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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

EFFECT OF PRENATAL HYPOXIA ON BLOOD COAGULATION IN POSTNATAL ONTOGENESIS OF RAT PUPS

Specialty:	2411.01 – Human and animal physiology
Field of Science:	Biology
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The work was performed at the laboratories "Environmental factors and formation of analyzers" and "Ecotoxicology" of the Institute of Physiology named after academician Abdulla Garayev of the Ministry of Science and Education of the Republic of Azerbaijan.

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Dissertation Council FD 1.08 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Institute of Physiology named after academician Abdulla Garayev of the Ministry of Science and Education of the Republic of Azerbaijan.

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GENERAL CHARACTERISTICS OF THE RESEARCH

Relevance and degree of the completion of the topic. The blood system is a physiological support mechanism that plays a key role in maintaining hemostasis and forming adequate regulation-adaptation reactions. On the other hand, regulation of blood circulation is known to be performed by close interaction of local and remote control mechanisms [1] . The formation of hemopoietic tissue response to various extreme effects of the environment belongs to the central ring of regulation. The main problem caused by the observed hypoxic condition in the body is not only the disruption of the regulatory mechanisms but also the dysfunctions in the defense mechanisms that determine the vital activity of living things [2] . A decrease in blood oxygen causes changes in its respiratory function leading to acidosis. Under these conditions, depending on the effect of hypoxia, many indicators of homeostasis change. Continuous lack of oxygen leads to severe disruption of blood circulation and microcirculation[3]. Monitoring the dynamics of the blood system and its defense components, which ensure the stability of the internal environment in living organisms, is considered one of the effective scientific research approaches for maintaining functional integrity under different

[1] Зимина Н.Н. Влияние острой и хронической внутриутробной гипоксии плода на формирование клеточного состава пуповинной крови доношенных новорожденных / Н.Н. Зимина, С.А. Румянцев, О.А. Майорова [и др.] // Современные технологии в диагностике и лечении, - Москва: - 2010, № 2 , с. 48- 57.

[2] Грачев В.И., Севрюков И.Т. Гипоксия и гипоксемия, их причины и последствия для человека // - Oslo: Norwegian Journal of development of the International Science , - 2018, No 17,- p. 12-30.

[3] Петров В.Н. Особенности влияния парциального градиента плотности кислорода в атмосферном воздухе на состояние здоровья населения, проживающего в арктической зоне РФ // - Апатиты: Вестник Кольского научного центра РАН 3, Естественные и технические науки, - 2015 (22), с. 82-92.

conditions[4].

The purpose and tasks of the research. The main purpose of the work was to study the changes in the dynamics of the blood coagulation system, which deviated from the physiological norm and were stable, and which could be observed in the dynamics of the blood coagulation system in the rats that passed the different stages of the intrauterine development period (embryonic, pre-fetal, and fetal) under the conditions of chronic hypoxia and were at the age of one, three, and six months.

To achieve the goal, the following tasks were set:

1. Study of blood coagulation dynamics in one-, three- and six-month-old rats born by rats, who passed the gestation period under normal conditions (normal food ration, optimal lighting, temperature, breathing, and free movement) and passed separate stages of intrauterine development (embryonic, pre-fetal and fetal) under conditions of maternal hypoxia.

2. Study of platelet activity in the peripheral blood of one-, three-, and six-month-old rats that underwent normal intrauterine development and animals subjected to maternal hypoxia during embryonic, pre-fetal, and fetal periods of intrauterine development.

3. Study of the morphohistological characteristics of the liver in one-, three- and six-month-old rats that underwent normal intrauterine development and animals subjected to maternal hypoxia during embryonic, pre-fetal and fetal periods of intrauterine development.

Main points presented to the defense of the dissertation:

1. The blood coagulation system is dynamic against the influence of prenatal hypoxia and is characterized by stable morphofunctional deviations in the ontogenesis of different age groups.

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[4] Шибенко, А.М. Современные направления в исследованиях свертывания крови. / А.М. Шибенко, А.Н. Баландина, Н.А. Подоплелова [и др.] // Вопросы гематологии онкологии и иммунопатологии в педиатрии, - Москва: - 2020.Т. 19, №3, - с.144–150.

2. The level of deviation of physiological functions from the norm was evaluated depending on the intrauterine development period (embryonic, pre-fetal and fetal) when the stresor factor occurred and it was found that the embryonic and pre-fetal periods of embryogenesis show greater sensitivity to the influence of the hypoxia factor.

3. Due to the influence of intrauterine hypoxia conditions, in the blood of one-month-old animals, a tendency to hypocoagulation is observed in the hemostasis system, according to the nature of changes in the platelet and coagulation hemostasis systems.

4. In the groups of 3- and 6-month-old animals, due to prenatal hypoxia, increased postnatal ontogenesis against the background of thrombocyte activity and hypercoagulation nature of the hemostasis system against the background of increased coagulation potential were found.

5. The defects caused by intrauterine hypoxia in the liver, which is one of the main organs in the regulation of the coagulation system, were more severe in one-month-old rats, and recovery processes were slow.

6. Despite the progress of morphological restoration processes in the liver in three- and six-month-old animals, hypercoagulation of the coagulation system is determined against the background of a number of pathologies observed in the liver parenchyma.

Scientific novelty of the research. For the first time, by using adequate methodical approaches in the fulfillment of the dissertation work, in order to assess the overall condition of the blood coagulation system, which is one of the body's defense systems against unfavorable conditions and hypoxia as a stres factor, the morphohistological study of the liver, which is the main organ of hemostasis and thrombocyte, plasma hemostasis. based on complex studies, serious changes in coagulation dynamics were discovered and the stable nature of these changes was determined.

For the first time, the state of the blood coagulation system under the influence of prenatal hypoxia was analyzed taking into account the separate stages (embryonic, pre-fetal and fetal) of the

morphofunctional maturity of the fetus during embryogenesis, and it was determined that the embryonic stage of intrauterine development is more sensitive to the influence of this stress factor.

For the first time, the effect of prenatal hypoxia on the coagulation system was carried out taking into account important age periods (one, three and six months) of experimental animals, and it was determined that the changes obtained by these age periods were of different nature. Thus, in one-month-old animals, the hypocoagulation character of the hemostasis system was determined against the background of a decrease in platelet activity and coagulation potential, and in three- and six-month-old animals, the hypercoagulation character of the hemostasis system was determined under the conditions of an increase in platelet activity and coagulation potential.

At the same time, it was discovered for the first time that the dysfunctions observed in the blood coagulation system during postnatal ontogeny under conditions of prenatal hypoxia are caused by deficiencies in platelet and plasma hemostasis rings of coagulation and pathologies manifested in liver tissue.

