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BIOETHICS AND TECHNOLOGIES OF REPRODUCTIVE MEDICINE

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With the development of biomedical technologies, scientists are faced with new thresholds of moral and ethical framework of society. Therefore, to conduct further experiments that can be in line with generally accepted norms of morality, it is necessary to develop a number of bioethical principles in order to be able to control the situation and to prevent "crimes against conscience". Among other biotechnological direction, the field of assisted reproductive technology (ART) is rapidly progressing with many new advances in the last decade. From these circumstances, it is necessary to point out areas of technology that may be controversial or new enough to require proper ethical control. The focus of this review was to analyze existing international documents related to biomedical research, to identify their advantages and disadvantages, and to describe the ethical problems of the use of the latest advances in the field of reproductive medicine. Thus, the main objectives described in the article were: 1) to analyze the feasibility of the current biomedical research and to highlight the main problems of bioethics; 2) to discuss existing international documents related to bioethics and biomedicine; 3) to describe the current achievements of reproductive medicine and to highlight the problems of their implementation in life.

Key words: bioethics, reproductive medicine, Convention on Human Rights and Biomedicine, human cloning, transplantation, assisted reproductive technology (ART).

Bioethics and its branching

Bioethics is one of the most up-to-date trends in philosophy and science in general. It has developed as a result of a large number of scientific breakthroughs and achievements. But in the pursuit of scientific discoveries, scientists began to forget about the ethical aspect of human existence as a person, to diminish the value and dignity of those people who participate in the experiments. This has become unacceptable in the context of a new stage in the development of human civilization, where everyone is equal in rights to the other, despite all the differences. Without the development of this science and the considerable influence of the humanistic views of world leaders, people would still be experimental in various experiments, which is unacceptable with the morals of modern society. Existing until the 30-s of the XX century the principles of ethics and morality of the doctor-patient relationship were rather outdated and needed adjustments to the requirements of the order of the new society. Thus the oldest principles between doctor and patient, known as the Hippocratic Oath, were transformed into the Geneva Declaration adopted by the UN General Assembly in 1948, which amended and supplemented the world-famous Oath, giving it the most humane sense and meaning. This is how bioethics works: the fundamental ethical principles of moral consciousness are transformed into principles that are humane in relation to the socio-cultural needs of the new modern society [1, 2].

At present, bioethics is a combination of research into ethical, philosophical and anthropological issues arising from the advancement of biology, medicine and

pharmacy, as well as the introduction of cutting-edge technologies into health care practice. This interdisciplinary field has attracted the attention of many well-known specialists in various fields of science: from philosophers and theologians to pharmacists, physicians and biotechnologists. As a result, the following branches of this science have emerged:

• "Medical ethics (Medical deontology) — a section of bioethics that examines the relationship between healthcare professionals with patients and colleagues.

• Biomedical ethics — an ethical and applied discipline, the subject of which is the moral attitude of society as a whole and professionals — physicians, biologists and pharmacists in particular — to the person, his life, health, death, and which sets the task to make their protection a priority right of everyone human.

• Pharmaceutical bioethics (biopharmaceutical ethics) — is a section of bioethics that studies the moral, law, social, environmental and jurisprudential issues that arise in the creation, clinical trials, registration, production, delivery to the consumer and use of pharmaceutical, parapharmaceutical and other pharmacy goods as well as in the provision of pharmaceutical scientific advisory services to protect the health of the population and individuals, quality of life, physical and mental integrity of the individual, protection of human dignity and safety, the study of the availability of pharmaceutical assistance to the general public" [3].

The main problem of bioethical research in the present day is that it is necessary to create such a legislative and regulatory framework that would satisfy the public from all points of view. The solution to this problem lies in the precise coordination of the actions of specialists in various fields of activity, including: lawyers, specialists in the natural sciences, industry, as well as philosophers. It is also very important to take into account the socio-cultural conditions of the future, to plan and forecast the consequences of the actions of the world governing bodies.

