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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

COMPARATIVE PHARMACOLOGICAL STUDY OF THE EFFECT OF CERTAIN CYTOSTATICS FROM THE DIAMIDOPHOSPHATE AND ANTHRACYCLINE GROUPS ON FETAL PRENATAL DEVELOPMENT

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OVERALL DESCRIPTION OF THE STUDY

Relevance and degree of study of the topic. Statistics show that the incidence of oncological diseases, one of the greatest scourges of our time, continues to increase with each passing day[1]. Every year, thousands of people worldwide are diagnosed with oncological diseases of various origins and localizations. It is estimated that the number of these diseases will double by 2030, reaching 20 million people, and the number of deaths from the disease will increase from 6 million to 12 million[2]. Although factors such as improper nutrition, obesity, inactivity, harmful habits (e.g. tobacco, alcohol, drug use), external factors (e.g. radiation, industrial waste), heredity, viruses, depression, weakened immunity, etc. are given priority in the etiopathogenesis, since the etiology of oncological diseases is unknown to science to this day, there is no etiotropic treatment for them[3].

As in all times, in our modern era, the indispensable role of surgical intervention, chemotherapy, and radiotherapy in the treatment of these diseases is an undeniable factor[4]. Although more than 70 years have passed since the beginning of the era of chemotherapy in oncology practice, it has not been possible to achieve the desired results with these treatment methods.

During this relatively short period of time, a large number of drugs with antitumor activity have been developed to provide the desired therapeutic effect for the treatment of oncological diseases of various origins and localizations.

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[1] Makimbetov, E.K. Cancer epidemiology in the world / E.K. Makimbetov, R.I. Salikhar, A.M. Tumanbaev [et al.] // Modern problems of science and education. 2020. No. 2. URL:https://science-education.ru/ru/article/view?id = 29718 (дата обращения: 03.03.2025).

[2] Amiraslanov, A. Oncological Gynecology, Monograph / Amiraslanov, A., Gaziyev A., Ibrahimov, A. East-West OJSC Publishing and Printing, Baku 2024, 1104 pp. p. 81-133.

[3] McGettigan, M. Cancer in pregnancy: treatment effects. / M. McGettigan, K. Thomas, A. Kamath //Abdom Radiol (NY). 2023; 48 (5): 1774–1783.

[4] Esposito, S. Chemotherapy against cancer during pregnancy. A systematic review on neonatal outcomes. /S. Esposito, R. Tenconi, V. Preti [et al.] //Medicine (Baltimore). 2016; 95 (38): 1–6.

Currently, these drugs are successfully used in mono- and combination forms in oncology practice. It is desirable that the use of chemotherapy has enabled long-term remission without complications in oncological patients and a significant extension of their life expectancy. On the other hand, almost all of these drugs are non-selective compounds with highly toxic properties, both in relation to the pathological process and the macroorganism. The target of these drugs is not only atypical cells and tissues that form in the body, but also the macroorganism itself (in particular, its rapidly growing cells and tissues, including fetal tissues in the prenatal development stage)[5].

A review of literature sources, reflecting both experimental and existing clinical studies, demonstrates that most chemotherapeutic drug preparations, when administered to pregnant women, cause various pregnancy and fetal pathologies, leading to severe, and in many cases irreversible, complications in the offspring[6]. Considering that the incidence of tumor diseases has significantly decreased in the last decade, especially during the reproductive age, it is necessary to conduct serious research in this direction.

The most important drugs used in the chemical treatment of these diseases include diamide phosphate and anthracyclines, antitumor agents. Currently, one of the main representatives of the first group is cyclophosphamide, and one of the main representatives of the second group is doxorubicin. Although both drugs are the most necessary chemotherapeutic agents in oncology practice, the molecular mechanism of their potential complications and side effects, especially with repeated administration, has not been fully elucidated and has not been comprehensively studied. The decisive condition for assessing the existing gaps in the mentioned direction is the deeper study of the clinical use of these drugs, in particular, their additional and toxic effects, such as teratogenic, mutagenic,

[5] Liu, P. Optimization of drug scheduling for cancer chemotherapy with considering reducing cumulative drug toxicity. / P. Liu, Q. Xiao, S. Zhai [et al.] // Heliyon, volume 9 (6) — 2023, Jun 15. Источник: ncbi.nlm.nih.gov

[6] Pauker, V. Oncological diseases and pregnancy. Oncogynecology 2017. No. 4. Pp. 59-67

carcinogenic, and embryotoxic, which is of fundamental interest and relevance in terms of developing experimental pharmacological correction methods. Considering that the incidence of tumor diseases has significantly decreased in recent decades, it is of great importance to study the effects of repeated administration of both drugs in this direction, especially on reproductive function. Taking into account the above, a study was conducted on the negative effects of mono- and combined use of both drugs on the concentration of reproductive hormones, the onset and course of pregnancy, and the prenatal development of the fetus, as well as on organs.

Aims and objectives of the study: The main goal of the planned study is to comparatively study the effects of cyclophosphamide and doxorubicin on the concentration of reproductive hormones, fertilization, pregnancy onset and development, as well as on the intrauterine and postnatal development stages of the fetus in pregnant rats, as well as the morphohistological changes they cause in internal organs, against the background of dose-dependent treatment of white rats of both sexes.

To achieve our goal, we completed the following tasks:

1. A comparative study of changes in the level of reproductive hormones in the blood of male and female rats after repeated administration of cyclophosphamide and doxorubicin separately and together, depending on the dose.

2. Comparative study of changes in the physical development of offspring born after repeated injection of cyclophosphamide and doxorubicin, separately and together, in a dose-dependent manner into female, male, and both sexes of rats.

3. A comparative study of the effects of cyclophosphamide and doxorubicin, separately and together, on the formation, development, and pre- and early postnatal development of offspring following repeated injections of cyclophosphamide and doxorubicin into female, male, and both sexes of rats, in a dose-dependent manner.

4. A comparative study of the effect of repeated injections of cyclophosphamide and doxorubicin, separately and together, depending on the dose, in pregnant white rats on the course of

pregnancy and on the pre- and early postnatal development of the offspring.

5. A comparative study of morphohistological changes in the internal organs of white rats after repeated administration of cyclophosphamide and doxorubicin separately and together depending on the dose.

Research methods:

Experimental studies were conducted on 350 sexually mature inbred white rats of both sexes, weighing 180-220 g, kept under normal conditions in a vivarium. 21 of these rats were euthanized.

The animals were grouped according to gender. Each group contained 10-20 white rats. When mating was performed, female and male rats were placed in a cage in a ratio of 1:2. Fertilization is considered to have occurred when sperm are detected in a smear taken from the cervix. The studies examined the effects of intraperitoneal injection of cyclophosphamide 10, 20 mg/kg (Russian Federation) and doxorubicin 2.5, 5 mg/kg (Germany) for one week on the concentration of reproductive hormones in white rats of both sexes, the onset, course of pregnancy, prenatal and postnatal outcomes, as well as the effect of administration to pregnant rats on the course of pregnancy, as well as the effect of the studied cytostatics on the morphohistological indicators of organs.

The studied substances were administered parenterally to experimental animals at the same time of day (in the first half of the day - until 12 noon to minimize the effect of circadian biorhythms), doxorubicin twice a week, and cyclophosphamide for 5 days. Animals in the control group were kept under the same conditions and feeding regimen and received the corresponding dose of 0.9% isotonic sodium chloride solution.

