EXTRAGENITAL PATHOLOGY OF THE MOTHER AND MORPHOLOGICAL FEATURES OF THE DEVELOPMENT OF THE THYMUS IN THE PERIOD OF EARLY POSTNATAL ONTOGENESIS

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ABSTRACT

The influence of chronic toxic hepatitis (CTH) of the mother on the development of the offspring thymus in the dynamics of early postnatal ontogenesis was studied. We used 120 female outbred rats weighing 110-120 g, and 120 male rat pups on days 1, 3, 7, 15, 21 and 30 after birth. Along with researches of changes in the thymus of the offspring, it was found that females with CTG had impaired fertility, only 84% of the females were pregnant after mating, only 64% of the pregnancy ended in childbirth, 8% miscarriages, and the rest had mortality during pregnancy, after childbirth rat pups showed up to 39.6% increase in infant mortality. There was a decrease in the average number of rat pups in the litter, a lag in weight and growth, as well as a decrease in the absolute and relative weight of the thymus of rat pups. The above processes in the offspring of CTG females were morphologically accompanied by a developmental delay and hyperplasia of the thymus and suppression of the T-cell immune system, that is, signs of accidental involution.

Key words: chronic toxic hepatitis, offspring, thymus, early postnatal ontogenesis, accidental involution.

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INTRODUCTION

It is known that the development and formation of the immune system in the pre- and postnatal periods of development depends on a number of factors, including the state of health of the maternal organism, which can affect the morphogenesis of the fetal immune defense organs. A number of authors express the opinion that changes in the functional state of the maternal organism during pregnancy, caused by infectious diseases, taking medications, can negatively affect the development of the immune system of the offspring [1, 4, 11, 19]. At the same time, despite the ongoing therapeutic and preventive measures, there is still a significant trend towards an increase in toxic liver damage, including among women of childbearing age, who, with or without acute viral hepatitis, often contribute to the development of chronic hepatitis and cirrhosis liver. It is also worrying that this extragenital pathology has a negative impact during pregnancy on the developing fetus, and after childbirth on the newborn [7, 9, 10, 18, 21].

Of particular interest are studies of the effect of chronic maternal hepatitis during pregnancy and lactation, on the development of the immune system of the offspring at different times of postnatal development, including the thymus, the central organ of immunity [8, 21]. The

thymus, as the primary organ of the immune system, largely determines not only the state of the peripheral organs of immunogenesis, but also the severity of the protective reactions of the whole organism [8, 15]. Immunodeficiency states in young children are quite common in clinical practice. Among the causes leading to immunodeficiency, the dominant ones are unfavorable exogenous influences of various etiologies in the prenatal period of ontogenesis, as well as the presence of maternal pathology, not only in the prenatal period, but also during breastfeeding [8, 16]. However, when studying the available literature, this issue is still poorly understood.

The aim of our research was to study the effect of extra genital pathology - chronic toxic maternal hepatitis on the formation of the offspring thymus in the period of early postnatal ontogenesis.

MATERIALS AND METHODS

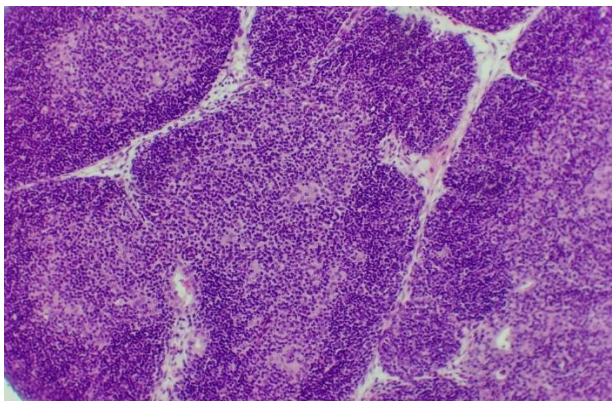
From the very beginning, it should be noted that the experimental studies were carried out in accordance with the requirements of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Scientific Purposes" and the principles of the "Helsinki Declaration on the Humane Treatment of Animals". The experiments were carried out on 120 female outbred rats weighing 110-120 g. To exclude infectious diseases, all animals were kept under quarantine for two weeks. Then the experimental animals were divided into 2 groups (60 rats in each): experimental and control. A model of heliothrin hepatitis was obtained by weekly administration of 0.05 mg of heliothrin per 1 g of body weight for 6 weeks [2]. The control group of animals received sterile saline instead of heliothrin. Males were added to the females 10 days after the last injection. Subsequently, the course of pregnancy was monitored.

