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PRENATAL GENDER SELECTION: MEDICAL, ETHICAL AND PSYCHOLOGICAL ASPECTS

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Abstract

The aim: to summarize the methodology of prenatal gender selection and the ethical aspects of its implementation.

Materials and methods: the authors conducted the review in the database of scientific periodicals PubMed.

Results: based on scientific publications, the principal techniques to determine sex in the pre-implantation period, in the embryo and fetus, are presented. Invasive and non-invasive procedures of prenatal diagnosis are described. Invasive procedures include examination of the fetus by chorionic villus sampling karyotyping of cells obtained by amniocentesis. Non-invasive techniques related to pregnant women's blood biochemistry and ultrasound markers of Down syndrome are given. Fetal blood DNA testing is a more sensitive diagnostic parameter that reduces the indication for invasive procedures. The newest and most effective method of sex determination in the pre-implantation period is sperm separation screening. Medical and non-medical reasons for prenatal gender determination, such as prevention of X-linked genetic disorders in a child, a couple's choice to balance the sex of children in the family and social gender preferences are shown. Gender selection for the prevention of X-linked disorders is justified. Ethical issues regarding the balance of children in the family, giving preference to certain sex with the help of advanced diagnostic techniques, and selective abortion are discussed. The bioethical principles for preventing selective abortion resulting from gender reasons are established.

Conclusion: for preventing prenatal gender discrimination is highlighted more strongly by the need legal regulation and the ethical control of scientific technologies in reproductive medicine.

Keywords: embryo and fetus sex determination, ethics of prenatal sex selection.

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1. Introduction

Prenatal gender selection is a medical technique to select the sex of offspring before the birth of a child. There are numerous ethical questions about the type and timing of gender selection, regarding the stage when it occurs – in the semen, embryo and even fetus with a focus on the risk-benefit ratio. During the creation and implementation of the latest technologies of prenatal gender selection, a critical analysis of the discourse of public debate on the moral and legal views on gender selection with the consequences in the form of selective abortion was carried out. Significant issues of individual freedom, legitimacy of reproductive choice and prevention of sex discrimination are reflected in publications, guidelines of leading international organizations and authorities of different countries. Therefore it is very important to summarize and generalize scientific materials in the area of medical, ethical and psychological aspects related to prenatal gender selection to improve doctors' awareness and knowledge on this topic.

2. Materials and methods

The review includes the analysis of publications in the database of scientific periodicals in PubMed aimed to identify articles with the keywords «prenatal gender selection». By aggregating the literature, special attention has been paid to medical materials devoted to the most important indications for prenatal sex determination, the advantages and the disadvantages of invasive and non-invasive procedures of prenatal diagnosis, the historical introduction of pre-implantation sex

diagnostics, the main justifiable indication for gender selection based on medical reasons, the ethical debate regarding prenatal gender selection due to non-medical reasons, an overview of the international documents regulating pros and cons of prenatal gender selection.

3. Results and discussion

Following modern data, there are certain reasons to use sex determination, which include three main areas:

1) prevention of X-linked genetic disorders in a child at risk;

2) a couple's choice in order to balance the sex of children in the family;

3) social gender preferences – giving preference to children of a particular sex [1].

The most important reasons for prenatal gender selection are medical indications, as more than 200 X-linked disorders affecting only males have been identified. A convincing example of a genetic X-linked disorder is haemophilia A, a disease with hemorrhagic syndrome, which results in disability at an early age with negative social consequences. 50 % of boys born by mothers who are carriers of haemophilia will have this pathology. Various mutations in the gene for factor VIII (F8) located on the Xq28 are considered etiological factors. Since the first sequencing of the F8 gene in 1984, more than 200 gene mutations that cause haemophilia have been described and presented in the Human Gene Mutation Database.

The next example of an X-linked pathology is the fragile X syndrome, the most recognized monogenic cause of human intellectual disabilities [2]. This pathology affects all ethnic groups worldwide, with a prevalence of 1 per 4000–5000 people. In more than 99 % of cases, this disorder is due to the unstable expansion of CGG repeats in 5 regions of the FMR1 gene, leading to abnormal hypermethylation followed by inhibition of FMR1 transcription and decreased protein levels in the brain [3]. If a mother is a carrier of an X-linked pathology, Duchenne muscular dystrophy, a male fetus has a 50 % chance of being affected by this disease, which manifests itself in early childhood with negative consequences and premature mortality because the disorder occurs due to mutations in the dystrophin gene, which is located on the X chromosome (Xp21) in humans.