The main provisions put forward for the purposes of defense: The concentration of reproductive hormones in the blood of white rats of both sexes administered cyclophosphamide and doxorubicin separately and together for 1 week is statistically significantly reduced. The effect of cyclophosphamide and doxorubicin on these parameters is significantly inferior to the effect of the combination of cyclophosphamide and doxorubicin used simultaneously.

2. When cyclophosphamide and doxorubicin were administered separately and together to female, male, and both sexes of rats for 1 week, serious quantitative and qualitative changes were observed in the health and mortality indicators, gender, quantitative composition, and physical development of the offspring born from them. These changes, which were statistically significant in a dose-dependent manner when comparing different drugs, were more pronounced in the offspring of rats receiving cyclophosphamide and doxorubicin in combination.

3. The significant changes in the quantitative and anatomical parameters of the offspring of female, male, and mixed-sex rats administered cyclophosphamide and doxorubicin separately and together for 1 week were less intense than those of the offspring of the group of rats receiving cyclophosphamide and doxorubicin in combination.

4. The significant changes observed in the course of pregnancy, quantitative and anatomical parameters of the offspring, and the results of the administration of cyclophosphamide and doxorubicin to pregnant white rats, both separately and together, were less intense compared to the offspring of the group of rats receiving cyclophosphamide and doxorubicin in combination.

5. Severe morphohistological changes occurred in the internal organs of rats after administration of cyclophosphamide and doxorubicin, both separately and in combination, for 1 week.

Scientific novelty of the study:

For the first time, the effects of cyclophosphamide and doxorubicin, both separately and in combination, on the blood levels of sex hormones in rats of both sexes, as well as on the number of offspring born and their physical development, have been comprehensively and comparatively studied. At the same time, the changes caused by the studied substances in the host organs were subjected to comparative histological examination. The results of the studies have shown that cyclophosphamide reduces hormone levels more than doxorubicin, depending on the dose. The combined use of cyclophosphamide and doxorubicin can cause a more pronounced decrease in the amount of sex hormones and even lead to

sterilization. Compared with doxorubicin, cyclophosphamide has a more negative impact on the number of offspring born, physical development, etc., depending on the dose. In comparison, the combined use of cyclophosphamide and doxorubicin has been shown to significantly reduce these parameters. At the same time, the effects of cytostatics administered individually and in combination to pregnant rats, depending on the dose, on the course of pregnancy, the number of offspring born, and their physical development were studied. For the first time, the morphohistological changes induced in the internal organs of white rats during chronic use of the studied drugs individually and in combination in a dose-dependent manner were studied.

Theoretical and practical significance of the study:

The increase in the number of oncological diseases in the 21st century, as well as the fact that people suffering from oncological diseases are more likely to be of reproductive age, in some cases these diseases coincide with pregnancy, and as a result, they are forced to undergo chemotherapy. The use of cytostatic drugs by any couple of reproductive age can lead to certain, very serious problems in monitoring the course of pregnancy, especially during unplanned pregnancies. From this point of view, the experimental proof that cyclophosphamide and doxorubicin, administered separately and together for 1 week, cause serious changes in the concentration of reproductive hormones in white rats, the onset and course of pregnancy, the development of defects in the fetus, and at the same time, the internal organs of the mother rats, as well as the confirmation of the negative effect of the cytostatic group on reproductive function, is of particular importance for practical medicine.

Based on the results of the studies, it is very important to identify the causes of the dose-dependent negative effects of chronic use of cyclophosphamide and doxorubicin separately and in combination on the reproductive system, and to develop an experimental model to eliminate the resulting harmful effects and as a primary source for the development of clinical protocols.

From a clinical point of view, the studies conducted allow pregnant women suffering from oncological diseases or couples

receiving cytostatic treatment, one or both of whom have initial information about pregnancy and fetal pathologies that may occur during planned pregnancies, and to take preventive measures to prevent them. The results obtained may also serve as an aid in planning oncological-gynecological surveillance for pregnant women who are receiving antitumor drugs from the cytostatic group out of necessity. At the same time, the results of the research conducted can be incorporated into the teaching process of pharmacology and used as a primary reference source when preparing textbooks, teaching aids, methodological work, and scientific articles.

Approval and implementation: Separate fragments of the dissertation work are presented in the materials of the international scientific conference dedicated to the 85th anniversary of the birth of Honored Scientist, Professor Asgarov Rafig Ashraf Baku 2018, in the materials of the scientific-practical conference dedicated to the 100th anniversary of the birth of Honored Scientist, Doctor of Medical Sciences, Professor Gahramanov Gahraman Mehdigulu Baku 2025, 9th International Izmir Congress on Medicine, Nursing, Midwifery, and Health Sciences Proceedings Book Volume – II. 2025, 5th international Asklepios congress on medicine, nursing, midwifery, and health sciences congress proceedings book volume – 2. Kosovo 2025, Congress proceedings book volume – ii June 27-29, 2025, Sakarya University faculty of health sciences, 7th International Latin American Scientific Research Congress. June 4-5, 2025, Universidad Peruana de Ciencias Aplicadas, Peru, 1. International Warsaw scientific research and innovation congress. June 19-22, 2025. Warsaw-Poland oprabated.

Name of the organization where the dissertation work was carried out: The topic of the dissertation work is part of the scientific work plan of the Department of Pharmacology of AMU (State registration number №01114090, UOT:61.577.1). Scientific research on the relevant sections was carried out at the Department of Pharmacology of AMU and the Scientific Research Center.

Scope and structure of the dissertation work.

The dissertation is printed on 183 pages (total, 223970 characters) on computer paper and consists of an introduction (13613

characters), a literature review (47170 characters), materials and methods of research (7624 characters), 2 chapters of personal research (Chapter III-50846 characters, Chapter IV-54154 characters), conclusion (45710 characters), conclusions (2722 characters), practical recommendations (1630 characters), and a list of literature (43585 characters).

The dissertation is illustrated with 19 tables and 9 figures. The list of references includes 262 sources, of which 38 are works by Azerbaijani, 120 Russian, and 110 are works by scientists from other countries.

RESEARCH RESULTS AND THEIR DISCUSSION

Study of changes in the concentration of sex hormones in the blood of white rats of both sexes following repeated dose-dependent administration of cyclophosphamide and doxorubicin separately and in combination

We injected cyclophosphamide 10 and 20 mg/kg intraperitoneally into male white rats for 1 week, and after 1 week, we collected blood from the tail vein of the animals and compared the concentrations of sex hormones Tü, Ts, FSH, LH, PL, PG, ER, and ED with the indicators of the control group. It turned out that during repeated administration of 10 mg/kg cyclophosphamide, the amount of T1 hormone in the blood of male animals decreased by 55%, the amount of T2 by 50.1%, the concentration of FSH by 60.3%, and the amount of LH by 62.2% compared to the control group ($P<0.001$). The amount of PL also decreased by 29.5%, the amount of PG by 78.7%, the amount of ER by 30.6%, and the amount of ED by 73.7%, compared to the control group. Against the background of repeated use of cyclophosphamide at a dose of 20 mg/kg, the amount of the hormone Tu is statistically significantly reduced by 73.2%, the amount of Ts by 65.3%, the amount of FSH by 60.4%, the concentration of LH by 77.1%, the amount of PL by 52.6%, the amount of PG by 88.3%, the amount of ER by 50.5%, and the amount of ED by 97.8% compared to the control group.