It should be noted that toxic hepatitis in female rats had a significant negative impact on fertility and the course of pregnancy. All animals in the control group became pregnant, which successfully ended in childbirth. Whereas in the experimental group of animals out of 84% of rats, pregnancy ended in childbirth in 64%, miscarriages - in 8%. The rest died during pregnancy. The average number of pups from one mother in the control group was 9.7+0.5, in the experimental group -6.3+0.6. With toxic hepatitis in the mother, postnatal mortality of the offspring increased to 39.6% (in the control 6.2%). Moreover, the highest mortality (28.7%) was observed on the 1-7th day after birth (5.4% in the control). Dead rat pups were excluded from the experiments. In total, 60 cubs from females of the control group and 60 from females of the experimental group were included in the studies.

Rats were decapitated under light ether anesthesia on days 1, 3, 7, 15, 21, and 30 after birth. To conduct a ***morphological*** analysis of the thymus, pieces of the obtained tissue were fixed with 10% buffered formalin for 24 hours. Dehydration, compaction and filling of tissues in paraffin were carried out according to the generally accepted method. Sections with a thickness of 3-5 µm were stained with hematoxylin-eosin according to the standard method. ***Morphometric*** researches were carried out using the Avtandilov grid per unit area according to the generally accepted method. ***Immunohistochemical studies*** were carried out on 60 samples. Tissues fixed with 10% buffered formalin for 24 hours were used. Routine tissue insertion was carried out on the STP120 carousel processor, ThermoFisher, Germany. Serial sections 3 µm thick were deparaffinized, dehydrated, unmasked, and stained with antigens using a specialized automated system Ventana Benchmark XT, Roche, Switzerland. The study was carried out in the thymus of 1, 3, 7, 15, 21 and 30 day old rats with CD3 and CD20 antibodies to detect T- and B-lymphocytes, respectively, on thymus biopsies from the control and experimental groups of animals. Statistical processing of the obtained data was carried out using computer programs.

RESULTS AND DISCUSSION

As a result of our morphological researches, it was found that in newborn rat pups (intact and control groups), the thymus is sufficiently formed and consisted of more than two lobes. Outside, the thymus was covered with a capsule, from which connective tissue partitions departed, dividing the lobes into lobules. For the lobules, it is characteristic that there is a clear differentiation into the cortical and medulla, a greater density of cell distribution in the cortical substance of the thymus lobule than in the medulla (see Fig. 1). The cortex was mainly represented by lymphocytes and accounted for two thirds. The location of lymphoblasts is noted mainly in the subcapsular space of the cortical substance, in some cases in rats a narrow non-epithelial space was found under the capsule. In addition, mitotically dividing lymphocytes and a large number of medium and small lymphocytes, as well as reticulo-epithelial cells and macrophages, were more often found in the cortical zone of the thymus lobules.



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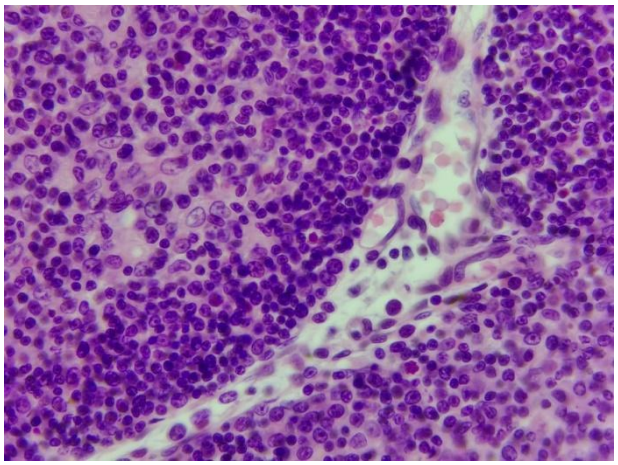