Theoretical and practical significance of the research:

Taking into account the dynamic nature of the blood coagulation system, which is one of the main defense systems of the body, and at the same time the unique physiological nature of this system during pregnancy, the study of the pathologies that can be observed in this system under the influence of unfavorable environment and various stress factors is of great scientific and practical importance for clinical medicine. The obtained results can be used to reveal the pathologies observed during embryonic development in the newborn generation and to assess the severity of stress factors. Since hematological and coagulation analyses are initially used in the diagnosis of many diseases, the results of our research can be used to reveal early pathologies in the body, in the early diagnosis of many diseases, and in the preliminary assessment of physiological dysfunctions that may occur in old age. At the same time, the obtained results can be used in the teaching of the protective properties of blood

in the "Human and Animal Physiology" subject in biologically oriented educational institutions in practical training manuals, seminars and lectures.

Approbation of the research. The materials of the dissertation work and the provisions derived from the research were discussed in a wide range of audiences at various symposia, conferences, seminars and congresses related to the subject of the research: Scientific conference of PhD students of Azerbaijan National Academy of Sciences (Baku, 2010; 2011); BSU, Scientific conference "Current problems of Biology in the 21st century" (Baku, 2010); Scientific Proceedings of the III Congress of Physiologists of the CIS (Yalta, Ukraine, October 1-6, 2011); II International Congress of Physiologists of Georgia (Georgia, Tbilisi, 2013); SSU, Modern problems of biology, Republican Scientific Conference, (Sumgayit, 2018); BEU, III International Conference of Young Scientists, (Baku, 2019); II International Scientific Conference of Young Scientists "Multidisciplinary approaches in solving modern problems of fundamental and applied sciences", Azerbaijan National Academy of Sciences (Baku, March 03-06. 2020); BEU, V International Conference of Young Scientists (Baku, 29-30 april, 2021); International Conference "Actual problems of contemporary natural and economic sciences"(Ganja, 2022);"International Asian Congress On Contemporary sciences –VI (Van, Turkey, May 27-29, 2022); Karabakh III. International Congress of Applied Sciences "Year of Shusha- 2022" (Karabakh/ Azerbaijan, June 7-10, 2022).

The name of the organization where the dissertation work was performed. The dissertation work was performed at the Institute of Physiology named after Academician Abdulla Garayev, Ministry of Science and Education of the Republic of Azerbaijan.

Publications. 25 scientific works have been published on the topic of the dissertation, 12 of them are theses and 13 are articles. 5 articles and 4 theses were published in foreign publishing houses.

Structure and volume of the dissertation work. The dissertation includes chapters: introduction, literature review, research results, discussion of results, summary, main conclusions, practical recommendations, and used bibliography, written according to the

requirements of the Supreme Attestation Commission.

The dissertation consists of 139 pages of text (184000 marks) - "Table of Contents" (1630 marks), "Introduction" (19310 marks), "Literature review" (51407 marks), "Materials and methods" (9964 marks), "Research results" (45846 characters), "Discussion of obtained results" (49533 characters), "Conclusions" (3216 characters), "Practical recommendations" (861 characters) and "List of abbreviations" (460 characters). 9 tables and 18 pictures are described in the dissertation work. The bibliography includes 184 sources. 17 of them are Azerbaijani, 105 are Russian, 62 are included in other foreign literature.

CONTENT OF THE WORK

CHAPTER I. LITERATURE REVIEW

Chapter I of the dissertation work is a review compiled on the basis of local and foreign literature. The modern approach to the coagulation system, ontogenetic features of the coagulation system, and literature data on the effect of the hypoxia factor of various origins on the dynamics of blood coagulation are presented in the chapter.

CHAPTER II. MATERIALS AND METHODS OF THE RESEARCH

The experiments were conducted during one, three, and six months of postnatal ontogenesis on 240 rat pups of 70 rats that passed the normal gestation period and its separate critical (conditionally: embryonic, pre-fetal, and fetal) stages under conditions of chronic repeated hypoxia. All experiments were carried out in accordance with the International Convention of the European Union (November 13, 1987, Strasbourg) and taking into account the principles of animal protection. Hypoxia conditions were created based on the method of Khvatova (1978).

Total blood coagulation time was determined by the Moravits method, plasma recalcification time by the Howell method,

prothrombin time by the Kwik method, thrombin time by the Sirmai method, plasma tolerance to heparin by the SIG method, fibrinogen richness by air drying, thrombus test by the Fuenta-Ita method.

The determination of platelets and the study of the main platelet indices were performed on the DIRUI BCC-3600 blood analyzer.

Histological examination of the liver was carried out by Hematoxylin and Eosin staining.

CHAPTER III. RESULTS AND DISCUSSION

3.1. Dynamics of blood coagulation in one-month-old rats that underwent normal intrauterine development and animals exposed to hypoxia at different stages of embryonic development (embryonic, pre-fetal, and fetal)

At the initial stage of the research, coagulation processes were studied in the blood of normal one-month-old rat pups and trial group animals exposed to prenatal hypoxia. The indirect effect of hypoxia on the fetus during embryonic development has been established to cause stable changes in the blood coagulation system from the first stages of postnatal development. According to the results of our research, the total coagulation time of blood in one-month-old rats from the control group is 153.8±7.4 seconds.

During the first 7-8 days of intrauterine development (embryonic period), under the influence of the hypoxia factor, the total blood coagulation time in one-month-old rat pups was prolonged by 13% ($p<0.001$) and amounted to 176.7±15.6 seconds [5] (Figure 3.1.1). In the pre-fetal period of intrauterine development (second week), the results we obtained for this indicator in rats exposed to the hypoxia factor were 170.4±8.4 seconds on average. In the fetal period of prenatal development (the last 7 days of intrauterine development), the total blood coagulation time was 168.3±10.3 seconds on average in

[5] Cəfərova G.Q. Antenatal hipoksiyanın siçovullarda qanın laxtalanmasına təsirinin yaş xüsusiyyətləri //- Bakı: Gənc tədqiqatçı, Elmi praktik jurnal, - 2019, V cild, № 1,- s.106-110.

pups exposed to the hypoxia factor [6]. Thus, the statistical analysis showed that as a result of prenatal hypoxia, blood coagulation potential decreases in animals from the trial group.

Plasma recalcification time (PRT) in animals from the control group was on average 81±4.1 seconds, whereas PRT slightly increased and lasted 91.3±5.2 seconds in the pups exposed to the hypoxia factor during the embryonic period of the development. PRT in pups exposed to hypoxia in the pre-fetal period of intrauterine development was 87.5±5.1 sec., and in pups exposed to hypoxia in the fetal period of development, PRT was 89.5±4.0 sec. on average. The statistical analysis of our results showed that the remote effect of the intrauterine hypoxia factor had a negative effect on the dynamics of plasma recalcification time as well as coagulation time in early postnatal ontogenesis and revealed the fact that the coagulation potential decreased [7].

A comparative analysis of the results obtained from our studies revealed a decrease in activated partial thromboplastin time (APTT) in animals from the trial group. Thus, it was found that thromboplastin activity in animals from the control group was 22.5±0.4 seconds on average. APTT in animals of the trial group exposed to the hypoxia factor during the embryonic, pre-fetal, and fetal periods of intrauterine development was on average 27.8±0.6, 26.8±0.3, and 27.6±0.2 seconds, respectively. Thus, thromboplastin activity in animals of the trial group had an average of 20% lower dynamics compared to the control group[8] (Figure 3.1.1).