When we continued our studies against the background of the dose-dependent use of doxorubicin, it was found that doxorubicin at a dose of 2.5 mg/kg statistically significantly reduced the amount of Tü hormone by 62.06%, the amount of Ts by 50.9%, the concentration of FSH by 34%, the amount of LH by 40.5%, the amount of PL by 28.7%, the amount of PG by 21.7%, the amount of ER by 23.6%, and the amount of ED by 97.2%. With repeated use of doxorubicin at a dose of 5 mg/kg, the amount of Tü hormone by 70.7%, the amount of Ts by 64.7%, the amount of FSH by 56.7%, the concentration of LH by 74.4%, the amount of PL by 55.4%, the amount of PG by 88%, the amount of ER by 57.6%, and the amount of ED by 97.8%.

With repeated intraperitoneal administration to male white rats of cyclophosphamide at a dose of 10 mg/kg in combination with doxorubicin at a dose of 2.5 mg/kg and cyclophosphamide at a dose of 20 mg/kg in combination with doxorubicin at a dose of 5 mg/kg, the amount of hormone T1 decreased by 75.9%, T2 by 62%, FSH by 51%, LH by 67.6%, PL by 65.6%, PG by 80.1%, ER by 61.2% and ED by 2.2 times compared to the control group.

Against the background of the combined use of cyclophosphamide at a dose of 20 mg/kg and doxorubicin at a dose of 5 mg/kg, it was found that the amount of the hormone Tu decreased by 83.5%, the amount of Tc - by 77.4%, the amount of FSH - by 77.4%, the concentration of LH - by 85.4%, the amount of PL - by 58.9%, the amount of PG - by 89.2%, the amount of ER - by 62.4%, and the amount of ED - by 2.7 statistically significant decrease.

Thus, analyzing the results of our studies, we conclude that the sharp decrease in the concentration of sex hormones against the background of repeated use of cyclophosphamide and doxorubicin separately and in combination in male white rats is associated with the cytotoxic effect of these cytostatics on hormone-secreting glands and organs[7].

[7] Gharwan, H. The role of reproductive hormones in epithelial ovarian carcinogenesis. / H. Gharwan, K. P. Bunch, C. M. Annunziata // EndocrineRelated Cancer. – 2015. – Vol. 22 (6). – P.339-363. – ISSN 1351-0088

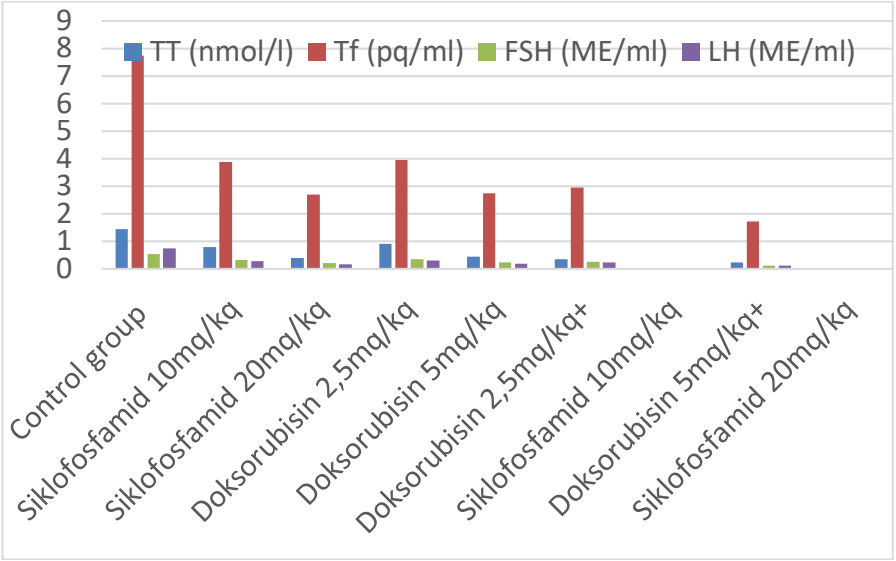

Figure 1. Effect of repeated administration of cyclophosphamide and doxorubicin separately and in combination on the concentration of reproductive hormones in the blood of male white rats in a dose-dependent manner

Against the background of the administration of a dose of 10 mg/kg of cyclophosphamide to female rats, we witnessed a statistically significant decrease in the amount of Tü by 52.2%, the amount of Ts by 53.1%, the amount of FSH by 48.7%, the amount of LH by 67.9%, the amount of PL by 57.8%, the amount of PG by 33.9%, the amount of ER by 74.2%, and the concentration of ED by 79.3%, compared to the indicators of the control group.

Against the background of repeated use of a dose of 20 mg/kg of cyclophosphamide, it was found that the amount of the hormone Tu was reduced by 69.6%, the amount of Ts by 70.4%, the amount of FSH by 61.25%, the amount of LH by 81.5%, the amount of PL by 50%, the amount of PG by 79.4%, the amount of ER by 82.8%, and the concentration of ED by 86%.

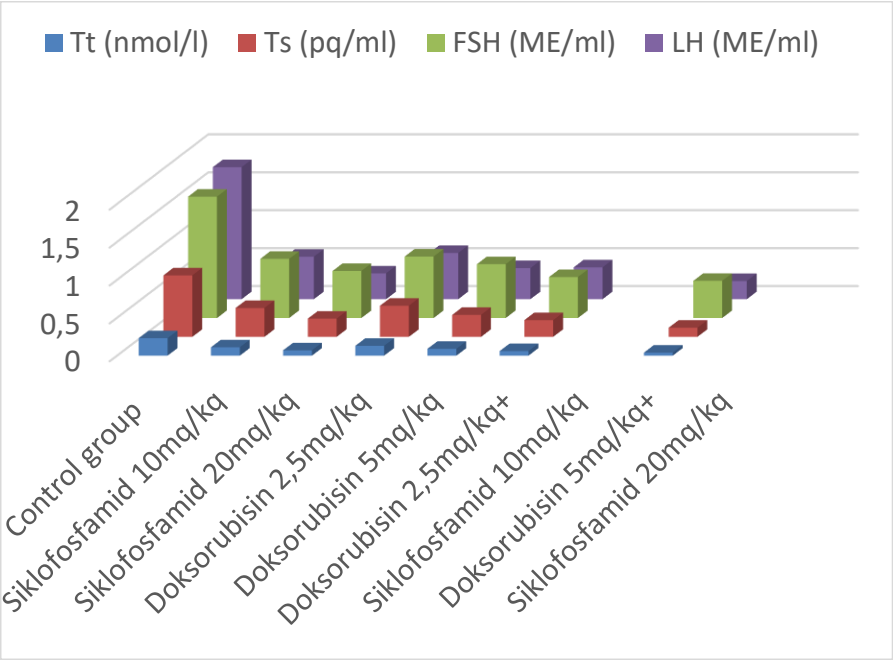

Figure 2. Effect of repeated administration of cyclophosphamide and doxorubicin separately and in combination on the concentration of reproductive hormones in the blood of female white rats in a dose-dependent manner

When determining the concentration of reproductive hormones in the blood of female white rats against the background of repeated administration of a dose of 2.5 mg/kg of doxorubicin, it was found that it statistically significantly reduces the amount of Tu by 43.5%, the amount of Ts by 50.6%, the amount of FSH by 50.6%, the amount of LH by 65%, the amount of PL by 40.6%, the amount of PG by 61.7%, the amount of ER by 72.6%, and the concentration of ED by 79.1%.

The dose of doxorubicin 5 mg/kg causes more serious hormonal disorders. Thus, against the background of the determination of a dose of 5 mg/kg of doxorubicin, compared to the indicators of the control group, the amount of the hormone Tu decreased by 60.9%, the amount of Ts by 64.2%, the amount of FSH

by 55.7%, the amount of LH by 76.5%, the amount of PL by 46.7%, the amount of PG by 85.6%, the amount of ER by 77.5%, and the concentration of ED by 79.2% were statistically significantly reduced.