There are reasons for gender selection not related to medical factors. Using modern techniques, parents have the opportunity to choose a child of a certain sex, thus planning and controlling the size and balance of children in the family, because in some cases, a couple gives birth to children of the same sex, a woman has new pregnancies, but cannot produce a child of a desired sex, and it even leads to conflicts in the family, since not all couples fully understand the biological nature of the conception process.

Gender preferences in choosing a gender for non-medical reasons are present in some countries due to historical, religious, cultural and other traditions. Males have an advantage over females for economic and social reasons in India and China. Thus, in some regions of India, giving daughters a dowry leads to a significant financial burden on the family, which has many female children [4]. In India, there are religious reasons to prefer male children in the family [5]. In China, sons are a source of financial and social security in the family [6]. The preference for sons is motivated in Asian countries because the family name is passed down from generation to generation through male descendants [7]. According to data from Pakistan, gender discrimination is reflected in the gender name, which compares the presence of daughters in a family to watering a neighbour's garden [8].

Undoubtedly, the introduction of prenatal gender selection requires scientific techniques that date back to the 70^{s} of the 20^{th} century and are relevant and informative today. Ultrasound examination of the fetus should be noted as a technique, in addition to many diagnostic parameters, is the primary historical means to determine sex before birth and is currently a routine examination of pregnant women [9, 10].

Introduced invasive procedures, such as fetal chorion biopsy and karyotyping of fetal cells obtained by amniocentesis, made it possible to diagnose prenatal genetic diseases and determine the fetal sex in the post-implantation period, much earlier than the ultrasound examination of the fetus. Amniocentesis is an invasive method of prenatal diagnosis performed at the beginning of the second trimester of pregnancy (16–19 weeks of gestation). The advantages of this procedure are obtaining high-quality chromosomes and parallel biochemical, immunological, molecular and

genetic testing [11]. However, it should be noted that fetal chorionic villus sampling should not be performed before 10 weeks of gestation, as there is an increased risk of limb malformations and spontaneous abortions. In many specialized genetic centres, amniocentesis is a routine procedure. At the same time, molecular analysis of chorionic villi is indicated in cases of high genetic risk, for example, to diagnose hemoglobinopathies and determine the fetal sex. The main advantage of chorionic villus sampling is the rapid receipt of results and its performance in early pregnancy. Its high efficacy and safety are observed during this period. If pathology is detected at these stages, it is possible to decide on the further course of pregnancy or elimination of the affected fetus. The disadvantage of chorionic villus sampling is a high risk of miscarriage (2.0–3.0 %), which, in this procedure, is higher than in amniocentesis [12].

Non-invasive testing has significant advantages over the listed techniques of fetal sex determination, which are primarily used for prenatal screening of trisomies and, in some cases, microdeletions. These techniques appeared in the United States when 2011 prenatal screening of pregnant women for fetal trisomy 21 was introduced for the first time, followed by a significant spread of this strategy in the world [13, 14]. This approach includes techniques based on studying DNA circulating in a pregnant woman's blood. The argumentation for this study is scientific studies that have shown that in addition to maternal DNA, the plasma of a pregnant woman contains fetal DNA from the placenta. Maternal DNA contains approximately 10 % of placental DNA, so-called fetal DNA, and 90 % of maternal DNA. These studies are considered significant achievements of prenatal diagnosis because the fetal cells present in the blood of a pregnant woman are available for cytogenetic examination and allow high accuracy, without risks and complications of pregnancy, to detect or exclude the most common chromosomal abnormalities: Down syndrome (trisomy 21), Patau syndrome (trisomy 13) or Edwards syndrome (trisomy 18) [15, 16]. This is a fairly accurate test for Down syndrome (trisomy 21) with high sensitivity (90 %) and specificity (99.5 %) both in the study of women at risk and in the general population [17]. Compared to non-invasive techniques, such as pregnant women's blood biochemistry and ultrasound markers of the Down syndrome, fetal blood DNA testing is a more sensitive diagnostic parameter that reduces the indication for invasive testing [18]. In certain indications, non-invasive testing can detect sex chromosome aneuploidies: Turner syndrome; Klinefelter syndrome; trisomy X in females and Jacobs syndrome [19, 20]. Microdeletion screening (subchromosomal abnormalities) also helps to diagnose the following pathologies: 22q11.2 deletion syndrome (DiGeorge), Prader-Willi syndrome, Angelman syndrome, 1p36 deletion syndrome, «cat's cry» syndrome [21]. This technique has been further developed with expanding capabilities for diagnosing recognized trisomies, sex chromosome aneuploidies, rare autosomal aneuploidies, copies of DNA fragments in one sample and their distribution by copy options [22]. It is very important that the results of the study of maternal blood samples when her DNA and fetal DNA are isolated from the plasma, have significant diagnostic value and can determine the fetal sex earlier than other methods (ultrasound, chorionic villus sampling) because fetal DNA appears in the mother's bloodstream from 5–7 weeks of gestation with maximum accumulation at 13–16 weeks of gestation [23–25].