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[6] Cəfərova G.Q. Antenatal dövrdə hipoksiyanın təsirinə məruz qalmış siçovullarda qanın koaqulyasyon xüsusiyyətləri // Azərbaycan MEA - da Fundamental və Tətbiqi elmlərin müasir problemlərinin həllində multidissiplinar yanaşması istiqamətində Gənc alimlərin II Beynəlxalq Elmi Konfransı, - Bakı: AMEA, 03-06 mart, - 2020, - s. 71-72.

[7] Джафарова Г.Г. Динамика свертывания крови крыс, подвергнутых воздействию гипоксии в период пренатального развития // - Тбилиси: Медицинские новости Грузии, – 2020. № 5 (302), с 132-135.

[8] Cəfərova G.Q. Antenatal hipoksiyanın siçovul balalarında qanın laxtalanmasının yekun fazasına uzaqlaşdırılmış təsiri // - Bakı: Azərbaycan Milli Elmlər

Prothrombin time (PT), which is the main indicator of the second phase of coagulation, lasted 18.1±0.2 seconds on average in one-month-old rats with normal embryonic development. In rats exposed to hypoxia in the embryonic stage, this period was prolonged by 24-30%, it lasted 23.7±0.1 seconds on average, and in rats exposed to hypoxia in the pre-fetal period, this period lasted 21.2±0.2 seconds. Prothrombin time in rats exposed to hypoxia in the fetal period of embryogenesis was recorded at an average of 20.6±0.2 seconds[9].

Thrombin time (TT) in one-month-old pups with normal embryonic development was 29.7±1.2 seconds on average. However, the average value of this indicator in animals exposed to hypoxia during the embryonic, pre-fetal, and fetal periods of intrauterine development, this period amounted to 39.5±0.2, 36.6±0.7, and 31.7±0.9 seconds, respectively. According to the available literature data, the prolongation of thrombin time indirectly leads to a decrease in the fibrinogen concentration in the plasma[10,11]. Thus, as a result of the hypoxia factor affecting the development of the fetus in the embryonic period, the concentration of fibrinogen in plasma decreased (34%) in animals of the trial group compared to the control group. The concentration of fibrinogen in animals from the control group amounted to 275±5.7 mg%. While in animals exposed to hypoxia in the embryonic, pre-fetal, and fetal periods, this parameter was found to be 183±11.3 mg%, 197±7.2 mg%, and 239±13.1 mg% on average,

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Akademiyasının Xəbərləri, Biologiya və Tibb Elmləri,- 2017, Cild 72, №2, - s. 132-135.

[9] Cəfərova G.Q. Prenatal hipoksiyanin hemostaz sisteminə təsiri // III Qarabağ beynəlxalq tətbiqi elmlər konfransı, "Şuşa ili- 2022" , - Bakı : İKSAD - 2022, - 07-10 iyun, - 2022, - s. 45.

[10] Долгов В.В. Лабораторная диагностика нарушений гемостаза / В.В. Долгов, П.В. Свирин – М. -Тверь: ООО «Издательство «Триада», - 2005. - 227 с.

[11] Шахматов, И.И. Гипоксическая гипоксия как фактор, активирующий систему гемостаза. / И.И. Шахматов, В.М. Вдовин, Ю.А. Бондарчук [и др.] // Бюллетень сибирской медицины,-Томск: - 2007. №1, – с. 67-72.

respectively[12]. A comparative analysis of the results obtained during the determination of plasma tolerance index to heparin (PTH) in animals from the control and trial groups using appropriate hematological tests showed that the total blood coagulation ability was reduced in the animals from the trial group. Thus, while in the control group, PTH was on average 53.7±7.1 seconds, in individuals exposed to hypoxic influence during the embryonic stage of development, this period was extended by 26% and was 71.8±3.5 seconds. In animals exposed to the hypoxia factor in the pre-fetal period of ontogenesis, PTH was found to be 73.4±3.7 seconds on average, and in animals exposed to hypoxia during the fetal period, it was 71.4±5.2 seconds, respectively (Figure 3.1.1).

3.2. Dynamics of blood coagulation in three-month-old rats whose intrauterine ontogenesis occurred under normal conditions and animals exposed to hypoxia at different stages of development.

According to our results, the 3-month-old rats from the control group had an average blood clotting time of 135±8.7 seconds. Whereas, the total blood clotting time (19-23% ($p<0.05$)) is slightly shorter in animals from the trial group (Figure 3.2.1). A statistical comparative study was also conducted on separate critical stages of intrauterine development (embryonic, pre-fetal, fetal) and blood clotting time was found to be 110.2±14.6, 113.8±6.5, 117.6±6.4 seconds in rats exposed to hypoxia in the embryonic, pre-fetal, and fetal periods of the prenatal development, respectively.

In 3-month-old rats of the control group, PRT was 101±7.9 seconds, while in the animals exposed to hypoxia during the embryonic period of intrauterine development, it was slightly shortened (13% ($p<0.05$)) and amounted to 88.4±5.8 seconds. Besides, PRT was 89.4±5.9 seconds in rats exposed to hypoxia in the pre-fetal

[12] Cəfərova G.Q. Axundova S.M. Bətndaxili inkişaf dövründə hipoksiyanın təsirinə məruz qalmiş bir ayliq siçovullarda qanda fibrinogenin qatılığı // Gənc tədqiqatçıların III beynəlxalq elmi konfransı, - Bakı: BMU, - 29-30 aprel,- 2019 , - s. 214-216.

period of antenatal development, and 90.5±5.4 seconds in rats subjected to hypoxia in the fetal period[13].

APTT in rats of the control group was 34.6±2.3 seconds, however, this period, which is a blood coagulation parameter, was slightly shortened in animals of the trial group exposed to intrauterine hypoxia (15-21% ($p<0.001$)); thromboplastin activity of the animals exposed to hypoxia in the embryonic, pre-fetal, and fetal periods of prenatal development amounted to 28.6±2.4, 27.4±3.9, and 29±3.3 seconds, respectively.

A comparative analysis of the results of our studies showed that although the prothrombin activity (PA) was relatively lower in animals from the trial group compared to the control group, statistically reliable different results were not observed. So, in animals of the control group, PA averaged 19.3±1.9 seconds. Whereas, PA in rats exposed to hypoxia during the embryonic period of intrauterine development was 24.3±3.3 seconds. Accordingly, prothrombin activity in rats that spent the pre-fetal period under conditions of intrauterine hypoxia was 21.5±4.9 seconds on average, and 21.7±3.1 seconds in rats exposed to hypoxia in the fetal period.