Convention on human rights and biomedicine

This convention arose from the awareness of the accelerated development of biology and medicine and the need for separate regulation of human rights in the protection of dignity and freedoms with regard to the use of modern science. It was adopted in 1997 along with the development of the Human Genome Project, one of the largest projects of humanity, the achievements of which concern everyone and everyone [4]. This document seeks to clarify the need for the international community to use the benefits of biology and medicine, the importance of publicly discussing issues and decisions related to the use of the latest developments, establishing human dignity and establishing measures for its integrity.

The Convention, setting the interests and well-being of the individual prevailing over the exclusive interests of the whole of society or science, recalls the term of reasonable selfishness, which must be at the heart of all decisions made by a man with respect to himself. It also stipulates that any intervention in human health must be carried out with the voluntary consent of the person, reminding us of the Belmont Principles, and in accordance with the relevant professional responsibilities and standards.

Subsequently, the Convention was supplemented by three additional protocols [4]:

1) Additional Protocol to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, on the Prohibition of Cloning Human Beings.

2) Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin.

3) Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research.

Protocol on the prohibition of human cloning

The only existing legislative instrument in the countries of Europe on the subject of prohibition of human cloning is the Additional Protocol to the Convention on the Protection of Human Rights and Dignity in the Application of the Advances of Biology and Medicine, concerning the Prohibition of Cloning of Human Beings, adopted by the Council of Europe in Paris on 12.01.1998. and its analogs in the legislative field of different countries where this protocol was taken as a basis. This instrument is open to signature and ratification by the member states of the Council of Europe as well as by non-member countries of the Council of Europe. Currently, out of 195 known countries in the world, the ban on human cloning has been partially or

fully accepted by about 70 countries as of 2018.

The basic principles of this Protocol are set out in Article 1 [5]:

1) "Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited.

2) For the purpose of this article, the term human being "genetically identical" to another human being means a human being sharing with another the same nuclear gene set".

There are 2 types of cloning:

• Therapeutic — its purpose is to obtain its own embryonic stem cells, as well as the organs and tissues synthesized from such cells.

• Reproductive — its purpose is to obtain a full-fledged adult organism [6–8].

There is controversy in global society about the urgency of canceling both types of cloning. To take therapeutic cloning as an example, it is acceptable within the protocol because it does not create a whole human being, but only part of it. With reproductive cloning it is more difficult, because as a result of it we get a genetically identical organism that has consciousness and the right to life as a representative of the human race. Considering that the formation of consciousness and personality traits are influenced to a greater extent by the social environment in which the subject is in development, and also that the environment and ability to maintain a healthy state remain a very important factor for the formation of health, it can be said that in many aspects of life, the genetic clone will be a separate link in society, not an identical repetition of an individual. However, despite this view, until the impact of human genetic information on the formation of its identity is fully understood, it will be advisable for the world community to act preventively, namely to protect human cloning entities from cloning by continuing to ban reproductive cloning, while assuming the existence of therapeutic cloning in the case of medical necessity [7–13].

Protocol on transplantation of human organs and tissues

This Additional Protocol, adopted on January 24, 2002, became the first worldwide document to validate the moral-ethical relationship of the donor-recipient physician. It establishes rules for the treatment of deceased and living donor persons, respect for the dignity of subjects, establishes the need for sanctions against persons who violate the dignity of another person and interferes with their will, takes into account the need to disseminate information about the lack of organs and tissues for transplantation. freedom of the donor person, etc. [14]. This document establishes only the moral, ethical and legal aspects of transplantation, and the transplant system itself remains the responsibility of the medical professionals who will perform the operation. I consider it expedient to establish an accelerated regime for the harmonization of the legal conditions necessary for transplantation and to state this in the Protocol or in analogues of this document adopted by other countries.

Such a measure, in my opinion, is appropriate, since with the mutual consent and voluntary decision of each party the only factor that remains to be resolved is the life of the recipient person. In such operations, time is important and therefore necessary, and therefore it is unacceptable to be distracted, in my opinion, by appealing to the authorities when a decision can be made locally, such as by a panel of physicians empowered to resolve such issues because they have in one way or another accepted the Geneva Declaration and, if they do not, they will be subject to legal penalties.