The implementation of revolutionary techniques in reproductive medicine, namely in vitro fertilization, has made it possible to create embryos in the laboratory using in vitro manipulations involving eggs and sperm, from which the cells are isolated after fertilization but before their transfer to the uterus, and to determine the sex of the embryo and possible pathologies, using pre-implantation diagnosis. Historically, a prerequisite for introducing pre-implantation diagnostics was the reports in the scientific literature on sex determination in rabbit embryos at the blastocyst stage [26]. Subsequently, pre-implantation techniques have become more common and practically used for the amplification of blastomere genes obtained by biopsy in order to study the genetic nature of haematological pathology and aneuploidy, as well as for sex determination [27].

The implementation of these techniques in clinical practice took place in 1990 when two married couples at risk of X-linked mental retardation had female twins born due to embryo biopsy at the pre-implantation stage. One cell was collected for the study, female embryos were selected, only embryos of the desired sex were transferred to women's uterus; thus, the birth of male children affected by X-linked recessive disorder was prevented [28]. These studies generated a concept

called «gender selection», namely the ability to choose the sex of the unborn child at the request of parents, both for medical and non-medical indications.

Therefore, pre-implantation genetic diagnostic technologies can prevent the transmission of monogenic defects to offspring in families, allowing couples with a family history of monogenic disorders associated with X-linked disorders and known chromosomal abnormalities to prevent embryo transfer with these specific genetic disorders [29]. Over the last years, preference has been given to a new generation of studies, the so-called pre-implantation diagnosis 2.0, which involves polar body or trophectoderm cells biopsy instead of biopsy of a three-day embryo with aneuploidy analysis of all 23 chromosome pairs [30].

An important achievement is that modern techniques can determine the sex of the unborn child before conception. The most effective method of sex determination is the Microsoft method. The principle of this non-invasive method is that the large X chromosome contains 2.8 % more DNA than the fragile Y chromosome. The procedure is as follows: the sperm is obtained from a potential father, treated with a fluorescent dye, and passed through a global detector that separates the sperm according to light intensity and separates samples containing X-sperm from Y-sperm. This technique is highly sensitive and effective for female sex selection in 93 % of cases and for male sex selection – in 82%. In the future, the necessary sperm can be used for artificial uterine insemination or in vitro fertilization. Microfluidic chips are also used for gender selection [31]. The newest methods of gender selection have been introduced in the United States, Israel, Cyprus and some other countries [32].

The introduction of assisted reproductive technologies has opened unprecedented prospects for basic medicine, including the study of fertilization mechanisms, visual observation of early human embryonic development, diagnosis of genetic defects and sex determination in the pre-implantation period. However, it creates an issue of the moral and legal status of the embryo as a component of reproductive technologies [33]. Due to scientific advances that open up space to the implementation of gender selection in practical medicine, many ethical, legal and social issues related to the introduction of a technique, which regulates the birth rate of male and female children, come to the fore.

The main justifiable indication for gender selection is undoubtedly medical reasons, namely the prevention of genetic diseases that affect boys. Methods for prenatal diagnosis using the study of the cells obtained from the embryo and fetus enable their sex determination. If the pathology is detected and the sex is determined to be male, the next step is to decide on the continuation of pregnancy or selective abortion on medical grounds. This situation can occur, for example, when there is a patient with haemophilia in the family, which requires constant and expensive treatment. In case of severe disease, early mortality is observed. Reproductive choices of families with haemophilia A and B aim to prevent the birth of a child with severe coagulation disorders. The family (woman) must make an informed decision on possible abortion, and a geneticist can give substantial advice using the techniques of non-directive counselling [34].

