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DUAL-USE TECHNOLOGIES OF CONCERN IN CONTEXT OF BIOSAFETY (REVIEW)

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Abstract

One of the main prerequisites for creation and dissemination of bioethics in the world was the concept of dual use in medical and biological sciences, which is defined as the direction of unintentional creation of biological threats in research or implementation of new biotechnologies. To determine the range of dual-use research that could potentially generate products, technologies, or knowledge whose misuse could harm large numbers of people or the environment and that are biosafety-relevant, the international term Dual Use Research of Concern (DURC) is used. Actualization of the debate on the dilemma of dual use in biomedical sciences is due to, on the one hand, the international community's attempt to minimize the potential for destructive use of biomedical research, on the other hand, the active search for effective ways to raise awareness of their social and moral responsibility for implementation of the results of scientific developments in the field of life. This article considers the definition of terms that define the field of DURC in the context of biosafety, which in recent decades have undergone a number of semantic changes. The article also outlines the modern general concept of DURC, defines the categories by which DURC is defined, and outlines the scope of policy on the implementation of control over DURC. Informing the scientific community engaged in biomedical research about the problem issues of DURC biotechnology is a key component of biosafety. Modern biotechnology and related biosafety issues should be applied to society needs, but without compromising human and environmental safety. Systematic consideration of all these disputable questions of the dual-use dilemma with the involvement of all stakeholders will allow to form a rational biosafety policy for biotechnology.

Keywords: *biosafety, investigation of DUAL-USE TECHNOLOGIES OF CONCERN, DURC criteria, DURC recommendations.*

At the global level, biosafety issues related to the protection of humans, animals, plants and the environment from biological threats are becoming increasingly important, especially in the context of modern information technology and access to global biosafety information [1].

One of the main prerequisites for the creation and dissemination of bioethics in the world was the concept of dual use in medical and biological sciences, which is defined as the direction of unintentional creation of biological threats in research or implementation of new biotechnologies. The knowledge cannot be safe or dangerous, it acquires either a benefit or a threat to society only in the process of implementing specific practical goals [2].

The biosafety strategy in biomedical sciences is mainly characterized by an approach that assumes that research results working with biological agents and designed to expand scientific knowledge can also be used for the purposes other than the original, predictable and legal. To refer to a range of dual-use studies that could potentially generate products, technologies, or knowledge whose misuse could harm large numbers of people or the environment and that are biosafety-relevant, the international term Dual Use Research of Concern (DURC) is used.

This article considers the definition of the terms that defines the scope of DURC in the

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context of biosafety, which in recent decades has undergone a number of semantic changes. The article also outlines the modern general concept of DURC, defines the categories used to define DURC, outlines the scope of policy on the implementation of control over DURC.

The actualization of the debate on the dilemma of dual use in biomedical sciences is due to, on the one hand, the international community's attempt to minimize the potential for destructive use of biomedical research, on the other hand, the active search for effective ways to raise awareness of their social and moral responsibility for the results of scientific development implementation in the field of life [3].

The use of the latest knowledge for destructive purposes is not a new problem of the modern science. This topic has undergone significant transformations in the recent decades in the context of the rapid development of scientific thought. Active discourse around modern biotechnology attracts the attention of scientists, politicians, regulators. A key aspect of DURC debate is whether biotechnology research should be active or whether this will not lead to the spread of diseases dangerous to humanity, whether these studies can become a threat to humanity. In other words, the concern of mankind is related to the question: Can the sciences about life become sciences about death? Researchers believe that such development is quite possible and therefore actively discuss the limitation of research and public information on the results of these studies in the field of biomedical research and the creation of potentially dangerous biotechnology [4].

The concept of dual use was in the past widely used to refer to the knowledge and technology for civil and military use. Today, in the context of the accumulation of dangerous knowledge in the life sciences, there is concern about how the new knowledge and methods may affect the development of biological weapons. The issue that biological agents (objects of medical and biological research) have the potential to be used as weapons of mass destruction is discussed [5]. In some cases, they also have the potential to spread worldwide through infection, thereby endangering the lives or health of large numbers of people, or harming the environment or other important interests, even in the case of local release [6]. Thus, DURC issue is a matter of potential biological weapons and bioterrorism that needs public scrutiny and attention.

The ethical problems of DURC danger are not a completely new moral and ethical challenge of the latest technologies. For example, physicists working on nuclear energy (Manhattan Project) discussed the ethical dangers of the possible use of nuclear research for military purposes, which proved justified after the first use of nuclear weapons against Japan. Another example of the possibility of dual use was the active debate after the start of the project on the creation of recombinant DNA. Biomedical scientists have been concerned about the implications of their research. The Asilomar Conference of 1975 was dedicated to recombinant DNA and was initiated because the scientists were concerned that DNA research, if left uncontrolled, could have unpredictable and devastating consequences for both human health and the global ecosystem. At the conference, geneticists discussed the possibility that common harmless microorganisms could become pathogenic to humans through the introduction of the genes that make them resistant to antibiotics, or allow microorganisms to produce dangerous toxins or transform them into carcinogens. The quote of the Nobel laureate, physicist Max Bourne: "Science destroys the ethical foundation of civilization" (1968), which can be interpreted as the fact that the latest technology always causes moral and ethical dilemmas, is world-known.

Biomedical sciences differ from nuclear research in that they are conducted worldwide in commercial and academic laboratories, rather than in the laboratories owned by national governments whose activities can be more strictly regulated and controlled at the governmental level. In the context of biomedical sciences, and, in particular, in the field of biotechnology, there are no clear boundaries and distinctions between defensive and offensive biological programs, and it is often difficult for scientists to justify a scientific biological experiment, although under the Convention on the Prohibition of Biological and Toxic Weapons, development of biological weapons is illegal, as is their production, acquisition, transfer, storage, accumulation and use.

DURC discussion has become active at the beginning of the new century. In 2000, Harvard University molecular biologist Matthew Messelson voiced the potential threats to the concept of dual use. In his opinion, over the next century, as our ability to change fundamental life processes continues to move rapidly, we will not only be able to invent additional ways to destroy life but also to obtain the possibility to manipulate it – including the processes of cognition, development, reproduction and inheritance. Therefore, the movement to such a world will distort the accelerating revolution in biotechnology, so as to

damage its huge potential for mutually beneficial application, and can have hostile consequences for the course civilization [7].

DURC concept originally referred to the technologies that had both civilian and military purposes. Following the terrorist attacks of September 11, 2001 and subsequent bioterrorist attempts to spread the anthrax to the United States, the term became broader, which was proposed in 2004 in a report by the Committee to Study Standards and Practices to Prevent the Destructive Application of Biotechnology to the US National Research Council (hereinafter referred to as Fink Committee) entitled "Biotechnological Research in the Age of Terrorism". The main premise of this report is the quote "Most of all biotechnology that serves human health can be used for hostile purposes. The main components of bioterrorism are likely to be based on the materials and techniques that are easy to obtain because they are accessible. The most important element of protection against bioterrorism is accelerated development of technologies to establish our ability to detect and treat diseases. The abuse between the spread of technologies that protect us and the spread of technologies that threaten us is a major component of the dual-use dilemma [8].

The dual-use dilemma, according to the report of Fink Committee, is that any advances in biomedical sciences can be easily used by dangerous subjects to develop biological weapons. Experts of Fink Committee formulated three potential definitions of the dual use of science and technology: 1. has both civilian and military applications; 2. can be used both for useful/good and for harmful/dangerous purposes; 3. has both useful/good and harmful/dangerous purposes related to weapons, in particular weapons of mass destruction [8].

Fink Committee based its recommendations on the analysis of the state of regulation of science and technology at the time. The Committee found that "current national and international directives and regulations for basic and applied research in the field of genetic engineering can guarantee the physical safety of laboratory workers and the environment by preventing contact with the pathogens or "new" organisms or the effects of such agents. However, they do not currently provide for measures to prevent the possible use of tools, technology, or research knowledge for aggressive military or terrorist activities. In addition, no national or international oversight body currently has the legal authority or self-responsibility to evaluate a proposed research activity to determine whether the benefits of the proposed research outweigh the risks associated with it and the likelihood of its abuse" [8].

Fink Committee identified 7 specific categories of research to be monitored. These include the following research areas:

1. a technique that demonstrates how to make a vaccine ineffective;
2. providing resistance to therapeutically useful antibiotics or antiviral agents;
3. enhancing the virulence of pathogens or providing virulence to non-pathogenic agents;
4. increase of pathogen transmissibility;
5. change in the range of hosts of pathogens;
6. techniques that make it possible to evade diagnostic methods;
7. conversion of biological substances or toxins into weapons.

Fink Committee also developed recommendations for the prevention/mitigation of possible misuse of biomedical research results [8]:

Recommendation 1: Education of the scientific community: We recommend that national and international professional associations and related organizations and institutions establish programs to train natural scientists on the dual-use dilemma of biotechnology and their responsibilities to reduce risks.

Recommendation 2. Review of Experimental Plans: We recommend that the Department of Health and Human Services (DHHS) strengthen the existing control system for recombinant DNA experiments conducted by the National Institutes of Health to establish a control system for seven classes of experiments (experiments of interest) using microbial pathogens that cause concern about their potential for proper use.

Recommendation 3. Verification at the stage of publications: We recommend, based on the self-government of scientific and scientific journals, to check publications for potential risks to national security.

Recommendation 4: Establishment of National Scientific Advisory Board on Biological Weapons: We recommend that the Department of Health and Social Services establish National Scientific Advisory Board on Biological Weapons (NSABB) to provide advice, guidance and leadership in the oversight and control system.

Recommendation 5. Additional elements of protection against misuse: We recommend that the federal government rely on current legislation and regulations on for periodic inspections of NSABB to ensure the protection of biological materials and the monitoring of personnel working with these materials.

Recommendation 6. The role of biomedical sciences in efforts to prevent bioterrorism and biological warfare: We recommend that the national security and law enforcement communities develop new channels of sustainable communication with the biomedical industry in order to reduce the risks of bioterrorism.

Recommendation 7. Coordination of International Supervision: We recommend that international political and scientific circles establish an International Biosafety Forum to develop and promote agreed national, regional and international activities in addition to the system we recommend for the United States".

One of the important recommendations of Fink Committee ("Biotechnological Research in the Age of Terrorism") was the formation of a standing committee to discuss the problems of potential threats associated with biotechnology in synthetic biology. In addition to creating such a new body, it was recommended that the mainstream scientific community improve education, namely, begin to study the ethics of dual use by changing existing publication requirements, and establishing the channels for communication between research laboratories and security and law enforcement agencies.

The debate, initiated by the report of Fink Committee, continued in 2006 when a report entitled "Globalization, Biosecurity, and the Future of Biomedical Sciences" was published under the auspices of the US National Academy. This program document was developed by the Committee on Technology Development and Prevention for the Requirements of Bioterrorism and Biological Weapons (Lemon-Relman Committee) [9]. This report not only addressed the issues highlighted in Fink's report, but also outlined a much wider range of scientific areas that may address the issue of dual use.

The main difference between the reports of Fink and Lemon-Relman was the scale of the study of biomedical technologies. Thus, Fink Committee focused mainly on the problems of threats in synthetic biology, while Lemon-Relman Committee did not limit itself to a specific area, but presented a more general concept of understanding biomedical threats and mechanisms for preventive response to them, and focused on that biomedical research is dangerous and requires development of control systems for all biomedical sciences.

Lemon-Relman Committee (2006) formulated a general concept for biotechnology. In particular, the experts concluded that biotechnology is a global and potential threat in their nature, and the potential threat of any biotechnology is much broader than just that posed by traditional pathogens and toxins. The report stated that the biological substance used in the mail attacks was anthrax, the 'classic' choice of those intending to wage biological warfare. Moreover, it is becoming increasingly important that biomedical scientist take all possible measures to ensure that their work is not used for criminal purposes. Correspondingly, this requires biomedical workers to pay much more attention to the danger than that currently exists and to be more willing to take on that responsibility. Finally, the experts of Lemon-Relman Committee conclude that a new standard is needed, and it must appear on a global scale [9].

Lemon-Relman Committee fully endorsed and reaffirmed the policy of promoting free and open exchange of information in the field of biomedical sciences and made several recommendations [9]:

1. to apply a broader view of the threat spectrum.

2. to strengthen and expand scientific and technical experience within and between security-related communities.

3. to accept and promote the general culture of awareness and the general sense of responsibility in the world community of scientists of medical and biological branch.

4. to strengthen .. the health care system ... and existing response and recovery capabilities.

One of Fink committee guidelines in 2004 was the recommendation to the Department of Health and Human Services to establish National Scientific Advisory Board on Biological Weapons (NSABB) to provide advice, guidance, and leadership in the oversight and control system. In accordance with these recommendations, the US Government established the National Scientific Advisory Board on Biosecurity (NSABB) in 2005. The NSABB is currently a federal advisory committee that reviews biosecurity and dual-use research commissioned by the US government. NSABB has up to 25 voting members with a wide range of experience in biomedical sciences such as molecular biology, microbiology, infectious diseases, biosafety, health, veterinary, plant health, national security, biosecurity, law enforcement, scientific publications and other related scientific and applied fields.

Regarding the responsibility of researchers for publishing the results of the study, DURC evaluations are currently conducted by the journal editors who may seek advice from the NSABB

staff. However, the NSABB is a federal advisory committee, and only the US government can delegate tasks to the board, which in turn can only advise the US government. Therefore, outside organizations, such as journals, cannot refer issues directly to the Board. Thus, the journal editors are the only arbiters for the publication of manuscripts describing DURC [10].

At present, various NSABB offices and programs work on a wide range of issues, including biosafety, biosecurity, genetic testing, genomic data sharing, subject protection, organization and management of the National Institutes of Health (NIH), and the results and value of research funded by the NIH [11]. This is achieved through a wide range of analyzes and reports, comments on the new policy proposals, and the development of policy proposals for consideration by the NIH, the federal government, and the public.

In 2007, the NSABB prepared a document entitled "Proposed Control System for Dual Use Life Sciences Investigation: Strategies for Minimizing the Potential Misuse of Research Information" [12]. This document identifies that some research has the potential to be "dual-use" and that it is the research that generates information and products that can be used for both beneficial and harmful purposes. The NSABB has introduced an international definition of DURC in the field of biomedical sciences, "Research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or material" [12].

In addition, the NSABB provided a roadmap and tools for identifying scientific work that could fall into the DURC category, and proposed mechanisms for disseminating such information, including writing of accompanying editorials.

The NSABB has proposed criteria for determining DURC, namely, it describes seven categories of experiments that can be used to identify the work that could potentially be DURC, with the wording according to which the studies ncluded in any of these categories "should be particularly carefully assessed for compliance with the criterion of dual-use studies of concern". The seven criteria are clear and easily applied to manuscripts to identify potential DURC.

The seven criteria of possible DURCs defined by the NSABB are [12]:

(1) Enhances the harmful effects of a biological agent or toxin (2) Violates immunity or the effectiveness of immunization without clinical and / or agricultural justification (3) Belongs to a biological agent or toxicity to clinically and / or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates its ability to avoid detection methodologies. (4) Increases the stability, transmission, or ability to spread a biological agent or toxin. (5) Changes the host range or tropism of a biological agent or toxin. (6) Increases susceptibility of the host population. (7) Forms a new pathogenic agent or toxin or restores a destroyed or extinct biological agent.

Informing the research biomedical community about the problematic issues of DURC biotechnology is a key component of biosafety. Modern biotechnology and related biosafety issues should be applied to social needs, but without compromising human and environmental safety. Systematic consideration of all these disputable aspects of the dual-use dilemma with the involvement of all stakeholders will allow to form a rational biosafety policy for biotechnology.

A key point here is the need to determine that the risks of dual use can and should be seen in the context of a range of surveillance measures, including monitoring the responsibility of scientists to minimize the risks of misuse of their research.

Thus, in order to solve the problems of DURC, there are approaches that, on the one hand, are aimed at developing a culture of biosafety based on social and moral responsibility of scientists in the field of high risk DURC, and on the other hand, to avoid their unnecessary restrictions or censorship in the direction of freedom of scientific thought.

Conflict of interests

The authors of the article declare no conflict of interests.

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ADIPONUTRIN LEVELS IN HYPERTENSIVE PATIENTS DEPENDING ON THE DEGREE OF OBESITY

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Abstract

Background. It is a well-known the fact that obesity, especially its abdominal (visceral) form, is one of the most important risk factors for hypertension. The purpose. to determine how excessive weight and obesity affect blood serum adiponutrin levels in patients with hypertension. **Materials and methods.** The study included 58 patients with hypertension. Grade 1 was diagnosed in 12 (20.69%), grade 2 – in 16 (27.59%), grade 3 – in 30 (51.72%) examined patients. Of these, 32 women and 26 men aged 32 to 79 years (mean age 57.5 ± 10.11 years). Patients underwent anthropometric measurements. Blood serum level of glucose was determined by glucose oxidase method, glycosylated hemoglobin was determined by photometric method, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined by enzymatic method according to standard biochemical method. The levels of very low density lipoprotein cholesterol, low density lipoprotein cholesterol, atherogenic factor were calculated by the formulas. Adiponutrin blood serum level was determined by enzyme immunoassay method. **Results.** Adiponutrin blood serum level in all groups of hypertensive patients with overweight and obesity was significantly increased compared to the control group, but the degree of hypertension did not affect the level of adiponutrin. However, the level of the latter in the serum gradually increases according to the duration of hypertension. In addition, the level of adiponutrin increased depending on the degree of obesity, which, in turn, was confirmed by a reliable direct linear relationship between adiponutrin and body mass index. **Conclusions.** Based on the data obtained, adiponutrin can be considered as a potential biomarker of metabolic disorders.

Keywords: *adiponutrin, hypertension, obesity, triglycerides.*

Introduction

Hypertension (HT) currently remains an actual problem of cardiology due to high prevalence and is a major risk factor for morbidity and mortality worldwide, resulting in 10.4 million deaths annually [1].

In addition to traditional factors of cardiovascular risk, a complex of factors such as obesity, dyslipidemia, insulin resistance in combination with hypertension attracted considerable attention of scientists. Nowadays, it is generally accepted that the level of increase in the obesity frequency among the population of developed countries is acquiring alarming rates, therefore this phenomenon is compared with a pandemic [2].

It is a well-known the fact that obesity, especially its abdominal (visceral) form, is one of the most important risk factors for HT. According to the World Health Organization (WHO), obesity is defined as «abnormal or excessive fat accumulation that presents a risk to health» [3, 4]. The actual prevalence of obesity in most European countries is around 20% [5]. These numbers have nearly tripled since 1986, when the European Association for the Study of Obesity was founded to address the emerging obesity problem [6]. In contrast to the opinion that obesity is only a risk factor for disease, the World Obesity Federation has declared obesity as a chronic recurrent progressive disease [7].

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Despite the presence of experimental and clinical evidence of the mutual burden HT and obesity, the mechanisms of formation of pathophysiological consequences of such a message remain insufficiently defined. Recently, an important role has been assigned to the adiponutrin (ADPN) protein as a marker for metabolic disorders [8]. ADPN, encoded by gene the patatin-like phospholipase domain-containing 3 (PNPLA3), consists of 481 amino acids responsible for the function of the endoplasmic reticulum, the structure and function of mitochondrial membranes and lipid inclusions in hepatocytes and adipocyte membranes [9]. This protein has hydrolase activity towards triglycerides (TG), acyltransferase activity towards lysophosphatidic acid, and esterase activity towards retinol palmitate [10–12].

The participation of adiponutrin in energy metabolism, triglyceride lipolysis and other metabolic processes has been proven earlier and presented in publications of previous years exclusively within the framework of liver pathology: non-alcoholic fatty liver disease with the risk of coronary heart disease [13], with the risk of chronic kidney disease [14], but data of clinical and experimental studies regarding adiponutrin blood serum level determination in patients with hypertension are very few, and there are almost no scientific data in comorbidity with obesity. Therefore, the study of ADPN - the marker of metabolic disorders to determine the character of the flow of HT in comorbidity with obesity is actually today.

2. Purpose, subjects and methods:

2.1. The purpose of the research was to determine how overweight and obesity affect blood serum adiponutrin levels in patients with hypertension.

2.2. Subjects & Methods

The study included 58 patients with HT, who were on inpatient treatment in the cardiology department. Of these, 32 women and 26 men aged 32 to 79 years old (mean age – 57.5±10.11 years), who previously have not been receiving regular antihypertensive therapy.

The diagnosis was verified on the basis of clinical, laboratory and instrumental methods of investigation. Exclusion criteria for patients of this study, in addition to patients with symptomatic hypertension, were patients with cancer, acute and chronic inflammatory processes, concomitant diseases of the thyroid gland, and diabetes mellitus. The control group included 20 age-and sex-matched healthy persons. The study was conducted in accordance with the current ethical requirements. The protocol of the study was approved at the meeting of the Committee of Bioethics of the Kharkiv National Medical University, department of Propedeutics of Internal Medicine No. 2 and Nursing Care (Minutes No 7 of 11 September 2018). All patients who participated in the study signed a voluntary informed consent to participate.

All patients had blood pressure (BP) measured in a sitting position after a 5-minute rest according to the Korotkov's method. The guidelines by of European Society of Cardiology (ESC) / European Society of Hypertension (ESH), criteria of Ukrainian Association of Cardiology were used for verification of the diagnosis and estimation of the hypertension grade [15]. Grade 1 HT was diagnosed in 12 (20.69%) patients, grade 2 HT – 16 (27.59%), and grade 3 HT – 30 (51.72%) examined patients.