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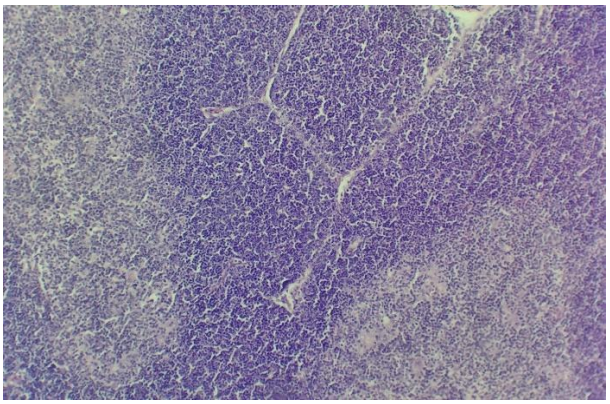

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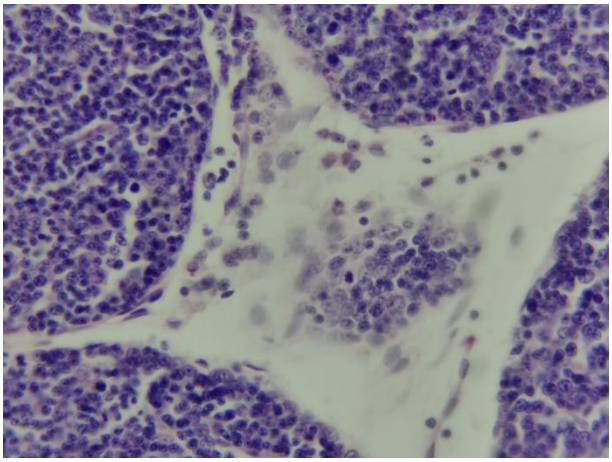

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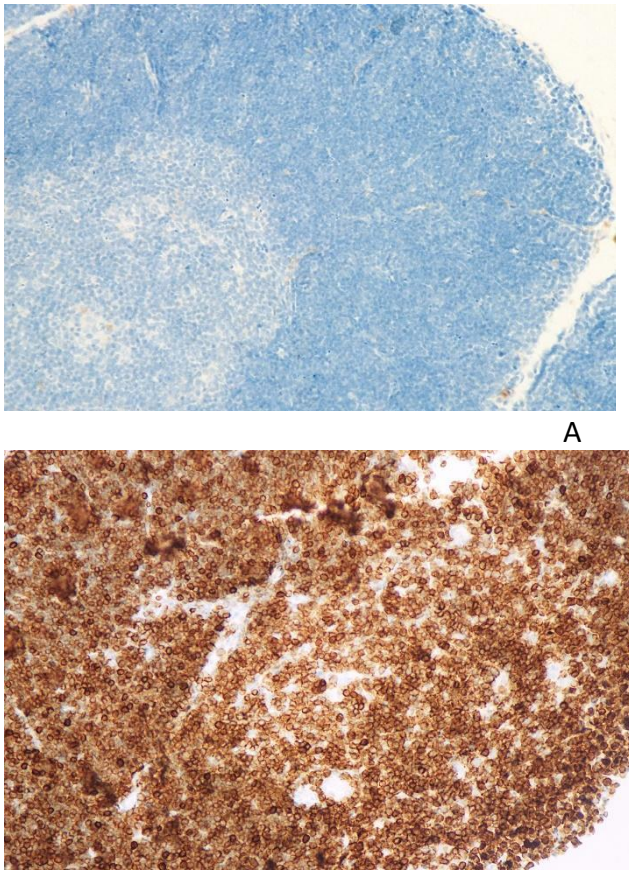
Figure 1. (A) Thymus of a rat pup of the control group of animals on the 15th day after birth. All structural and functional zones of thymus lobules are well expressed. Paraffin cut. Hematoxylin-eosin staining. Magnification x 130 times. (C) Thymus of a rat pup of the control group of animals on the 15th day after birth. Connective tissue trabeculae of the thymus are infiltrated with cellular elements. Paraffin cut. Hematoxylin-eosin staining. Magnification x 200 times.