Problems of transplantation in Ukraine and the world

In modern bioethics, certain principles have been developed that should determine the functioning of transplantology first and foremost as a medical practice [15]:

1) Protecting the life of the donor and the recipient — this principle provides for a homoplastic transplant (from one person to another), provided that the life of the donor cannot be irreparably harmed (transplanted by one of the paired organs, such as a kidney, or part of an organ, such as a liver, lungs); transplantation is only possible if the recipient's health improvement exceeds the donor's health. This principle also requires that the sacrifice of the donor should be proportionate to the real possibility of the rescue of the sick patient [16, 17].

2) Protection of the identity of the recipient and his descendants. Organ transplantation causes a deep shock to the whole organism, which raises questions about the patient's personal identity and the validity of the transplant, even for the purpose of survival, which in this case can only be reduced to a biological form. Today, science is working on the technical possibility of brain

transplantation, which exacerbates the problem of self-identity both corporeally and spiritually, since the human brain stores "personal memory". Moreover, the brain transplant must be carried out as long as irreversible processes have begun in it, that is, there must be a living brain, which is murder because it contradicts even the modern criterion of human death — brain death [17–19].

3) The transplantation of the reproductive glands and organs is not a sufficient motive for using transplant methods. This transplant is considered by many researchers to be a threat to the biological and psychological identity of the recipient and his or her descendants and is not adequately reasoned for its transplantation. Since the purpose of transplantation should be to save lives and not to treat certain defects in the patient [20–24].

4) Informed consent. It provides information on the risks of both the donor — the risk of the consequences and the recipient — the risk of implantation; therefore, there can be no donation to the body solely on the grounds of sacrifice, solidarity, without clearly aware of the consequences of this action [25, 26].

Active transplant practice is practically operating in the world almost to the north, introducing technological activities from year to year. But the problems created by this practice remain as relevant as in the bowls of the first steps. Do you adhere to what time of life this person has for conscious traumatization, permanent deterioration of health and as a consequence — reduction of life expectancy of another? In sociocultural practice, the people of the world are worshiped with respect to the body of the dead, worship of the dead is a condition of respect for the living. Is it possible to find the body of a dead person a thing for common usage and use it for the social good of living [19, 26, 27]?

Transplantation, like any bioethics dilemma, has a complex component and needs to be taken into account, which remains a case-by-case delay (often in extremely limited periods of time) to make a sound decision. But the obvious fact is that by working out the paths of productivity of bioethical problems, one cannot be ensured on the technological attempt of ability and medico-social expediency. Pragmatism in medicine leads the hospital to the consumer as a person. Therefore, the rationale for the name of the problem can be attached to the entry into ethical and philosophical life [27, 28].

Today, this problem is very diverse, but there is also a significant biological transplant for surgery [29]. Until recently, the main problem was reduced to the legislative database on transplant surgery [30] (the Law of Ukraine "On transplantation of state and other anatomical human beings" was adopted in 1999), but in 2018. The new Law of Ukraine "On Transplantation of Human Anatomical Human Transplants" has been adopted, which will further aggravate the situation at this station. Legally, the law sounds pretty good, but there were no people needed for it to work. Because of this, you will not register for your people and because of this, you need to cooperate with the logistics situation with the authorities. Transplantologists were blocked and could not do surgery because of the complexity of the law — they could go to jail for criminal prosecution for "black transplantology". But at the moment, the law was rejected in December 2019, which also worked on operations through a survey of Uniform Transplant and Tissue Information [31].

Review of reproductive medicine technologies

Infertility treatment is an important demographic and socio-economic problem worldwide, using assisted reproductive technology (ART) to solve this problem. ART is a collection of infertility treatments that include various types of gametes manipulation, some or all stages of reproductive cell preparation, and the processes of fertilization and embryo development prior to transfer to the uterus are performed in vitro. Today, these are not only ways of overcoming various forms of male and female infertility, but also the possibility of preventing and treating hereditary diseases through preimplantation molecular diagnostics and cell technologies that have been developing rapidly in recent decades. But despite all of its advantages it needs to be controlled, observed and researched to prevent negative repercussions [32–36].

