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Study of the Effect of Cyclophosphamide and Doxorubicin on the Progress of Pregnancy and Histomorphological Structure of the Ovaries of White Rats

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Abstract

The article is devoted to the study of changes in the course of pregnancy and final outcomes against the background of the introduction of cyclophosphamide and doxorubicin to pregnant female white rats, as well as morphohistological changes developing in organs against the background of the introduction of cyclophosphamide and doxorubicin. The results of the studies showed that the duration of pregnancy in pregnant females receiving cyclophosphamide at a dose of 10 mg / kg decreased by 27.1% compared with the control group, the prenatal weight of animals decreased by 39.3% compared with the control group, and the postnatal weight decreased by 33.4%. The difference between prenatal and postnatal weight was 56.8%. The number of cubs decreased by 40.6%, and their weight by 43.9% compared with the number of cubs in the control group. When cyclophosphamide was prescribed at a dose of 20 mg / kg, the changes that occurred in the mother and offspring during pregnancy were more serious. In pregnant rats given doxorubicin at a dose of 2.5 mg/kg twice a week from the 8th day of pregnancy, the duration of pregnancy was 18.5% shorter compared to females in the control group, the prenatal weight of the animals decreased by 28.2% compared to the control group, and the postnatal weight by 29.9%. The difference between prenatal weight and postnatal weight was 25.4%. The number of pups also decreased by 29.8% compared to the number of pups in the control group. The birth weight of pups also decreased by 27.3% compared to the control group. These parameters decreased more significantly with the introduction of doxorubicin at a dose of 5 mg/kg. In pregnant rats given cyclophosphamide at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg from the 8th day of pregnancy for 1 week, the duration of pregnancy was reduced by 50.5%. The prenatal weight of the animals decreased by 50.2% compared to the control group, and the postnatal weight by 47.7%. The difference in prenatal and postnatal weight was 57.6%. A decrease in the number of pups by 90.1% was noted. The weight of the pups at birth also decreased by 50.7%. Against the background of the combined administration of cyclophosphamide at a dose of 20 mg/kg and doxorubicin at a dose of 5 mg/kg, the pregnancy did not end normally, and since the birth of cubs was not observed, the number of cubs was not determined, and since cubs were not born, it was not possible to determine their weight. When studying the histomorphological changes developing in the ovaries against the background of the administration of cytostatics to female rats for a week, it was shown that destructive changes, leukocyte infiltration and cellular edema are observed in the organs.

Keywords: Cyclophosphamide, Doxorubicin, Pregnancy, Stillbirth, Ovaries

Introduction

Relevance

Statistics show that the incidence of cancer, one of the greatest disasters of our time continues to grow up[1, 2, 3, 4]. Every year thousands of people in the world are diagnosed with cancer of various origins and localizations. Sadly tracking the dynamics of the growth of these diseases gives reason to say that by 2030 the number of such patients will double and amount to 20 mil-

lion, and the number of deaths from this disease will increase from 6 million to 12 million [3, 4]. In etiopathogenesis priority is given to such factors as poor nutrition, obesity, physical inactivity, bad habits (e.g., smoking, alcohol, drugs), external factors (e.g., radiation, industrial waste), heredity, viruses, depression, weakened immunity, etc., there are still serious gaps in the study of the causes of cancer, the dynamics of aggressive development, especially when etiotropic therapy and methods of pharmacological correction are unknown [5, 6, 7].

To this day, the irreplaceable role of chemotherapy as one of the methods of pharmacological treatment in the treatment of these diseases is an indisputable factor in achieving stable remissions, returning patients to an active life and prolonging relapse-free life [6, 7, 8]. An examination of the literature reflecting the results of both experimental and existing clinical studies shows that most chemotherapeutic drugs, when prescribed to pregnant women, cause various pathologies of pregnancy and the fetus, leading to the development of very serious, in most cases uncorrectable complications in the offspring [9, 10, 11]. Considering the fact that tumor diseases have significantly become younger in the last decade, especially the growth rates, coinciding with the reproductive age period, it is necessary to conduct serious research in this area. The most important drugs used as chemotherapeutic agents for various localizations and forms of these diseases include diamide phosphate and antitumor agents from the anthracycline group. Currently, cyclophosphamide is widely used among the main representatives of the first group, and doxorubicin is among the main representatives of the second group [12, 13, 14, 15]. Drugs included in both groups combine the pharmacological properties of this group. Although both drugs are currently considered the most necessary chemotherapeutic agents in oncological practice the spectrum of their pharmacological action especially the molecular mechanism of complications and side effects that they can cause upon repeated administration, have not been fully elucidated and studied [5, 16, 17, 18]. A decisive condition for assessing the existing gaps in this area is the relevance of the clinical use of these drugs in particular in terms of a more in-depth study assessment, analysis of their side and toxic effects such as teratogenic, mutagenic, carcinogenic and embryotoxic.