Methods of pre-implantation sex determination provide significant diagnostic information. Some women at risk of haemophilia during the in vitro fertilization procedure will not agree to transferring the male embryo to the uterus, not to pass on this pathology to the offspring. Thus, only a female embryo transplant is justified from a medical point of view in cases of X-linked recessive diseases. This strategy has already been adopted in some clinics. The report from the Department of Genetics and Reproductive Medicine (Spain) contains the program's results with the inclusion of pre-implantation genetic diagnosis [35]. The study involved 34 couples, 30 couples with haemophilia A and 4 couples with haemophilia B. A total of 60 reproductive cycles were performed, and 508 embryos were obtained. Gender identification of each embryo was performed using pre-implantation genetic diagnosis. According to follow-ups since 2005, 10 healthy children were born to 34 married couples (29.4 %).

A great deal of controversy arises regarding prenatal gender selection due to non-medical indications, which should be identified as gender discrimination by favouring offspring of a particular sex as the first child or a purposeful choice of offspring sex in general. However, there are some differences in opinions on this issue depending on the individual preferences of married couples, as well as religious, ethical, economic and social principles. According to a report from the United States, 90 % of couples who have used gender selection services have announced their

intention to have a balance in the family, and 89 % of them wanted a girl as the first child in the family [36]. In Germany, a representative sample of 1094 men and women aged 18–45 was surveyed to determine their gender preferences for children and their consent or refusal to select the sperm using flow cytometry followed by intrauterine insemination [37]. 58 % of the respondents said they did not care about the sex of their children, 30 % wanted to have an equal number of sons and daughters, 4 % preferred sons, 3 % – daughters, 1 % – only sons, 1 % – only daughters, 14.2 % wanted to have a boy as their first child, 10.1 % – a girl. Even with a hypothetical consideration of the medical availability of gender selection, 90 % of respondents did not want to use this technology. An anonymous sociological survey of geneticists in Ukraine in 2018 showed that only 6.0 ± 3.4 % of geneticists assumed social gender selection for the fetus for ethical reasons, and 76.0 ± 6.0 % did not assume it. This allows us to conclude that gender discrimination is not typical for the respondents who were surveyed [38].

The publications present a debate on the pros and cons of gender selection based on non-medical indications [39]. Advocates of this strategy insist on respect for human autonomy according to T. Beauchamp and D. Childress's bioethical framework and human reproductive freedom [40]. The application of the prenatal sexual determination technique gives preference to parents (or one of the parents) in their desire to have a child of a certain sex. However, from a moral point of view, such a strategy leads to the creation of a race of «desired» infants in favour of «undesired» infants, which can be assessed as manifestations of discrimination and elements of negative eugenics [41].

The need for selective abortion is a consequence of inappropriate control over the characteristics of children in some situations, such as the presence of an embryo or fetus of the opposite sex. It should be borne in mind that this approach does not preclude psychological disorders in the offspring selected using gender selection techniques. Thus, prenatal gender selection in order to have children of the desired sex and artificial balance in the family should be considered a «slippery slope» [42]. Nowadays, critical views on prenatal gender determination and selective abortion dominate because they harm the mother and the child and contradict the rule of biomedical ethics – nonmaleficence [43].

If the sex of the child is determined during pregnancy, the family does not want to keep the child of a certain sex; it results in selective abortion. Sex determination before conception does not harm the embryo or the fetus. Therefore, a sperm separation procedure is preferred because it reduces a woman's suffering, both physical and psychological [44].

The scenario of prenatal artificial change in the ratio of children for non-medical reasons, dominated by patriarchal preferences in favour of male children, which is typical of some countries in South, East and Central Asia, is considered threatening. In these countries, males have an advantage over women in social and economic spheres, so there have been attempts to use medical advances to select the offspring sex. The fundamental consequences of this phenomenon result in a violation of the natural balance and, as a result, gender imbalance. An article published in 2002 notes that gender selection of children has become an «epidemic» in countries such as India and China. In India, among other reasons to prefer male children, prenatal gender selection has become important. In Spain (2007–2015), deliveries from Indian and Chinese mothers present a higher than expected male: female ratio with the phenomenon of «missing girls» [45].

Selective abortions have a significant impact on demographics. Thus, in China, the number of young men who are unable to find a partner has increased, which reduces the quality of life and social status [46]. This trend is typical for countries with a high proportion of immigrants from Asia, such as the United States, Canada and now Europe [47].