Assisted reproductive technologies include [37]:

- Insemination;
- In vitro fertilization — IVF;
- Intracytoplasmic Sperm Injection — ICSI;
- Selection of the highest quality sperm as a result of motile sperm organelle morphology examination (MSOME) for better ICSI — IMSI method;
- PICSI (PICSI — Petri Dish ICSI, Petri dish for ICSI) is an auxiliary method for the selection of sperm for ICSI procedure;

• Testicle biopsy — a method of surgical diagnosis and treatment of male infertility (PESA, TESA, MESE);

• Auxiliary hatching (embryo sheath intersection);

• Embryo biopsy followed by preimplantation genetic diagnosis (PGD);

• Non-invasive methods of embryo research (proteomic and metabolic analysis);

• Vitrification (cryopreservation method of embryos and oocytes);

• Semen donation;

• Oocyte donation;

• Surrogate motherhood.

Insemination is a method of infertility treatment that involves the introduction of sperm of a man or a donor into the uterine cavity during ovulation, which makes it possible to overcome the cervical factor of infertility. Insemination requires semen preparation. In modern conditions, the procedure can be performed both in the natural cycle and by induction of ovulation. The insemination is carried out during one menstrual cycle in the periocular period. For women with normal menstrual function and full ovulation, one insemination is sufficient. However, due to the difficulty of accurately setting the time of ovulation, 2–3 procedures are performed. In this case, due to the long functional capacity of sperm (72 h), the probability of fertilization increases [38].

In vitro fertilization (IVF) — Fertilization of an egg cell outside a woman's body consists of several steps:

1) Examination of patients;

2) Induction of superovulation;

3) Follicular puncture;

4) Fertilization of eggs and culturing of embryos;

5) Transfer of embryos into the uterine cavity;

6) Support phase II stimulated menstrual cycle;

7) Diagnosis of pregnancy [39].

IVF is serious topic for discussion between bioethics specialists, for example can we use embryos from IVF as research materials and use genome editing technologies, like CRISPR-Cas9, on it [40–43].

The ICSI method enables effective treatment of infertility of the married couple in the presence of a pronounced oligozoospermia and asthenozoospermia in a man. To use the method, it is sufficient to have only a single sperm in the semen sample, whereas previously the only way to obtain pregnancy in such pairs was to use donor sperm. The practical use of the ICSI method increases the effectiveness of the treatment of male infertility and enables the man to have a genetically born child. In connection with the introduction of the ICSI method, the technique of obtaining individual spermatozoa in men with azoospermia, necrosospermia, and aspermia by direct transcutaneous aspiration of sperm from the testicle has been successfully used. This method is often used with measurement of follicular output rate (FORT) as a predictor of oocyte competence, embryo quality and clinical pregnancy after intracytoplasmic sperm injection [44–46].

Testicle biopsy — a method of surgical diagnosis and treatment of male infertility (PESA, TESA, MESE). This technique is not complicated from a surgical point of view. As a rule, in the case of obstructive azoospermia, in most cases, it is possible to obtain enough sperm to perform the ICSI procedure [39].

The IMSI method is exclusively ancillary to the ICSI methodology. According to ESHRE, the probability of pregnancy in the ICSI method is about 35%. IMSI technology is based on a good semen evaluation, after which the performance of IVF + ICSI is greatly enhanced. In this method, the laboratory is screened for sperm before the introduction into the egg under a microscope with a powerful magnification (7000 and more). Here, first of all, the sperm morphology and its proper structure are taken into account [47].

PICSI method. The method is practically indistinguishable from ICSI and can be used in conjunction with ICSI. When using this method, the sperm passes an additional "check for maturity". Only fertilizable sperm interact with hyaluronic acid. Non-fertilizing sperm do not contain specific receptors, so they do not come into contact with hyaluronic acid and are therefore not used further for ICSI. Spermatozoa capable of contacting hyaluronan have a lower rate of chromosomal abnormalities and DNA fragmentation [48].