In the next stage of our research, we administered a dose of 10 mg/kg cyclophosphamide to female white rats in combination with a dose of 2.5 mg/kg doxorubicin. It was found that the combined use of cyclophosphamide and doxorubicin statistically significantly reduced the amount of testosterone by 73.02%, the amount of testosterone by 72.9%, the amount of FSH by 66.3%, the amount of LH by 75.9%, the amount of phospholipids by 54.4%, the amount of prostaglandins by 73.3%, the amount of estrogens by 80.2% and the concentration of estrogens by 83.9% compared to the control group.

Against the background of repeated use of cyclophosphamide at a dose of 20 mg/kg and doxorubicin at a dose of 5 mg/kg, the amount of T hormone decreased by 82.7%, the amount of Ts hormone by 85.2%, the amount of FSH by 69.4%, the amount of LH by 86.06%, the amount of PL by 57.9%, the amount of PG by 82.6%, the amount of ER by 88.2%, and the concentration of ED by 89.3%.

Thus, analyzing the results of our research, we come to the conclusion that both cyclophosphamide and doxorubicin are cytostatics with a toxic effect; they cause growth retardation and death of both normal and atypical cells, and also lead to atrophy and damage to hormone-synthesizing glands, which, in turn, leads to a decrease in the amount of synthesized reproductive hormones.

Study of changes in the development of the newborn offspring during the antenatal and postnatal periods following repeated administration of cyclophosphamide and doxorubicin separately and in combination in a dose-dependent manner to white rats

Although the parameters studied in the control group of animals were within the normal range, the following phenomenon was observed when female rats that received cyclophosphamide at a dose of 10 mg/kg for 5 days mated with males. Thus, in females receiving cyclophosphamide at a dose of 10 mg/kg, the duration of pregnancy was shortened by 30.5% compared to the control group. The animals' prenatal weight decreased by 43.3% and postnatal

weight by 40.2% compared to the control group. The difference between prenatal and postnatal weights was 52.7%. The number of puppies born decreased by 67.4% compared to the control group. A 56.1% decrease in puppies' birth weight was also observed.

After administering a dose of 20 mg/kg of cyclophosphamide to female rats for 5 days, when they were placed in the same cage with males in a 1:2 ratio, neither fertilization occurred, nor pregnancy, nor birth of offspring was observed because they were unable to impregnate the females.

Female rats that received doxorubicin at a dose of 2.5 mg/kg twice a week became pregnant, and the duration of pregnancy was shortened by 27.6% compared to control group females. The animals' prenatal weight was 38.3% lower than the control group, and their postpartum weight was 37.1%. The difference between prenatal and postpartum weight was 58.2%. The number of puppies decreased by 56.5%, and birth weight decreased by 53.1%. Against the background of the administration of doxorubicin at a dose of 5 mg/kg, the duration of pregnancy was reduced by 32.8%. The prenatal weight of pregnant rats decreased by 54.7%, the postpartum weight by 42%, and the difference between prenatal and postpartum weight by 44.9%. The number of pups also decreased by 79.3%, and the weight of pups by 57.6%, statistically significant, compared to the control group.

We placed female rats, which were given cyclophosphamide at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg for 1 week, in a cage with intact male rats at a ratio of 1:2 and monitored them. As a result of our long-term observation, although spermatozoa were detected in the uterus of some female rats, we did not observe pregnancy in general.

We observed a similar trend in animals receiving cyclophosphamide at a dose of 20 mg/kg in combination with doxorubicin at a dose of 5 mg/kg. We believe that the primary cause of unsuccessful conception is the combined toxic effects of the two cytostatics used.

Regarding the number and anatomical characteristics of the new generation born from females against the background of repeated administration of cyclophosphamide and doxorubicin separa-

tely, it was found that the number of offspring born against the background of administration of a dose of 10 mg/kg of cyclophosphamide was statistically significantly reduced by 83.4% compared to the indicators of the control group ($p<0.001$). 40% of the puppies were born alive, and 60% were stillborn. Of the 10 puppies born, 3 were male and 7 were female. The period of opening of the auricle in newborn puppies was increased by 3.7 times, and the formation of fur occurred in 5.3 days in puppies of the control group, while in puppies born with cytostatics this period was 8.1 days. No reverse geotaxis response was observed in offspring born to pregnant rats administered cyclophosphamide at a dose of 10 mg/kg, which is due to the general weakness in muscle strength in these animals. Abnormalities were observed in all offspring born to rats that became pregnant after administration of cyclophosphamide at a dose of 10 mg/kg.

After repeated administration of 20 mg/kg cyclophosphamide to female rats, we placed them in the same cage with male rats in a 1:2 ratio. As a result of our long-term observations, no pregnancy was observed in any rat that received this dose of the drug, although spermatozoa were detected in the vagina.

When female rats were given doxorubicin at a dose of 2.5 mg/kg for one week, the number of pups born was 12, which was 80% less than in the control group. Of the cubs born, 5 were found to be alive and 7 were found to be dead. Of these pups born, 3 (25%) were male and 9 (75%) were female. The duration of ear flap opening in newborn pups was 2.6 times longer, reaching 4.9 days. Hair growth was delayed by 2.3 times. No reverse geotropism reactions were observed in newborn puppies, and all puppies exhibited various anomalies.

In rats that became pregnant after administration of 5 mg/kg of doxorubicin for 1 week, 93.4% fewer pups were born, that is, 4 pups, compared to the control group. No live pups were observed among the born pups, all of the pups were stillborn. One of these pups was male and 3 were female.

Despite the dose-dependent administration of cyclophosphamide and doxorubicin to female rats for 1 week, and the fact that they were housed in a cage with male rats in a 1:2 ratio, we observed that pregnancy did not occur as a result of our long-term observations.

From the figures obtained in our study, we can conclude that cytostatics administered to female animals for a week cause serious

changes in the number and weight of the newly born offspring. These changes can be attributed to the fact that the cytostatics we studied affect the mother's body, causing serious disruptions in hormonal balance and the development of sex cells[8].

On the other hand, the difference in antenatal quantitative parameters of offspring born to females exposed to long-term exposure to cytostatics from control group offspring demonstrates that the relevant research drugs have a negative effect on female germ cells[9,10].

Visual observation of the offspring after birth, following the administration of cytostatics to female rats, showed that all offspring born in all groups receiving cytostatics had anomalies in their external appearance.

There were no stillborn puppies in the control group, however, cases of stillbirth were observed in all groups receiving both cytostatics separately.

Pregnancy has not been observed in general when cytostatics are administered together, regardless of dose.

It should be noted separately that in some pups born after long-term use of both cytostatics in female rats, the skull and facial skeleton were asymmetrical, and anomalies of the limbs, tail, eye sockets, nostrils and oral cavity were also recorded. This is due to the fact that chronic administration of research drugs causes hormonal changes and damage to germ cells in female rats, as well as toxic effects on the mother and teratogenic effects on the newborn offspring[ ].

Male white rats were dose-dependently treated with cyclophosphamide and doxorubicin for 1 week, placing them in the same cage with intact females, and after pregnancy, the males were separated from the females and the progress of pregnancy in the females was monitored. When males treated with cyclophosphamide

[8] Sher, S.A. Teratogenic effects of drugs on the body of the unborn child during intrauterine development // Pediatric pharmacology. Moscow, 2014, Vol. 7, No. 6 (8), Pp. 57-59.