Thrombin time as one of the main indicators characterizing the total antithrombin activity of blood was 19.3±2.0 seconds in rats of the control group, while it was 23.7±2.7 seconds in animals exposed to intrauterine hypoxic. In other words, compared to the control group, thrombin activity decreased by 15% ($p<0.001$) in rats subjected to hypoxia during the embryonic period of intrauterine ontogenesis. However, no statistically significant differences in ontogenetic development were identified in rats exposed to hypoxia during the pre-fetal and fetal periods compared to the control group.

Based on the results of our analysis of the plasma tolerance index to heparin, a slightly higher tolerance index was found in the trial group compared to the control group. This parameter was equal to 93±11.3

[13] Cəfərova G.Q. Antenatal dövrdə hipoksiyanın uzaqlaşdırılmış təsirinə məruz qalmış üç aylıq siçovul balalarında qanın laxtalanmasının yekun fazasında koaqulyasyon xüsusiyyətlər // Gənc alimlərin V Beynəlxalq Elmi Konfransı, - Bakı: BMU, - 29-30 aprel,- 2021, - s. 1118-1120.

seconds in the control group rats. Based on the comparative analysis of the results, the plasma tolerance index to heparin was shortened by 16-18% to 76.6±9 seconds in rats exposed to the hypoxia factor during the embryogenic period of intrauterine development, while this indicator was 82.6±12.2 seconds in the rats exposed to the hypoxia factor during the pre-fetal development. No statistically significant difference was recorded in rats exposed to this factor during the fetal period of ontogenetic development; the plasma tolerance index to heparin was found to be 87.7±10.9 seconds (Figure 3.2.1).

Analysis of the results revealed that the concentration of fibrinogen slightly increased in animals from the trial group compared to the control group. Thus, while the concentration of fibrinogen in animals from the control group was 260 ± 13 mg%, it was found that this indicator slightly increased and amounted to 289 ± 11.9 mg% due to the effect of the hypoxia factor during the embryonic period of intrauterine development. Similarly, in three-month-old rats exposed to the hypoxia factor during the pre-fetal period, the concentration of fibrinogen slightly increased compared to the control group and was found to be 281±8.2 mg%. Similar results were observed in rats exposed to hypoxia during the fetal period of intrauterine development. Thus, the concentration of fibrinogen in plasma in the trial group was 282±11.3 mg% [14].

3.3. Dynamics of blood coagulation in six-month-old rats whose intrauterine ontogenesis occurred under normal conditions and animals exposed to hypoxia at different stages of development.

The comparative analysis of the results obtained with the control and trial animals showed that the blood coagulation time (CT) is slightly shorter (29% ($p<0.05$)) in rats exposed to intrauterine hypoxia at the maturity stage of ontogenesis (age period of 6 months). So, in

[14] Cəfərova G.Q. Embriogenezdə hipoksiya təsirinə məruz qalmış siçovullarda qanda fibrinogenin dəyişmə dinamikası / Cəfərova G.Q., Qazıyev A.Q., Rüstəmov Q.D. [və b.] // Sağlamlıq, Elmi-praktik jurnal, - Bakı: - 2019, №2, - s. 105-108.

animals from the control group, CT was 148±5.6 seconds, while it was shortened in rats exposed to hypoxia during the embryonic stage of prenatal development and amounted to 106±4.2 seconds on average. Similarly, in adult rats exposed to hypoxia in the pre-fetal period, this indicator was 122±7.1 seconds, and in rats exposed to hypoxia in the fetal period, the coagulation time was 128±7.6 seconds[15].

The determination of the plasma recalcification time (PRT) in six-month-old rats also confirmed that the coagulation process was accelerated in animals from the intrauterine hypoxic group compared to the control group. Thus, it was found that the normal recalcification period was 105±4.1 seconds in animals from this group. In animals exposed to the remote effect of intrauterine hypoxia, this period was relatively shortened and ended quickly. Thus, PRT in rats exposed to hypoxia during the embryonic period of prenatal ontogenesis was 83.5±1.4 seconds, which indicated a 21% decrease ($p<0.001$) compared to the control group (Figure 3.3.1). Similarly, the shortening of PRT was detected in rats exposed to hypoxia during the pre-fetal and fetal periods of prenatal development. In rats subjected to hypoxia during the pre-fetal period, this period was on average 87.5±2.5 seconds, and in rats subjected to hypoxia during the fetal period, the plasma recalcification time was 92.5±3.4 seconds[16].

APTT was 34.8±2.4 seconds in six-month-old rats from the control group. However, the statistical analysis of the results revealed that thromboplastin activity was slightly higher in trial group animals. This was especially observed in rats exposed to hypoxia during the embryonic period of intrauterine development. Thus, APTT in rats from this group was 26.5±1.9 seconds. Compared to the control group,

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[15] Cəfərova G.Q. Prenatal dövrdə hipoksiyaya məruz qalmış siçovullarda qanın laxtalanma dinamikasının cinsi xüsusiyyətləri // Sumqayıt Dövlət Universiteti Biologiyanın müasir problemləri Respublika elmi konfransının materialları, - Sumqayıt: SDU, 23-24 oktyabr, - 2018, - s. 19-20.

[16] Cəfərova G.Q. Antenatal dövrdə hipoksiyanın təsirinə məruz qalmış siçovullarda qanın koaqulyasyon xüsusiyyətləri // Azərbaycan MEA - da Fundamental və Tətbiqi elmlərin müasir problemlərinin həllində multidissiplinar yanaşması istiqamətində Gənc alimlərin II Beynəlxalq Elmi Konfransı, - Bakı: AMEA, 03-06 mart, - 2020, - s. 71-72.

statistically unreliable, almost close results were obtained in rats exposed to hypoxia in the pre-fetal and fetal periods of prenatal development: 30.3±1.4 seconds in rats exposed to hypoxia in the pre-fetal period of prenatal development (p<0, 01), and in rats exposed to hypoxia in the fetal period, this indicator was 30.7±0.9 seconds[17].

In rats with normal intrauterine development, PT amounted to 21.4±2.1 seconds, whereas, the level of prothrombin activity decreased slightly and was 27.2±2.0 seconds in animals exposed to hypoxia during the embryogenic stage of the development. Similar results were obtained in rats exposed to hypoxia during the fetal period of development: 27.6±1.7 seconds. In the animals exposed to hypoxia during the fetal period of antenatal development, this difference was more evident and amounted to 33.4±2.2 seconds (36% (p<0.001))[18].

In another series of our study, similar dynamics in the thrombin time were detected. While the thrombin time was 15.8±1.2 seconds in rats from the control group, this duration was extended to 28.8±1.0 seconds, especially in rats exposed to hypoxia during the fetal stage. Similarly, in rats exposed to hypoxia during the embryonic stage, this indicator was slightly prolonged and amounted to 19.6±1.5 seconds, and in rats exposed to hypoxia during the pre-fetal period, it was 22.8±1.9 seconds[19].