The Aim of the Study

Taking into account all of the above we conducted a comprehensive and all-round experimental study of the effect of mono- and combined use of cyclophosphamide and doxorubicin depending on the dose on the progress of pregnancy in rats as well as on the prenatal development of the fetus and the postnatal periods of development of the offspring, as well as the cytotoxic effect of these drugs on the ovaries.

Materials and Methods of the Study

The studies were conducted on 87 female white mongrel rats grown up in the vivarium of the Scientific Research Center of the Azerbaijan Medical University, weighing 180-200 g. 21 of them were decapitated. Animals of the first experimental group were divided into 7 groups. In the control group, 6 females were used and in the experimental groups 10 females in each group. Female rats of all groups were placed in one cage with intact males in a ratio of 1:2 and after pregnancy. The males were separated from the females and the females were taken as controls. The onset of pregnancy was assessed by the detection of spermatozoa in a smear prepared from the vaginal contents of the rats and by the increase in the weight of the animals after 1 week. In the second experimental group the cytotoxic effect of the studied drugs on the organs was studied histologically individually and in combination depending on the dose. The animals of the first experimental group were administered intraperitoneal cyclophosphamide at a dose of 10 mg/kg for 1 week after the onset of pregnancy, the second group - 20 mg/kg (Russian Federation), the third - 2.5 mg/kg, the fourth - 5 mg/kg doxorubicin (Germany), the fifth - 10 mg/kg cyclophosphamide and 2.5 mg/kg doxorubicin, the sixth - 20 mg/kg cyclophosphamide and 5 mg/kg doxorubicin. The animals of the second experimental group were also divided into 7 groups. Morphological and histological changes in the ovaries caused by the use of cytostatics for a week were studied, in each group of 3 female white rats. After that, the removed ovaries were fixed in a formalin solution. For histological studies, preparations were prepared using standard methods, sections were stained with hematoxylin and eosin, and preparations were studied using electron microscopy [19]. The course of pregnancy in pregnant rats was then visually observed and the offspring born were assessed. During the scientific research, the rules recommended by the European Parliament and the European Union for the proper treatment of animals in scientific research were observed [20]. To calculate the experimental data, parametric Student's t-test and nonparametric Wilcoxon-Mann-Whitney U-test were used. The results were processed using the statistical program Microsoft Excel (Office-2010).

Results and Discussion

The course of pregnancy: duration, parturition, postpartum condition, quantitative composition and weight of the offspring were studied further against the background of the introduction of cyclophosphamide and doxorubicin separately and in combination to pregnant rats for a week from the 8th day of pregnancy.

In the control group it was again confirmed that the onset of pregnancy its duration, pre- and postnatal weight of animals, the difference between weights, the number of cubs and the weight of cubs at birth were within normal limits [21]. The results of the study showed that in pregnant females receiving cyclophosphamide at a dose of 10 mg/kg, the duration of pregnancy was reduced by 27.1% compared to the control group. The prenatal weight of animals decreased by 39.3%, and the postnatal weight by 33.4% compared to the control group. The difference in pre- and postpartum weight was 56.8%. The number of pups decreased by 40.6% compared to the number of pups in the control group. A decrease was also observed in the birth weight of the pups. Thus, if in the control group the birth weight of the cubs was 6.6±0.1 g, then in the group receiving cyclophosphamide at a dose of 10 mg/kg, this indicator statistically significantly decreased by 43.9% and became 4.1±0.1 g. When pregnant rats were given cyclophosphamide at a dose of 20 mg / kg for one week, the changes that occurred in the mother and offspring were more serious [19, 22]. Thus, against the background of the introduction of cyclophosphamide to pregnant rats at a dose of 20 mg/kg, the duration of pregnancy was reduced by 36.8%. Such a decrease was also observed in other study parameters. Against the background of the introduction of cyclophosphamide at a dose of 20 mg/kg, the prenatal weight of pregnant rats decreased by 46.6%, and the postnatal weight by 43.8%, the differences

amounted to 54.8%. Cyclophosphamide at a dose of 20 mg/kg reduced the number of born offspring by 77.3%. A decrease was also observed in the weight of born offspring. The weight of the offspring born decreased by 45.4%. The results of the study are presented in Table 1.