Auxiliary hatching is the process of cutting the embryo shell into a specific phase of its development to facilitate the hatching of the embryo. This procedure may increase the likelihood of pregnancy. Indications for use of this method: age factor (women over 37 years), the presence of several unsuccessful attempts at HIV. The following variants of hatching are distinguished: mechanical, chemical, laser and using a piezo method [49].

Embryo biopsy with subsequent preimplantation genetic diagnosis (PGD) is not completely safe and often impairs

further embryo development because it is due to alteration of the integrity of the embryo (chemically or mechanically). Recently, a biopsy laser has been used to reduce the integrity of the shell. The laser beam makes an opening in the embryo shell through which the blastomer is easily and easily released. Usually, a biopsy of one blastomer in an embryo undergoing fragmentation (4–10 blastomeres) is performed for analysis. In recent years, there has been a tendency to switch to a biopsy of the troptoderm (outer layer of cells) at the blastocyst stage (the fifth day of embryo development) [50]. Preimplantation genetic diagnosis is considered as a way of alternative prenatal diagnosis. Its main advantage is that it uses no selective termination of pregnancy, and the probability of having a baby without a genetic disease is quite high.

Non-invasive embryo research methods (proteomic and metabolic analysis) are methods based on the study of metabolites of embryo culture media. Studies of media in which embryos were cultured revealed different metabolites of the implanted embryo's life and non-implanted embryos [51].

Vitrification is a cryopreservation method that combines highly concentrated cryoprotectant solutions and rapid (almost instantaneous) cooling by immersing the samples directly into liquid nitrogen. This achieves the main purpose of vitrification — minimizing the formation of ice crystals, which can damage the structure of the cell. Vitrification is a process in which highly concentrated cryoprotectant solutions in the process of rapid cooling acquire an amorphous glassy state without the formation of ice crystals [52, 53].

The main advantages of vitrification are that the high concentration of cryoprotectants and the high rate of cooling-thawing eliminate the damage caused by the formation of intracellular ice, as well as the undesirable osmotic effects of dehydration and rehydration due to extracellular crystallization [46, 53, 54].

Sperm donation is one of the most advanced infertility treatments available. The indications for insemination or IVF are:

– male infertility caused by aspermia, primary azoospermia, necro- and teratozoospermia;

– the presence of genetically determined hereditary diseases in men;

– retrograde ejaculation in the absence of normal sperm;

– lack of a sexual partner in a woman [39].

Oocyte donation is indicated for women who have no ovaries or no ovaries, and are at high risk for inherited fetal diseases. In such cases, the eggs are obtained from a healthy female donor [55].

Surrogate motherhood. The program of surrogate motherhood includes women who, due to the pathology of the reproductive sphere, cannot bear a baby (the uterus is absent due to surgery or may not be fecundity, extragenital diseases, a large number of unsuccessful attempts at extracorporeal fertilization, etc.). Genetically native embryo is transferred into the uterine cavity of a woman who has consented to have a baby [53, 55–58].

Ethical and legal problems in the use of reproductive medicine technologies in Ukraine and in the world

Scientists, doctors, and donors of gametes face a number of philosophical, ethical and moral issues when using the latest technologies in the field of reproductive medicine. One of the major bioethical problems of today is the solution of the question: what is the moral status of the embryo, from what stage of embryo development should it be considered a human being, to what extent does it have human rights? Ukrainian and world scientists, focusing on the ethical issues of ART, refer to them: biological rights and social problems of the embryo; the risk of a kind of racism when targeted or a random selection of donors — carriers of the "best" genes; destruction or preservation of the embryo in case of possible or detected anomalies; the problem of ownership of "extra" embryos, etc. [50, 59–65].

Scientists, as an alternative to solving problems related to the use of embryos, suggest determining the status of the embryo. V.G. Tretyakova stresses that the question arises as to the legal status of the embryo and the legal consequences of its use or destruction. It is understood that the law should establish all the necessary procedures, procedures, and rules for the handling of embryos, in particular in relation to their application for artificial insemination [66, 67].