Comparative analyses of plasma tolerance to heparin between control and trial groups revealed a high tolerance of plasma to heparin

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[17] Cəfərova G.Q. Antenatal hipoksiyanın yetkin siçovullarda protrombin müddəti və aktiv parsial tromboplastin müddətinə təsiri //- Bakı: Azərbaycan Milli Elmlər Akademiyası A.İ.Qarayev adına Fiziologiya İnstitutunun və Azərbaycan Fizioloqlar Cəmiyyətinin Elmi Əsərlərinin külliyatı, - 2018, cild XXXVI, - s. 97-101.

[18] Mustafayeva G.Q. Prenatal hipoksiyanın yetkin siçovullarda qanın laxtalanmasının ilkin fazasına təsiri // - Bakı: A.İ.Qarayev adına Fiziologiya İnstitutunun və Azərbaycan Fizioloqlar Cəmiyyətinin Elmi Əsərlərinin Külliyatı, - 2012, XXX cild, - s. 122-125.

[19] Mustafayeva G.Q. Ontogenezin dölönü dövründə xroniki hipoksiya edilmiş siçovullarda qan laxtalanmasının ikinci fazasında müşahidə olunan dəyişkənliklər // AMEA Aspirantların elmi konfransının materialları, - 25-26 may, Bakı: -"ELM", - 2011, - s. 120-125.

(44% ($p<0.01$)) in animals that underwent hypoxia during their prenatal ontogenesis (Figure 3.3.1). Thus, PTH in the control group averaged 86.6 ±7.1 seconds, while in animals exposed to hypoxia during the embryonic period of antenatal development, this parameter amounted to 66.4±3.5 seconds. Similarly, PTH was 59.2±4.9 seconds in rats subjected to hypoxia during the pre-fetal period of antenatal development.

While the amount of fibrinogen was 234±0.5 mg% in rats from the control group, the results of our research showed an increase in the amount of fibrinogen (13-15% ($p<0.01$)) in rats exposed to hypoxia during the antenatal period (Figure 3.3.1). This ratio was more pronounced in rats exposed to hypoxia during the fetal period. The concentration of fibrinogen was found to be 268±0.2 mg%. The concentration of fibrinogen was 251±0.5 mg% in rats exposed to hypoxia during the embryonic period, and similarly, it was 247±0.4 mg% in rats subjected to hypoxia during the pre-fetal period[20].

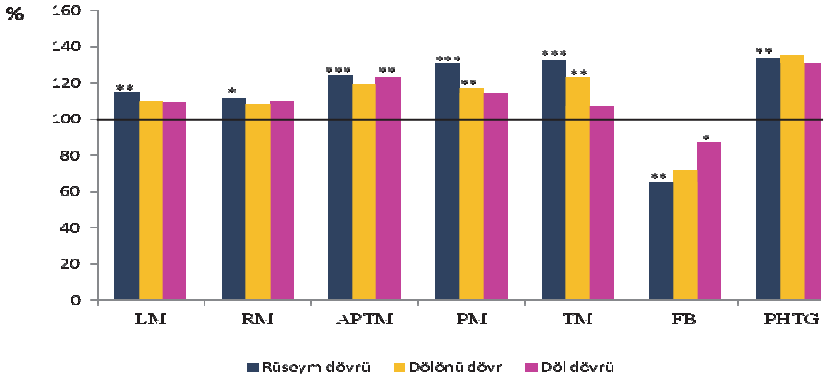

Figure 3.1.1. Percentage indicators of coagulation dynamics in one-month-old animals with prenatal hypoxia (*-$p<0.05$; **- $p<0.01$; ***- $p<0.001$).

[20] Джафарова Г.К. Некоторые особенности свертывания крови крыс, подверженных воздействию гипоксии в плодный период пренатального развития // - Прага: Scientific discussion, - 2017. Vol 1, № 8, ISSN 3041-4245, с 16-20.

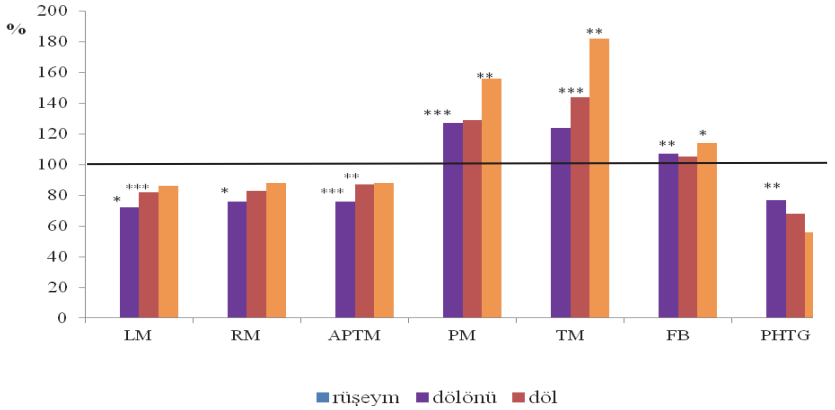

Figure 3.2.1. Percentage indicators of coagulation dynamics in three-month-old animals with prenatal hypoxia (*-p<0.05; **- p<0.01; ***- p<0.001).

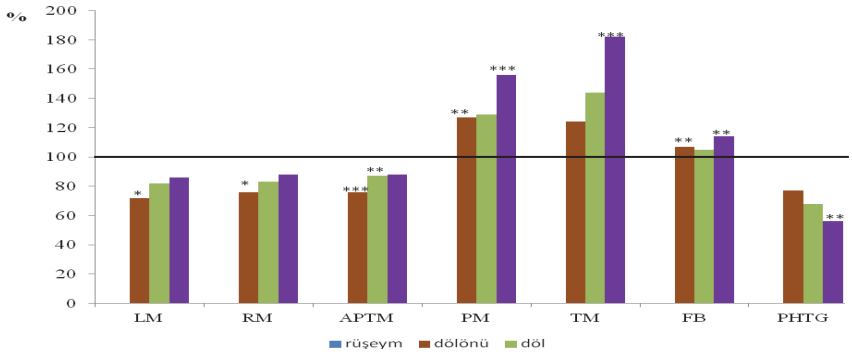

Figure 3.3.1. Percentage indicators of coagulation dynamics in six-month-old animals with prenatal hypoxia (*-p<0.05; **- p<0.01; ***- p<0.001).

3.4. Dynamic characteristics of platelets in the peripheral blood of one-, three- and six-month-old rats that underwent normal intrauterine development and were exposed to hypoxia at different stages

Statistical analysis of the results showed a significant decrease in the number of platelets in animals exposed to hypoxia during

intrauterine development. This difference was more pronounced (up to 40-53%) in animals exposed to hypoxia during the embryonic period. Thus, while PLT averaged 617.4*109 /l in animals that spent the embryonic development period under normal conditions, this indicator changed in the range of 326÷374 (*109 /l) in animals exposed to antenatal hypoxia. Besides, the fraction of large platelets (P-LCC) was significantly lower (50-56%) in the animals of the trial group compared to the control group. The obtained results show that intrauterine hypoxia leads to a decrease in the number of platelets in the peripheral blood and a decrease in platelet indices (Figure 3.4.1), which can be accompanied by thrombotic and thrombohemorrhagic deficiencies[21].