Table 1: Changes in mother and offspring after repeated administration of cyclophosphamide and doxorubicin separately and in combination to pregnant white rats depending on the dose (M±m)

Groups	Gestation period (day)	Prenatal weight of animals (Gram)	Postnatal weight of animals (Gram)	Differences (Gram)	Number of offspring	Weight of offspring at birth (Gram)
Kontrol (n=6)	20,98±0,1	300,1±1,5	224,3±1,3	75,8±1,2	10,1±0,9	6,6±0,1
Ciclofosfamid 10mq/kq (n=10)	15,3±0,01 *** (-27,1%)	182,2±0,06 *** (-39,3%)	149,4±1,25 *** (-33,4%)	32,8±1,2 *** (-56,8%)	6,0±0,01 *** (-40,6%)	4,1±0,1 *** (-37,9%)
Ciclofosfamid 20mq/kq (n=10)	12,9±0,03 ** (-38,6%)	160,4±1,03 *** (-46,6%)	126,1±0,3 *** (-43,8%)	34,3±0,3 * (-54,8%)	2,3±0,01 * (-77,3%)	3,0±0,01 ** (-45,4%)
Docsorubicin 2,5mq/kq (n=10)	17,1±0,02 *** (-18,5%)	215,5±1,2 *** (-28,2%)	157,4±0,9 *** (-29,9%)	58,1±1,1 ** (-25,4%)	7,1±0,3 * (-29,8%)	4,8±0,02 ** (-27,3%)
Docsorubicin 5mq/kq (n=10)	14,1±0,02 ** (-32,8%)	171,3±1,02 *** (-42,92%)	139,2±0,7 *** (-38%)	33,1±0,4 * (-56,4%)	4,9±0,1 * (-48,5%)	3,8±0,02 ** (-42,5%)
Docsorubicin 2,5mq/kq+ Ciklofosfamid 10mq/kq (n=10)	10,4±0,01 ** (-50,5%)	149,6±0,9 *** (-50,2%)	117,4±0,25 *** (-47,7%)	32,2±0,2 * (-57,6%)	1,0±0,01 * (-90,1%)	2,6±0,01 ** (-50,7%)
Docsorubicin 5mq/kq+ Ciklofosfamid 20mq/kq (n=10)	9,1±0,01 ** (-56,7%)	140,2±0,5 *** (-53,3%)	110,3±0,1 *** (-50,9%)	32,2±0,2 * (-57,6%)	-	-

The significance of the difference is at *p<0.05; **p<0.01; ***p<0.001.

In pregnant rats, which were administered doxorubicin at a dose of 2.5 mg/kg twice a week from the 8th day of pregnancy, the duration of pregnancy was reduced by 18.5% compared with females in the control group. The prenatal weight of the animals was 28.2% less than in the control group, and the postnatal weight was 29.9%. The difference between the prenatal and postnatal weight was 25.4% less than in the control group. As for the number of cubs, it was found that there was also a serious decline in the number of cubs. Thus, if in the control group the number of cubs was 10.1±0.9, then against the background of the introduction of doxorubicin at a dose of 2.5 mg/kg this indicator decreased by 29.8% and was 7.1±0.3. The weight of the pups at birth also decreased by 27.3% compared to the control group. With the introduction of doxorubicin at a dose of 5 mg / kg, the duration of pregnancy decreased by 32.8% to 14.1 ± 0.02 days. The prenatal weight of pregnant rats decreased by 42.9% and became 171.3±1.02 g. When studying the postnatal weight, it was found that, compared to the control group, this indicator decreased by 38% and became 139.2±0.7 g. The difference between the prenatal and postnatal weight changed towards a decrease of 56.4%. The number of offspring also decreased by 48.5% compared to the control group, and the weight of the offspring at birth statistically significantly decreased by 42.5%.