The history of increased blood pressure less than 5 years was observed in 27% of patients, from 6 to 10 years-in 33%, more than 10 years-in 40%. Surveys of the examined patients showed the presence of asthenic-neurotic complaints in 98.3%, cerebral complaints – 84.5%, cardiac complaints – 84.5%. It should be noted that in patients with obesity-associated HT, the symptoms were more pronounced. The diagnosis of obesity is established in accordance with the classification based on the determination of body mass index (BMI). This classification is developed by the National Health Institutes by the United States of America, and approved by the WHO. Anthropometric measurements included height (cm), weight (kg), waist circumference (WC, cm) and hips circumference (HC, cm). It was followed by calculation of BMI (kg/m^2), according to the formula BMI = body weight / height^2 as well as calculation of the waist to hip ratio (WHR). A WC / HC value > 0.90 for male and > 0.85 for female attesting to the presence of abdominal (visceral) type of adipose tissue distribution. Blood for biochemical research was carried out in the morning on the next day after admission of the patient to the hospital after 12–18 hours starvation. Blood was taken from the ulnar vein. All patients were in the same physical activity conditions.

Adiponutrin levels (pg/mL) were determined by enzyme immunoassay method using The RayBio® Adiponutrin Enzyme Immunoassay (EIA) Kit, (USA).

In order to control carbohydrate metabolism, the glucose level was determined by the fasting

glucose oxidase method, the content of glycosylated hemoglobin (HbA1c) in blood serum was determined by photometric method by reaction with thiobarbituric acid using a commercial test system of the company «Reagent» (Ukraine). The levels of total cholesterol (TC, mmol/l), high-density lipoprotein cholesterol (HDL CS, mmol/l) and triglycerides (TG, mmol/l) were determined by enzymatic method using standard kits. The level of very low-density lipoprotein cholesterol (VLDL CS, mmol/l) was calculated using the by the value of the ratio: VLDL CS = TG/2.2. Low – density lipoprotein cholesterol (LDL CS, mmol/l) was determined using the formula Friedewald: LDL CS = TC – (HDL CS + TG/2.2). Coefficient of atherogenicity (CA) was calculated by the Klimov formula: CA = (TC - HDL CS) / HDL CS.

Mathematical computer processing of results was carried out with the help of the software package Statistica 10.0 (StatSoft Inc.). The mean value (Mean) and standard deviation (SD) were determined. Analysis of the data was carried out by methods of nonparametric statistics. In samples with the non-parametric data distribution the results are presented as Me (LQ; UQ), where Me – median of index, LQ – lower quartile, UQ – upper quartile. The Kruskal-Wallis ANOVA, the Mann–Whitney U-test, was used for comparison of the results between groups. Spearman's rank correlation coefficient was used for estimation of the relationship between two variables. The difference in parameters was considered statistically significant at $p<0.05$.

3. Results & Discussion

During our research, we found a significant increase in ADPN blood serum level in hypertensive patients. The median ADPN in patients of the main group was 5.16 with an interquartile range of 2.78 to 11.33 (pg/mL). Compared with the control group, median 1.55 with an interquartile range of 1.37 to 1.68 (pg / mL) (*Fig. 1*).

The patients were divided into 3 groups depending of the degree of HT. To identify differences when comparing these groups using the Kruskal-Wallis ANOVA, statistically significant differences were found ($H = 36.58$; $p<0.001$). For a more accurate description of the differences in the groups, they were compared in pairs, taking into account the median.

The level of the studied ADPN in all groups of patients with HT was found to be significantly increased compared with the control group: 8.64 [2.94 – 10.60] – 3.81 [1.72 – 7.85] – 8.14 [3.12 – 12.00] and 1.55 [1.37 – 1.68] (pg / mL) ($p< 0.001$), respectively to HT 1 group, HT 2 group, HT 3 group and control group. As seen from the *Fig. 2*, the level of the latter in the blood serum does not depend on the grade of HT. When studying the effect of the duration of the increase in blood pressure on the level of ADPN found that $H = 7.28$; $p = 0.028$. Pairwise comparison of groups, which is shown in *Fig. 3*, shows that the level of ADPN is higher in patients with the duration of HT of more than 5 years and was significantly increased compared with the hypertensive patients lasting up to 5 years group:

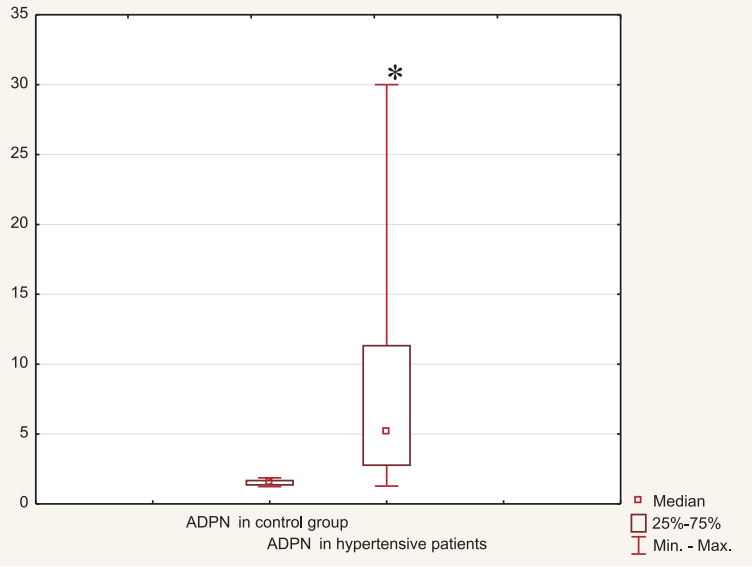

Fig. 1 The level of ADPN (pg/mL) in control group and hypertensive patients.
Note: * the difference is statistically significant compared with control group ($p < 0,05$)

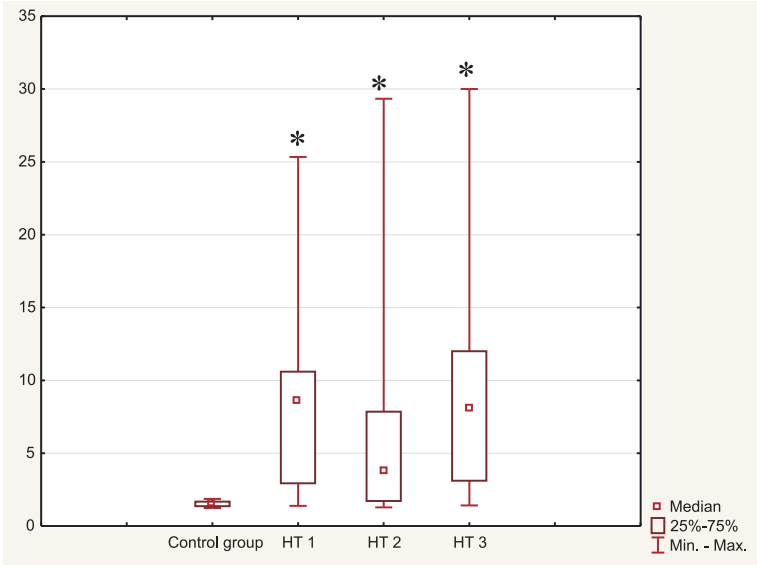

Fig. 2. The level of ADPN (pg/mL) depending of the grades of HT
Note: * the difference is statistically significant compared with control group (p < 0,001)

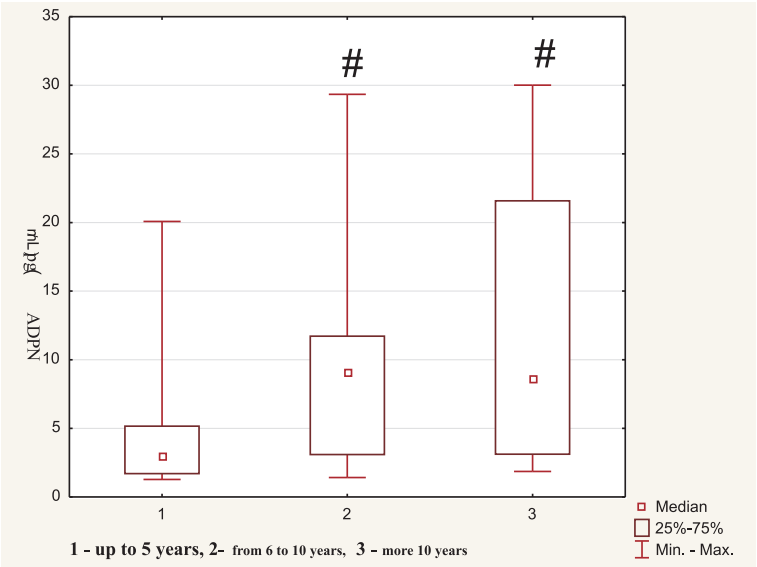

Fig. 3. The level of ADPN (pg/mL) in hypertensive patients depending on the duration of hypertension, Me [LQ; UQ]
Note: #the difference is statistically significant compared with 1 group (p < 0,05)

9.03 [3.09–11.72] – 8.63 [3.12–21.58] – 2.96 [1.71–5.16] (pg/mL) (p<0.05), respectively to hypertensive patients lasting from 6 to 10 years group, hypertensive patients lasting more 10 years group and hypertensive patients lasting up to 5 years group.

To analyze the effect of the level of increase in body weight for the the level of ADPN, groups of patients with obesity and without obesity were identified. When comparing these groups using the Kruskal-Wallis test, statistically significant differences were found (H = 56.29; p<0.001). For a more accurate description of the differences in the groups, they were compared in pairs, taking into account the median (*Table 1*). As seen from the *Table 1*, the indices of the concentration of the latter in the blood serum significantly differed between the control group in comparison with the patients of the above groups, as well as directly and in the groups among themselves (p<0.001). At the same time, in obese patients, the median of 10.45 [5.08–20.08] (pg/mL) had the greatest value compared to the group of patients without obesity, 2.03 [1.68–3.09] (pg/mL).

In order to study the effect of the degree of obesity on the concentration of ADPN, both in the group of obese and non-obese patients, subgroups were identified depending of the body

Table 1

ADPN level in hypertensive patients depending of the level of increase in body weight and in the control group, Me (LQ; UQ)

Index	Control group (n=20)	Hypertensive patients without obesity (n=19)	Hypertensive patients with obesity (n=39)	P (Mann–Whitney U-test)
ADPN (pg/mL)	1.55 [1.37–1.68]	2.03 [1.68–3.09]	10.45 [5.08–20.08]	$p_{0-1} < 0.001$ $p_{0-2} < 0.001$ $p_{1-2} < 0.001$

mass index. When comparing these groups using the Kruskal-Wallis test, statistically significant differences were found (H = 68.27; p<0.001). To find out which groups differed among themselves, they were pairwise compared with the median taken into account. We see that the level of ADPN in all of the above subgroups of patients was significantly increased compared to the control group: 3.09 [2.78–3.22] – 4.42 [3.85–8.63] – 10.86 [10.45–11.72] – 27.11 [24.72–29.13] – 1.55 [1.37–1.68] – (pg/mL) (p<0.05), respectively to overweight group, grade 1 obesity group, grade 2 obesity group, grade 3 obesity group and control group, excluding the subgroups of patients with normal body weight group – 1.71 [1.42–1.94] (p>0.05).

As seen from the *Fig. 4*, the level of the latter in the blood serum gradually increases according to the degree of obesity, and the maximum level of ADPN was noted in the subgroup of patients with obesity of the third degree.

To identify the relationship between ADPN and other indicators, a correlation analysis was carried out (*Table 2*). There were no significant correlations with systolic blood pressure (SBP), diastolic blood pressure (DBP), heartbeats (HB), indicators of the carbohydrate profile, lipid profile, with the exception of VLDL CS and TG. Namely, a reliable direct linear relationship between ADPN and VLDL CS (r = 0.34, p<0.05) and a reliable direct linear relationship between ADPN and TG (r = 0.35, p<0.05) in both cases, the strength of the bond was moderate. Also, a significant direct linear relationship between ADPN was noted with WS, HC, WHR, body weight, and noteworthy with a BMI (r = 0.90, p<0.05), which has very high character.

There are a large number of hypothetical pathogenic mechanisms through which obesity can lead to HT. They include the activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, metabolic disorders (including

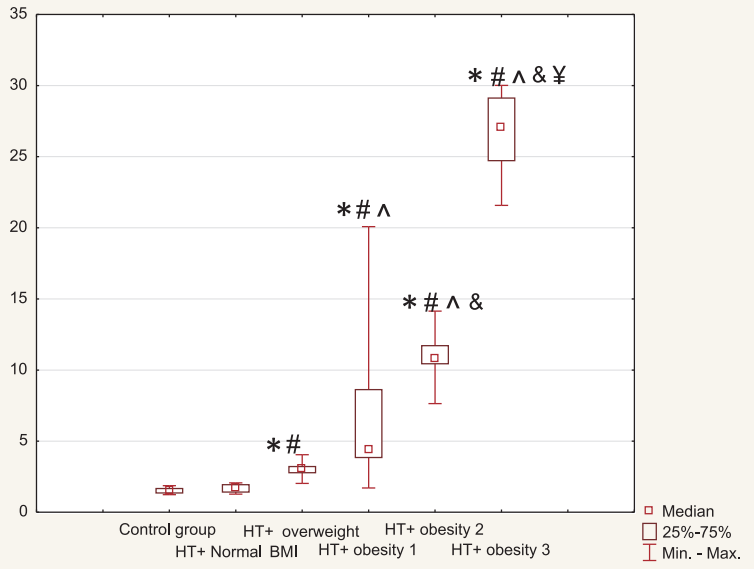

Fig. 4 ADPN level (pg/mL) depending from the presence and degree of obesity

Note: * – the difference is statistically significant compared with control group (p < 0,05),
– the difference is statistically significant compared with HT+ Normal BMI group (p < 0,05),
^ – the difference is statistically significant compared with HT+ overweight group (p < 0,05),
& – the difference is statistically significant compared with HT+ obesity 1 group (p < 0,05),
Ґ – the difference is statistically significant compared with HT+ obesity 2 group (p < 0,05).

Table 2

Correlation links between ADPN and SBP, DBP, HB, parameters of carbohydrate and lipid metabolism, BMI and anthropometric parameters of patients (n=58)

Index	r	p
SBP, mmHg	0.20	0.14
DBP, mmHg	0.15	0.27
HB, beats per minute	0.09	0.48
Glucose, mmol/L	0.16	0.22
HbA_{1c}	0.17	0.19
HDL CS mmol/L	-0.03	0.83
LDL CS mmol/L	-0.09	0.50
VLDL CS mmol/L	**0.34**	**0.009**
TC mmol/L	-0.07	0.62
CA	-0.11	0.40
TГ mmol/L	**0.35**	**0.007**
BMI	**0.90**	**0.001**
WC, cm	**0.80**	**0.001**
HC, cm	**0.55**	**0.001**
WHR	**0.65**	**0.001**
Weight, kg	**0.86**	**0.001**

hyperinsulinemia, imbalance of adipokines, an increase in the number of cytokines). The influence of adipokines, in particular ADPN, in conditions of overweight and obesity, is possibly one of the key processes in the development of hypertension. Here it is necessary to take into account the general effect of the imbalance of adipokines, their maintenance of oxidative stress and inflammation, which leads to endothelial dysfunction.

According to most literature assumptions, ADPN, encoded by gene the patatin-like phospholipase domain-containing 3 (PNPLA3), is a liver-specific human protein [16, 17]. In particular, in studies by Johansson L.E., in 2009 it was shown that the G-allele of the PNPLA3 gene positively correlates with the content of triglycerides in liver tissue [18]. But Qadri S. et al. concluded that this protein is found not only in the human liver, but also in large quantities in the abdominal tissue, and in particular human abdominal tissue to contain approximately nine-fold more PNPLA3 protein than the liver at the level of the whole body, which contradicts most previous assumptions [19]. Excessive accumulation of TG is a hallmark of obesity. Fatty acids released during hepatic TG hydrolysis can be used for β-oxidation, signaling, and for VLDL-CS synthesis. Lipolysis was initially thought to be concentrated in adipose tissue and catalyzed by only two lipases, hormone-sensitive lipase (HSL) and monoacylglycerol lipase. However, genetic elimination of HSL expression in mice failed to eliminate TG hydrolysis in adipocytes, leading to the identification of a third lipase termed adipose triglyceride lipase (ATGL). Although these three enzymes are considered major players that regulate lipolysis in adipocytes, other lipolytic enzymes that promote TG metabolism in the liver have been described. One of them is ADPN [20].

In our study, patients with hypertension with overweight and obesity showed a significant increase in adiponutrin blood serum level compared with the control group. (5.16 pg/mL vs. 1.55 pg/mL, $p<0.05$). It was estimated that blood serum adiponutrin levels depend on the duration of hypertension. It was estimated that the level of adiponutrin in blood serum depends on the body mass index, which is confirmed by a reliable direct linear relationship ($r = 0,90$; $p<0,001$).

Based on the data obtained, adiponutrin can be considered as a potential biomarker of metabolic disorders. It is important to conduct further studies to evaluate the activity of adiponutrine with a longer observation period in broader populations. The results of new studies will help to study the pathogenetic mechanisms of this comorbidity, namely hypertension with obesity and its use in clinical practice as a potential biomarker of metabolic disorders.

Conclusions

– Hypertensive patients with overweight and obesity showed a significant increase in adiponutrin blood serum level compared with the control group.

– It was estimated that blood serum adiponutrin levels depend on the duration of hypertension.

– It was estimated that the level of adiponutrin in blood serum depends on the body mass index, which is confirmed by a reliable direct linear relationship.

Conflict of interests

The authors of the article declare no conflict of interests.

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CURRENT UNDERSTANDING OF THE PEDIATRIC METABOLIC SYNDROME (REVIEW)

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Abstract

According to the World Health Organization, 68% of the causes of global mortality are due to noncommunicable diseases that include cardiovascular pathology, obesity, atherosclerosis and diabetes mellitus. The combination of abdominal obesity, hypertension, hyperglycemia and hyperlipidemia against a background of insulin resistance and chronic subclinical inflammation are components of metabolic syndrome (MetS). MetS in pediatric population is also a complex problem associated with the potential cardiovascular risk in young adults. There are lots of debates around definitions and diagnostic cut-offs for the MetS components due to age dependent fluctuations of the metabolic and cardiovascular parameters. This leads to the unclear incidence of the syndrome in children. Meantime, healthy lifestyle, nutrition and sleep are best strategies for both preventing and treating MetS in children and adolescents. Despite the large number of studies in this area, pediatric metabolic syndrome remains the subject of controversy.

Keywords: *Metabolic syndrome, diagnosis, children.*

According to the World Health Organization, the prevalence of overweight and obesity among children and adolescents aged 5 to 19 years increased dramatically from 4% in 1975 to more than 18% in 2016, when the number of children with obesity and overweight reached 340 million [1]. 17.77% children in Ukraine were obese in 2014 [2] with an annual upward trend in the incidence of new cases [3].

Overweight and obese children have a high probability to become obese adults and develop cardiovascular problems [4] and diabetes in the early adulthood [5]. The combination of abdominal obesity, insulin resistance, hyperglycemia, hypertension, violation of hemostasis was combined into the concept of "metabolic syndrome" (MetS). The main concept of the MetS theory is in the timely patient stratification into a group of high cardiovascular risk [6].

Despite numerous studies, common criteria for diagnosing MetS in childhood are still under debates. Current diagnostic criteria for the pediatric practice were published in the IDF report in 2007 and were based on similar MetS criteria for adults. These criteria include: waist circumference > 90 percentile, triglycerides level > 1.7 mmol/l, high-density lipoproteins (HDL) level < 1.03 mmol/l, fasting glucose level > 5.6 mmol/l or diagnosed diabetes mellitus, systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg [7].

Unfortunately, these cut-offs do not meet modern requirements for the parameters included and it has been shown in the results of the investigation in the IDEFICS study [8]. That is why the prevalence of MetS differs in dependently on the definition (ranged from 6 to 39%) [9]. Furthermore, there are lot of controversies around the pediatric MetS diagnosis [10, 11]. Despite confirmed association between childhood and adolescent MetS with long-term outcomes, further prospective studies are needed to clarify the true value of diagnosing MetS in youth [12].

Insulin Resistance was mentioned as a main background for all MetS components development [13]. Homeostasis model assessment-insulin resistance (HOMA-IR) was proposed to evaluate insulin resistance [14] and became the most

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popular for both adults and children despite the fact that many other surrogate indices were elaborated [15–18].

Meanwhile, there is still unknown how to properly measure Insulin Resistance in children, according to the conclusion of the Insulin Resistance in Children Consensus Conference Group (2010) [19].

The problems of determining the clinical criteria for MetS in children include physiological changes that occur throughout childhood and puberty. For example, insulin resistance increases in early puberty, but stabilizes in the middle of adolescence as well as lipids and can also vary depending on gender [20].

Insulin secretion is affected well before blood glucose concentrations are within the range of prediabetes and diabetes. It is well established that abnormal β-cell function and peripheral insulin resistance are associated with elevated 2-h glucose levels, even within the normal glucose tolerance range, without meeting the criteria for impaired glucose tolerance and impaired fasting glucose [21, 22]. There is a linear dependence of fasting and average insulin concentration on BMI. Thus, there is a strongest insulin response at the standard glucose load at the second phase in overweight and obese subjects that differs from normal weight and skinny children [23].

It may well explain why the elevated blood glucose 2 hours after the standard load is a strong predictor for the development of T2DM in adults [22], but not in children [24].

According to the European Society of Cardiology elevated triglycerides and LDLs and decreased HDLs are direct cause of cardiovascular disease in adulthood [25]. Decreased HDL and elevated triglycerides are components of the metabolic syndrome in children according to the IDF Consensus [7]. It is estimated that about 42% of obese children have lipid abnormalities, particularly those with visceral obesity [26].

The leading document that allows assessment of the level of lipid metabolism, taking into account the age of the child are the recommendations of the National Cholesterol Education Program (NCEP) [27]. These recommendations effectively establish variants of hyperlipidemia in obese children [28].

Associations between MetS and non-alcoholic fatty liver disease, hyperuricemia, sleep apnea, and several other potential biomarkers, useful for early identification of patients with a higher cardiometabolic risk, have been described in obese children. But these are still not considered when MetS is defined [29].