Similarly, a slight decrease in thrombocrit (PCT) was detected in the blood of one-month-old animals. Thus, in the control group, the PCT was 0.562%, while this indicator was 0.151%, 0.198%, and 0.187% in pups exposed to hypoxia during the embryonic, pre-fetal, and fetal periods of intrauterine development, respectively. A decrease in thrombocrit is an indicator of a faster breakdown of platelets in the body, a state of thrombocytopenia[22].

PDW was found in the range of 8.2÷11.8 fl in the animals from the control group, while it was observed in the range of 5.3÷9.2 fl in the animals from the trial group. Thus, the anisocytosis of platelets in trial-group animals decreased slightly.

A slight increase in mean platelet volume (MPV) was found in experimental animals. Thus, MPV was observed in the range of 5.2÷6.7fl in animals from the control group, and in the range of 6.7÷8.9fl (more in the embryonic period) in the animals of the trial group. A slight increase in mean platelet volume (MPV) was found in trial animals. Thus, MPV was observed in the range of 5.2÷6.7fl in animals from the control group, and in the range of 6.7÷8.9fl (more in

[21] Cəfərova G.Q. Embrional inkişafın müxtəlif mərhələlərində hipoksiyanın təsirinə məruz qalmış siçovullarda trombositar komponentlərin dinamikası //Sağlamlıq, Elmi-praktik jurnal , - Bakı: - 2021 , cild 27, №3, - s. 126-129.

[22] Cəfərova G.Q., Abdullayeva G.M. Antenatal hipoksiyanin postnatal ontogenezin müxtəlif yaş dövrlərində əsas trombositar göstəricilərə təsiri //Müasir təbiət və iqtisad elmlərinin aktual problemləri beynəlxalq elmi konfrans, - Gəncə: GDU, 06-07 May, - 2022, - s. 152-153.

the embryonic period) in the animals of the trial group. An increase in the average volume of platelets indicates a relatively large number of immature cells in the peripheral blood, a tendency to thrombocytopenia, and a decrease in coagulation ability, which proves that insufficient platelets are formed in the bone marrow as a result of hypoxia occurring in the embryonic period.

The determination of P-LCR (Platelet larger cell ratio) confirms similar results. Thus, compared to the control group, P-LCR decreased by 33-39% ($p<0.001$) in the trial group. This also confirms the fact that blood coagulation ability decreases due to the weakening of platelet activity in one-month-old animals under conditions of prenatal hypoxia.

The results of our laboratory analyses with both 3- and 6-month-old animals showed a slight increase in the average number of platelets in animals from the trial group compared to the control group. Thus, PLT increased by 10-15% ($p<0.01$) in the trial group compared to the control group in three-month-old animals. In six-month-old animals, this rate was higher, at the level of 22-25% ($p<0.001$). This fact indicates that the hypoxia occurring at different critical stages of embryonic development causes thrombocytosis in adult animals. At the same time, a positive trend was detected in the fraction of large thrombocytes. Thus, in 3-month-old animals, this indicator was in the range of 45÷55 *109/l in the control group, while in trial animals it increased by 13-18% ($p<0.01$) and was recorded at the level of 57÷65 $*10^9$/l (Figure 3.4.2). Similar results were obtained for the group of 6-month-old animals. Compared to the control group, P-LCC increased by 18-21% on average (Figure 3.4.3). As a whole, these positive dynamics increased the risk of the tendency to thrombosis and determined the hypercoagulability of the hemostasis system in 3- and 6-month-old animals.

Thrombocrit, which is the main platelet index, was also slightly elevated in both age groups compared to the control group. In 3-month-old animals, PCT fluctuated between 0.363÷0.421 and increased by 12-14% on average ($p<0.01$) compared to the control (Figure 3.4.2). In 6-month-old animals, the ratio of this indicator increased slightly and amounted to 21-24% ($p<0.001$) (Figure 3.4.3).

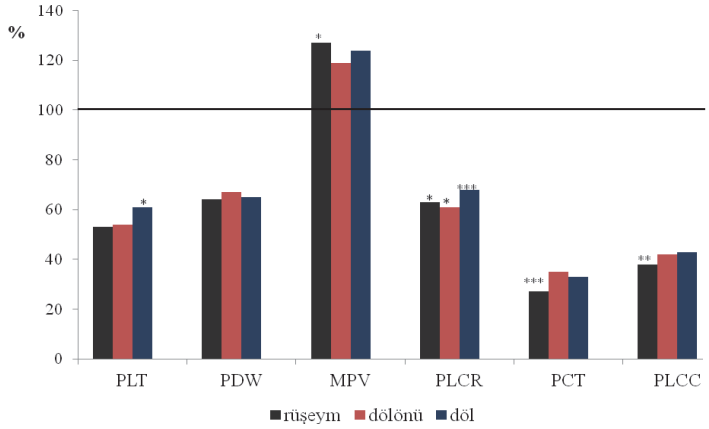

Figure 3.4.1 Percentage indicators of thrombocytic indices in one-month-old animals exposed to hypoxia during prenatal development (*-p<0.05; **- p<0.01; ***- p<0.001).

However, in our studies on 3- and 6-month-old animals, no significant variability was observed in the average volume of platelets. Similarly, the heterogeneity of platelets was also observed within the norm.

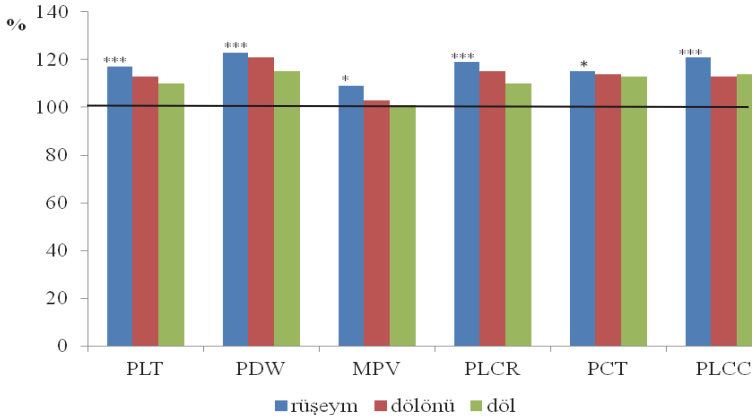

Figure 3.4.2. Percentage indicators of thrombocytic indices in three-month-old animals exposed to hypoxia during prenatal development (*-p<0.05; **- p<0.01; ***- p<0.001).