[9] Schaefer, K. Drug therapy during pregnancy and lactation. / K. Schaefer, K. Shpilman, K.M. Fetter M.: Logosfera; 2016. 768 p

[10] Esposito, S. Chemotherapy against cancer during pregnancy. A systematic review on neonatal outcomes. /S. Esposito, R. Tenconi, V. Preti [et al.] //Medicine (Baltimore). 2016; 95 (38): 1–6.

for 1 week were mated with intact females, the number of offspring born to them was 90% lower than that of the control group. Of the puppies born, three were stillborn, and three survived. Two puppies were male and four were female. In the surviving puppies, ear opening was observed 2.9 times later, and fur development was 2.4 times later, compared to the control group. No reverse geotactic response was observed in live-born puppies. Anomalies were detected in both stillborn and surviving puppies.

Males given cyclophosphamide at a dose of 20 mg/kg show no interest in females and do not even attempt to mate. Therefore, no spermatozoa were detected in a preparation prepared from the vaginal contents of any of the intact females involved in the experiments. As a result, female rats housed in the same cage with male rats that were given cyclophosphamide at a dose of 20 mg/kg did not become pregnant and, consequently, did not give birth to offspring.

When male rats in a long-term experimental setting were given a dose of 2.5 mg/kg doxorubicin and then placed in a cage with unspayed females in a 2:1 ratio to await pregnancy, it was found that the males given the 2.5 mg/kg dose of doxorubicin gave birth to 8 pups. This indicator was 86.7% lower than the control group. Of the pups born to males administered 2.5 mg/kg of doxorubicin, 5 were alive, 3 were stillborn, and 4 were male and 4 were female. In these puppies, ear flap opening was delayed 3.4 times, and hair coat development was delayed 4 times. No reverse geotropism reaction was observed in newborn puppies, and the anomaly was noted in all puppies, both stillborn and live.

The number of pups born to males given a dose of 5 mg/kg of doxorubicin was statistically significantly reduced by 91.7% compared to the control group, to 5 pups. All pups were confirmed to be born with anomalies[11].

When we repeatedly administered cyclophosphamide and doxorubicin together in a dose-dependent manner to male white rats

[11] Andreev, D.A. The role of doxorubicin in the formation of cardiotoxicity - a generally accepted statement. Part I. Prevalence and mechanisms of formation (review). /D.A. Andreev, E.I.Balakin, A.S.Samoilov [et al.] // Development and registration of drugs. 2024; 13 (1): 190-199. https://doi.org/10.33380/2305-2066-2024-13-1-1508

and placed them in the same cage with female rats in a 2:1 ratio and kept them together for a certain period of time, we witnessed that the males did not approach the female rats. No sperm were detected in a smear prepared from the contents of the vagina of any of the females involved in the study[12].

Cyclophosphamide doses of 10 and 20 mg/kg, compared with doxorubicin doses of 2.5 and 5 mg/kg, have very serious adverse effects on the offspring following chronic administration to male rats and are dangerous in terms of fetal appearance and prenatal developmental profile. A more serious teratogenic effect is shown by cyclophosphamide doses of 10 and 20 mg/kg compared to different doses of doxorubicin.

With long-term administration of cyclophosphamide to male rats at doses of 10 and 20 mg/kg in combination with doxorubicin at doses of 2.5 and 5 mg/kg, no offspring were observed.

In the context of the administration of cyclophosphamide and doxorubicin separately and together to white rats of both sexes, it was found that the absence of spermatozoa in the smear prepared from the uterine contents of rats that received cyclophosphamide at a dose of 10 mg/kg was an indicator of the failure of pregnancy. Administration of cyclophosphamide to rats of both sexes at a dose of 20 mg/kg for 1 week almost certainly also caused sterilization in rats.

Based on visual observations we conducted during the administration of a 2.5 mg/kg dose of doxorubicin to rats of both sexes for 1 week, as well as the absence of spermatozoa under a microscope in a preparation prepared from the contents of the female vagina, pregnancy in the animals was assessed as not having occurred.

When rats of both sexes were given a dose of 5 mg/kg of doxorubicin, fertilization and pregnancy were not observed in females, as it reduced the amount of sex hormones in the animals'

[12] Lapin, K.N. The effect of cyclophosphamide on the reproductive system of male rats /K.N.Lapin, I.A.Ryzhkov, N.M.Zakharova // Experimental and clinical pharmacology. 2020. Vol. 83. No. 11. Pp. 16-19

blood and inhibited the formation of sex cells, weakening libido, that is, sexual desire[13].

When studying the reproductive ability of animals against the background of the combined administration of cytostatics to rats of both sexes, it was found that no pregnancies were observed after using cyclophosphamide at a dose of 10 mg/kg with doxorubicin at a dose of 2.5 mg/kg, or cyclophosphamide at a dose of 20 mg/kg with doxorubicin at a dose of 5 mg/kg, when the animals were housed in a cage in a ratio of 2:1.

Thus, the results of our studies call into question the possibility of obtaining a new generation of rats under conditions of chronic use of cytostatics by both sexes. More specifically, it can be concluded that the administration of cyclophosphamide and doxorubicin, separately or together, by both sexes has the potential to have toxic effects on both sexes of rats, their hormonal balance, and germ cells, and they can be considered dangerous drugs for both sexes of rats and the new generation derived from them.

At this stage of our study, when we continue to study the effects of repeated administration of cyclophosphamide and doxorubicin, separately and in combination, in a dose-dependent manner, on the course of pregnancy, its duration, birth process, postpartum condition, quantitative composition and weight of the offspring in pregnant rats, it becomes clear that cytostatics administered to pregnant rats separately and in combination for treatment from the 8th day of pregnancy in all study groups lead to the development of serious disorders compared to the indicators of the control group. In pregnant females receiving cyclophosphamide at a dose of 10 mg/kg, the duration of pregnancy was shortened by 27.1% compared to the control group, the prenatal weight of the animals was reduced by 39.3% compared to the control group, and the postpartum weight was reduced by 33.4%. The difference in

[13] Asanov, M.A. Comprehensive assessment of subchronic low-dose exposure to doxorubicin in a Wistar rat model. /M.A.Asanov, A.O.Poddubnyak, R.A.Mukhamadiyarov [et al.] // Siberian Journal of Clinical and Experimental Medicine. 2024; 39 (4): 171-179. https://doi.org/10.29001/2073-8552-2024-39-4-171-179

weight before and after birth was 56.8%. The number of pups decreased by 40.6% compared to the number of pups in the control group. The birth weight of the pups also decreased by 43.9%, which was statistically significant.

When pregnant rats were given cyclophosphamide at a dose of 20 mg/kg for one week, the changes occurring in the mother and offspring during pregnancy were more severe. Thus, against the background of the administration of cyclophosphamide at a dose of 20 mg/kg to pregnant rats, the duration of pregnancy was shortened by 36.8%. The prenatal weight of pregnant rats decreased by 46.6%, the postpartum weight by 43.8%, and the differences were 54.8%. The number of offspring also decreased by 77.3%. The birth weight of the offspring also decreased by 45.4%.