A number of recent studies also indicate that epigenetic mechanisms may play an important role in MetS initiation [30] and its course in both adults [31, 32] and children [33]. Meanwhile, excessive nutrition, low physical activity, social environment and stress have even stronger influence on the development of obesity and related metabolic disorders, that can be preventable [1].

Regardless of many different approaches to treating metabolic syndrome (MetS) in children and adolescents, early screening and treatment of the individual components that contribute to its development play a key role in reducing cardiometabolic risk. Therefore weight loss and lifestyle interventions can have a positive effect on the components of MetS [34].

Also, according to numerous studies, special attention should be paid to the sleep duration as poor or insufficient quality of sleep (less than 8 hours) in children and adolescents are associated with MetS elements such as hypertension with/or non-dipping profiles of BP [29]. Furthermore, acute sleep restriction increases food intake associated with the deteriorated lipid content [35].

Conclusions

Metabolic syndrome in pediatric population is a complex of problems associated with the potential cardiovascular risk. There are lots of debates around definitions and diagnostic cut-offs for the MetS components due to age dependent fluctuations of the metabolic and cardiovascular parameters. This leads to the unclear incidence of the syndrome in children. Healthy lifestyle, nutrition and sleep are best strategies for preventing and treating MetS in children and adolescents.

Despite the large number of studies in this area, pediatric metabolic syndrome remains the subject of controversy.

Conflict of interests

The authors of the article declare no conflict of interests.

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INFLUENCE OF AGE AND MORPHOLOGICAL FEATURES ON THE CLINICAL MANIFESTATIONS AND TREATMENT EFFICACY OF HEMANGIOMAS IN CHILDREN

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Abstract

Background. Infantile hemangioma (IH) is a neoplasm that is most common in childhood. Morphologically, hemangiomas are divided into superficial, deep and mixed, focal, segmental, indeterminate and multifocal. The course of IH includes phases of rapid growth followed by slow involution. The degree of involution of hemangioma is variable. Hemangiomas can lead to the appearance of permanent deformities of soft tissues or functional disorders, especially when localized on the face and vital structures. Clinical heterogeneity of hemangiomas creates significant difficulties for physicians in resolving issues of treatment tactics. Specific characteristics of the clinical behavior of hemangiomas of various morphological types can be crucial in the choice of management tactics for such patients. **Objectives.** The aim of the work is to study the effect of different morphological types of hemangioma in children on the effectiveness of treatment of age-related clinical features. **Subjects and Methods.** The study group consisted of 100 children in age from birth to 6 years who have hemangiomas of different morphological types and localizations and did not receive previous treatment. All research participants for hemangioma severity scale (HSS), hemangioma activity scale (HAS), visual analogue scale (VAS) before, during and after treatment were scored. Serum levels sFas/sFasLs before and during treatment evaluated. **Results.** With increasing the child's age, the indicator as for HAS reliably decreases for all types of hemangiomas. In all types of hemangiomas predominantly an active growth took place. An abortive growth in 10% of patients was noted. For focal hemangiomas, the indicator of sFas decreases with age, and for multifocal hemangiomas it increases. In both cases, there is an increase in the sFasL indicator with increasing age of the child. In our study, in age group before 1 year in the factor structures, "age" factor was considered to be the main one and manifested by a decrease in the activity of hemangioma with an increase in the age of the child. Among children over 1 year age, during the course of treatment, the greatest contribution the "hemangioma severity factor", the influence of which leads to a decrease in the cosmetic effect of hemangioma treatment against the background of its high severity and an increase in the indicator of apoptosis inhibition of sFas. The influence of the "treatment efficacy" factor leads to a decrease in its cosmetic effect and an increase in the severity of the manifestations of hemangioma against the background of blocking the manifestations of apoptosis. **Conclusions.** When starting treatment of hemangioma in the early stages, the cosmetic effect increases significantly. A decrease in sFasL in the younger age group may indicate a decrease or absence of apoptosis processes, which is clinically expressed by active proliferation. An increase in sFas in the older age group (over a year old) may indicate a blockage of apoptosis processes and, as a consequence, a slow regression of hemangioma.

Keywords: *hemangioma, children, morphological type, age, sFas/sFasL, hemangioma activity scale, visual analogue scale.*

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Introduction

Infantile hemangioma (IH) is a neoplasm that is most common in childhood [1, 2]. According to the 2018 classification of the International Society for the Study of Vascular Anomalies (ISSVA), hemangiomas are considered to be benign vascular tumors. The latter include infantile hemangiomas and congenital hemangiomas of three types: rapidly involuting (RICH), partially involuting (PICH), non-involuting (NICH) [3].

Hemangiomas in clinical practice differ in localization, morphological type and stage of development [4]. Morphologically, hemangiomas are divided into superficial, deep and mixed, focal, segmental, indeterminate and multifocal [5, 6]. The predominant localization of hemangiomas is on the head, face, neck [7, 8].

The characteristic course of IH includes phases of rapid growth due to proliferation followed by slow involution. Most hemangiomas have the first clinical manifestations in the form of pale spots, telangiectasias, pink macules, "scratches" or "bruises" in the neonatal period, followed by the rapid development of the tumor [9, 10].

In general, hemangiomas proliferate by the age of 6–9 months [11]. According to some studies, the growth of hemangiomas ends at the age of 3 months [12], according to others, the completion of their growth was observed at 5 months [13]. Subcutaneous hemangiomas, in comparison with superficial ones, have a much longer proliferative activity [14], sometimes up to 14 months and even over 2 years. The growth of hemangiomas in children over 3 years of age is an atypical phenomenon [15].

The degree of involution of hemangioma is variable. Recent studies have shown that in untreated hemangioma, in almost 90% of cases, involution is completed by 4 years of age [16].

Despite the fact that most hemangiomas do not cause considerable problems, a significant part of them can lead to the appearance of permanent deformities of soft tissues or functional disorders, especially when localized on the face and vital structures [17, 18]. The presence or consequences of hemangiomas can affect the quality of life of both children and their parents due to anxiety, low self-esteem of children and peer bullying due cosmetic defects [19].

The average age of contacting a pediatric dermatologist is 5 months, at this time the main growth and possible complications are already developing [20, 21]. Clinical heterogeneity of hemangiomas creates significant difficulties for physicians in resolving issues of treatment tactics [22, 23].

For hemangiomas that require treatment, the best time to start is before or immediately after the onset of obvious risks of complications [24]. It was found that IH treatment in the proliferative phase allows achieving the best result [25, 26].

Despite the fact that the general signs of the course of hemangiomas have been studied for a long time, there is not enough description of the specific details of the growth of hemangiomas and information about the variety of manifestations of growth among hemangiomas of different subtypes. Specific characteristics of the clinical behavior of hemangiomas of various morphological types can be crucial in the choice of management tactics for such patients.

2. Purpose, subjects and methods:

2.1. The purpose of the work is to study the effect of different morphological types of hemangioma in children on the effectiveness of treatment of age-related clinical features.

2.2. Subjects & Methods

The study group consisted of 100 children who were consulted on an outpatient basis and who received treatment at the Regional Children Clinical Hospital No. 1 in Kharkiv from September 2017 to October 2019. The selection criteria were: the age of children from birth to 6 years, children who had neoplasms with clinical signs of hemangiomas of external location, their complications and consequences, children who did not receive previous treatment, children whose representatives have agreed to participate in the study.

The methods used in this study were agreed and approved by the ethics committee of Kharkiv National Medical University No. 6 dated 04.10.2017, in accordance with the 1975 Declaration of Helsinki.

In almost all cases, the diagnosis was made during an outpatient visit. The age, sex, birth weight, the period of hemangioma occurrence and its morphological type, growth peculiarities (active or abortive), the maximum size of the hemangioma, its localization and depth of spread, the presence of complications, the period of appearance of hemangioma regression signs were determined in children.

The indicators of the general clinical blood analysis, clinical urine test, blood glucose levels, sFas and sFasL indicators before and during treatment, and electrocardiography data were evaluated. Children receiving systemic propranolol therapy were consulted by a cardiologist. According to the indications, echocardiography was performed, consultations of other specialists (ophthalmologist, ENT) were appointed.

To determine the clinical state of hemangioma, we used the severity scale (HSS), which was assessed once during the initial examination, as well as the hemangioma activity scale (HAS), which was used before the appointment of treatment (HAS1) and after three months of treatment (HAS2). The achieved cosmetic result was determined using a visual analogue scale (VAS) based on photographs taken before treatment, during its treatment (VAS1) and after completion (VAS2). A comparison of photographs taken before treatment and three months after the start of treatment was made in order to assess the dynamics of the process.

Determination of sFas and sFasL indicators in blood serum was carried out by the enzyme-linked immunosorbent assay using a commercial test system manufactured by "Elabscience" (ELISA, USA) on an enzyme-linked immunosorbent analyzer "Labline-90" (Austria), according to the instructions that were added to the kit.

Taking into account the different activity of hemangiomas and their size, the treatment was prescribed according to individual indications such as: active growth of the neoplasm, cosmetic defects caused by them or obvious risks of their formation, as well as the desire of the parents to get rid of the hemangioma.

Treatment of complicated, large and active hemangiomas was carried out according to the appointment of systemic therapy with propranolol (17 children). Children with superficial flat lesions were prescribed topical treatment with 0.5% timolol maleate solution (15 children). In cases of focal (deep, mixed and superficial), some multifocal and indeterminate hemangiomas, protruding above the skin surface and spread subcutaneously, combined treatment with 0.5% timolol maleate solution and local compression was prescribed (52 children). Children with volumetric formations up to 1 cm in diameter underwent intratumor administration of triamcinolone acetonide, followed by topical application of 0.5% timolol maleate solution (8 children). Intratumor administration of triamcinolone acetonide was performed in children with active mucosal hemangiomas that were small (1 child). Surgical removal of hemangiomas was performed in children over a year old due to the presence of a cosmetic defect and at the request of the parents (5 children). Two children, 3 and 5 years old, were not prescribed treatment due to unexpressed residual changes.

During the treatment, the heart rate and blood glucose levels were monitored.

Statistical processing of the research results was carried out using the Statistica 6.0 software package. Average values of indicators, standard errors, and, if necessary, medians (Me) and quartiles (25%; 75%) were calculated. Nonparametric Wilcoxon, Mann-Whitney, Pearson χ^2 criteria were used to compare the samples due to the absence of normal distributions of the studied indicators..

3. Results & Discussion

There were 32 (32±4.7)% boys and 68 (68±4.7)% girls in the study group. Children aged 0-6 months – 62 (62±4.9)% persons consisted the largest age group; there were 17 (17±3.8)% children aged 7–12 months; 18 (18±3.8)% children aged 13–36 months and 3 (3.0±1.7)% children aged 37–72 months.

The children of the study group had four morphological types of hemangiomas: focal – 71 (71±4.5)% persons; segmental – 4 (4.0±2.0)% persons; indeterminate – 7 (7.0±2.6)% persons; multifocal – 18 (18±3.8)% people. Thus, children with focal and multifocal hemangiomas consisted the significant ($p<0.05$) majority in the study group.

The average values of the indicator as for HAS1, taking into account the age of the child and the morphotype of the hemangioma are given in *Table 1*.

The table shows that with increasing the child's age, the indicator as for HAS1 reliably decreases for all types of hemangiomas.

In 30 children, abortive growth of hemangioma was noted, among them in 22 up to the age of 6 months inclusively, in 6 children under 1 year and in two children at the age of 12 months. Clinical signs of independent regression were observed in 17 children with active growth and in 2 children with abortive growth of hemangiomas. In 6 children, signs of regression appeared before the age of 6 months, in 7 children – in the period from 7 to 12 months, and in 6 children – from 12 months to 24 months.

According to *Table 2*, it can be noted that among all morphotypes of hemangioma, its active growth is reliably more often observed in both boys and girls. In the group with active growth, girls are reliably more common than boys.

The results of the study of the dynamics of Fas and FasL indicators in children of different ages during treatment are shown in *Fig. 1* and *Fig. 2*.

According to the histograms shown in *Fig. 1* and *Fig. 2*, it can be noted that in both cases there is a tendency to change in the sFas indicator, but in different directions. For focal hemangiomas,

Table 1

Average values of the indicator as for HAS1 in age groups of children with different morphotypes of hemangiomas

Morphotype	Values of HAS1, point			
	0–6	7–12	13–36	37–72
Focal (n=71)	10.5±1.2	7.7±1.6* U=36.5	6.1±0.9* U=8.5	3.0±1.7* ** U=0; U=0
Segmental (n=4)	11.0	0	7.0	0
Indeterminate (n=7)	12.2±1.0	5.7±1.2* U=0	0	0
Multifocal (n=18)	9.5±1.4	7.0* U=3.5	6.0±1.7* U=1.5	0

Notes: * – differences in the values of the indicator between the age group (0–6) months and other age groups are reliable ($p<0.01$); ** – differences in the values of the indicator between the age group (7–12) months and other age groups are reliable ($p<0.01$).

Table 2

Distribution of children with different morphotypes of hemangiomas by growth characteristics, (%)

Morphotype	Growth characteristics of hemangioma			
	Active growth		Abortive (Minimal growth)	
	boys	girls	boys	girls
Focal (n=71)	21 (28±5.3)^2 χ^2=20.6	47 (66±5.6)	2 (4.0±2.3)^3 χ^2=14.99	1 (2.0±1.7)^1 χ^2=66.79
Segmental (n=4)	1 (25±21.7)	1 (25±21.7)	1(25±21.7)	1 (25±21.7)
Indeterminate (n=7)	0^2 χ^2=10.5	6 (86±13)	0	1 (14±13)^1 χ^2=7.14
Multifocal (n=18)	4 (22±9.8)^2 χ^2=5.6	11 (61±11.5)	3 (17±8.9)	0^1 χ^2=15.84
Total (n=100)	25 (25±4.3)^2 χ^2=32.32	65 (65±4.8)	7 (7.0±2.6)^3 χ^2=12.05	3 (3.0±1.7)^1 χ^2=85.65

Note: 1 – differences in the incidence of active and minimal hemangioma growth in girls are reliable ($p<0.05$); 2 – differences in the incidence of active hemangioma growth between girls and boys are reliable ($p<0.05$); 3 – differences in the incidence of active and minimal growth of hemangiomas in boys are reliable ($p<0.05$).

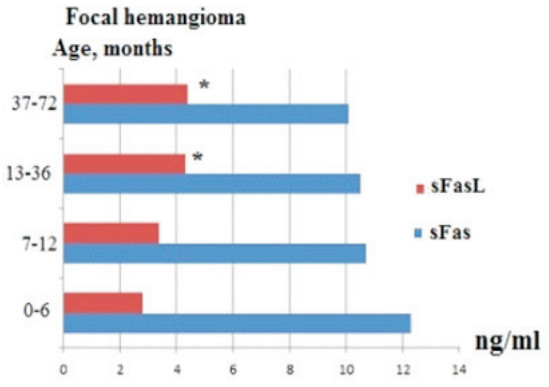

Fig. 1. Age-related dynamics of sFas and sFasL indicators in children with focal hemangioma. * – differences in the sFasL content in the blood of children of the age group (0–6) months and children of other age groups are reliable according to the Mann-Whitney criteria ($p<0.01$)

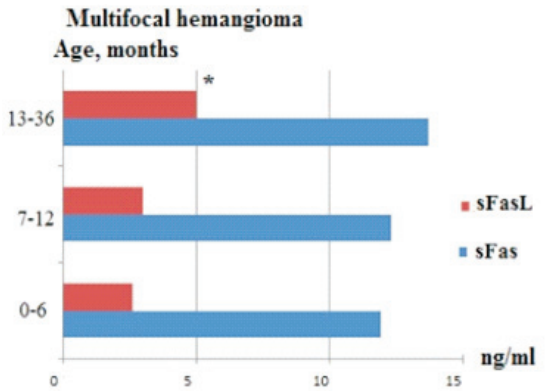

Fig. 2. Age-related dynamics of sFas and sFasL indicators in children with multifocal hemangioma. * – differences in the sFasL content in the blood of children of the age group (0–6) months and children of other age groups are reliable according to the Mann-Whitney criteria ($p<0.01$)

the indicator decreases with age, and for multifocal hemangiomas it increases. In both cases, there is an increase in the sFasL indicator with increasing age of the child. According to this indicator, reliable differences were revealed between the first and third, and the first and fourth age groups for the focal hemangioma, and between the first and third - for the multifocal one. There were no reliable differences between the indicators for other morphotypes of hemangioma, which is associated with the insufficient volume of the respective groups of children.

To identify the relationship of clinical history and laboratory indicators in children of different ages, factor analysis was carried out and factor structures were plotted (*Fig. 3*). Since the distribution of the proportion of the studied indicators did not correspond to the normal one, the pairwise Spearman's correlation coefficients were used as input indicators.

Currently, studies are being done on various factors, including biomarkers that affect: the clinical behavior of hemangiomas during treatment [27–29], the development of unwanted side effects during treatment [30], the risk of complications [31], and factors of the appearance of hemangioma in general [32].

In our study, in all age groups in the factor structures, two factors were found, which indicates their plasticity. In the younger age group (*Fig. 3,a*), the first factor of the factor structure, plotted according to the indicators obtained during the course of treatment, called the "age factor of activity", explains 41% of the total variance. The action of this factor leads to a decrease in the activity and severity of hemangioma against the background of an increase in the child's age. The action of the second factor, called the "weight factor", which explains 27% of the total variance, leads to a decrease in apoptosis indicators against the background of an increase in the child's weight at birth. It is known that low birth weight is one of the risk factors for hemangioma, and it also determines the severity and activity [33]. The sFas and sFasL indicators characterize the level of intensity of apoptosis processes. The sFasL concentration can be proportional to the intensity of apoptosis processes [34]. The exact mechanism of interaction between membrane and soluble forms of Fas and FasL (sFas, sFasL) remains unknown [35]. It has been suggested that soluble Fas has an inhibitory effect on Fas/FasL-mediated apoptosis [36]. The total contribution of factors to the total variance is 68%, which

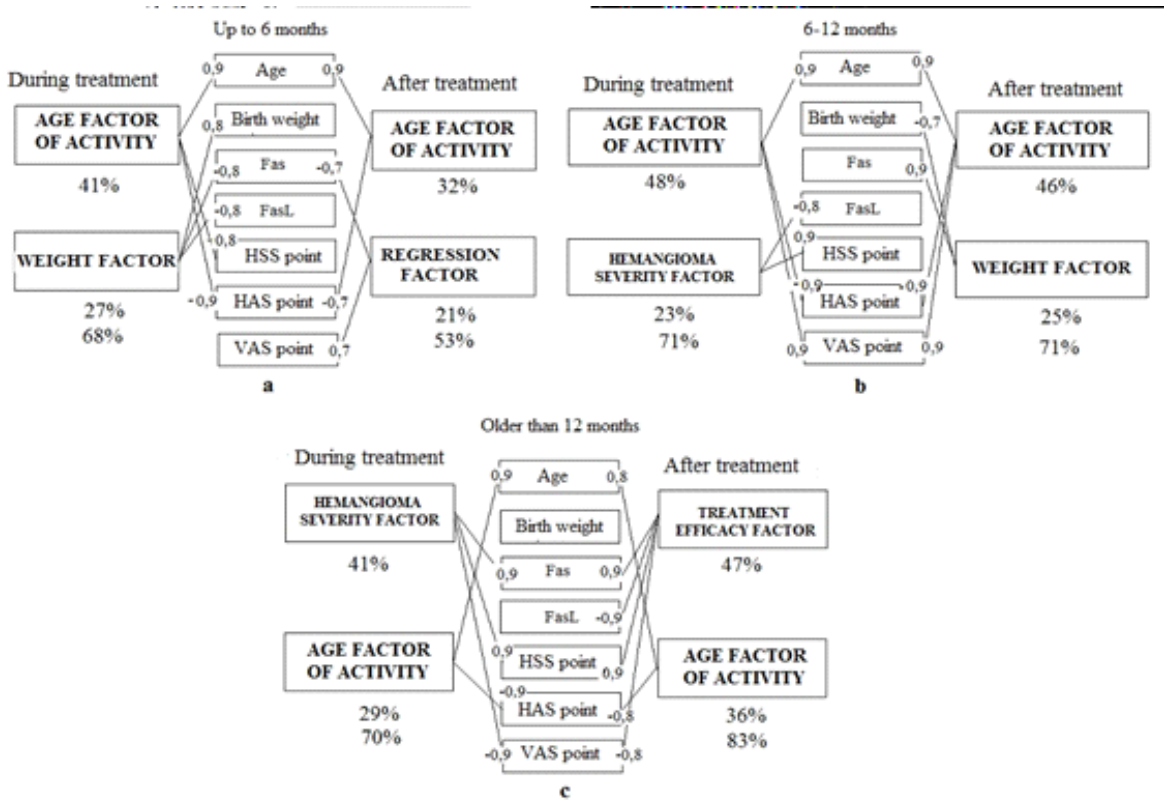

Fig. 3. Factor structures of indicators of patients of different age groups with hemangioma

indicates the presence of a random component, which has increased after treatment. This is a sign of significant external influences on the studied system of indicators in young children. After treatment, the first factor has changed its configuration, it only affects the activity of the hemangioma, which decreases with increasing age of the child. The contribution of this factor to the total variance has decreased and is 32%. The second factor, called the "regression factor", leads to an increase in the VAS indicator after treatment, which happens in parallel to a decrease in the sFas indicator.