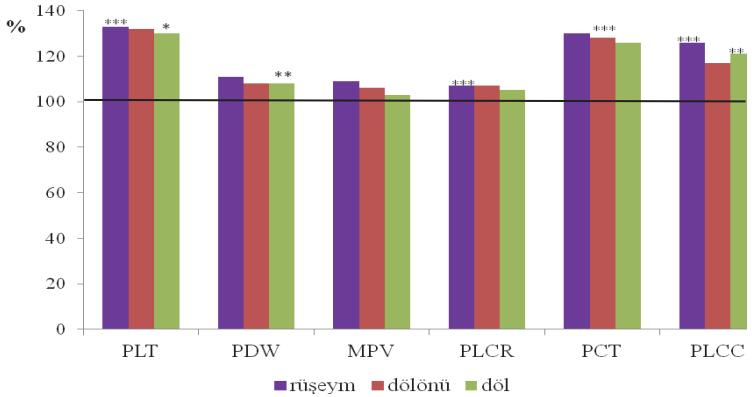

Figure 3.4.3 Percentage indicators of thrombocytic indices in six-month-old animals exposed to hypoxia during prenatal development (*-p<0.5; **- p<0.01; ***- p<0.001).

3.5. Morphohistological characteristics of liver tissue in one-, three- and six-month-old rats with normal intrauterine development and animals exposed to hypoxia during different periods

First, the morphometric parameters of the liver were studied in one-month-old rats. The initial difference between the control and trial groups was recorded in the absolute mass of the liver corresponding to the body mass. Thus, the analysis of the obtained data showed a decrease of 20-26 % (p<0.001) in the absolute mass of the liver relative to the body mass in trial-group animals compared to the control group, especially in the animals exposed to hypoxia during the embryogenic stage of development. Besides, the mass of the liver relative to the body mass in the animals of the trial group was statistically reliably reduced by 20-23% (p<0.01). Histological studies of the liver showed no pathological changes in the liver of the control-group animals. In the liver parenchyma of animals whose embryonic development occurred under normal conditions, hepatocytes with normal borders and one nucleus were recorded (Figure 3.5.1). In the critical periods of prenatal development (embryonic, pre-fetal, and fetal), in the liver of animals exposed to

hypoxia, along with slight vacuolization, expansion of hepatocytes and an increase in the size of their nuclei were observed (figure 3.5.2). Thus, the diameter of the hepatocytes in the animals of the trial group increased by 16-18%, and the diameter of the nucleus increased by 25%, compared to the control group. Since the area of hepatocytes and their nuclei are indirect indicators of polyploidization of hepatocytes, these indicators were determined in the control and trial groups, and an increase in the area of hepatocytes (31%) and their nuclei (44%, $p<0.01$) was found to be statistically reliable in animals exposed to hypoxia during embryonic development. Besides, NSI (nuclear cytoplasmic index) increased by 17% ($p<0.01$). A significant increase (12%) in the number of binucleated hepatocytes in the liver of trial-group rats was also detected compared to the control group.

As a result, expansion of hepatocytes led to compression and expansion of sinusoids in the parenchyma. At the same time, the increase in the number of binucleated hepatocytes can be an indicator of the continuation of recovery processes in accordance with the decrease in the absolute liver mass and mass relative to the body mass in the animals of the trial group.

During the comparative study of histological data, no statistically reliable different results were obtained in the liver of three-month-old rats. Binucleated hepatocytes were rarely found in the parenchyma (Figure 3.5.3). These results can be evaluated as an indication of the completion of recovery processes aimed at eliminating the negative effects of antenatal hypoxia in animals of this age group. However, severe blood stasis was observed in the liver samples of experimental animals and disorders in the hemodynamic sphere were detected (Figure 3.5.4). The mentioned pathologies were recorded in the venous structures of the liver.

Similarly, no statistically reliable different results were obtained in the morphometric indicators of the liver parenchyma in the control and trial groups of six-month-old rats. Thus, in 6-month-old control animals, the diameter of the nucleus of hepatocytes was 22.67 ± 2.07 μm, the average size of the area of hepatocytes was 406

± 74.81 μm^2, the average value of the diameter of the nucleus of hepatocytes was 12.3 ± 0.82 μm, the average area of the nucleus was 119.83 ±16.73 μm^2, while the nuclear-cytoplasmic index (NSI) was on average 0.30±0.01 (Figure 3.5.5). In adult animals exposed to the hypoxia factor during the embryonic period, the diameter of hepatocytes, the diameter of the nucleus, the area of hepatocytes, the area of the nucleus, and NSI were 22.83±1.8 μm, 12.6±1.24 μm, 409.1±83.1 μm^2, 124.6± 17.9 μm^2, and 0.30±0.02, respectively. Similar results were recorded in animals exposed to hypoxia during the pre-fetal and fetal periods, and no statistically significant changes were observed in the morphometric parameters of the parenchyma.

Although the obtained evidence showed that the recovery processes were completed in six-month-old rats as well as in three-month-old animals, blood stasis observed in the parenchyma and macrophages (Figure 3.5.6) revealed traces of the remote effect of hypoxia[23].

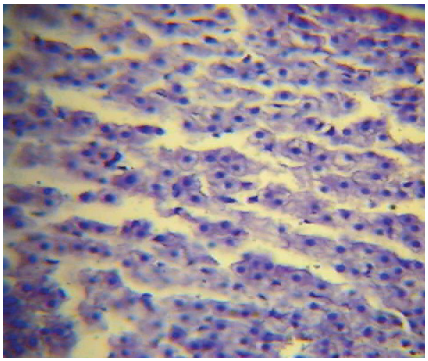

Figure 3.5.1. Liver parenchyma in one-month-old animals with normal embryonic development. Normal structure of the liver.

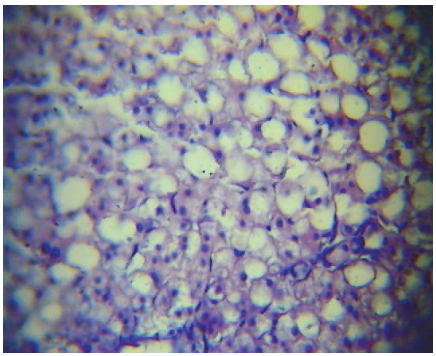

Figure 3.5.2. Liver parenchyma in one-month-old animals exposed to the hypoxia factor during the embryonic stage of development. Vacuolization in the parenchyma.

[23] Джафарова Г.Г. Влияние пренатальный гипоксии на печень крыс // - Нижневартовск: Бюллетень науки и практики. «Наука и практика» Россия, - 2022. Т. 5, №3. - с. 34-39.

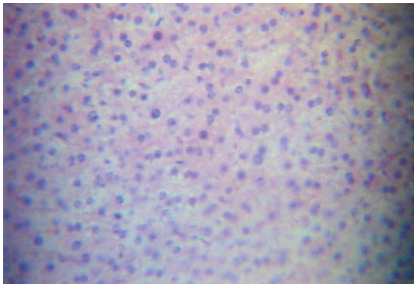

Figure 3.5.3. Liver parenchyma in three-month-old animals with normal embryonic development. Normal structure of the liver.