An article from Pakistan attempts to assess the attitude of rural women towards abortion caused by gender preferences following historical traditions [8]. Based on ethnographic observations using interviews and group interviews, the attitude of women to the devaluation of daughters compared to sons as a result of forced actions – selective abortion was established. These data showed a decrease in the autonomous paradigm in the feminist direction due to women's loss of individual identity in the family. Social and cultural legitimacy due to the patriarchal regime encourages women to balance autonomy and reproductive choice. This study demonstrates gender-based discrimination against women, which is manifested in the violation of women's ability to exercise their preferences for reproductive behaviour. The article raises an important question about how

to make a selective gender abortion legal, considering the legal actions of parents and mothers with an understanding of medical regulations, laws and traditions of the countries, as well as biotechnological advances. This study may also encourage the development of controls on reproductive violence against vulnerable populations.

In 1994, the Indian government issued the Diagnostic Techniques (Regulation and Prevention of Misuse), which introduced restrictions on the use of prenatal diagnosis for some congenital conditions and prohibited using this methodology to determine the sex of the fetus.

The international regulative document, in particular, the Convention for the Protection of Human Rights and Dignity of the Human Being concerning the Application of Biology and Medicine, explicitly prohibits sex selection, «…assisted reproductive technologies are not allowed to select the sex of the future child, except in cases where this is done to prevent the future child from inheriting a sex-liked disease».

The Declaration of the World Medical Association continues the preliminary consideration of ethical principles of medical research with human involvement. Attention is drawn to the need for new methods that change medical practice and deepening the ethical views of perception and evaluation of the concept of design, usefulness and management of methods. It is emphasized that the primary purpose of research is to generate new knowledge, but it should not have priority over the rights and interests of the subject.

The Ethics Committee of Australia notes the growing disapproval of techniques related to gender selection, arguing that giving life to a child should not depend on gender. Moreover, further consideration of this issue by society is needed [48].

In general, gender selection using modern methods depending on the different characteristics of participants (age, sex, education, religion, social status) is possible only for the prevention of transmission of genetic diseases and the birth of a sick child.

The Resolution of the European Parliament, which defines the term gendercide, is of paramount importance for the prevention of the elimination and discrimination of women [49]. The semantic meaning of this expression should be considered in accordance with the interpretation of two terminological elements of Latin origin: genus – genus and credo – kill. According to the provisions of the Resolution, gendercide is defined as the systematic, deliberate and prejudiced killing of persons belonging to a particular sex. The report emphasizes the specific causes, existing trends and consequences of the medical practice of gender selection. Gendercide is a global practice in Asia, Europe, and North and Latin America. The Resolution provides impressive data showing that since 1990 more than 100 million women have demographically «disappeared» from the world's population as a result of gender-based violence, with a tendency to increase to 200 million women over the last few years. It is emphasized that gender-biased medical practice leads to gender imbalance in the population, which has negative economic, psychological and social consequences [50]. Shifting the normal, natural biological ratio in favour of the male sex causes social instability, frustration, violence and increased crime.

The European Parliament Resolution calls for the prevention of gender-based selection, not by significantly restricting access to reproductive health technologies and services, but by increasing responsibility, creating recommendations, and special training in prenatal gender selection. European Parliament resolution of 15 February 2023 on the EU priorities for the 67th session of the UN Commission on the Status of Women to highlight the need to ensure universal and full access to online information on sexual and reproductive health and rights [51].

Research limitation. The main points presented in the article are given from the point of view of reproductive genetics and bioethics specialists working in a country with a multi-religious population, loyal legislation to human rights, and a separate state policy from religion.

Prospects for further research. We are the witness of fundamental achievements in the field of embryo and fetus sex determination. The implementation of invasive and non-invasive procedures in medical practice gave the opportunity to prevent the transmission of X-linked disorders. Nevertheless, the integrated application of advanced technologies in various reproductive stages highlights not only comprehensive information for genetic counselling and clinical decision but also demonstrates significant ethical problems with non-medical reasons for gender selection.

Hence the prospects for further research should be considered as an integral part of the genetic approach shifting to non-invasive prenatal methods. It is important to strengthen the social and moral arguments against prenatal sex discrimination and selective abortion.

4. Conclusions

1. Prenatal gender selection is a rapidly evolving field of knowledge and medical practice in reproductive medicine. In general, this process should be considered a promising approach aimed at solving urgent problems of preventing the inheritance of X-linked diseases based on the principles of confidentiality, procedural justice and non-discrimination on medical grounds.

2. At the same time, the use of modern techniques for gender selection for non-medical reasons and gendercide requires unquestionable observance of both moral and legal regulations related to social challenges.

3. A necessary condition for progress is constant deepening and improvement of control of new scientific technologies at the level of society, professional organizations and state agencies.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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Data availability

The manuscript has no associated data.

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