In the second age group of children (*Fig. 3,b*), the action of the first factor, plotted according to the indicators obtained during the course of treatment, leads to an increase in the cosmetic effect of treatment against the background of a decrease in hemangioma activity (according to HAS) and an increase in the child's age. The contribution of this factor to the total variance is 48%. The second factor of the structure – the "hemangioma severity factor" – causes an increase in the indicator according to HSS against the background of a decrease in apoptosis. The total contribution of both factors to the total variance is 71%, which indicates a smaller influence of the random component on the system of the studied indicators than in the first age group (*Fig. 3,a*). The action of the first factor of the structure, plotted according to the indicators obtained after treatment, leads to an improvement in the results of treatment with an increase in the child's age against the background of a decrease in hemangioma activity (according to HAS). The structure of relationships in the system of indicators in the factor and its contribution to the total variance is similar to that obtained during the course of treatment. The same configuration of connections in the factor indicates the continuation of positive trends in hemangioma regression under the influence of the treatment. The action of the "weight" factor in this age group leads to a decrease in apoptosis indicators with an increase in the age of the child. The total contribution of factors after treatment is also 71%.

In the first and second age groups, the greatest contribution to the total variance was made by the "age" factor, which is considered to be the main one. In the third age group (*Fig. 3,c*) during the course of treatment, the greatest contribution (41%) to the total variance is made by the first factor – the "hemangioma severity factor", the influence of which leads to a decrease in the cosmetic effect of hemangioma treatment against the background of its high severity and an increase in the indicator of apoptosis inhibition of sFas. This coincides with modern ideas about the need for early treatment of hemangioma and a decrease in the cosmetic effect of treatment with its late initiation [37, 38]. The influence of the "age" factor is manifested by a decrease in the activity of hemangioma with an increase in the age of the child. The contribution of both factors to the total variance is 70%. After treatment in the older age group, in comparison with the state during the treatment and with other groups, there is an increase in the number of connections in the structure from 5 to 6, which indicates an increase in the determinism of the system. The influence of the "treatment efficacy" factor leads to a decrease in its cosmetic effect and an increase in the severity of the manifestations of hemangioma against the background of blocking the manifestations of apoptosis. The structure of connections in the second factor confirms the idea of a decrease in hemangioma activity with an increase in the age of the child. The total contribution of both factors to the variance is 83%, which indicates an insignificant influence of the random component.

Thus, the analysis of the structure of relationships between indicators in factors obtained in different age groups during and after treatment confirms modern clinical concepts of the course and outcomes of treatment of hemangioma in children.

Conclusions

1. Before treatment, the activity of hemangioma decreases with the age and, accordingly, the severity of hemangioma decreases.

2. The activity and severity of hemangioma decreases after treatment, but with predominance in the younger age group (up to 1 year), which affects the outcome of treatment, that is, when starting treatment of hemangioma in the early stages, the cosmetic effect increases significantly.

3. A decrease in sFasL in the younger age group may indicate a decrease or absence of apoptosis processes, which is clinically expressed by the opposite manifestations – active proliferation. An increase in sFas in the older age group (over a year old) may indicate a blockage of apoptosis processes and, as a consequence, a slow regression of hemangioma.

Conflict of interests

The authors of the article declare no conflict of interests.

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SURGICAL TREATMENT OF PRIMARY INTRA-ABDOMINAL COMPLICATIONS: ABSCESSES AND INFILTRATES

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Abstract

Purpose of the work. improving the results of surgical treatment of patients with primary intra-abdominal infiltrates and abscesses. **Material and research methods.** From 2006 to 2019, 191 patients with primary intra-abdominal infiltrates and abscesses were treated. The patients' age ranged from 16 to 85 years. There were 96 male patients (50.26%), 95 female patients (49.74%). **Results.** The patients were divided into 3 subgroups depending on the underlying disease. The first group included 74 (38.74%) patients with destructive appendicitis, of which 39 (20.42%) were in the control group, and 35 (18.32%) were studied. The second group included 48 (25.13%) patients suffering from perforated gastric ulcer and 12 duodenal ulcer, of which the control group was 26 (13.61%), and the studied group was 22 (11.52%). The third group included 69 (36.13%) patients with cholecystitis, of which 37 (19.37%) were in the control group, and 32 (16.76%) were studied. All patients were operated on. **Conclusions.** Surgical treatment is individualized depending on the disease, so with destructive appendicitis from 74 (38.74%) laparotomic in 42 (21.99%), laparoscopic in 32 (16.75%), and in 12 (6.28%) with conversion; perforated gastric ulcer and 12 duodenal ulcer in 48 (25.13%) open laparotomy; with cholecystitis from 69 (36.13%) in 48 (25.13%) laparotomic and in 21 (11.00%) laparoscopically. The use of water-jet technologies in 64 (33.51%) patients made it possible to minimize damage to the serous membrane and cleanse the peritoneum from acquired formations.

Keywords. *Abscesses and infiltrates of the abdominal cavity, surgical treatment.*

Introduction

Today, urgent abdominal pathology is complicated by formation of abscesses and infiltrates in 20–25% of cases. Typically, the causes of intra-abdominal formation can be acute appendicitis, acute cholecystitis, perforated gastric and duodenal ulcers, Meckel's diverticulum, as well as serious of other diseases [2]. Despite significant developments, these diseases do not tend to decrease, on the contrary, the number of patients with abdominal perforations, destructive appendicitis and cholecystitis, as well as pancreatitis increases every year [2, 6].

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According to various authors, postoperative abscesses develop in 0.8–2% of operated patients, and mortality in these cases ranges from 10.5 to 26%. Intra-abdominal abscesses and infiltrates rank second among the causes of repeated laparotomies in the early postoperative period. In case of inadequate treatment, mortality from this pathology reaches 45% and more [2, 6, 7]. The main causes of intra-abdominal abscesses and infiltrates development and mortality in acute appendicitis in Ukraine are the following: disease severity – 19.7%; late hospitalization – 46.1%; technical mistakes during the operation – 5.2%; tactical mistakes – 6.8%; defects of postoperative treatment – 7.7%; concomitant diseases – 9.3%; late operation – 5.2%. The problem has not been solved, and all complications and mortality rates indicate organizational problems and late referral [1, 6].

Thus, all of the above requires further study in order to predict the course of the disease and its adequate surgical treatment, for the sake of

reducing both postoperative complications and mortality, which in general will improve patient's quality of life.

2. Purpose, subjects and methods:

2.1. The purpose: to improve the results of surgical treatment of patients with primary intra-abdominal infiltrates, abscesses and fluid masses by introducing the latest innovative diagnostic and treatment technologies.

2.2. Subjects & Methods

191 patients aged 16–85 (96 male (50.26%) and 95 female (49.74%)) with primary intra-abdominal infiltrates, abscesses and fluid masses were treated at the hospital of the Department of Surgical Diseases, at the Surgery Center of Kyiv City Clinical Hospital No. 1 from 2006 to 2019. Only the patients with primary fluffy infiltrates, abscesses and fluid masses were included in the study, and patients with dense infiltrates were not included in the study, because that group provided for conservative and then operative treatment. Depending on the time of hospitalization and use of diagnostic and therapeutic measures, the patients were divided into a control group – from 2006 to 2012 – 102 (53.40%) patients and the study group – from 2013 to 2019 – 89 (46.6%) patients. General clinical and biochemical blood and urine tests were performed in all patients during hospitalization. Radiological examination (vertical and polypositional plan radiography of the abdominal cavity organs) was performed in 85 (44.50%) patients. Ultrasound examination of the abdominal cavity organs was done in 78 (40.84%) patients. Rectal and bimanual examination was performed in 100 (52.36%) patients. Thermometry of the anterior abdominal wall was performed in 61 (31.94%) patients.

3. Results & Discussion

The patients were divided into 3 subgroups depending on the underlying disease; however, these were patients who were urgently hospitalized and had surgical treatment. The first group included 74 (38.74%) patients with destructive appendicitis complicated by primary infiltrates and abscesses, of which 39 (20.42%) control group patients and 35 (18.32%) study group patients. The second group included 48 (25.13%) patients with perforated gastric and duodenal ulcers, of which the control group was 26 (13.61%), and the study group was 22 (11.52%). The third group included 69 (36.13%) patients with cholecystitis with primary complications in 69 (36.13%) patients, including 37 (19.37%) in the control group and 32 (16.76%) in the study group.

First of all, it is reasonable to emphasize that the type of surgical treatment depended on the study group, since the study group included laparoscopic surgery and technology of tissue ligation and separation. Considering that each nosological unit is an independent disease, further percentage calculations were performed in each group.

Surgical treatment of 74 (38.74%) patients with destructive appendicitis was complicated by primary infiltrates and abscesses differed in time of surgery. Thus, surgical access in 39 patients in the control group was laparotomy and was associated with the localization of infiltrative abscessed mass, of which 11 (14.86%) had midline laparotomy and 28 (37.84%) had right-sided transrectal laparotomy. However, among 35 (47.30%) patients of the study group right-sided transrectal laparotomy was performed in 3 (4.05%) of them, laparoscopy in 20 (27.03%) and diagnostic laparoscopy with conversion in 12 (16.22%) patients. The reasons for conversion during surgery were: beginning of the introduction of laparoscopic techniques and subhepatic, retroperitoneal location of the appendix in 5 (6.76%) patients and in the pelvic cavity in 1 (1.35%) patient, which made it impossible to separate it. Separation of the infiltrative-abscess formation in the control group was purely mechanical using instruments and cotton swab, and hemostasis was performed using monopolar coagulation and tissue piercing. On the other hand, in the control group of 35 (47.40%) patients, a water-jet device for tissue preparation was used in 15 (20.27%) patients to separate infiltrate-abscess formations, as well as bipolar coagulation and intracorporeal suturing for the purpose of hemostasis. During laparoscopy, infiltration-abscess formations were separated in 20 (27.03%) patients using bipolar coagulation. The next stage of surgery differed depending on the successful separation of the infiltrative-abscess formations. During the separation of formations in 39 (54.6%) patients in the control group, staged resection of the greater omentum with vascular stitching (non-resorbable thread), as well as monopolar coagulation of blood vessels were used. In contrast, bipolar coagulation of the greater omentum and soft tissues was used in 35 (47.40%) patients of the control group, of which in 15 (20.27%) patients openly, and in 20 (27.03%) by laparoscopy. Separation and mobilization of the appendix and the mesentery was performed as follows. In the control group, the appendix and the mesentery were separated, and then non-resorbable sutures were applied, of which 25 (33.78%) patients had two sutures. The

stump of the appendix was tied and implanted under the cisternal and Z-shaped sutures in 23 (31.08%) patients, and in 16 (21.62%) other patients, separate stump invaginations in number from 6 to 8 were placed because of a pronounced inflammatory process (suture cutting out). In the study group, the mesentery of the appendix was sutured with bipolar in 20 (27.03%) patients, stapler and Z-shaped sutures were applied to the base of the appendix in 20 (27.03%) patients. Debridement of the abdominal cavity was of great importance. Thus, in the control group we performed debridement with antiseptics, and in the study group we used physiological solution until complete removal of purulent contents and fibrin. Later there was a question of abdominal cavity drainage, and single-lumen (control group) and double-lumen (study group) drains were used, and the number of drains was determined individually depending on the spread of inflammatory process. However, we consider it necessary to arrange the drainage through a separate access, which was performed in 35 (47.40%) patients of the control group and in 12 (16.22%) patients of the study group. Pelvic cavity drainage was performed in 46 (62.16%) patients, which allowed avoiding postoperative complications. The following complications were found in the postoperative period: postoperative wound infiltrate in 14 (18.92%) patients, postoperative wound seroma in 9 (12.16%) patients, suppuration of the wound channel in 3 (4.05%) patients control group). The drains were removed in the absence of discharge.

Surgical treatment of 48 (25.13%) patients with perforated gastric and duodenal ulcers who had infiltrative-abscessing complications of greater omentum. Surgical access in all 48 patients was made by midline laparotomy with revision and separation of the perforated-inflammatory process caused by the action of hydrochloric acid and bile on the peritoneal walls. Localization of perforated gastric ulcer: 5 cm to the duodenal bulb in 7 (14.58%) patients, closer to the small curvature in 12 (25.0%) patients, at the bottom of the stomach in 14 (29.17%) patients, in the center of the stomach in 9 (18.75%) patients, at the level of duodenal bulb in 10 (20.83%) patients, the anterior part of the duodenum in 3 (6.25%) patients, the lower part of the duodenum in 5 (10.42%) patients. Surgical differences between the control and study groups consisted in the use of vicryl sutures instead of Capron ones, as well as the use of mono and bipolar for hemostasis. Mobilization and separation of the infiltrated greater omentum with resection and stitching in the control group in contrast to the study group using water-jet scalpel in 18 (37.5%) patients for precise "bloodless" tissue separation. In all patients the perforated ulcer margins were cleaned of callous tissues and double-row sutures "resorbable sutures with an interval of more than 40 days" were applied against a background of the probe in the stomach and duodenum, with mandatory control of the tightness of the sutures. After the defect was eliminated, the abdominal cavity was examined, washed and drained. In the study group, two-lumen drainages were placed both to the perforation site and the pelvic cavity. In the postoperative period, the postoperative wound infiltrate was diagnosed in 2 (4.17%) patients in the study group, where the conservative treatment was effective and the postoperative wound seroma in 3 (6.25%) patients in the control group, where the removal of one suture (debridement and drainage) treatment was effective. Drainage in all patients was performed through a separate access, and removal was performed when there was no discharge and peristalsis was restored on the 3rd–5th day. Suture failure was not detected in the control and study groups.

Surgical treatment of 69 (100%) patients with cholecystitis had primary infiltrative abscessed complications that differed by groups. Thus, in the control group 37 (53.62%) patients had the laparotomy access along the costal arch, in 32 (46.38%) patients of the study group, the access was performed by laparotomy in 6 (8.69%) of them, laparoscopy in 26 (37.68%) patients, of which 5 (7.25%) underwent conversion due to a pronounced sclerotic adhesions of the greater omentum and the walls of the large intestine. The greater omentum was involved in the infiltrative-abscess formation of all 69 patients, as well as the walls of the large intestine (transverse colon) in 18 (26.08%) patients. In 37 (53.62%) patients of the control group, the infiltrative-abscess process was separated mechanically, and in 11 (15.94%) patients of the study group, water-jet device was used. Mobilization and resection of the greater omentum was performed by stitching the area of the mobilized omentum with non-resorbable threads in 37 (53.62%) patients, using bipolar in 32 (46.38%) patients of the study group. Biliary bile extraction in patients of the control group was carried out using monopolar, which led to certain difficulties and bleeding, and in the patients of the study group - using bipolar, which allowed performing almost bloodless surgical intervention. Laparoscopic cholecystectomy was performed in 21 (30.43%) patients using bipolar

coagulation. In the postoperative period, drainage of the abdominal cavity was performed, with the difference that in the study group it was performed by double-lumen drainage. In the postoperative period, the postoperative wound suppuration occurred in 2 (2.90%) patients of the control group and in one (1.4%) patient of the study group.

Thus, primary intra-abdominal abscesses and infiltrates were associated with the organ, of which destructive appendicitis was found in 74 (38.74%) patients, perforated gastric and duodenal ulcers in 48 (25.13%) patients, cholecystitis in 69 (36.13%) patients. Visualization of primary and secondary disease was based on ultrasound in 78 (40.84%), abdominal and thoracic radiological examination in 85 (44.50%), anterior abdominal wall thermometry in 61 (31.94%), and rectal examination in 100 (52.36%) patients. Surgical treatment was individualized depending on the disease. In destructive appendicitis of 74 (38.74%) patients, laparotomy was performed in 42 (21.99%) patients, laparoscopic procedure in 32 (16.75%), and in 12 (6.28%) patients with conversion. 48 (25.13%) patients perforated gastric and duodenal ulcer underwent open laparotomy. Of 69 (36.13%) patients with cholecystitis, 48 (25.13%) underwent laparotomy and 21 (11.00%) – laparoscopy. The use of the recent water-jet technique in 64 (33.51%) patients to separate infiltrative abscesses allowed minimizing the damage to the serous membrane and cleaning the peritoneum from the acquired formations. The control group demonstrated better results of surgical treatment, taking into account the quality of life.

Surgical treatment of intra-abdominal abscesses and infiltrates is always controversial with regard to diagnostic methods, that is, imaging of the disease, surgical treatment methods, as well as drainage and use of suture material, and antibacterial therapy aimed at stopping the spread of infection.

Among acute surgical diseases of the abdominal cavity, acute appendicitis (AA) accounts for 89.1%, ranking first in Ukraine. Appendectomy accounts for about 20–30% of all surgical procedures. Based on the protocol, the proportion of patients hospitalized later than 24 hours from the onset of the disease ranges from 4.9 to 31.2% and averages 20.9% in the country, and postoperative mortality among them is 0.15% (0 to 0.4%) [1]. It is known that the incidence of AA has been steadily decreasing since the late 1940s. Thus, in developed countries, AA occurs in 5.7–50 patients per 100,000 inhabitants per year, with a peak between the ages of 10 and 30 years. Geographic differences have also been established: the lifetime risk of AA is 9% in the United States, 8% in Europe, and 2% in Africa. Moreover, there are large differences in clinical manifestations, disease severity, radiological examination, and surgical treatment of patients with AA, which are related to the income of the country [10].

According to the EAES (European Association for Endoscopic Surgery) summary regarding the diagnosis of AA, diagnostic imaging can reduce the negative appendectomy rate, which reaches 15%. Ultrasound, abdominal computed tomography (CT) and magnetic resonance imaging (MRI) are most commonly used methods. Ultrasound has a sensitivity of 71 to 94% and a specificity of 81 to 98%. The incidence of purulent-septic complications after appendectomy ranges from 0 to 11%, and other complications (stump suture failure, adhesive obstruction) range from 3.0 to 28.7% [25].

Thus, according to Di Saverio et al. (2020), the incidence of appendix perforation ranges from 16% to 40%, with a higher incidence in younger age groups (40–57%) and in patients over 50 years of age ranging from 55 to 70%. The risk of death from non-gangrenous appendix is less than 0.1%, but the risk increases to 0.6% in gangrenous appendix. On the other hand, perforated appendix has a higher mortality rate of about 5% [10]. The same authors established the role of diagnostic imaging, such as ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) in the diagnosis of the disease [10].

Further studying the diagnosis of destructive appendicitis (DA), Matthew Fields J. et al. (2020) found that sensitivity and specificity of ultrasound is 91% and 97% respectively with a positive and negative predictive value of 91% and 94% respectively [21]. A meta-analysis by Duke E. et al. (2016) on the use of MRI in the diagnosis of appendicitis during pregnancy found a sensitivity of 90.5%, 94% and 91.8%; specificity of 98.6%, 97% and 97.9% respectively, and a positive predictive value of 86.3% and a negative predictive value of 99.0% [12].

In order to diagnose infiltrative inflammatory appendicular complications of abscesses and infiltrates, Rybalchenko V.F., Demidenko Yu.G. (2016) used infrared thermometry of the anterior abdominal wall and self-developed axillary pain factor in order to interpret the increased temperature. In all observations, the method resulted to be informative [5].

The issue of both appendix extraction and suture fusion is still relevant today. Diamantis T. et al. (2006) compared LigaSureTM and Harmonic Scalpel with monopolar electrocoagulation and bipolar coagulation: the first two had minimal thermal tissue damage than other methods [11]. However, studies by Pogorelic Z. found higher thermal damage of the mesoappendix and its base in patients during surgery using LigaSureTM than in patients using Harmonic Scalpel [23]. The studies by Skyba V.V. et al. (2017) proved that the use of water-jet scalpel to separate infiltrative inflammatory process and mobilize the appendix is a bloodless method [6].

The treatment of the mesentery and the base of the appendix is an important problem, since isolated cases of appendix ligature failure have been described in the literature. Thus, Wright G.P. et al. (2015) suggested the use of a single stapler line to dissect the mesoappendix and apply to the appendix as a safe and effective method that leads to a shorter duration of surgery and excellent surgical results [31]. A meta-analysis by Antoniou S.A. et al. (2017) involving more than 5000 patients showed that the use of suture material, that is, appendix ligation is superior to other methods given the combined parameters of infection of the organ and the surface of the operating field [8]. In another study, Qian D. et al. (2015) compared simple ligation and stump invagination, and no significant difference was found, and as a consequence, clinical results showed that simple ligation was significantly superior to stump invagination [24]. Abdominal drainage is also debated. According to the retrospective study by Schlottmann F. et al. (2016), the placement of intra-abdominal drainage in complicated appendicitis did not bring benefits in terms of reducing the infectious process, and was characterized by an increase in the duration of hospital stay [26].

Regarding the development of cholecystitis, it has been established that in 10-15% of patients, gallbladder wall ischemia develops against a background of intravesical hypertension, which leads to necrosis, perforation and peritonitis. The most frequent forms are perivesical (subhepatic, subdiaphragmatic) abscesses. In gas-forming flora, emphysematous gallbladder is more common. Ultrasound allows to differentiate between acute obstructive (catarrhal) and acute destructive cholecystitis and distinguish gangrenous cholecystitis and establish gallbladder wall integrity disorder and peripapillary abscess [3]. According to Kimura Y. (2013), Pisano, M. (2020), 20 to 40% of patients with gallbladder stones develop gallbladder stone-related complications with an incidence of 1–3% annually [17]. In order to verify the disease, Gurusamy et al. (2015) performed a meta-analysis of ultrasound verification with a sensitivity of 95% and specificity of 95% [15].

Cholecystectomy is the most common approach and is considered the standard of care for gallstone disease for most patients. The causes of gallbladder obstruction can vary and may be related to obesity, adhesions, acute or chronic inflammation, gallbladder bloating and cirrhosis. Options include subtotal cholecystectomy [16]. A meta-analysis by Elshaer et al. (2015) showed that subtotal cholecystectomy was performed using laparoscopic (72.9%) open (19.0%) and laparoscopic, convertible to open (8.0%) techniques. The number of patients was more than 1200, and the most frequent indications were severe cholecystitis (72.1%), cirrhosis and portal hypertension (18.2%) and empyema or perforated gallbladder (6.1%). [13].

Conservative treatment of acute cholecystitis is relevant, and therefore Schmidt M. (2011) with long-term observation for 14 years approximately 30% of patients who received conservative treatment developed recurrent complications associated with gallstone disease, and 60% of patients who underwent cholecystectomy [27].