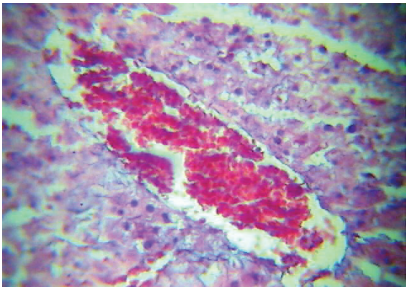

Figure 3.5.4. Liver parenchyma in three-month-old animals exposed to the hypoxia factor during the embryonic stage of development. Blood stasis in the parenchyma.

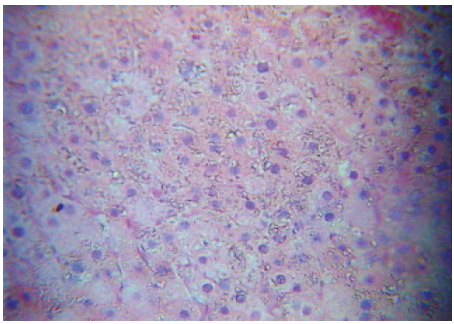

Figure 3.5.5. Liver parenchyma in six-month-old animals with normal embryonic development. Normal structure of parenchyma.

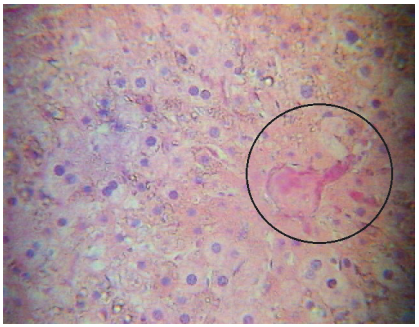

Figure 3.5.6. Liver parenchyma in six-month-old animals exposed to the hypoxia factor during the embryonic stage of development. Macrophage in the parenchyma.

CONCLUSIONS

1. Prenatal hypoxia has been found to cause significant changes in the dynamics of most stages of the blood coagulation system during the individual development of the organism. The level of these changes depends on the separate stage of intrauterine development (embryonic, pre-fetal, fetal) at which the hypoxia factor occurs and is stable until the maturity stage of ontogenesis.

2. The number of platelets in the platelet chain of blood coagulation and the main platelet indices decrease, and a decrease in platelet activity occurs in one-month-old pups exposed to the hypoxia in separate periods (embryonic, pre-fetal, and fetal) of intrauterine development. The hypocoagulation character of the hemostasis system is revealed in one-month-old animals exposed to hypoxia during the embryonic period of development.

3. It was found that in one-month-old pups exposed to prenatal hypoxia, blood coagulation time is prolonged, recalcification activity and plasma tolerance to heparin decrease, prothrombin demand decreases, blood coagulation potential, characterized by a decrease in fibrinogen level against the background of prolongation of thrombin time is weakened. It was detected that the observed changes in the coagulation ring are caused by deficiencies in the platelet chain, and a more severe effect of hypoxia was recorded in the embryonic stage.

4. Serious changes in the liver tissue are observed in one-month-old animals exposed to hypoxia during the critical stages of intrauterine ontogenesis. Thus, the decrease in the absolute and relative weight of the liver, the expansion of hepatocytes, the increase in the size of their nuclei, and the positive dynamics observed in the number of binuclear hepatocytes prove that the recovery processes aimed at eliminating the negative effects of this stres factor occur.

5. The number of platelets in the peripheral blood, the thrombocrit indicator, and the fraction of large platelets increase in the animals of sexual maturity (3 months) and adulthood (6 months) periods that have been exposed to the hypoxia factor during the embryonic, pre-fetal and fetal periods of prenatal development. These facts indicate

deficiencies in the hemocoagulation process by characterizing the increased clotting potential.

6. In 3-month-old and 6-month-old animals exposed to hypoxia during the separate periods of ontogenesis, shortening of blood coagulation time, increase in recalcification time, high tolerance of plasma to heparin, increase in prothrombin demand, shortening of thrombin time, and increase in fibrinogen level, which characterize a partial increase in blood coagulability, are revealed. These show deficiencies in the coagulation ring and determine the hypercoagulation nature of the hemostasis system.

PRACTICAL RECOMMENDATIONS

1. The results of the research can be important in the assessment of homeostasis in organisms at different stages of ontogenesis, under the influence of physical and chemical stress factors in the early stages of development.

2. The results can be applied to the detection and diagnosis of blood defects in the new generation that has been caused by hypoxia during sensitive stages in the dynamics of fetal development in pregnant women working in extreme labor conditions (chemical industries, high altitude, underwater, etc.).

3. The obtained results can be used in teaching the protective properties of blood in seminars and lectures and in practical training manuals on the subject of "Human and animal physiology" in biologically oriented educational institutions.

The main content of the dissertation is reflected in the following published works of the author:

1. Mustafayeva G.Q., Qazıyev A.Q. Prenatal ontogenezi hipoksiya olunmuş bir aylıq siçovul balalarında qanın laxtalanma göstəriciləri // - Bakı: A.İ.Qarayev adına Fiziologiya İnstitutunun və Azərbaycan Fizioloqlar Cəmiyyətinin elmi əsərlərinin külliyatı, - 2010, XXVIII cild. s. 68-72.

2. Mustafayeva G.Q. İnkişafın rüşeym mərhələsini anaların hipoksiyası şəraitində keçirmiş siçovul balalarında qanın laxtalanma və rekalsifikasiya müddəti // AMEA aspirantların elmi konfransının materialları, - Bakı:-"Elm", 20-21 may, - 2010, - s. 240-245.
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8. Cəfərova G.Q. Antenatal hipoksiyanın siçovul balalarında qanın laxtalanmasının yekun fazasına uzaqlaşdırılmış təsiri // - Bakı: Azərbaycan Milli Elmlər Akademiyasının Xəbərləri, Biologiya və Tibb Elmləri,- 2017, cild 72, №2, - s. 132-135.
9. Джафарова Г.К. Некоторые особенности свертывания крови крыс, подверженных воздействию гипоксии в плодный период пренатального развития // - Прага: Scientific discussion, - 2017. Vol. 1, № 8, ISSN 3041-4245, с 16-20.

10. Cəfərova G.Q. Antenatal hipoksiyanın yetkin siçovullarda protrombin müddəti və aktiv parsial tromboplastin müddətinə təsiri //- Bakı: Azərbaycan Milli Elmlər Akademiyası A.İ.Qarayev adına Fiziologiya İnstitutunun və Azərbaycan Fizioloqlar Cəmiyyətinin elmi əsərlərinin külliyatı, - 2018, cild XXXVI, - s. 97-101.
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13. Cəfərova G.Q. Embriogenezdə hipoksiya təsirinə məruz qalmış siçovullarda qanda fibrinogenin dəyişmə dinamikası / Cəfərova G.Q., Qazıyev A.Q., Rüstəmov Q.D. [və b.] // Sağlamlıq, elmi-praktik jurnal, - Bakı: - 2019, №2, - s. 105-108.
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