To achieve a high pharmacotherapeutic effect in chemotherapy, combination therapy is usually carried out. Taking this into account, we administered cyclophosphamide and doxorubicin together depending on the dose to pregnant rats to determine the course of pregnancy and the final result. Initially, we observed pregnant female rats that were administered cyclophosphamide at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg from the 8th day of pregnancy for 1 week. The combined use of cytostatics in the indicated doses caused a reduction in the pregnancy period by 50.5%. The prenatal weight of the animals decreased by 50.2% compared to the control group, and the postnatal weight - by 47.7%. The difference in prenatal and postnatal weight was 57.6%. As for the number of pups, we observed a decrease of 90.1%. The reduction in birth weight of the cubs also amounted to 50.7%. In our studies, with the combined use of cyclophosphamide 20 mg/kg and doxorubicin 5 mg/kg in pregnant rats, the following picture was observed. Thus, the duration of pregnancy decreased by 56.7%, the prenatal weight of animals decreased by 53.3%, the postnatal weight by 50.9%, and the difference was 57.6%. Since the pregnancy did not end normally, the birth of offspring was not observed, so the number of offspring was not available, and since the offspring was not born, it was not possible to determine its weight. Thus, our visual observations showed that against the background of the introduction of both studied cytostatics separately and together to pregnant rats from the 8th day of pregnancy, significant deviations in their behavior were observed compared to the females of the control group. Thus, unlike the pregnant rats of the control

group, the mucous membranes of the rats of the study group were not clean, the outer hair was not smooth and thick, and they did not build nests of straw to accommodate their offspring 2-3 days before giving birth. On the other hand, compared to similar indicators of females in the control group, a significant difference was found in the course and nature of the birth process in pregnant rats of the corresponding experimental groups. In our studies, the postpartum body weight of pregnant rats was also determined and the difference and changes between the body weight in the last days of pregnancy and the postpartum weight were assessed. During visual observation of lactating females during the lactation period, a tendency was noted for them to fail to care for newborn cubs. Compared with the control group, the rats in the corresponding experimental group did not protect or shelter their young from the environment, and indifference to the young was observed. The results of our research once again proved that cytostatics have a negative effect on the reproductive system. The idea that even optimal antitumor doses of the studied cytostatics have a negative effect on the amount of sex hormones and reproductive capacity was confirmed [15, 18, 21]. When the drugs we studied were administered to pregnant female rats, they caused serious defects in the normal development of their pregnancies. At the same time, the administration of the drugs we studied separately and together to pregnant rats from the 8th day of pregnancy also caused serious disturbances in the course of pregnancy, abnormal births and stillbirths. We believe that this is due to the toxic effect of these drugs. On the one hand, these drugs have a toxic effect on the mother's body, which ultimately disrupts the normal development of the fetus in the womb, and on the other hand, they have a direct teratogenic effect on the fetus itself. Thus, according to the results of our studies, the number of offspring born in the six study groups was significantly lower than in the control group, especially against the background of high doses and combined use of cytostatics. During the study, all six variants of the experimental drug were compared with each other in the relevant aspect and it was found that the effect of these drugs on the number of offspring was similar. A statistically significant difference was determined between the results of the studied drugs ($p < 0.05$).

The fact that changes in pre- and post-natal body weight of pregnant animals were lower than in the control group can be explained by the lower total weight of both mothers and offspring, which is confirmed by the decrease in the number of offspring.

Other studies examined histomorphological changes developing in the ovaries against the background of the introduction of cytostatics to female rats for one week. Although there is sufficient information in the literature on the negative effect of the cytostatics we studied on the heart, there is very little information on their effect on other organs [19, 23]. Analyzing the results of our studies, we came to the conclusion that, although very minor, destructive changes and inflammatory processes were detected in the ovarian tissues of rats that were administered cyclophosphamide at a dose of 10 mg/kg for 1 week.