Postoperative complications are more frequently diagnosed in men, ranging from 10 to 15%, with increased conversion to open cholecystectomy from 16 to 48.5% and, according to the author, are associated with increased skeletal muscle mass [28]. Meanwhile, Campanile F.C. (2014) presented hospital mortality and cholecystostomy incidence ranging from 4 to 50% and from 8.2 to 62%, respectively [9].

Perforated gastric and duodenal ulcers are clinically manifested by sudden abdominal pain with the development of localized or generalized peritonitis and may be present in only two-thirds of patients [29, 30]. In terms of diagnosis, the first diagnostic test is an abdominal and chest X-ray to determine the presence of free air in the abdomen and varies widely among studies reported in the literature, ranging from 30 to 85%. Meanwhile, a negative X-ray does not exclude a possible perforation, and therefore a CT scan is advisable [14, 30].

The work of Lee F.Y. (2001) is of scientific and practical significance, involving 374 patients who had surgical treatment for perforated ulcer disease, of whom 219 patients received open treatment (suturing), 109 patients received laparoscopic treatment with fibrin glue, and the remaining 46 patients were treated with laparoscopic

suture. At the beginning of treatment, laparoscopic fibrin glue plastics were performed on 149 patients, but 40 had to be transferred to suturing. The overall conversion rates for laparoscopic fibrin glue plastics and laparoscopic suture plastics were 27 and 15%, respectively. The main reasons for conversion were a large (1 cm or more) perforated ulcer, as well as the inability to determine the location of the perforation. Mean-while, the overall rate of leaks after laparoscopic glue plastics and laparoscopic suture plastics was 16 and 6%, respectively, and the rate of reope-ration for clinical leaks after laparoscopic glue plastics and laparoscopic suture plastics was 10 and 4%, respectively [18, 30]. Instead, studies by Lin et al. (2017) analyzed the surgical treat-ment of 118 patients with perforated ulcers who underwent laparoscopic plastics with simple suturing (n = 27) and omentopexy (n = 91), and found three failures of sutures after closure: 1 after simple closure and 2 after closure and omento-pexy, but no patient died [19].

Based on the results of treatment, an analysis of the Massimo S. at al. [2017] was studied, as well as multicenter observation conducted in 132 medical institutions around the world over a 4-month period (October 2014 – February 2015), and included 4553 patients who had intra-abdominal infection. According to the results of the study, the established overall mortality was 9.2% [20].

In conclusion, it is worth emphasizing that the diagnosis and adequate treatment of primary infiltrative and abscessing formations, despite the achievements, remains an extremely difficult problem.

Conclusions

1. The frequency of primary intra-abdominal complications in the form of infiltrates and abscesses is associated with anatomical localization: most often it is destructive appendicitis, to a lesser extent destructive cholecystitis and perforated gastric ulcer and duodenal ulcer, and among postoperative it is adhesive obstruction and hernia strangulation.

2. Visualization of primary and postoperative secondary intra-abdominal complications is based on a comprehensive examination with the account the informativity and safety: thermometry of the anterior abdominal wall, ultrasound, X-ray examination of the abdominal cavity and rectal examination of the patients.

3. The use of a water-jet scalpel and bipolar coagulation allows precise and bloodless separation of infiltrative-abscessing formations, which yields better results of surgical treatment, taking into account the quality of life.

Conflict of interests

The authors of the article declare no conflict of interests.

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BIOMECHANICAL SUBSTANTIATION FOR EXTERNAL FIXATION OF THE PELVIS USING RODS WITH DIFFERENT THREAD HANDS

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Abstract

Background. External fixation devices (EFD) have found wide application in pelvic fractures treating, but it is not always that strength characteristics of these devices make it possible to realize early rehabilitation. **Objective:** the biomechanical justification for external pelvic osteosynthesis with use of rods having different thread hands on the basis of analysis of the stress-strain state (SSS) of the "EFD – pelvis" system and an experimental study of the strength of threaded connections of different rods and the pelvic bone under the effect of alternate cyclic loads. **Materials and Methods.** Was analyzed the SSS of the "EFD – pelvis" system verified in an experimental study of the strength of threaded connections of different rods and the pelvic bone under the effect of alternate cyclic loads. **Results:** standing on a single basis in the AVF rods with the same thread, there are torques directed in different directions: on the right – clockwise (screwing in), on the left – counterclockwise (screwing out).A change in the thread direction does not lead to change in the moment values, but directions of the action of the moments of force for the left rod will correspond to the direction of its screwing both in the left- and right-sided one-support position. **Conclusions:** Bar-connected rods with a differently directed thread create a reciprocally interlocking structure, which counteracts self-unscrewing. Such a structure significantly increases the strength of connection of an EFD with the pelvic bone and creates conditions for an effective use of the early rehabilitation of patients with pelvic fractures.

Key words: *pelvis, stress-strain state, external fixation, experimental study.*

Introduction

The results of medical rehabilitation of patients with consequences of unstable pelvic fractures (UPF) depend upon many factors, among which the strength of fixation of the fragments that makes possible early recovery of the staticodynamic function of the lower girdle is particularly important,

External fixation rod devices are widely used in treating fresh UPF and their consequences, but it is not always that strength characteristics of these devices make it possible to realize modern tendencies in medical rehabilitation, which call for early verticalization of the patients and use of constant passive movement and application of electromechanical splints. This is explained by the fact that in patients with UPF, who have underwent external osteosynthesis with a rod device, both axial load and repeated cycles of hip flexion and extension reduce the strength of rod fixation in the iliac bone.

In order to improve strength characteristics of the "external fixation device – pelvis" system, experimental studies and mathematical modeling with use of the finite element method (FEM) have been conducted [1–4]. Recently, assessment of the stress-strain state (SSS) of biomechanical systems with FEM has become widely used [5–

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8]; herewith good prospects of this method in modeling both internal and external pelvic fixation are indicated [9–11].

2. Purpose, subjects and methods:

2.1. The purpose of the present study was to substantiate biomechanically external pelvic osteosynthesis with the use of rods having different thread hands on the basis of analysis of the stress-strain state of the "external fixation device – pelvis" system and an experimental study of the strength of threaded connections of different rods and the pelvic bone under the effect of alternate cyclic loads.

2.2. Subjects & Methods

At the first stage of this study we analyzed the stress-strain state of the "external fixation device – pelvis" system on a finite element mathematical model, which was built on the basis of tomographic sections of the pelvic bones, drawn through 0.5–1 cm for irregular zones. Two variants of the calculation model were built (*Fig. 1*). The first one was intact. The second one was the model of a rotationally unstable pelvic fracture of B1 type (AO) (rupture of the pubic symphysis and left ventral sacroiliac ligament), fixed with a rod device. The model consisted of 59,713 finite elements (10-noded isoparametric tetrahedrons) and had 111,420 nodes. All contact pairs of model elements, apart from external fixation device (EFD) rods and pelvic bone, were performed by the "bonded" type. The contact pair between the threaded portion of fixing screws and the iliac bone was performed by the "frictional" type with the metal-bone friction coefficient equal to 0.3. The geometric model was built using the Solid Works program. The calculations were carried out in the ANSYS program.

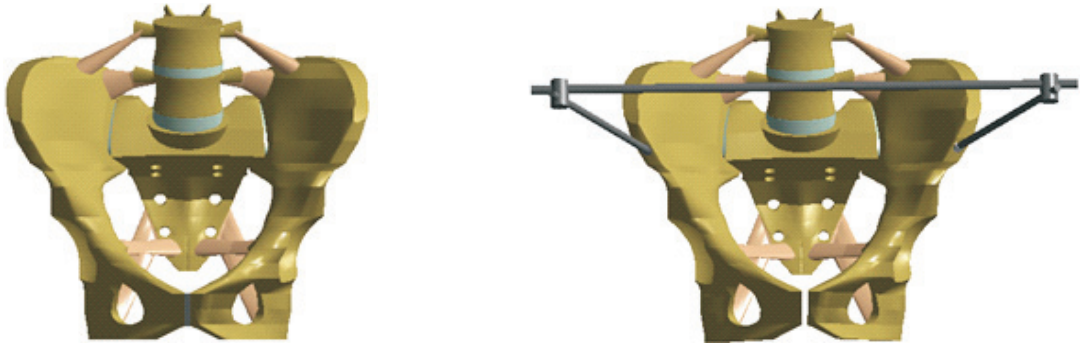
Previous studies took into consideration different kinds of biological tissues: cortical and cancellous bones, cartilaginous tissue, ligaments. In our study the material was regarded to be homogeneous and isotropic. We used the data, which are most commonly found in literature [12–14]. The mechanical characteristics of biological tissues are summarized in *Table 1*.

Table 1

Mechanical characteristics of biological tissues

Tissue	E (MPa)	ν	Source
Cortical bone	12240	0.3	[12]
Cancellous bone	380	0.3	[12]
Cartilage	5.58	0.45	[13]
Ligaments	330	0.4	[14]

The values of resultant muscle forces and angles of their power for the pelvis were taken in compliance with the data from the study of L. Modenese, A.T.M. Phillips, A.M.J. Bull (2011) [15]. The pattern of loading and fixation of the model is shown in *Fig. 2*. The body mass, equal to 700 N, was the major load. In one-support standing the applied force value was 540 N (without including the weight of the weight-bearing extremity).



a *b*

Fig. 1. Calculation models: a) intact model; b) model with a fracture of B1 type fixed with EFD

3. Results & Discussion

Analysis of the performed calculation of SSS (*Fig. 3*) shows that the region of the sacroiliac joint on the weight-bearing side is the most stressed element of the model. The stressed state level in this region reaches to 11.5 MPa. In the study by Ding S. et al (2020) [4] the authors received on an intact model in one-support standing the maximum values in the same region equal to 28 MPa. It should be emphasized that higher values of the stressed state in the above study resulted from modeling with a higher load, 600 N, as well as from using higher values for the elastic modulus of materials. In the anterior pelvic ring, the most stressed regions are as follows: the superior pubic ramus from the weight-bearing side – 4.7 MPa, and the anterior acetabular rim from the non-weight-bearing side – 3.7 MPa.

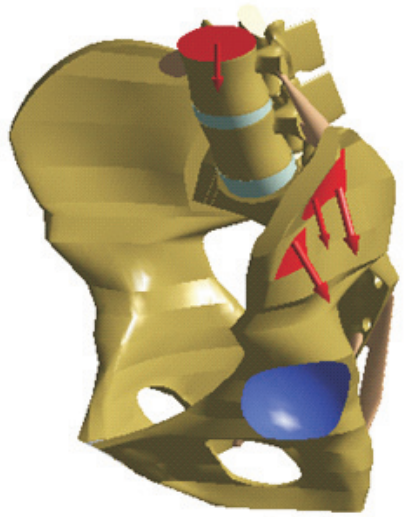


Fig. 2. The pattern of loading and fixation of the model: red color – applied load and muscle forces, blue color – the area of fixation

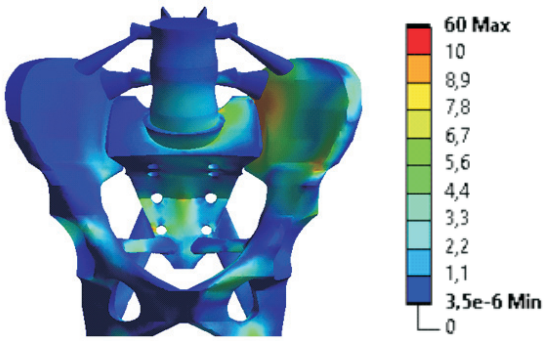


Fig. 3. Von Mises stresses in the intact model

Fig. 4 shows the displacement of the model. With a support from the left leg, displacements of the iliac bone and sacroiliac joint from the non-weight-bearing side do not exceed 0.4 mm.

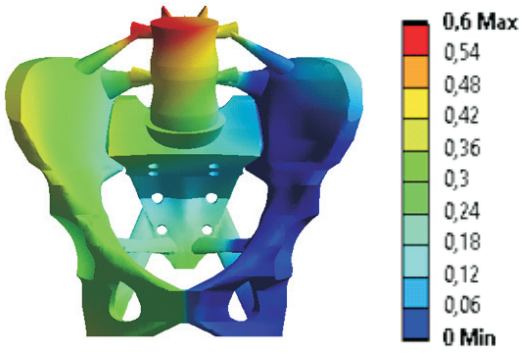


Fig. 4. Displacements of the intact model

Analysis of SSS of the intact pelvis revealed the following facts:

1. The sacroiliac joint from the weight-bearing side, the pubic rami from the weight-bearing side and the anterior acetabular rim from the non-weight-bearing side are the most stressed regions of the model with the stressed state level not exceeding 11.5 MPa.

2. The right (non-weight-bearing) pelvic side slightly moves down (not more than by 0.4 mm.

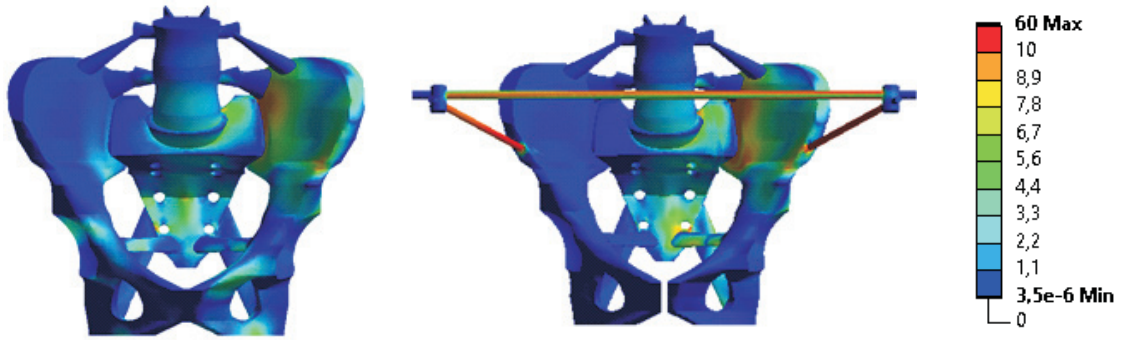
3. The stressed state level in the bone structure is not critical from the perspective of strength.

The next stage of our study consisted in examination of SSS of the pelvic model with a rotationally unstable pelvic fracture of B1 type and fixation with a rod device in one-support standing. Analysis of the performed calculation (*Fig. 5*) shows that EFD rods are the most stressed elements of the model. The stressed state level in them does not exceed 60 MPa. For bone structures, the most stressed regions are as follows: the sacroiliac joint from the weight-bearing side – 14.1 MPa (11.5 MPa for the intact model) and the entrance of rods into the bone, where the maximum value of von Mises stresses is 11.9 MPa for the weight-bearing side (5 MPa for the intact model) and 8.9 MPa for the non-weight-bearing one (0.2 MPa for the intact model).

Fig. 6 demonstrates the distribution of SSS along the passage of EFD rods in the bone in more detail. Our analysis revealed that on the weight-bearing side the stressed state level in the rod was higher and its distribution was more homogeneous along the whole length of the threaded portion. As for the weight-bearing side (*Fig. 6a*), the stressed state level on the rod-bone border changed within 9.5–11.9 MPa. On the non-weight-bearing side, the stressed state distribution was not homogeneous, a higher level was observed approximately on one-fourth of the threaded portion length of the rod and changes (*Fig. 6b*) within 3.5–8.9 MPa.

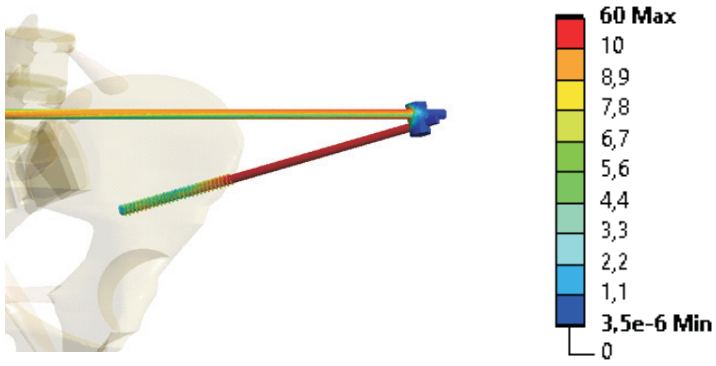
Fig. 7 shows comparison of the deformed and undeformed model (the gray color). With a support from the left leg, the largest displacement is performed by the right node of rod fixation – 4.7 mm.

The above displacement creates a rotary moment of force around EFD rod axes, which acts on the left rod in the counterclockwise direction from a front view (*Fig. 8*). The performed calculation results in the value of the moment in the node of fixing of the transverse bar and the left rod equal to 4.1 Nm. The value of the moment in the right rod in the section of the node of intersection with the transverse bar is less and equals to 0.02 Nm. The direction of the moment action corresponds to a clockwise turn from a front view. When the support is changed for the right leg we receive a symmetrical pattern of SSS distribution, and the direction of moments in the nodes of rod fixing is

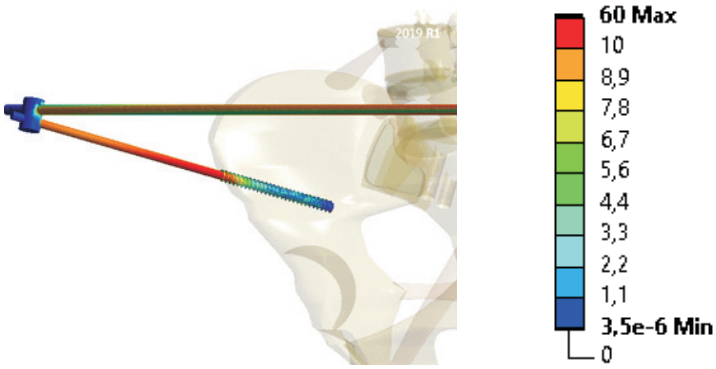


a *b* *c*

Fig. 5. Von Mises stresses: a) in the intact model;
b) in the model with a fracture of B1 type fixed with EFD



a



b

Fig. 6. Von Mises stresses in section: a) the left rod; b) the right rod

preserved (clockwise for the right screw and counterclockwise for the left one).

Analysis of SSS of the pelvic model with a fracture of B1 type fixed with EFD revealed the following facts:

1. EFD rods are the most stressed elements of the model, the rod from the weight-bearing side of the pelvis being more stressed.

2. The right (non-weight-bearing) pelvic side slightly moves down thereby creating a moment of force, which acts on the left rod counterclockwise and facilitates unscrewing of the left rod (in case of a right-handed thread).

3. The stressed state level in the bone structure is not critical from the perspective of strength.

The comparative analysis of calculations of SSS demonstrated that one-support standing develops rotary moments with different directions in EFD rods. For the right fixing screw, both in left and right one-support standing, a moment of force was created, which was clockwise and facilitated screwing (strengthening of fixation) of the rod. For the left fixing rod, a moment of force was created, which was counterclockwise and facilitated unscrewing of the rod (destabilization of EFD) both in left and right one-support standing.

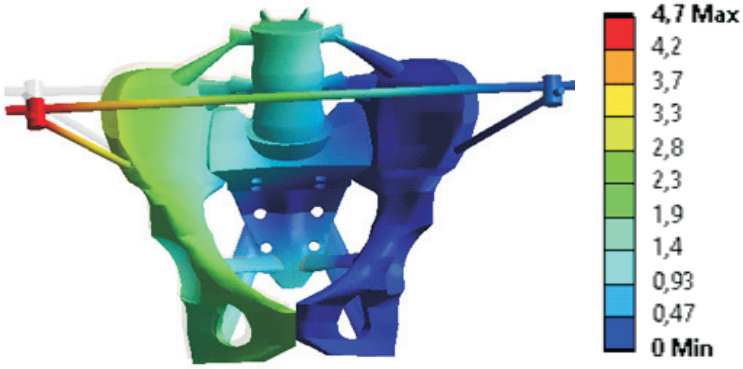


Fig. 7. Displacements of the model
(the scale of deformity is multiplied by 2.5 times for illustration purposes)

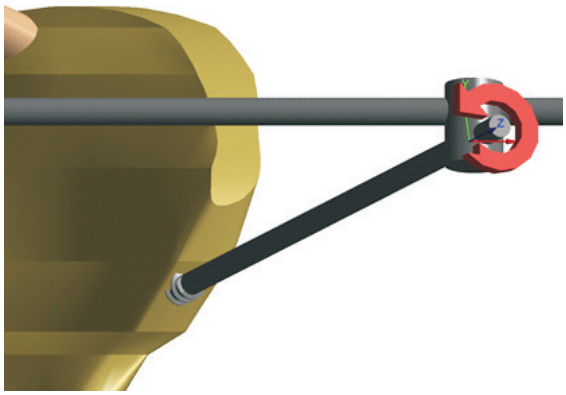


Fig. 8. The direction of the moment
in the section of the left EFD rod

Results of the mathematical modeling were verified in an experimental study of the strength of threaded connections of different rods and the pelvic bone under the effect of alternate cyclic loads.

The experimental studies were conducted on the specimens of the pelvic bones of a pig. We used external fixation devices having rods with a cylindrical unidirectional thread and rods, where one had a right-handed thread and the other was with a left-handed thread (*Fig. 9*).

Fig. 9. The experimental model on the testing device

For each type of rods, three preparations were used. Cyclic alternate loads were performed with help of a shaker device (*Fig. 10*) with vibration frequency of 25 Hz and amplitude of 2.5 mm [16].

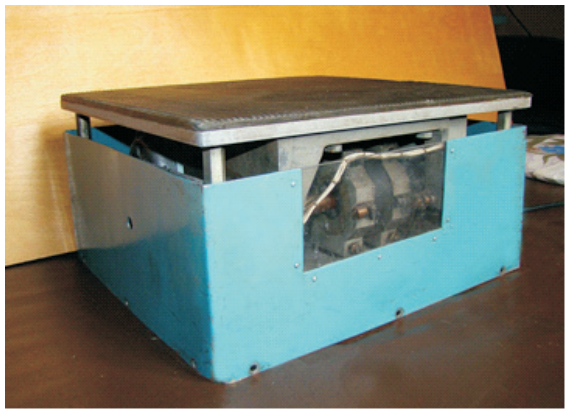


Fig. 10. The shaker device

The vibration lasted for 30 minutes, this duration corresponding to 45,000 gait cycles. Contact places of the rods with the bone were treated with brilliant green.