A dose of 2.5 mg/kg of doxorubicin shortened the duration of pregnancy in pregnant rats by 18.5% compared to control females. The prenatal weight of the animals was 28.2% lower than in the control group, and the postnatal weight was 29.9%. The difference between prenatal and postnatal weight was 25.4% lower than in the control group. As for the number of puppies, it was found that there was a 29.8% decrease in the number of puppies. The birth weight of the puppies also decreased by 27.3% compared to the control group. Against the background of administration of doxorubicin at a dose of 5 mg/kg, the duration of pregnancy is reduced by 32.8%, the prenatal weight of pregnant rats is reduced by 42.9%, and the postpartum weight is reduced by 38%. The difference between prenatal and postnatal weights decreased by 56.4%. The number of puppies also decreased by 48.5%, and the birth weight of puppies decreased by 42.5%, which is statistically significant compared to the control group.

In pregnant rats administered cyclophosphamide at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg for 1 week from the 8th day of pregnancy, the duration of pregnancy was shortened by 50.5%, the prenatal weight of the animals was reduced by 50.2%, and the post-partum weight was reduced by 47.7% compared to the control group. The difference between prenatal and postpartum weight was 57.6%. The number of pups also decreased by 90.1%, and their weight

decreased by 50.7%. When a dose of cyclophosphamide 20 mg/kg and a dose of doxorubicin 5 mg/kg were administered to pregnant rats, we witnessed a 56.7% reduction in gestational age, a 53.3% reduction in pre-natal weight, and a 50.9% reduction in post-natal weight, with a difference of 57.6%. Because the pregnancy ended abnormally, the birth of the puppies was not observed, so the number of puppies was unknown, and because the puppies were not born, their weight could not be determined.

Thus, our visual observations showed that, upon administration of both cytostatics studied separately and together, depending on the dose, to pregnant rats from the 8th day of pregnancy, the mucous membranes of these rats were not clean, the outer hair coat was not smooth and dense, and 2-3 days before giving birth, it was observed that they did not build nests from straw to place their offspring. On the other hand, it has been determined that there is a significant difference in the course and nature of the birth process in pregnant rats.

During visual observation of lactating females, a tendency was noted for them to not care for their newborn calves. Compared to the control group rats, the rats in the corresponding experimental group did not protect or cover their pups from the environment, and were indifferent towards the pups.

The results of our study shed light on the controversial claim that cytostatics have a negative impact on the reproductive system[14]. The hypothesis that even optimal antitumor doses of the studied cytostatics have a negative impact on the level of sex hormones and reproductive function has been confirmed. When these drugs are administered to pregnant female rats, serious defects occur in the normal development of their pregnancies. These defects cause serious disorders during pregnancy, abnormal births, and stillbirths. We believe that, on the one hand, these drugs have a toxic effect on the mother's body, which ultimately disrupts the normal development

[14] Kheibatova, M.F. Study of the onset of pregnancy and changes in subsequent outcomes against the background of the administration of cyclophosphamide and doxorubicin to female albino rats. YAKUT MEDICAL JOURNAL. 3(91)2025, DOI: 10.25789/YMJ.2025.91.08 UDC 618.2: 615.256.5

of the fetus in the womb, and on the other hand, they have a direct teratogenic effect on the fetus itself.

Repeated administration of cyclophosphamide and doxorubicin also causes serious abnormalities in the number and anatomical characteristics of offspring born from pregnant female rats.

The number of puppies born after administration of a cyclophosphamide dose of 10 mg/kg was statistically significantly reduced by 50% compared to the control group, the number of live-born puppies was 14, i.e. 46.6%, and the number of stillborn puppies was 16, i.e. 53.4%. Of the 30 pups born, 13 were male and 17 were female. Serious deterioration in quality indicators was observed in the newborn pups. Thus, the duration of ear flap opening in newborn puppies was 3.2 times longer, and the formation of hair cover was 6.9 days in puppies born in the drug group. No reverse geotaxis reaction was observed in newborn puppies, and anomalies were observed in 70% of puppies.

It was confirmed that the total number of puppies born during the administration of a dose of 20 mg/kg cyclophosphamide was statistically significantly 70% lower than in the control group. Of the 18 puppies born, 6 were alive and 12 were stillborn. Nine puppies were male and nine were female. Ear opening time was 3.8 times slower than in the control group, and hair growth time was 2.6 times longer. While no reverse geotaxic response was observed, anomalies were observed in all born pups.

Following administration of 2.5 mg/kg of doxorubicin to pregnant rats for 1 week, the total number of pups born was statistically significantly reduced by 43.4% to 34. Of these, 22 were born alive and 12 were stillborn. Of these born, 15 (44.1%) were males and 19 (55.9%) were females. In newborn puppies, the opening of the ear flap was delayed by 2.8 times, and the formation of the hair coat was delayed by 2.1 times. No reverse geotaxis reaction was observed in newborn pups in the experimental group. Various anomalies were observed in 35.2% of the newborn pups.

When pregnant rats were given 5 mg/kg of doxorubicin for 1 week, the number of pups born was 60% lower than the control group, i.e. 24 pups. Of the cubs born, 10 were reported alive and 14 were stillborn. Of these, 11 were male and 13 were female.

When cyclophosphamide was administered at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg to pregnant rats, 14 pups were born. This is 78.7% less than the control group. Of the pups born, 4 were alive and 10 were stillborn. Seven of the pups were male and seven were female. The opening of the ear flap took up to 6.4 days, and the formation of the hair coat took 2.7 times longer. No reverse geotaxis reaction was observed, and various anomalies were observed in all of the born pups.

When cyclophosphamide 20 mg/kg was used in combination with doxorubicin 5 mg/kg, the number of pups born was reduced by 88.4%. There were no live births among the puppies, all 7 were stillborn. Of the stillborn puppies, 3 were male and 4 were female. Various anomalies were observed in all of the stillborn puppies.

From this, we can conclude that cytostatics administered to pregnant animals for a week cause serious changes in the number and weight of the newborn offspring. These changes can be explained by the negative impact of the cytostatics we studied on the mother's body and the teratogenic effect on the fetus.

Due to the occurrence of stillbirths in the offspring of pregnant rats that received cytostatics, it was not possible to observe physical development parameters such as eye opening, tooth eruption, opening of the uterus in female offspring, and testicular development in male offspring.

Visual observations show that repeated administration of both study drugs, either separately or together, results in dose-dependent changes in the behavior of pregnant rats. Pregnant rats were noted to have pale mucous membranes and sparse and sparse outer hairs. Pregnant females in all study groups did not build straw nests to house their pups until 2-3 days before parturition. A significant difference was found in the course and nature of the birth process in pregnant rats in the corresponding experimental groups compared to similar parameters in the control group

females. During visual observation of lactating females during the lactation period, it was noted that they did not care for their newborn cubs. Compared to the control rats, no signs of protection or sheltering of the pups from the environment were found, and indifference towards them was observed.

Thus, visual observations in our research study showed that the cytostatic drugs under study have a serious impact on the course of pregnancy, the course and nature of childbirth[15]. Based on the postnatal examination, we can say that all representatives of the offspring in all study groups were found to have an external anomaly or physical defect. It was determined that pregnancy generally did not occur against the background of the combined use of cytostatics.

This is due to the repeated administration of research drugs to pregnant rats, which causes serious hormonal disruptions, toxic effects on their bodies, and teratogenic effects on the fetus, leading to a sharp decrease in the number of pups born, as well as the birth of offspring with certain anomalies and stillbirths.

There is sufficient scientific evidence to confirm that treatment with cytostatics not only causes disruption of the reproductive system, but also has a negative impact on various organs[16,17].