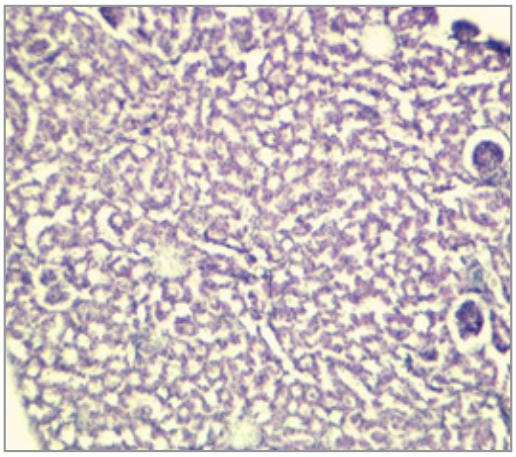

Figure 1: Section of rat ovary. Normal staining with hematoxylin eosin x400

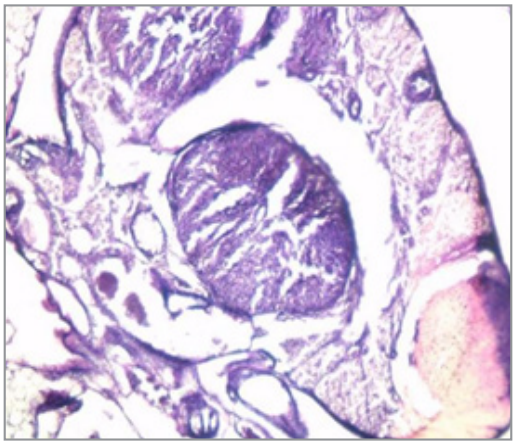

Figure 2: Section of rat ovary against the structure. of repeated administration and of cyclophosphamide t a dose of 10 mg/kg changes in the structure of the ovaries are observed the formation of oocytes is delayed Hematoxylin and eosin staining x400.

Cyclophosphamide at a dose of 20 mg/kg for 1 week leads to destructive changes in histological preparations prepared from animal organs. Thus, the use of cyclophosphamide at a dose of 20 mg/kg caused serious destructive lesions in the ovaries.

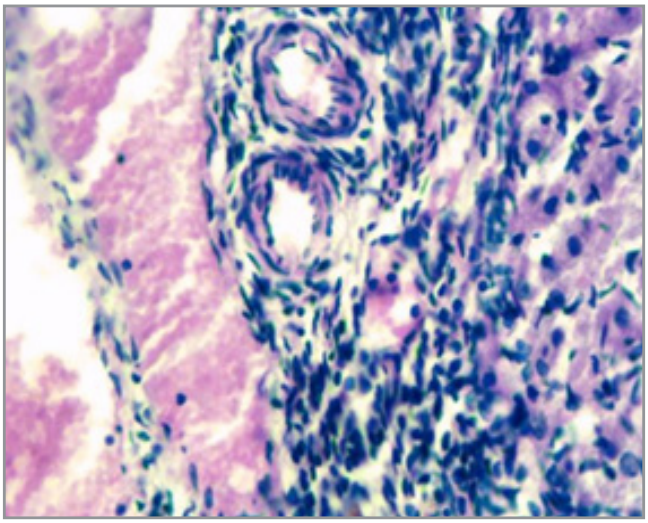

Figure 3: Section of rat ovary, against background of repeated administration of cyclophosphamide at a dose of 20 mg/kg serious changes in the structure of the ovaries of white rats are observed: follicles are underdeveloped, oocyte formation is delayed. Stained with hematoxylin and eosin x400

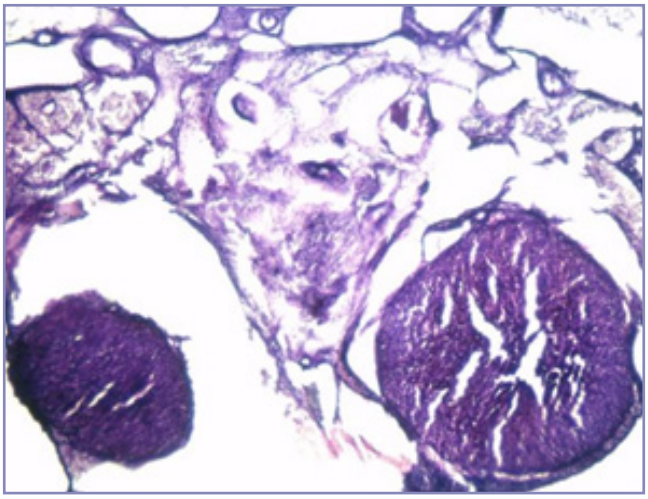

Figure 4: Section of rat ovary after the administration of doxorubicin at a dose of 2.5 mg/kg. Pathological changes are observed.