In the end of the experiment the value of self-unscrewing of the screws from the bone was determined with help of an optical micrometer (*Fig. 11*).

Besides, the value of the unscrewing moment during screwing of the rod into the bone tissue was experimentally studied. For this purpose we used a rigidly fixed preparation of the hip bone of a pig. With help of a tommy bar the rod was screwed into the mid-diaphysis across its entire width. The scheme of the experiment is shown in *Fig. 12*.

The length of the lever of action of the unscrewing force in our experiment was:

$l = 100$ mm.

A photograph of the experiment procedure is presented in *Fig. 13*.

The unscrewing force was applied to the tommy bar, and its value was measured with help

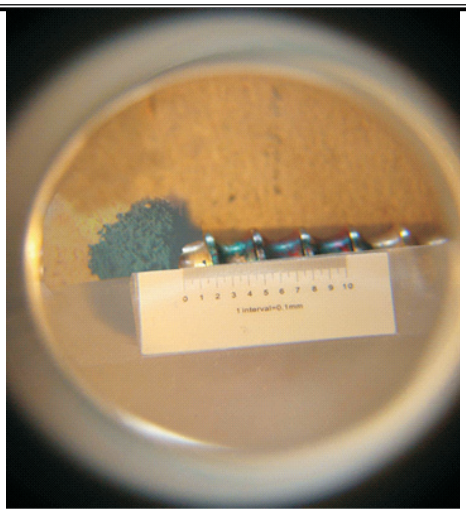


Fig. 11. The view of the specimen under an optic micrometer

geometrical characteristics of thread and forces in the threaded connection are given in *Fig. 15*.

According to [17], the moments, which are necessary for unscrewing a threaded connection, can be presented in the form of:

$$M_{\text{вгв}} = M_{\text{вигв}} \frac{\left[tan(\phi + \psi) + f_T \frac{d_{cp}}{d_2}\right]}{\left[tan(\phi - \psi) + f_T \frac{d_{cp}}{d_2}\right]} \qquad (2)$$

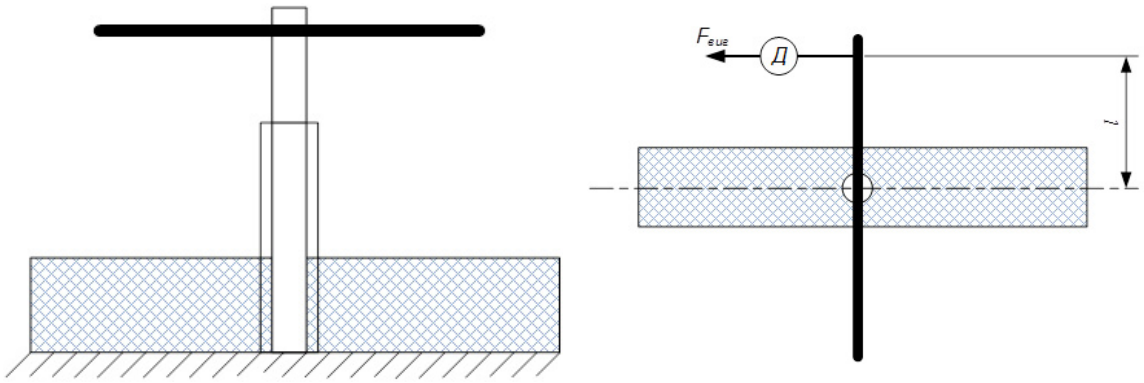
where Munscr, Mscr – the moments, required for unscrewing/screwing a threaded connection;

fR – friction ratio on the thread edge;

dm – mean diameter of a contact ring;

d2 – pitch diameter.

Results of our experimental study of the unscrewing moment value for a rod, screwed into



a *b*

Fig. 12. The scheme of the experiment with unscrewing of the rod:
a – view in the sagittal plane; *b* – top view (D – dynamometer; Funscr – force of unscrewing; l – length of the lever of action of the unscrewing force)

of a tensometric sensor SBA-100L and a CAS registration device of CI-2001 type (*Fig. 14*).

The unscrewing moment value was calculated using the formula [16]:

$$Munscr = Fl, \qquad (1)$$

where F – value of the unscrewing force;

l – length of the lever of action of the unscrewing force.

By results of the experiment we calculated the value of the screwing moment [17] and critical values of the amplitude and frequency of vibration, with which a rod can unscrew [18].

The experimental data were subjected to statistical processing. We calculated the mean value (M) and its standard deviation (SD) as well as the minimum and maximum values. Analysis of the findings was performed in a pack for statistical analysis IBM Statistic SPSS 20.0 [19].

In order to understand the alternate cyclic loads on the strength of threaded connections let us use the method of calculations presented in [16]. The

the diaphyseal portion of the hip bone of a pig, are shown in *Table 2*.

According to the results of our experimental study the mean value of the unscrewing moment was 3.3±0.32 Nm. Therefore for calculating we take the mean value:

Munscr = 3,3 Нм.

In compliance with additional data [16] we chose the value of the friction ratio for the metal-bone pair:

fT = 0.3.

We chose the last parameters according to the design of the rod, engaged in the experiment:

Dm = 5 mm;

d2 = 6 mm;

$\psi = 10^0$;

$\phi = 30^0$;

P = 3 mm.

If the above values are inserted into the equation (2), the value of the screwing moment of our rod is received:

M_{unscr} = 4.9 Nm

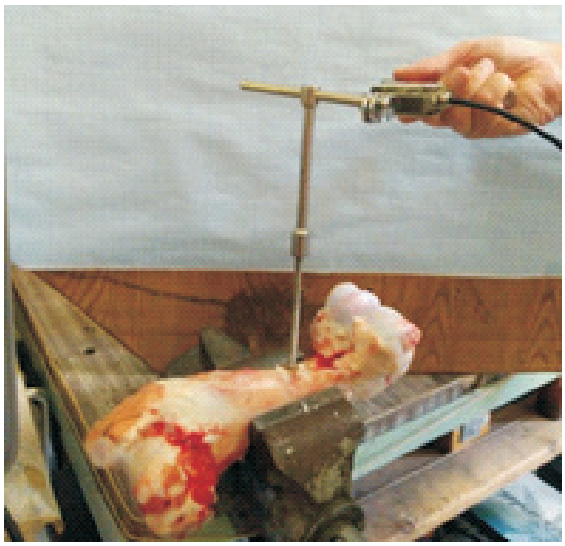


Fig. 13. An experimental study of the unscrewing moment value, when a rod is screwed into the bone tissue

Fig. 14. The device for registering the value of loading with a tensometric sensor

According to the results of our experimental study the mean value of the unscrewing moment was 3.3±0.32 Nm. As it can be seen, the main factors that produce their effect on the forces, required for unscrewing a threaded connection,

Table 2. The values of the unscrewing moment for a rod, which is screwed into the diaphyseal portion of the hip bone of a pig

No. of test	Unscrewing moment M_{unscr}, Nm		
	M_{unscr}	M±SD	min÷max
1	2.80	3.3±0.32	2.80÷3.60
2	3.50		
3	3.40		
4	3.20		
5	3.60		

are as follows: the moment of the previous tightening and the friction force on turns and edges of the thread. Consequently, lowering of the unscrewing moment is directly caused by a change of the friction force in turns and edges of the thread. One study [2] has examined the effect of vibration on the friction ratio and demonstrated that longitudinal vibration is its major cause. The conditions for absence of slipping are as follows:

$$\frac{2M_{\text{ВГВ}}\left[tan(\phi-\psi)+f_T\frac{d_{cp}}{d_2}\right]}{d_2\left[tan(\phi+\psi)+f_T\frac{d_{cp}}{d_2}\right]} > mA\omega^2 \qquad (3)$$

where m – rod weight, in our case m = 20 g;
A – vibration amplitude;
ω – vibration frequency.

Having transformed the equation (3), we can receive an equation for determining critical values of vibration frequency depending upon its amplitude:

$$\omega < \sqrt{\frac{2M_{\text{ВГВ}}\left[tan(\phi-\psi)+f_T\frac{d_{cp}}{d_2}\right]}{mAd_2\left[tan(\phi+\psi)+f_T\frac{d_{cp}}{d_2}\right]}} \qquad (4)$$

Let us insert the necessary values into the equation (4) and calculate critical values of vibration frequency for its amplitude in the range from 1.0 mm to 5.0 mm with the pitch of 0.5 mm.

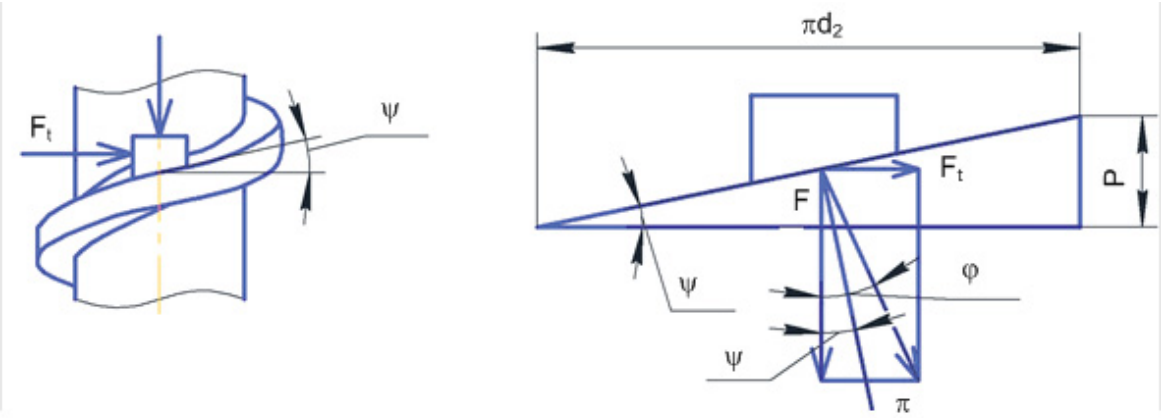


Fig. 15. Interacting forces in a threaded connection: where Ft – circumferential driving force; F – axial force on a screw; ψ – lead angle; ϕ – friction angle; d2 – pitch diameter; P – thread pitch

Results of the calculations are presented in *Table 3*.

Table 3. Critical values of vibration frequency from its amplitude for unscrewing a rod from the bone

Amplitude, mm	Frequency, Hz
0	681
0.5	305
1.0	215
1.5	176
2.0	152
2.5	136
3.0	124
3.5	115
4.0	108
4.5	102
5.0	96

A better visualization of critical values of vibration frequency from its amplitude, for rod unscrewing from the bone is possible with help of a graph given in *Fig. 16*.

Table 4. Values of unscrewing of rods under vibrational effect

Sl. No.	Values of unscrewing of rods, μm	
	Unidirectional threads	Differently directed threads
1	713	0
2	823	0
3	936	0
M±SD	824±112	0
min÷max	713÷936	0

the device that had rods with a differently directed thread they did not unscrew at all (0 μm). We explain it by the fact that the presence of bar-connected screws with a differently directed thread creates a reciprocally interlocking structure, which counteracts self-unscrewing.

The stability of threaded connections is based on the presence of the friction force in the thread plane that in its turn depends upon the pressing force of the centralizer. Vibration is one of unfavorable factors for stability of threaded connections. Vibration causes microdisplacements

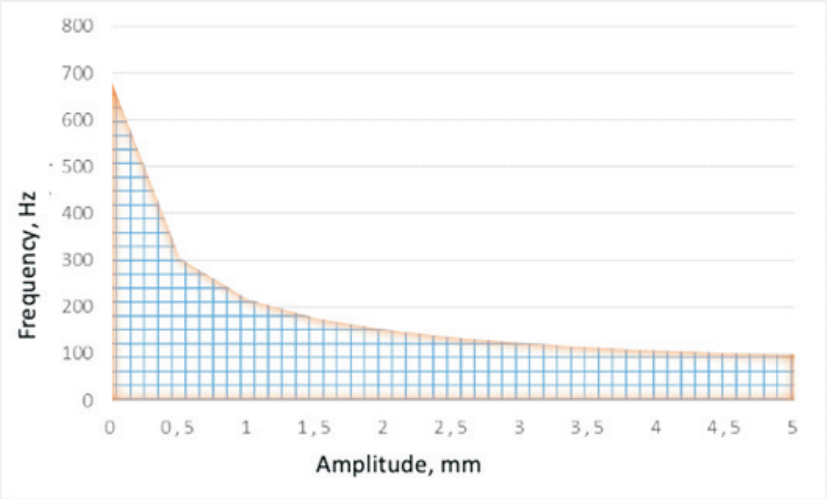


Fig. 16. Diagram of vibration frequency dependence upon its amplitude, which is critical for unscrewing a rod from the bone tissue

The above graph vividly demonstrates that the region above the shaded area is especially dangerous from the viewpoint of possible self-unscrewing of rods.

Table 4 contains the results of testing of the pelvic bones of a pig for vibrational effect; the above bones were connected with an external fixation device in variants with rods having unidirectional and differently directed threads.

As a result of the conducted studies it has been revealed that screws with a unidirectional thread are less resistant to cyclic alternate loads. The mean value of screw unscrewing was 824±112 μm. In

of the centrator with a resultant reduction of the friction force in some cases down to zero. The studies of the unscrewing moment value have shown that the rod used for fixing the pelvic bones creates a sufficient pressing force, but with regard for the structure mass tends to its reduction under the effect of low-frequency mechanical vibrations. This fact was confirmed by the results of tests on a shaker device. One of the methods for counteracting a negative effect of vibration waves on threaded connections consists in creating an additional pressing force by using spring washers, plastic or silicone sealants, etc. Another method involves blocking of a threaded connection, for example with help of

a check nut. In our case the blocking was achieved by using rods with differently directed threads, which provide self-locking of the rods. Experimental studies on a shaker device completely confirmed the effectiveness of such an approach.

Conclusions

We believe that in order to increase the stability and reliability of pelvic fixation with EFD it is necessary to use a left-handed thread for the left rod, thereby making it possible to avoid loosening of its fixation in the bone, since the "behavior" of the left rod will be similar to that of the right one.

A change in the thread direction does not lead to redistribution of SSS and change in the moment values, but directions of the action of the moments of force for the left rod will correspond to the direction of its screwing both in the left- and right-sided one-support position, i.e. both in standing and walking.

Bar-connected rods with a differently directed thread create a reciprocally interlocking structure, which counteracts self-unscrewing. Such a structure significantly increases the strength of connection of an external fixation device with the pelvic bone and creates conditions for an effective use of the technique of CPM in rehabilitation of patients with unstable pelvic fractures.

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Conflict of interests

The authors of the article declare no conflict of interests.

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THE IMPACT OF SMOKING ON THE MORPHOFUNCTIONAL STATE OF PERIODONTAL TISSUES OF YOUNG ORGANISM

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Abstract

Background. The interrelation of disorders in periodontal tissues with metabolic changes caused, in particular, by a violation of microcirculation, observed namely in smoking but the fact that the effect of smoking on the condition of periodontal tissues at a young age has been studied less than other risk factors deserves special attention. The aim of our study was to experimentally assess the effect of smoking on the morphofunctional state of periodontal tissues in young animals. **Materials and methods.** Simulation of smoking has been performed with ten-week-old WAG rats using the Boyarchuck chamber. Morphometric studies were performed in the gingival zone which was chosen for morphological interpretation of volumes of specific vascular density in microcirculatory bed, specific density of connective tissue in lamina propria and specific area of tissue with ischemia. The obtained digital data were processed by the methods of variation statistics. **Results.** Simulation of smoking for four weeks in experimental animals leads to pathological changes in the morphofunctional state of the periodontium with reducing vascular density from 19,44±1,97% to 11,03±1,38 %, increasing area of connective tissue from 18,33±2,71% to 26,49±1,24%, spreading area of tissue with ischemia from 1,14±0,70% to 6,35±1,67%. **Conclusions.** Morphofunctional changes in the periodontium with damage to the structure of the epithelial membrane and changes in its permeability, microcirculatory disorders, sclerotic changes are a manifestation of the initial inflammatory and dystrophic processes that can lead to persistent chronic pathology.

Keywords: *smoking, oral mucosa, ischemia, microcirculatory bed, periodontitis, histology, experiment.*

Introduction

The interest in determining the epidemiological situation with periodontal disease worldwide is high and raises many unanswered questions, despite significant advances in science and practice in this area for young persons and children especially [1]. In particular, this is due to numerous risk factors that directly or indirectly participate in the occurrence of gingivitis [2]. A close look at this problem is based on the fact that the inflammatory process in periodontal tissues is a potential precursor to periodontitis, which can have negative health consequences, including systemic conditions that affect quality of life [3, 4]. Epidemiological data on the occurrence of gingivitis in adults worldwide have been significantly studied and analyzed [5]. Most studies examining the prevalence and distribution of gingivitis in young children and adolescents carry the context of some controversy. In childhood, a number of diseases can be prevented or treated, including gingivitis, before they become irreversible, such as preventing the evolution of gingivitis to periodontitis and possibly worsening pre-existing systemic conditions [2, 6]. This can affect the quality of life of children from the beginning of the disease. Therefore, it is especially important to know the factors associated with gum disease in childhood, which, in turn, will justify and implement better programs for primary and secondary prevention, as well as identify more effective therapeutic approaches.

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One of the unresolved issues of pediatric dentistry is the impact of smoking on the condition of periodontal tissues [7]. The high prevalence of tobacco addiction, difficulties in its diagnosis and treatment, contradictions of ideas about the links of etiopathogenesis have led to a constant interest of researchers in this problem [8, 9]. Such local factors are most often considered among the starting points in periodontal pathology as dental debris, traumatic injuries, infectious agents, and general, in particular, a constant stress factor which could be presented in smoking [10]. Despite sufficiently elucidated morphological and histochemical aspects of periodontal pathology, there is no clear idea of the primary mechanisms of structural and functional changes in periodontal tissues, the relationship between local disorders of homeostasis and the general state of metabolism [11]. This circumstance explains the need for new comprehensive studies using methods that will eliminate the error in the results, leading to contradictions in the reports on periodontology.

One of the postulates of modern periodontology is the interrelation of disorders in periodontal tissues with somatic metabolic changes caused, in particular, by a violation of microcirculation, observed namely in smoking [12–14]. At the same time, the fact that the effect of smoking on the condition of periodontal tissues at a young age has been studied less than other risk factors deserves special attention.

2. Purpose, subjects and methods:

2.1. The purpose of our study was to experimentally assess the effect of smoking on the morphofunctional state of periodontal tissues in young animals.

2.2. Subjects & Methods

Twenty ten-week-old WAG rats (male 86–94g) were obtained from the Vivarium of Kharkiv National Medical University. They were kept at a controlled temperature (21 ± 20C) and relative humidity (50–70%), at 12–12 h light-dark cycle and free access to rodent chow and water ad libitum. All experimental procedures were carried out in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. The animals were randomly divided into two groups by 10 animals: group 1 (control group) and group 2 consisted of 10 animals exposed to smoking.

Smoking was generated using the Boyarchuck chamber operated in a one-pass mode with the smoking feed controlled externally by a metering pump. This prevented smoking recirculation that could lead to the physical damage of the respiratory epithelial cells. Functionality of the Boyarchuck chamber is based on smoking and fresh air mixing caused when incoming air forced through a small orifice meets a flow of incoming smoking. At the beginning of the experiment, the rats were allowed a period of 2 weeks to adapt to the Boyarchuck chamber. For time adaption, all rats were exposed to the fresh airflow.

The Boyarchuck chamber was turned on, and the rats of Group 2 were exposed to smoking for 15 min. To exposure dilution air was delivered at 6 l/min and smoking was added at 6 l/min. The smoking was delivered at a rate of 1 l/min per port, a value close to the puffing flow rate.

The animals were removed from the experiment by decapitation under ether anesthesia, after which the lower jaws were prepared. For further histological and histochemical examination, the gum-bone-tooth blocks of the right jaw and the gums of the left jaw were fixed in neutral 10% formalin. Sections after decalcification of the gum-bone-tooth blocks and standard paraffin proceeding were stained with hematoxylin-eosin, with picrofuxin according to van Gieson, according to Rego. The slides were studied on "Olympus BX-41" microscope with subsequent processing using "Olympus DP-soft, version 3.2" software. Morphometric studies were performed in the gingival zone which was chosen for morphological interpretation [15]. Volumes of specific vascular density in microcirculatory bed (MCB), specific density of connective tissue in lamina propria and specific area of tissue with ischemia [16] were estimated for each group (%). Black area of tissue was detected as area of ischemia is slides staining according to Rego. The obtained digital data were processed by the methods of variation statistics. Statistical significance was accepted in $p < 0.05$.

3. Results & Discussion

The study of histological specimens of the experimental group showed moderate hyperkeratosis of the epithelium of the intercostal papillae and gingival sulcus, the epithelial attachment with thickening of the stratum corneum on the background of thinning of the spiny and granular layers, papillary smoothing. Own plate was found to have acanthotic cords with increased number of fibroblasts, single leukocytes and sclerosis of reticular layer.

The vessels of microcirculatory bed have been characterized by uneven blood filling with background of isolate vessels that have fallen lumens and presence of blood-empty arterioles and

capillaries with signs of constriction. Mucoid and fibrinoid swelling have been observed in vascular wall. Endotheliocytes are flattened more often, with signs of desquamation in focus of ischemia in slides stained according to Rego. Simultaneously initial signs of sclerotic processes have been noted in perivascular space in lamina propria. Vascular density of microcirculatory bed (*table*) according to morphometric studies in comparison with the intact group ($p<0.05$).