Although there is sufficient scientific information about the cardiotoxic effects of both cyclophosphamide and doxorubicin, there is very little information about the negative effects of these drugs on the ovaries, lungs, liver, and adrenal glands, and this information has not been scientifically confirmed[18]. To study the toxic effects of these drugs on other

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[15] Heybatova M.F. Study of changes in pregnancy course, prenatal and postnatal outcomes following administration of cyclophosphamide and doxorubicin to pregnant white rats. HEALTH № 2. 2025. Səh:170-177 DOI: 10.36719/2706-6614/2/170-178

[16] Adıyaman M. Effects of grapeseed extract on doxorubicin-induced cardiotoxicity in rats /M. Adıyaman, Ö. A. Adıyaman, A.F. Dağlı [et al.]// Herz. – 2021. – V. 46, № Suppl 1. – P. 103-108. 10.1007/s00059-019-04888-w.

[17] Subramaniam S.R. Low-dose cyclophosphamide-induced acute hepatotoxicity. /S.R. Subramaniam, R.A. Cader, R. Mohd [et al.] //Am J Case Rep 2013; 14: 345-349

[18] F.M.Heybatova STUDY OF THE EFFECT OF CYCLOPHOSPHAMİDE AND DOXORUBİCİN ON THE PROGRESS OF PREGNANCY AND HİSTOMORPHOLOGİCAL STRUCTURE OF THE OVARİES OF WHİTE RATS Journal of National Surgery. Crossref Scopus .25.08.2025 https://doi.org/10.63682/jns.v14i32S.8438

organs besides the heart, cyclophosphamide at doses of 10, 20 mg/kg and doxorubicin at doses of 2.5, 5 mg/kg were injected intraperitoneally into the animals for a week. After that, the animals were euthanized, the liver, lungs, ovaries, and adrenal glands were removed, fixed with the help of special fixatives, then sections were made, histological preparations were prepared using standard methods, and these preparations were stained with hemotoxylin and eosin.

Analyzing the results of our studies, we concluded that cyclophosphamide causes, albeit very slight, infiltrative changes in the ovaries, liver, lungs, and adrenal glands of rats administered 10 mg/kg for 1 week. Histological examination of the lungs and adrenal glands of these rats revealed the presence of a slight inflammatory process in these tissues. The results of the studies are shown in the pictures.

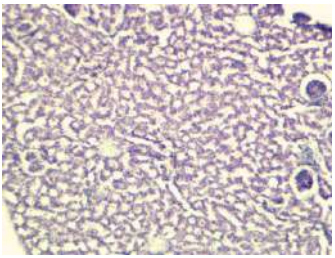


Figure 1. Control group cut made from the ovaries of animals. Stained with hematoxylin and eosin x 400

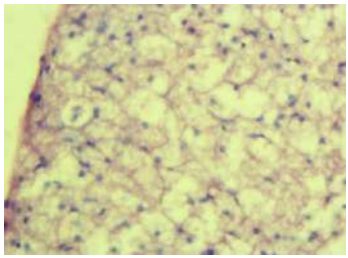


Figure 2. Control group a cut made from the adrenal gland. Stained with hematoxylin and eosin

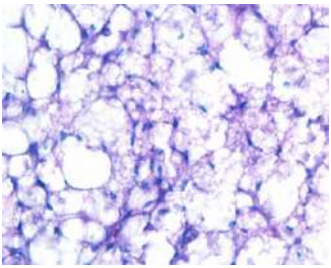


Figure 3. Sections prepared from lung tissue of control group animals. Stained with hematoxylin and eosin x 400

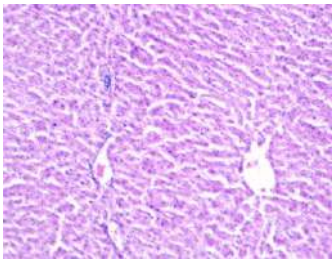


Figure 4. Sections prepared from liver tissue of control group animals. Stained with hematoxylin and eosin x 400

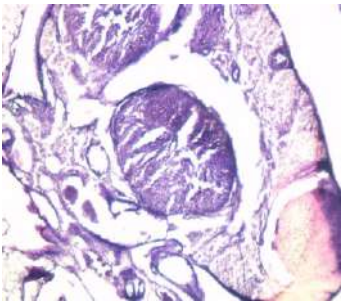


Figure 5. Ovarian excision against the background of cyclophosphamide administration at a dose of 10 mg/kg Edema is noted in ovarian cells Stained with hemotoxylin and eosin. x 400

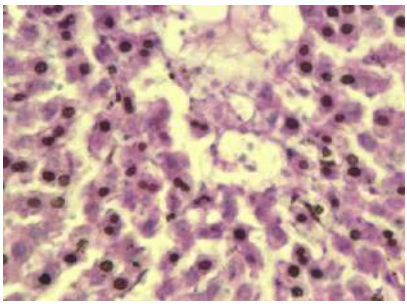
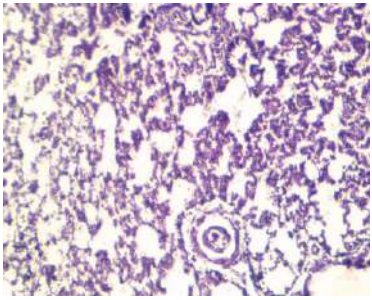


Figure 6. Liver tissue section after administration of cyclophosphamide at a dose of 10 mg/kg. The tissue shows punctate hemorrhage and edema. Stained with hemotoxylin and eosin. x 400



Şəkil 7. Lung tissue damage to the alveoli is more common after administration of cyclophosphamide at a dose of 10 mg/kg. bleeding and the formation of large lesions are observed Stained with hemotoxylin and eosin. x 400

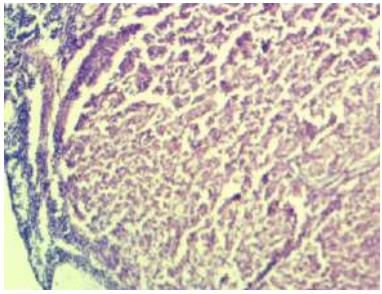


Figure 8. Dotted hemorrhages and edema are observed in the adrenal gland after administration of cyclophosphamide at a dose of 10 mg/kg. Stained with hemotoxylin and eosin x 400

Histological examination of the ovary, liver, lung, and adrenal gland against the background of the administration of a dose of 20 mg/kg of cyclophosphamide confirmed the presence of destructive changes in histological preparations prepared from the animals' organs.

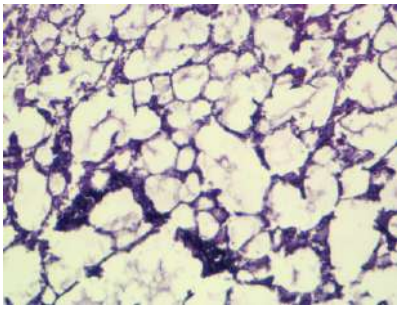


Figure 9. Against the background of the administration of doxorubicin at a dose of 2.5 mg/kg no signs of damage are observed in the majority of lung tissue-alveoli. Stained with hemotoxylin and eosin. x 400

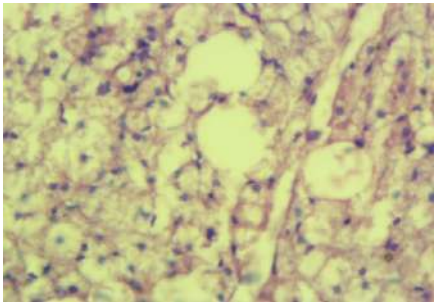


Figure 10. Mild signs of adrenal insufficiency were observed against the background of the administration of 2.5 mg/kg of doxorubicin. Stained with hemotoxylin and eosin. x 400

