingdom, embryos are governed by the HFE Act up to 14 days post-fertilization. Beyond that, the Abortion Act, or locally, the Abortion Law applies. Although abortion carried out on grounds of the foetal sex alone does not come within the terms of this Law, when a pregnancy is terminated by a registered medical practitioner if two such doctors in good faith form the opinion that 'the continuation of the pregnancy would involve risk to the pregnant woman, or an injury to the physical or mental health of the pregnant woman, greater than if the pregnancy were continued', no abortion offence is committed. Morgan advances reasons whereby in strict terms, abortion of a healthy foetus on the grounds of its sex alone remains permissible under the Abortion Act, e.g., where sex-linked disorders have a high chance of affecting a male foetus, or in exceptional circumstances where the mental health of the mother was so disturbed by the particular sex of the foetus.[21] Nevertheless, the General Medical Council was to express a contrary view in the context of considering a serious professional misconduct. The issue is at yet unsettled.

Ethical considerations

The ethics of the issue of sex selection still lies on the established facts concerning the efficacy of individual methods employed, the interests of patients, the duty of the doctor to serve those interests, and the interests of the community as a whole. Unreliability of available commercial methods must be a factor in the advice given to a patient. Post-fertilization methods involving chromosomal analysis, such as embryo biopsy, chorionic villus biopsy and amniocentesis are highly accurate, but the procedure related risks of embryo or foetal wastage must be stressed. It must be realized also that ultrasound assessment of foetal phenotype, although non-invasive, can never be relied on to replace chromosomal sex determination. Pre-fertilization methods poses an even more controversial issue. As has been reviewed in the preceding section, no known method of sperm separation is entirely reliable and satisfactory at present. Sperm filtration gradient methods claiming 75% male birth ratio[8,9] are not considered clinically helpful because of the substantial proportion of failures. There is, therefore, a serious risk of patient deception if, by commercial pressure and media propaganda, the public are given false expectations and are persuaded to invest their resources in attempts to fulfil them. Moreover, such in vitro sperm processing methods may dilute total sperm number albeit increasing the percentage of motile sperm. Decreased fertility per cycle may result, and patients should be properly warned of the possible costs and inconvenience involved. The use of flow cytometry methods of X and Y sperm separation appears more efficient than albumin gradients, but the results have not been tested with human insemination and the probable decrease in fertility rate after sperm processing is similarly anticipated.

Sex selection is already medically advised and practiced where there is evidence of a familial inheritance of a sex-linked genetic disorder. Termination of a male foetus is offered when there is a high statistical risk of a linked serious genetic defect. If it became possible to identify genes for sex-linked disorders in the gametes, there would be no inconsistency in selecting against them at this earliest stage to reduce the need for subsequent abortion procedures.[22]

Claims for sex selection have commonly been made on the grounds of culture and cult — the 'wanted child'. Parents may imagine an ideal family of predesigned number of offspring and birth order of different sexes. The cultural background that predisposes to the selection of sex of the offspring are varied and complicated. A boy is desired by many couples as their first born, often because of inheritance issues, but in agrarian societies male infants are priced for their usefulness on the farm, and in others because they bring wealth to the family when they marry.[19] In cultures like the British where titles and entailed inheritance descend by the male line, sex selection could assure a male heir.[1] The situation is probably similar amongst Chinese communities.

In modern society, consumer demand for sex selection may be expressed ideologically as the 'right to choose', simply as a right without even the need to justify a practical benefit or reason. Even renowned authors expressed no objection to people trying to

achieve this by sex selection.[23] Moreover, gender selection by means other than abortion to provide a child of the sex opposite to existing children would be acceptable to many people, including some noted medical ethicists.[24] The question remains, however, as to whether this request constitute a claim to the medical profession that the doctor is professionally bound to meet. Moreover, if the doctor deems his task as that of primarily to promote health and alleviate suffering, then he must realize that sex, whether male or female, is an endowment, not a disease and indeed cannot, except under extremely rare circumstances, be considered a cause of suffering.[1]

The Ethics Committee of the Royal College of Obstetrics and Gynaecology of the United Kingdom does not regard sex selection as a matter on which the medical profession can stand ethically neutral. The Committee accepts as ethical the determination of sex in the embryo or foetus, when there are reasons to investigate the possibility of serious sex-linked disorders, and to offer selective implantation or selective termination of pregnancy. As regards pre- and post-fertilization sex selection for other purposes, the Committee would urge a strong presumption against the practice, except under very discretionary circumstances; and termination of pregnancy for no other reason than the unwanted sex of the foetus would also be regarded as unethical. In this respect, the advice given by the National Institutes of Health and the President's Commission of the United States has been remarkably similar.[25]

Since 1979, government policies in Mainland China have forbidden families to have more than one child. Kumar estimated that 250,000 baby girls were subjected to infanticide between 1979 and 1984 in the country.[26] The result is that now there are 111 boys for every 100 girls. This means that many men will not find a woman to marry, and will be unable to provide the family the needed grandchildren, let alone male grandchildren. Thus, it is expected that Nature will again drive the population to an equilibrium,[27] albeit the turmoil and social conflicts in between.

Conclusion

Many authorities argue that allowing sex selection would not greatly disturb the existing sex proportions in the long run,[27,28] and would not alter in any sensible way our social structure. Furthermore, planned parenthood organizations have always proclaimed that all children should be desired, and this principle has not so far been strongly contested. In those families where the sex of the children is a problem for whatever reasons, a child of the wanted sex would be a desired child. Demographers worldwide will agree that the world is over-populated. If reliable, safe and simple sex selection procedures were available, population growth might be slowed if couples could have the exact number of children of the wanted sex. It is to be expected, therefore, that sex selection will continue to have a consumer demand, and the medical practitioner of today must be ready to meet this need within the norms of ethical medical practice.

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