Morphometric changes of the oral mucosa

Groups / Index	Intact	Smoking
Specific vascular density MCB (%)	19.44±1.97	11.03±1.38*
Specific area of connective tissue (%)	18.33±2.71	26.49±1.24*
Specific area of tissue with ischemia (%)	1.14±0.70	6.35±1.67*

* $p < 0.05$ significant difference between groups.

Connective tissue of lamina propria was shown to have edema and isolate lymphocytes and plasma cells in the perivascular space. There was an increase in the number of fibroblasts. Reticular fibers were less coiled than in the control group, thickened and compacted, in some places with partial homogenization. Collagen fibers were collected in bundles with microfocal hyalinization.

Lymphocytes, macrophages and neutrophilic leukocytes were found in the periodontal space. Capillaries were full-blooded with focal paravasal hemorrhages and hyaline thrombi. Certain morphological changes in periodontal tissues were considered to be a manifestation of inflammatory and dystrophic processes in microcirculation disorders and metabolic disorders [17].

The issue of the role of smoking in the etiopathogenesis of many non-communicable diseases ranks high, and the possible consequences of smoking in periodontal tissues have been regarded as contradictory and require further careful study especially in young age [8] as it could be risk for future changes [18, 19] due to widespread form of Tabaco addiction [20, 21] in different countries. In our opinion, smoking can be the basis not only for the intensification of pathological changes in the periodontium, but also be a trigger for the emergence of these processes [8, 20].

Keeping experimental animals for weeks with continuous simulation of smoking led to morphofunctional changes in periodontal tissues. Four weeks of experimental smoking simulation caused changes in the structure of the epithelial membrane, resulting in violation of its permeability, disruption of the microvascular bed of the connective tissue base of the gums, lymphomacrophage infiltration of varying degrees, as well as sclerotic changes. All these signs underlie the pathogenesis of chronic periodontal disease [22, 23]. Further progression of the pathological process in the gums along with an increase in the damaging effects lead to the destruction of the gingival junction of periodontal pockets, destruction of the circular connection [24] with the development and deepening of resorptive changes in bone tissue. In our study, the uncertainty of cellular infiltrates is noteworthy, which should not be interpreted as a favorable course. Probably, this fact testifies to the gradual development of the chronic pathological process, as edema and alteration of periodontal structures are most often dominant in the morphological picture of the chronic process with a sluggish course, as noted by some researchers [2]. Moreover, changes in the microcirculatory tract, identified in the course of our study, were quite significant in periodontal pathology and were confirmed in a number of scientific studies [17, 22].

Thus, our study revealed changes corresponding to the initial stages of chronic pathological process. Disorganization of connec-tive tissue, disturbance of MCB development, consequences of ischemic injuries are important for development of periodontitis. We have shown that vascular dysfunction may link development of hypoxia with activation of connective tissue that leads to sclerotic changes in oral mucosa [16, 24] and surrounding organs [25]. However, taking into account the smoking of young people [20], development of adequate treatment and prevention measures [26, 27] requires a longer simulation of this condition in experimental animals.

Conclusions

1) Simulation of smoking for four weeks in experimental animals leads to pathological changes in the morphofunctional state of the periodontium with reducing vascular density from 19,44±1,97% to 11,03±1,38 %, increasing area of connective tissue from 18,33±2,71% to 26,49± 1,24%, spreading area of tissue with ischemia from 1,14±0,70% to 6,35±1,67%.

2) Morphofunctional changes in the periodontium with damage to the structure of the

epithelial membrane and changes in its permeability, microcirculatory disorders, sclerotic changes are a manifestation of the initial inflammatory and dystrophic processes that can lead to persistent chronic pathology.

Thus, the studies and conclusions indicate the need for further study of the effects of smoking on the condition of periodontal tissues. In the future, it is necessary to study the above indicators after 6 months of the experiment, which will clarify the possibility of adaptation mechanisms, or deepening of dystrophic-inflammatory processes with prolonged chronic exposure to smoking. In addition, special attention needs to be paid to the state of the microcirculatory tract and endothelial disorders in periodontal tissues under the influence of smoking.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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THE FEATURES OF ENDOMETRIUM STRUCTURE IN ALCOHOL-ABUSED HIV-INFECTED INDIVIDUALS

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Abstract

Background. Patients with comorbid pathology occupy leading positions in the practice of a doctor of any specialty especially in patients with HIV. The reproductive system is known to be the gateway for viruses. This fact could explain severity of changes developing in the female reproductive system infected with HIV, in particular in the endometrium. The purpose of this study was to assess the morphological changes of the endometrium caused by the combined effects of HIV infection and chronic alcoholism. **Materials and Methods:** The study involved autopsy material taken from 60 women of reproductive age (20–40 years). They were all divided into two groups. Group 1 (30 persons) consisted of HIV-positive individuals in whom, according to the relatives and according to the autopsy findings (the main symptom was the presence of alcoholic cirrhosis of the liver), alcohol abuse was confirmed. The following parameters were determined: the average diameter of the endometrial glands (proliferative type), the minimum diameter of the endometrial glands (proliferative type), the maximum diameter of the endometrial glands (proliferative type), wall thickness (proliferative type), the relative volume of the epithelium (proliferative type), the average diameter of the glands (secretory type), the minimum diameter of the glands (secretory type), the maximum diameter of the glands (secretory type), the relative volume of the epithelium (secretory type), the thickness of the epithelium. **Results.** The average diameter of the endometrial glands (proliferative type) decreased from $51.71 \pm 2.90 \times 10^{-6}$ m compared to $39.42 \pm 2.35 \times 10^{-6}$ m in the HIV-infected group, which was 23.77%. The minimum diameter of the endometrial glands (proliferative type) reduced from $32.47 \pm 1.83 \times 10^{-6}$ m to $27.13 \pm 1.73 \times 10^{-6}$ m (16.45%), the maximum diameter from $72.14 \pm 2.21 \times 10^{-6}$ m to $63.84 \pm 3.29 \times 10^{-6}$ m (11.5%). the relative volume of the epithelium (proliferative type) decreased by 5.41% (from 54.43 ± 1.79% in the study group to 49.02 ± 2.65% in the control group). The thickness of the uterine wall was also significantly reduced from $15.18 \pm 1.60 \times 10^{-6}$ m to $14.52 \pm 1.19 \times 10^{-6}$ m, which was 4.35%. The maximum volume of glands (secretory type) changed from $127.98 \pm 2.10 \times 10^{-6}$ m to $97.18 \pm 3.12 \times 10^{-6}$ m (24%). Changes by 3.6% were also observed when examining the wall thickness (from $13.02 \pm 1.36 \times 10^{-6}$ m to $12.55 \pm 1.68 \times 10^{-6}$ m). **Conclusion.** We can conclude about significant severity of pathological changes in the endometrium in HIV-infected women who were addicted to alcohol. This fact makes it possible to assume that the presence of alcohol addiction increases the changes caused by HIV infection in the endometrium. The described changes are mainly expressed in the maximum and average diameter of the endometrial glands in both the proliferative and secretory phases of the menstrual cycle.

Keywords: *endometrium, HIV, alcohol, histology, morphometry.*

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Introduction

In Ukraine, the number of HIV-infected people is growing every year with the overwhelming majority the young persons (77.6% of reproductive and working age (15–49 years)), the number of HIV-infected pregnant women is also increasing [1], which is explained by the high proportion of women of reproductive age among the patients with HIV infection [2].

The patients with comorbid pathology occupy leading positions in the practice of a doctor of any specialty especially deaing with HIV patients [3]. Working with such a group of people, the physician needs to assess the risks of the combined influence of several abnormal processes, which often reinforce each other, leading to an even more pronounced reaction to the development of the pathological process in various organs and tissues [4]. Such patients always require an individual approach in sense of diagnostic procedures, diagnosis confirmation and selection of therapy [5].

HIV infection is the leader in the frequency and severity of comorbid pathology among all diseases. In almost one hundred percent of cases [3], HIV infection is combined with a variety of diseases that drastically aggravate its course, and often cause the death of patients. Meanwhile, it is known that alcohol abuse is the cause of cancer deveopment in women [6, 7]. Considering the behavior of people who abuse alcohol, their low social responsibility, concomitant diseases of chronic alcoholism are often infectious diseases, including HIV infection (AIDS) [9, 10].

The reproductive system is known to be the gateway for viruses. This fact could explain severity of the changes developing in the female reproductive system infected with HIV, in particular in the endometrium. It can be assumed that these changes may increase in the presence of any of the diseases associated with HIV infection, especially alcohol abuse [10].

Today there are many studies covering the influence of chronic alcoholism on the state of the reproductive organs in women, as well as the impact of HIV infection. However, there are practically no data on the combined effect of these factors.

2. Purpose, subjects and methods:

2.1. The purpose

Considering all of the above, the purpose of this study was to assess the morphological changes in the endometrium caused by the combined effects of HIV infection and chronic alcoholism.

2.2. Subjects & Methods

The study included autopsy material taken from 60 women of reproductive age (20–40 years). They were all divided into two groups. Group 1 (30 persons) consisted of HIV-positive individuals in whom, according to their relatives and according to the autopsy findings (the main symptom is the presence of alcoholic cirrhosis of the liver), alcohol abuse was confirmed. HIV infection was determined by a serum enzyme-linked immunosorbent assay (ELISA) with confirmation by Western blot. CD4 lymphocyte count <100 cells/μL was considered "low" [2]. The control group (30) consisted of women without any concomitant diseases, with a negative HIV status, who had no confirmed alcohol abuse, who died as a result of accidents.

The material was fixed in 10% neutral buffered formalin, then the selected samples were embedded in paraffin. At the next stage, sections with a thickness of 5×10^{-6} m were made from the prepared paraffin blocks. Subsequently, staining with hematoxylin and eosin was performed. Microscopic examination was carried out on an Olympus BX41 microscope, followed by morphometric examination using the Olympus DP-soft 3.12 software [11].

The following parameters were determined: the average diameter of the endometrial glands (proliferative type), the minimum diameter of the endometrial glands (proliferative type), the maximum diameter of the endometrial glands (proliferative type), wall thickness (proliferative type), the relative volume of the epithelium (proliferative type), the average diameter of the glands (secretory type), the minimum diameter of the glands (secretory type), the maximum diameter of the glands (secretory type), the relative volume of the epithelium (secretory type), the thickness of the epithelium.

Statistical processing was performed using the methods of variation statistics. Correspondence of the distribution to the norm was determined by the Shapiro-Wilk test, which showed that the samples were close to the normal distribution. Statistical indicators are presented in $M \pm \sigma$ format, where M is the arithmetic mean, σ is the standard deviation, Student's t-test. Correlation analysis was carried out using Spearman's rank correlation coefficient. The statistical difference between the studied parameters was considered significant at p less than 0.05.

The procedure was done strictly in compliance with Helsinki Declaration after approval from the Re-gional Ethical Review

Board at Odessa National Medical University, records No. 3 dated 17 October 2011.

3. Results & Discussion

The results of the study carried out in a group of HIV-infected women suffering from chronic alcoholism and in the control group are presented in *Table*.

Indicators of the endometrium structure

The investigated indicator	Comparison group	HIV infection and alcoholism
Average diameter of the endometrial glands (proliferative type), $\times 10^{-6}$ m	51.71±2.90	39.42±2.35*
Minimum diameter of the endometrial glands (proliferative type), $\times 10^{-6}$ m	32.47±1.83	27.13±1.73*
Maximum diameter of the endometrial glands (proliferative type), $\times 10^{-6}$ m	72.14 ±2.21	63.84±3.29*
Wall thickness (proliferative type), $\times 10^{-6}$ m	15.18±1.60	14.52±1.19
Relative volume of the epithelium (proliferative type), %	54.43±1.79	49.02±2.65*
Average diameter of the glands (secretory type), $\times 10^{-6}$ m	101.55±3.12	82.44±3.59
Minimum diameter of the glands (secretory type, $\times 10^{-6}$ m	33.86±1.17	30.81±1.79*
Maximum diameter of the glands (secretory type), $\times 10^{-6}$ m	127.98±2.10	97.18±3.12*
Wall thickness (secretory type), $\times 10^{-6}$ m	13.02±1.36	12.55±1.68
Relative volume of the epithelium (secretory type), %	61.24±1.11	47.18±1.62*
Thickness of the epithelium, $\times 10^{-6}$ m	49.14±1.44	53.04±1.13*

* $p < 0.05$ significant between groups.

As it can be seen from *Table*, the presence of HIV infection in patients with chronic alcoholism caused significant morphological changes in the structure of the endometrium. In the group of HIV-infected women who abused alcohol, practically all studied parameters significantly decreased in comparison with the control group.

Namely, the average diameter of the endometrial glands (proliferative type) decreased from 51.71 ± 2.90 $\times 10^{-6}$ m in the comparison group to 39.42 ± 2.35 $\times 10^{-6}$ m in the HIV-infected group, which was 23.77%. The minimum diameter of the endometrial glands (proliferative type) reduced from 32.47 ± 1.83 $\times 10^{-6}$ m to 27.13 ± 1.73 $\times 10^{-6}$ m (16.45%), the maximum diameter from 72.14 ± 2.21 $\times 10^{-6}$ m to 63.84 ± 3.29 $\times 10^{-6}$ m (11.5%) according to the above order.

Obviously, the changes affected not only the glands, but also the epithelium itself. Meanwhile, the relative volume of the epithelium (proliferative type) decreased by 5.41% (from 54.43 ± 1.79% in the study group to 49.02 ± 2.65% in the control group). The thickness of the uterine wall was also significantly reduced from 15.18 ± 1.60 $\times 10^{-6}$ m to 14.52 ± 1.19 $\times 10^{-6}$ m, which made 4.35%.

As can be seen from the table, the changes affected the endometrium, both in the proliferative and secretory phases.

The average diameter of the glands (secretory type) in the comparison group was 101.55 ± 3.12 $\times 10^{-6}$ m, which was 18.82% more than in the study group (82.44 ± 3.59 $\times 10^{-6}$ m). The minimum diameter of the glands (secretory type) was reduced by 9% and in the comparison group it was 33.86 ± 1.17 $\times 10^{-6}$ m; 30.81 ± 1.79 $\times 10^{-6}$ m in the group of HIV-infected women with alcoholism.

The maximum volume of glands (secretory type) changed from 127.98 ± 2.10 $\times 10^{-6}$ m to 97.18 ± 3.12 $\times 10^{-6}$ m (24%). The changes by 3.6% were also observed when examining the wall thickness (from 13.02 ± 1.36 $\times 10^{-6}$ m to 12.55 ± 1.68 $\times 10^{-6}$ m).

The relative volume of the epithelium in the study group compared with the comparison group decreased from 61.24 ± 1.11% to 47.18 ± 1.62%.

The thickness of the epithelium increases by 7.35% (from 49.14 ± 1.44 in the control group to 53.04 ± 1.13 in the study group).

As can be seen from the table, the parameters that maximally reacted to the combined effect of HIV infection and chronic alcoholism on the endometrium were the maximum and average diameter of the glands both in the proliferative and secretory phases of the menstrual cycle that could be coordinated with the earlier findings [12].

Thus, it can be assumed that the effect of HIV infection on the endometrium may be enhanced by the presence of chronic alcoholism. HIV is known to cause a violation of the immune status of a person, which affects the state of all organs and tissues, including the endometrium [13, 14]. Many authors have shown a violation of the supervisory functions of the immune system, which regulate the processes of cell proliferation. These changes can be both hereditary and developed during the expression or mutations of the corresponding genes during life. The results of other studies allow suggestion that there is a genetic predisposition to the development of endometrial hyperplastic processes, and the main risk factor and trigger of the pathogenic

mechanisms of proliferative processes in the uterus are genetic determinants (PL-AI allele of the GP-IIIa gene), xenobiotics, PTEN [15, 16].

There are reports of the "inflammatory" origin of endometrial hyperplastic processes [17, 18]. It is known that in the presence of long-term, often exacerbated inflammatory processes of the genital organs, the risk of endometrial cancer increases 20 times, and 15 times against a background of hyperplastic processes of the endometrium. Long-term persistent infection of the genitals leads to a change in estradiol and progesterone receptors in the tissue of the endo- and myometrium [19, 20].

Nevertheless, it is probably fair to consider the fact that in the development of hyperplastic processes, the main role is traditionally assigned to an increase in the concentration of estrogens [21].

It should be considered the most frequent problem of the state of the endometrium and as a consequence of the pressing issue in the female population and oncological alertness due to its high prevalence [22]. Today, it is officially recognized that endometrial hyperplastic processes are one of the important and potentially health-damaging medical problems that challenge doctors around the world [23, 24]. A steady increase in the number of patients suffering from endometrial hyperplastic processes, unclear etiology, variable clinical manifestations and a high recurrence rate and risk of malignancy, as well as low treatment efficacy have led to the fact that in recent years, the scientific interest in this problem has increased significantly [25].

Currently, interesting and at the same time contradictory statistical data are cited in relation to the combined pathological processes of the endo- and myometrium, which to some extent can be explained by a fairly frequent asymptomatic course [24]. Hyperplastic processes of the endometrium constitute 15–40% in the structure of all gynecological diseases, and up to 80% when combined with adenomyosis. Contradictory data can be found as to the combination of endometrial hyperplastic processes and uterine leiomyoma, the frequency of which ranges from 13% to 80%. In the asymptomatic course of uterine leiomyoma in postmenopausal women, every sixth patient has endometrial hyperplasia, at the same time, when uterine bleeding appears, the parallel development of hyperplasia is diagnosed in every other woman [26, 27]. Endometrial hyperplasia in our study manifested by thickening of the epithelium. Thus, it can be assumed that additional ultrasound diagnosis of the state of the endometrium is required in this group of women as a way to determine the endometrium thickness. Such persons should be especially wary in connection with the increased risks of developing cancer and bleeding. The risk of malignant neoplasms can also be enhanced by the direct toxic effect of ethanol, the main component of alcoholic beverages [7]. Ethanol is known to exert a carcinogenic effect at prolonged and excessive use.

In addition, one should not forget that HIV infection, similar to chronic alcoholism, leads to the changes in the structure of the endometrium also due to the development of hormonal imbalance. Under the influence of both diseases, dystrophic-sclerotic changes occur in the ovaries. Thus, there is a decrease in the size of all types of follicles in the ovaries, a decrease in the number of primordial follicles. The described changes lead to a violation of the ovarian-menstrual cycle, a change in the production of estrogen and progesterone [19].

Thus, the women with concomitant pathology in the form of HIV infection and alcoholism should be especially alert in terms of infertility development. Follicle-stimulating hormone hypoproduction entails a decrease in the production of estrogen by the ovaries. These effects can also be enhanced by the occurrence of dystrophic-sclerotic changes in the ovaries themselves. These pathological processes are known to be manifested by the proliferation of the connective tissue, a violation of the relationship between the cortex and medulla, a decrease in the size of all types of follicles (primary, secondary and tertiary), and even a decrease in the number of primordial follicles. The described changes inevitably lead to a decrease in the production of estrogen. The endometrium is regarded as a target organ for estrogen. Proliferative changes occur under their influence. Thus, hypoproduction or complete absence of estrogen by the ovaries, which is also due to dystrophic processes in them, can cause oligomenorrhea or even cause early menopause. This fact could explain the changes obtained in the course of the study, namely: a decrease in the average diameter of the endometrial glands, the minimum diameter of the endometrial glands, the maximum diameter of the endometrial glands, wall thickness, the relative volume of the epithelium, which were calculated in the proliferation phase of the menstrual cycle [28]. Based on the study and literature data, it can be assumed that gynecologists sometimes need to look for concomitant factors that influence

the female body for the correct selection of therapy for women with oligomenorrhea and early menopause [29, 30].

In addition, an imbalance in the concentration of FSH and LH can lead to the development of follicular and corpus luteum cysts, which, although functional, are sometimes associated with the development of complications and require urgent surgical treatment.

In the course of the study, data were obtained that could help in the diagnosis, selection of adequate therapy for gynecological diseases. In addition, this study can be used for the timely diagnosis of conditions that threaten the life of women (bleeding, rupture of cysts) and even malignant neoplasms [31–35], which is intended to reduce the percentage of mortality or disability among this group of patients.

Conclusions

Our findings indicate a significant severity of pathological changes in the endometrium in HIV-infected women who were addicted to alcohol. This fact makes it possible to assume that the presence of alcohol addiction increases the changes caused by HIV infection in the endometrium. The described changes are mainly expressed in the maximum and average diameter of the endometrial glands in both the proliferative and secretory phases of the menstrual cycle.

Conflict of interests

The authors of the article declare no conflict of interests.

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ON THE ISSUE OF REPRODUCTIVE LOSSES PREVENTION IN UKRAINE

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Abstract

The aim of the study was to determine the compliance of the existing medical care system in Ukraine for pregnant and married couples planning a pregnancy (its organizational and financial capabilities), the need to reduce the high level of reproductive losses. **Materials and methods.** Statistical methods and system analysis were used. The national programs of reproductive health, demographic data, data on morbidity (received from the national medical statistics for the period 2017–2018), reports of the national survey "Health Index. Ukraine" (2018), data on appeals for obstetric-gynecological, genetic care (in connection of reproductive losses, fertility) were analyzed. A comparison between the indicators of Ukraine and Kharkiv region, as well as with other countries, according to the cost of the survey, requested for medical care for the examination of genetic and infectious diseases associated with reproductive losses, was made. The organization of outpatient care for pregnant and married couples planning a pregnancy was analyzed in terms of availability and sources of payment for the services. **Results.** The number of Ukrainian women planning their first pregnancy aged 35 and over was increasing as well as the number of genetic pathologies. The indicators of infectious pathology remained high. Meanwhile, women visited less gynecologists and family doctors, which is due to the high cost of the part of medical care that the patients have to pay for themselves. Genetic screening programs for genetic diseases were poorly developed. The professional contacts of physician of various specialties required improvement. These facts negatively affected the level of reproductive losses, complicate their prevention. **Conclusions.** Our findings suggest that to reduce reproductive losses, it is necessary to create a national disease monitoring center, increase the availability of obstetric-gynecological and genetic care for the population, increase coverage of genetic screening programs, and give birth to children at the optimal age of 20–34.