Bioethics is the science of modernity that has emerged from the huge number of biomedical breakthroughs. Without an understanding of its moral and ethical principles it is impossible to have human dignity, its personality is invulnerable to the immoral intentions of individuals. It is also necessary for the co-operation of research around the world and the implementation of their achievements in all countries of

the world at the legislative level. Today there are still ethical problems with the implementation of modern technologies due to lack of attention to these problems in world organizations. I think, there should one more additional protocol to Convention on Human Rights and Biomedicine about genome editing in all spheres of life and in all purposes due to impetuous growth of using of genome editing technologies. Can we use genome editing technologies in embryos to prevent future pandemics? That is the question arising in today's situation with COVID-19. The moral and ethical philosophical questions surrounding the introduction of new technologies into reality will always remain as long as technological progress is true, because, despite all attempts to predict the future, there will still be such a problem that will in one way or another touch on the philosophical principles of worldview. Of all contemporary issues of bioethics, I consider that one of the most important issues is to determine the moral status of the embryo and its rights as a separate element of society.

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БІОЕТИКА ТА ТЕХНОЛОГІЇ РЕПРОДУКТИВНОЇ МЕДИЦИНИ

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З розвитком біомедичних технологій науковці стикаються з новими порогами морально-етичних рамок суспільства. Тому для проведення подальших експериментів, що можуть межувати із загальноприйнятими нормами моралі, потрібно розробити низку біоетичних принципів для можливості контролю ситуації та застереження від «злочинів перед сумлінням». Серед інших напрямів біотехнології в останнє десятиріччя суттєвих досягнень та стрімкого прогресу набула галузь допоміжних репродуктивних технологій. Із цих позицій існує необхідність виявити ті галузі технології, які можна вважати неоднозначними або досить новими для застосування належних етичних норм.

Поданий огляд сфокусовано на аналізі чинних міжнародних нормативних документів, які стосуються біомедичних досліджень, ідентифікації їхніх переваг та недоліків, а також обговорення етичних проблем використання новітніх розробок у сфері репродуктивної медицини.

Таким чином, головними завданнями статті є: 1 — проаналізувати доцільність сучасних біомедичних досліджень та виокремити основні проблеми біоетики; 2 — обговорити існуючі міжнародні документи, що стосуються біоетики та біомедицини; 3 — описати сучасні досягнення репродуктивної медицини та виділити проблеми їх упровадження в життя.

Ключові слова: біоетика, репродуктивна медицина, Конвенція про права людини та біомедицину, клонування людини, трансплантація, допоміжні репродуктивні технології (ДРТ).

БИОЭТИКА И ТЕХНОЛОГИИ РЕПРОДУКТИВНОЙ МЕДИЦИНЫ

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С развитием биомедицинских технологий ученые сталкиваются с новыми порогами морально-этических рамок общества. Поэтому для проведения дальнейших экспериментов, которые могут граничить с общепринятыми нормами морали, следует разработать ряд биоэтических принципов для возможности контроля ситуации и предостережений от «преступлений перед совестью». Среди других направлений биотехнологии за последнее десятилетие значительных успехов и стремительного прогресса достигла область вспомогательных репродуктивных технологий. С этих позиций существует необходимость выявления тех отраслей технологии, которые могут считаться неоднозначными или достаточно новыми для применения надлежащих этических норм.

Представленный обзор сфокусирован на анализе существующих международных нормативных документов, касающихся биомедицинских исследований, идентификации их преимуществ и недостатков, а также обсуждении этических проблем использования новейших разработок в сфере репродуктивной медицины.

Таким образом, главные задачи статьи: 1 — проанализировать целесообразность современных биомедицинских исследований и выделить основные проблемы биоэтики; 2 — обсудить существующие международные документы, касающиеся биоэтики и биомедицины; 3 — описать современные достижения репродуктивной медицины и указать проблемы их имплементации в жизнь.

Ключевые слова: биоэтика, репродуктивная медицина, Конвенция о правах человека и биомедицине, клонирование человека, трансплантация, вспомогательные репродуктивные технологии (ВРТ).