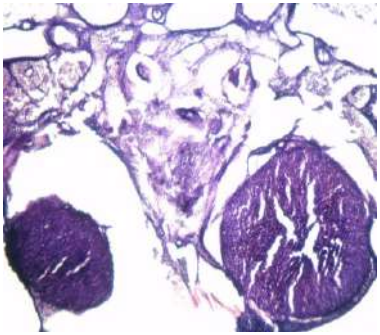


Figure 11. Mild signs of ovarian stasis are observed against the background of the administration doxorubicin at a dose of 2.5 mg/kg. Stained with hemotoxylin and eosin. x 400

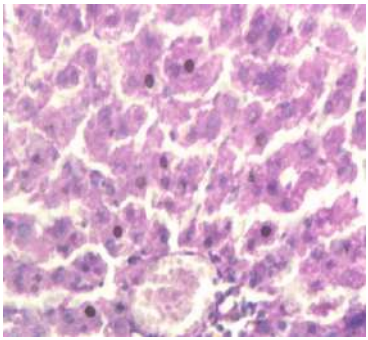


Figure 12. Liver tissue after administration of 2.5 mg/kg doxorubicin. Hepatocytes are mainly damaged around the central vein. Capillaries are dilated, and signs of mild hemorrhage are observed. The the structural changes are muchless than in cyclophosphamide. Stained with hemotoxylin and eosin. x 400

Thus, the use of cyclophosphamide at a dose of 20 mg/kg caused the appearance of small destructive foci in the tissue of the ovary, liver, lung, and adrenal gland. Doxorubicin at a dose of 5

mg/kg also caused relatively mild changes in the organs studied compared to cyclophosphamide at a dose of 20 mg/kg. More severe changes in the organs were observed with the combined use of cyclophosphamide and doxorubicin in a dose-dependent manner.

In general, when comparing preparations prepared from individual organs of female white rats with preparations from the control group, it was found that we witnessed the formation of vacuolization in individual organs of animals that received either cyclophosphamide or doxorubicin for 1 week, depending on the dose. At the same time, we witnessed atrophy, myocytolysis, necrosis, and mononuclear infiltration of hepatocytes, lung cells, and ovarian cells against the background of the administration of these cytostatics. These changes I have mentioned were observed during light microscopy. When these preparations were examined with the help of an electron microscope, three types of structural changes were observed. Vacuolization, edema and disintegration of mitochondria, dissolution of myofibrils. We believe that the development of this toxic effect and the detection of pathology in preparations prepared from organs is due to the accumulation of cytostatics in the body during 1 week of use. The results of our studies are almost consistent with scientific data that the studied drugs have a cardiotoxic effect.

Thus, as a conclusion of our studies, we can conclude that cyclophosphamide and doxorubicin administered to female white rats for 1 week caused dose-dependent growth of cells in the liver, lungs, ovaries, and adrenal glands, the formation of dystrophic changes in them, the formation of diffuse leukocyte infiltration, and the enlargement of cell nuclei.

CONCLUSIONS

1. Repeated administration of cyclophosphamide and doxorubicin, separately and in combination, in a dose-dependent manner, produces statistically significant changes in the levels of reproductive hormones in the blood of white rats of both sexes. Cyclophosphamide dose-dependently reduced the levels of all reproductive hormones studied more significantly than doxoru-

bicin. The most potent inhibitory effect on reproductive hormone levels was demonstrated by the combination of cyclophosphamide and doxorubicin dose-dependently [2,3,5,8,12].

2. Cyclophosphamide and doxorubicin, when administered separately and together to rats of only female, only male, and both sexes, cause significant changes in the onset, course, and physical development of the offspring. Both doses of cyclophosphamide injected shorten the duration of pregnancy more than both doses of doxorubicin injected. Cyclophosphamide significantly reduces prenatal and postnatal weight gain in pregnant rats compared to doxorubicin. The decrease in postnatal weight and number of pups born against the background of repeated administration of both cytostatics is observed more often against the background of cyclophosphamide administration. The most negative effect on all these indicators is shown by the dose-dependent combination of cyclophosphamide and doxorubicin.[4,10,11].
3. When cyclophosphamide and doxorubicin are repeatedly administered to female rats, male rats, and both sexes, separately and together, in a dose-dependent manner, significant changes occur in the quantitative and anatomical parameters of the offspring. In the offspring born against the background of repeated administration of both cytostatics, delays in ear flap opening, reverse geotaxis response, hair coat formation, and an increase in the number of defective offspring are observed. Developmental defects are observed more often in offspring born from rats of both sexes administered cyclophosphamide. The combined use of cyclophosphamide and doxorubicin causes very serious changes in the quantitative and anatomical parameters of the offspring, depending on the dose [10,11,12].
4. Repeated administration of cyclophosphamide and doxorubicin, separately and in combination, to pregnant white rats, depending on the dose, has a serious negative effect on the course of pregnancy, the pre- and early postnatal development of the offspring, and leads to the termination of pregnancy with various complications. Cyclophosphamide has more serious adverse effects on pregnancy outcome and outcome than doxorubicin. The

most adverse effects are seen with the dose-dependent combination of cyclophosphamide and doxorubicin [2,3,5,8,12].

5. Comparison of the morphohistological changes in the internal organs of white rats against the background of chronic administration of cyclophosphamide and doxorubicin separately and in combination, in a dose-dependent manner, showed that cyclophosphamide has a stronger organotoxic effect in a dose-dependent manner compared to doxorubicin. The most potent organotoxic effect is shown by the dose-dependent use of cyclophosphamide and doxorubicin in combination [6].

PRACTICAL RECOMENDATIONS

1. When prescribing cytostatic drugs to men and women planning a family with oncological diseases, it should be taken into account that they have a high probability of causing pregnancy and fetal pathologies, and that the cytotoxic effect of cytostatics on healthy cells as well as on tumor cells, which is the basis of these pathologies, plays a significant role.
2. When planning a family for men and women who are periodically treated with cytostatics and suffer from oncological diseases, specialists should seriously consider the fact that cytostatics reduce the concentration of reproductive hormones, shorten the duration of pregnancy in experiments, cause physical retardation of the fetus, intrauterine developmental defects, as well as intrauterine death.
3. Couples planning a family with oncological diseases, especially pregnant women, should not be prescribed drugs from the cytostatic group. In cases of necessity and in desperate situations, the doctor should consult with geneticists and oncogynecologists and either monitor the pregnancy or terminate it.
4. Couples receiving cytostatic treatment, suffering from oncological diseases, planning a family, as well as during the course of an existing pregnancy, may be recommended to use drugs from various groups for correction purposes in the event of additional toxic effects observed in the experiment.

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4. Kheibatova M.F. Study of the onset of pregnancy and changes in subsequent outcomes against the background of the administration of cyclophosphamide and doxorubicin to female white rats. Yakut Medical Journal. 3(91)2025, DOI: 10.25789/ymj.2025.91.08, UDC 618.2: 615.256.5

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Https://doi.org/10.63682/jns.v14i32s.8438

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LIST OF CONVENTIONAL ABBREVIATIONS

WCS	- World Cancer Society
T	- Testosterone
Tf	- Testosterone free
T t	- Testosterone total
FSH	- Follicle Stimulation Hormone
LH	- Luteinizing Hormone
P	- Prolactin
ED	- Estradiol
ER	- Estriol
LP	- Lipid peroxidation
AFO	- Active forms of oxygen
WHO	- World health organisation
CNS	- Central Nervous System

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