Keywords: *reproductive health, reproductive losses, fertility rates, screening genetic examinations.*

Introduction

A key paradigm of the world health concept transformation is the transition from a responsive work model to a preventive, towards the so-called "4P medicine" model ("Predictive, Personalized, Preventive and Participatory approach to medicine"), where medicine proclaims, personalizes, prevents and requires patient involvement [1]. In such circumstances, the responsibility for maintaining physical and mental health lies with the patient. In this case, health care becomes a service. But the emphasis is forced to shift in the preservation of the life and health of the pregnant and the fetus, due to the particular condition of the woman, who during pregnancy feels less controllable in her life and health, because she focuses on the preservation of the fetus at all levels of body functioning and the mind (conscious, subconscious, at the instinct level).

In a demographic crisis reality, the birth of every healthy baby is a priority for medical services at all levels and for medical science. The main concepts in the national programs "Health 2020: The Ukrainian Dimension" [2] and "Reproductive and Sexual Health of the Nation for the period

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2017–2021" have been outlined. According to these programs, the health status of the Ukrainian population is estimated to be unsatisfactory, including because of low birth rates combined with high mortality rates. The health care system is primarily aimed at treating patients rather than preventing diseases and detecting them early. This approach leads to an increase in primary disability and preventable mortality. To eliminate the negative impact of the social determinants of health, a responsible attitude of each person to personal health is needed, optimization of the care delivery system and intersectoral interaction both in medicine and between medicine, education system, public, etc. Specialists in prevention and early detection of diseases should also be trained.

From an anthropological point of view, reproduction of a population is necessary for its survival in conditions of relative isolation, and all factors that hinder it need to be studied for their elimination. Miscarriages, developmental disabilities (birth defects) incompatible with life, spontaneous abortions and other reproductive losses (RL) causes are actively studied in developed affluent countries of Western Europe, in the United States, but not enough in the poorer countries of the world. In addition, approaches to the study of these issues in many countries in South America, Africa and Asia are difficult to call complete [3, 4]. The strange situation is in Ukraine: according to the declarations, the approaches to the study are modern, in practice, even statistical data are not fully collected.

2. Purpose, subjects and methods:

2.1. The purpose

of the study was to determine the compliance of the existing medical care system in Ukraine for pregnant and married couples planning a pregnancy (its organizational and financial capabilities), the need to reduce the high level of reproductive losses.

2.2. Subjects & Methods

In the context of the identified problems, the methods of statistical and systems analysis were applied. The female fertility rate of different ages, the ratio of the female population to the number of permanent population, the frequency of genital pathology and pregnancy complications, which affected the RL rates, the frequency of women seeking medical help from family doctors on reproductive health issues were examined. The indicators for the Kharkiv region were compared with the national ones, for which official statistics and data from the annual national survey "Health Index. Ukraine" [5] were used.

In 2018 [6], the "Health Index. Ukraine" survey was conducted by Kyiv International Institute of Sociology, the Social Indicators Foundation, the School of Health of the National University "Kyiv-Mohyla Academy" with the support of the International Renaissance Foundation and the World Bank. The survey is conducted annually to determine the actual level of satisfaction of Ukrainian citizens with medical care, covers each of the 24 regions of Ukraine (in Donetsk and Luhansk regions only in the territories controlled by Ukraine) and the city of Kyiv. More than 10,000 people took part in the survey. Survey indicators were either declared in the national "Health Reform Strategy 2015–2020" [7], or are considered important for evaluation attributes, or were available for the calculation of the Index. Assessment of 10 sub-indicators (e.g., visit to physicians in case of illness, satisfaction with medical care, cost of examination and treatment, knowledge of the symptoms of own disease) was conducted from 0 to 10 points per skin indicator (up to 100 points for each region). The results of the current year were compared with the results of the previous year.

Analysis of the state medical statistical reporting of treatment and prevention institutions of Kharkiv region according to the State Statistics Service of Ukraine, the Center for Medical Statistics of the Ministry of Health of Ukraine, the Main Department of Statistics in Kharkiv region (for the period 2008–2018), of the national annual statistical survey "Health Index. Ukraine" (for the 2018 compared to 2017) was completed. We studied the data on fertility, diagnosed malformations, visits to physicians of the relevant profile. Data sampling from forms No. 21 ("Report on medical care for pregnant, mothers and parturients" and No. 49 ("Report on the provision of medical and genetic care") are used.

The method of systems analysis [8] with modified by E.P. Golubkov was used. It involves setting a problem, research, analysis, preliminary judgment, confirmation, final judgment and implementation of the decision.

The preconception preparation, which was the focus of the study, applies to both married couples who are planning a pregnancy, but have a diagnosis of infertility, a high risk of hereditary diseases and history of RL, and pregnant with a high risk of miscarriage, birth defects, ectopic pregnancy and premature birth. Long-term observation of patients from the moment of planning the next pregnancy to the birth of a child is important both for the individual health of the

offspring and for planning organizational measures to RL reduction at the regional and national levels. This fact is taken into account in the proposed system of preconception training and verified by the method of system analysis.

Analysis of the state medical statistical reporting of treatment and prevention institutions of Kharkiv region according to the State Statistics Service of Ukraine, the Center for Medical Statistics of the Ministry of Health of Ukraine, the Main Department of Statistics in Kharkiv region (for the period 2008–2018), of the national annual statistical survey "Health Index. Ukraine" (2018 compared to 2017) was completed. We studied the data on fertility, diagnosed malformations, visits to physicians of the relevant profile. Data sampling from forms No. 21 ("Report on medical care for pregnant, mothers and parturients" and No. 49 ("Report on the provision of medical and genetic care") were used.

3. Results & Discussion

In Ukraine, Western Europe and the United States, pregnancy planning is gradually shifting towards the advanced age of parents. But the reasons are different: in affluent countries it is the pursuit of career growth that hinders the birth of children [9], in Ukraine – socio-economic difficulties that do not allow having not only another but at least one child. According to the literature in Western Europe countries, such cases are now about 5 %. Our calculation indicates a similar trend in Ukraine, at both regional and national level, which is shown in *Table 1*. Thus, since 2008, a gradual increase in the birth rate at the Ukraine and Kharkiv region in the age groups of 35–39 and 40–44 years was observed. In the

Table 1

Number of permanent population, pregnancies, occurring in women over 35 years in Ukraine and Kharkiv region for the period 2008–2018, according to state statistics*

Year**	Number of permanent population*** on January 1 of the current year, thousands				Birth rates**** by mother's age, ‰					
	In Ukraine		In Kharkov region		In Ukraine			In Kharkov region		
	in all	women	in all	women	35-39 years	40-44 years	45-49 years	35-39 years	40-44 years	45-49 years
2008	46372.7	24894.6	2780.3	1504.9	19.7	3.3	0.2	19.0	2.9	0.1
2009	46143.7	24778.4	2766.8	1497.3	21.5	3.8	0.2	20.3	3.6	0.2
2010	45962.9	24675.5	2753.5	1489.6	22.3	4.2	0.2	20.1	4.3	0.2
2011	45778.5	24565.6	2739.4	1480.8	24.6	4.6	0.2	22.4	4.2	0.3
2012	45633.6	24476.6	2726.5	1473.4	26.4	5.0	0.3	25.6	4.7	0.4
2013	45553.0	24410.0	2728.8	1469.9	27.2	5.2	0.3	24.8	5.0	0.5
2014	45426.2	24327.6	2721.6	1464.3	27.6	5.5	0.4	28.0	5.4	0.7
2015	42929.3	22971.9	2715.7	1459.3	27.3	5.6	0.4	25.6	5.4	0.3
2016	42760.5	22873.0	2703.0	1451.3	27.3	5.8	0.5	25.3	5.1	0.4
2017	42584.5	22770.3	2685.6	1440.9	26.7	5.9	0.7	24.4	5.4	0.5
2018	42386.4	22658.6	2678.4	1437.8	26.4	6.1	0.7	24.4	5.6	0.5
Sources	[10, 11]		[12]		[13, p. 5]			[12]		

Notes:

* For our study, we selected a group of women who gave birth at first time after the age of 35 (so-called age-old primaparas) [14]. In these women, the incidence of genital pathology and complications in childbirth exceeds similar rates in women 20–30 years [15]. Thus, cases of uterine myomas account for 27.8 %, cervical ectropion – 17 %, chronic adnexitis – 6.7 %, infertility – 11.1 %, ureaplasmosis – 5.6 %, preeclampsia at 32 weeks of gestation and over – 50 %, anemia – 27,8 %, chronic placental insufficiency – 16.7 %, pregnancy termination threats – 16.7 %, gestational diabetes – 5.5 %. With increasing of birth age, the frequency of the following states increased as well: premature birth, premature outflow of amniotic fluid (up to level 27.8 %), primary weakness of childbirth activity (11.1 %), cervical ruptures (11.1 %), threatening perineal rupture (5.5 %), delays of litter parts (5.5 %). This age was also considered to be the safest for pregnancy and childbirth [16, 17].

** Since 2015, data have been submitted without taking into account the temporarily occupied territories of Donetsk, Luhansk region, Crimea and Sevastopol. Population calculations were made on the basis of available administrative data on state birth and death registration, as well as changes in residence registration.

*** Permanent Population - population that is permanently resident at the time of the census in a certain territory, including temporarily absent persons, if their absence in the place of permanent residence did not exceed 12 months.

**** Age-specific fertility rates (live births per 1,000 women of the appropriate age) – the ratio of live births per year in women of this age group to the average annual number of women at this age. In fact, this is the birth rate for the hypothetical generation, which does not depend on the age of the population [18].

age group of 45–49 years there is a trend of growth only at the national level noted, but this indicator fluctuated over the years in Kharkiv region.

Age-specific fertility rates in all countries of the world are traditionally calculated per 1,000 of the population corresponding age and in age groups of 5 years during the reproductive age (15–49 years) [19]. The state statistics organizations annually publish statistical data on fertility rates for all age groups of women, and the researchers select the age for which they conduct their research. The result of the arithmetic mean for the nearest age groups is not correct in cases where the researcher needs to show the age group, for example, women at 40–49 years age. In this case, it is necessary to process the primary data of the region or country, which includes the number of women of the appropriate age group and the number of children born by them. Similarly, total fertility rate of women aged 15–49 calculated as:

$$F_{15-49} = \frac{N}{W_{15-49}} \times 1000, \qquad (1),$$

where F_{15-49} – fertility rate of women aged 15 to 49 years;

W_{15-49} – the average number of women aged 15 to 49 years;

N – number of births.

At present, the availability of affordable, effective and safe contraceptives, as well as assisted reproductive technologies help to correct the reproductive cycle. The incidence of use of such technologies increases significantly ($p<0.001$) with the age of pregnant at times after 40 years [20]: in the group younger than 40 years – 3.3 ‰, in the group 40–44 years – 7.9 ‰, older 45 years – 23,7 ‰. Obviously, extracorporeal fertilization can overcome the problem of infertility, but the hope of it and allows you to postpone pregnancy until later. While it is known that with increasing maternal age, the possibility of pregnancy fertilization and delivery decreases [21], increases the number of chromosomal abnormalities, pathological pregnancy [22, 23]. The use of contraception allows delay in pregnancy beyond the parent's age, but also reduces the risk of sexually transmitted infections, which are responsible for a significant RL incidence.

Pregnancy planning for Ukrainian women under 35 should be facilitated by improved socio-economic living conditions, as well as coordinated efforts by family doctors (general practitioners, GP), obstetrician and genetic services, prevention of unwanted pregnancies under 20 years by available contraceptive methods and family planning knowledge.

According to the annual national survey "Health Index. Ukraine-2018" [6], less than half (46.7%) of women surveyed have visited a gynecologist for prophylactic purposes in the last 12 months (*see Table 2*). Among men, reproductive treatment rates are traditionally lower by about half (in 2017 – 24.0 %, in 2018 – 20.5 %). In addition, these figures decreased compared to 2017 for both women and men. There is also a strong statistical trend: as the age of women increases, the percentage of those who undergo screening is declining. In 2018, it was 66.4 % in women aged 18 to 29 years, in 30-44 years – 58.3 %, 45–59 years – 48.2 %, over 60 years – 24.9 %. Another constant observation: more women with higher education are turning to medics for prevention.

Table 2

Number of women who visited a gynecologist with a preventive purpose in 2017 and 2018 in different regions of Ukraine (% of the total number of respondents)

Region, city	Year	
	2017	2018
Vinnitsa region	52.4	44.3
Volyn region	15.0	18.7
Dnipropetrovsk region	68.7	55.0
Donetsk region *	38.6	43.7
Zhytomyr region	57.0	63.1
Zakarpattya region	47.6	41.4
Zaporizhzhya region	31.0	42.5
Ivano-Frankivsk region	56.0	54.6
Kyiv region	55.8	50.3
Kirovograd region	20.0	25.0
Luhansk region *	39.1	53.4
Lviv region	45.6	47.7
Mykolaiv region	67.4	60.9
Odessa region	43.2	33.8
Poltava region	54.4	62.9
Rivne region	50.8	48.3
Sumy region	48.9	44.9
Ternopil region	45.9	46.8
Kharkiv region	43.5	47.6
Kherson region	56.4	59.3
Khmelnytsky region	41.8	32.1
Cherkasy region	68.1	56.8
Chernivtsi region	69.8	56.3
Chernihiv region	63.4	60.2
City of Kyiv	32.0	29.7
All Ukraine	47.5	46.7

Note: * except the occupied part.

The number of referrals to GP is increasing: in 2016 this figure was 25.5 %, in 2017 – 30.1 %, in 2018 – 34.8 %. This was facilitated by the fact that in the last two years, declarations have been signed between the population and GP [24]. Interviewed Ukrainians consider the main barriers to receiving medical care to be large queues, lack of confidence in the qualifications of doctors, poor treatment of patients, high cost of treatment, lack of transportation, lack of understanding of which doctor to consult, others. The cost of treatment is seen as a barrier to an increasing proportion of patients (24.6 % in 2016, 22.9 % in 2017 and 17.0 % in 2018). In 2018, residents of Zakarpattya region (39.6 %) and Kyiv region (31.1 %) were most concerned with treatment, while residents of Ternopil region (0 %) and Volyn region (2.1 %) were the least concerned. Among the residents of Kharkiv region, 21.5 % of respondents indicated this factor in the survey. Large queues should be positively impacted by electronic enrollment systems, at high cost by the state system of medical guarantees and the introduction of insurance medicine.

Outpatient care for all issues was addressed by 36 % of Ukrainians in 2016, 37 % in 2017, and only 33 % in 2018 [25]. The establishment of a primary care system, in which a GP now plays a leading role, will allow the patients receiving medical referrals to narrow specialists to obtain reimbursement of the costs of secondary and tertiary care professionals at the expense of state medical guarantees. Only two out of five interviewed patients who received help from a narrow specialist had a referral (41.7 %), but this is 1.5–2 times more than in previous years.

The number of referrals to GPs in 2018 was in fact equal to the number of referrals to specialists of all profiles (35 % and 34 %, respectively). Other referrals were to district internists (29 %) and general practitioners (2 %). Among the residents of Kharkiv and Kirovohrad regions, the numbers of referrals to GPs were 13.6 % and 11.0 %, respectively), among the residents of Volyn region - the highest (68.5 %). The largest number of appeals to specialists was among the residents of Ivano-Frankivsk region (51.4 %). Among those who referred to a GP or a district internist/pediatrician, they had 20.9 % of patients in 2016, 28.5 % in 2017 and 41.7 % in 2018. In 2018, this was the highest in Dnipropetrovsk region (60.2 %), the lowest in Vinnytsia region (11.5 %). Among the reasons for seeking outpatient care to highlight our topic are the most important infectious diseases, which is one of the main causes of miscarriage and RL. Such cases, together with complaints about pregnancy in 2018 in different regions of Ukraine are shown in *table 3*. Among other investigated reasons of complaints were diseases of the circulatory system (25.2 %),

Table 3

Specific reasons for the last outpatient visit to physicians in 2018 in Ukraine related to fertility and reproductive losses (regional distribution, %)

Region, city	Reason for appeal	
	Pregnancy	Infectious diseases
Vinnitsa region	0.0	1.5
Volyn region	8.3	1.8
Dnipropetrovsk region	0.5	0.4
Donetsk region *	1.2	1.3
Zhytomyr region	5.6	3.4
Zakarpattya region	0.0	1.1
Zaporizhzhya region	0.9	1.0
Ivano-Frankivsk region	0.7	1.6
Kyiv region	1.2	0.0
Kirovograd region	1.1	0.4
Luhansk region *	0.0	1.2
Lviv region	0.0	0.0
Mykolaiv region	0.0	0.0
Odessa region	0.9	2.0
Poltava region	4.1	0.4
Rivne region	3.2	0.5
Sumy region	0.7	0.0
Ternopil region	0.0	0.0
Kharkiv region	0.0	2.0
Kherson region	0.7	0.0
Khmelnytsky region	0.0	3.1
Cherkasy region	2.1	0.6
Chernivtsi region	1.0	1.7
Chernihiv region	0.0	0.0
City of Kyiv	0.0	0.0
All Ukraine	1.2	0.9

Note: * except the occupied part.

respiratory organs (30.7 %), locomotive system and connective tissues (5.9 %), trauma, poisoning and other external influences (6.4 %), diseases of the genitourinary system (4.7 %), neoplasms (1.5 %), diseases of the endocrine system (3.7 %), nervous system (1.7 %), eye and its accessory organs (1.2 %), skin and subcutaneous tissue (1.2 %), ears (0.9 %), mental and behavioral disorders (0,2 %), diseases of blood and hematopoietic organs (0,2 %), digestive organs (4,5 %).

Interaction of GPs with obstetric and genetic health services should give Ukrainians the opportunity to receive timely information about the risks of pathological pregnancy, miscarriage, fetal malformations, the development of rare (orphan) diseases (that are progressive chronic diseases, with frequency in a population 1:2000 or less, with risk of death or disability [25]). The

presence of such diseases is closely linked to the overall RL rate. Therefore, the state must allocate the necessary resources for their timely diagnosis. The rare diseases should be offset by well-planned genetic screening studies [26] that cover all at-risk groups (including infertility, miscarriage and birth defects in obstetric anamnesis), and not high-cost [27].

According to the same principles, treatment and prevention measures should be planned. Such a goal is easily achievable, given the absence of specific pathogenetic pharmaceuticals for the treatment of genetic diseases. Conversely, it is known [28] that the use of natural therapeutic factors, vitamins and rehabilitation measures contribute to the improvement of cytogenetic status, burdened with anthropogenic influences. Therefore, the scheme of preconception medical care for pregnancy should include individual cofactor therapy, taking into account the results of biochemical and molecular examination of women [29], taking probiotics, which according to the studies of Kirihara et al. [30] significantly reduces the risk of prematurity.

In addition to low-cost examinations (for example, ultrasound, biochemical tests for the exchange of amino acids of the folate cycle), the practice of genetic genetics also uses complex and costly methods of chromosomal and gene analysis. The cost factor has repeatedly prompted researchers from different countries to conduct an economic analysis to determine the feasibility of mass surveys. Thus, Van Leeuwen et al. [31] determined the cost of preventing the birth of one child in the range of 226,000 to 6,556,000 thousand euros, with the difference depending on the pathology detected, the number of previous miscarriages and other obstetric history, examinations (for example, whether a chromosomal history was combined with an amniotic history). The economic feasibility of prophylaxis during recurrent pregnancies ranged from 2,000 to 223,000 euros for each case of preventing the birth of a disabled child.

The use of an extended model of care assistance in cases of suspicion instead of the standard one was also economically justified in the case of early pregnancy loss [32]. The experience of many countries (e.g., India [33] and Zambia [34]) points to the economic losses in the health care system as a result of the abortion ban, which also increases the risk of dangerous abortion and maternal mortality. Thus, the Ministry of Health of Zambia could save $ 400,000 a year in treating the effects of dangerous abortions. Upgrading aid schemes to women in need of termination of pregnancy on medical grounds reduces the direct economic losses of national health care systems and families in which children with genetic pathologies are born.

For the planning of reproductive loss prevention measures, it is advisable to use models of predicting the detection of genetically induced diseases [35], which are based on statistical observations of population morbidity, and take into account the potential of national and regional health systems, as well as the dynamics of changes during reform. At the present stage, the Ministry of Health of Ukraine is developing processes of power distribution between several new structures, which are responsible for certain areas of medical, preventive work and medical education. At the time of making proposals for improving genetic monitoring programs, as well as establishing a Ukrainian National Center for Disease Prevention and Control at the Ministry of Health of Ukraine, which should operate under the scheme of the US Center of the same name (CDC in Atlanta), and carry out those studies for which budget funds will be available, on the list in order of weight for the community and the medical community. But unlike the US Center, we suggest that genetic diseases will receive high priority.

Conclusions

1. When planning preventive measures to reduce reproductive losses, statistics from previous years, the possibilities of regional and national health care systems, models and ways of reforming them, public perceptions of these initiatives, barriers to receiving medical assistance should be considered.

2. For the full compilation in the regions of medical statistics data used in reproductive loss reduction planning, centralized analysis and public discussion in professional circles requires a national disease control and prevention center in Ukraine, where genetic monitoring programs should be prioritized along with infectious, oncological and cardiovascular diseases, despite the higher prevalence of the latter.

3. Ukraine needs a program to promote pregnancy planning at the optimum age of 20 to 35 years. All key medical specialties – GPs, gynecologists, internists and geneticists – should be involved in its implementation. Preconceptual health care for pregnancy should include individual cofactor therapy, taking into account the results of instrumental, biochemical and molecular genetic examination of a woman.

Conflict of interest

The authors declare no conflicts of interest.

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