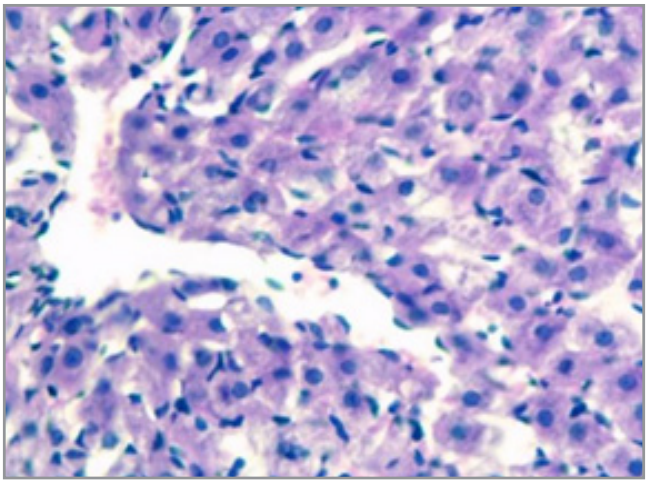

Figure 5: Section of the rat ovary against the background of repeated administration of doxorubicin at a at dose of 5 mg/kg in the ovary pathological changes are observed. Hematoxylin and eosin staining

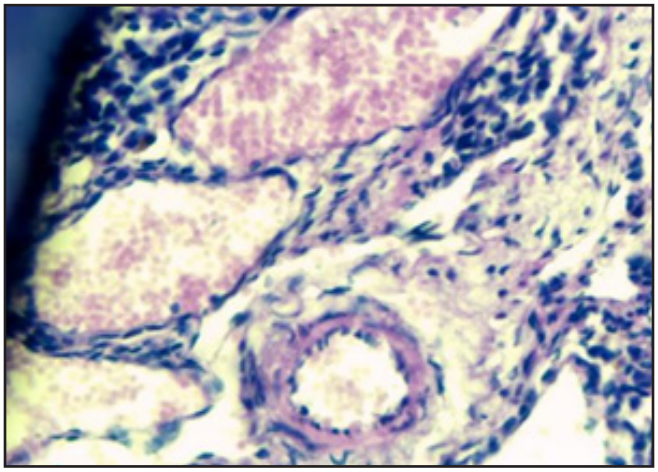

Figure 6: Section of rat ovary against the background of administration of cyclophosphamide at a dose of 10 mg/kg and doxorubicin at a dose of 2.5 mg/kg; administration inhibits the development of follicles in the ovaries and disrupts the formation of eggs. Staining with hematoxylin

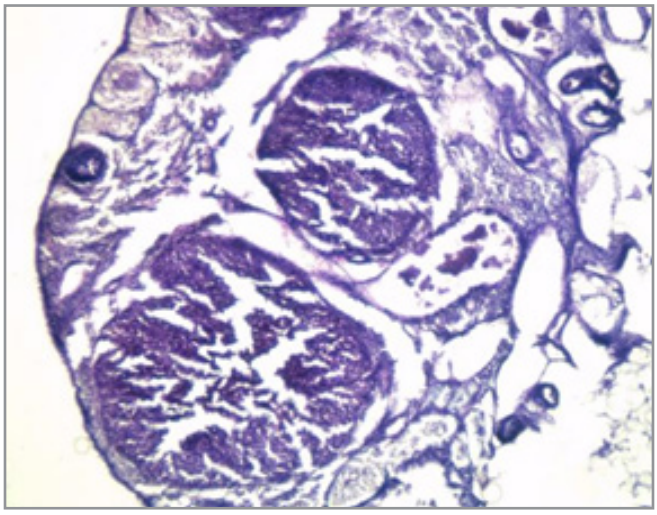

Figure 7: Section of rat ovary against the background of the introduction of cyclophosphamide at a dose of 20 mg/kg and doxorubicin at a dose of 5 mg/kg in the ovary micro follicles and suppression of egg formation. Staining with hematoxylin and eosin x400.

We observed the same effects when using doses of doxorubicin 2.5, 5 mg/kg, which are somewhat weaker than cyclophosphamide. More pronounced destructive changes were observed when using cyclophosphamide and doxorubicin in a dose-dependent combination.

Conclusions

1. Cyclophosphamide and doxorubicin when used separately and together, depending on the dose in pregnant rats cause serious quantitative and qualitative changes in the course and final result of pregnancy.
2. Cyclophosphamide and doxorubicin when used separately and together, depending on the dose, cause serious morpho-histological changes in the ovaries of white rats.

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