Figure 2. (A) Thymus of a rat pup from a mother with CTG on the 15th day after birth. All structural and functional zones of thymus lobules are well expressed. Some increase in the area occupied by the brain zone of the thymus lobule is noted. Paraffin cut. Hematoxylin-eosin staining. Magnification x 130 times. (B) Thymus of a rat pup from a mother with CTG on the 15th day after birth. There is a decrease in the density of cells in the subcapsular zone, an increase in the area occupied by connective tissue, vessels filled with blood cells. Paraffin cut. Hematoxylin-eosin staining. Magnification x 200 times



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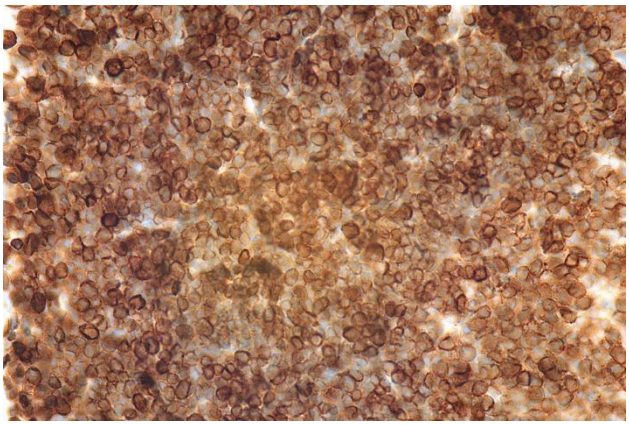

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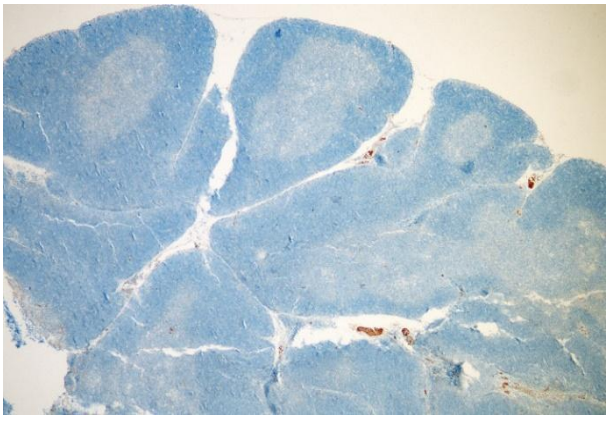
Figure 3. Thymus of a rat pup from the control group on the 7th day after birth: (A) treated with CD20 monoclonal antibodies; Paraffin cut. Magnification x 200 (B) Treated with CD3 monoclonal antibodies. Paraffin cut. Magnification x 200; (C) treated with CD3 monoclonal antibodies. Paraffin cut. Magnification x 400



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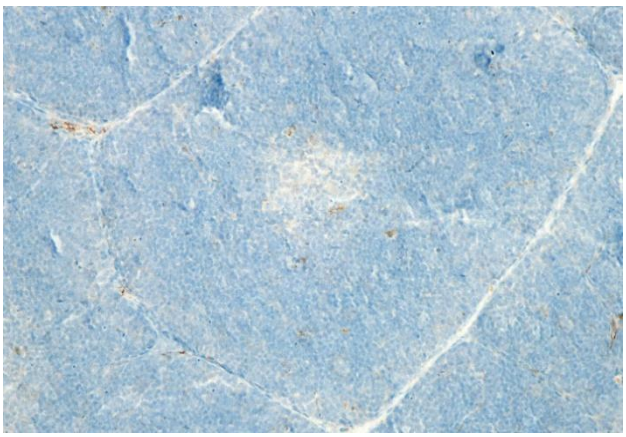

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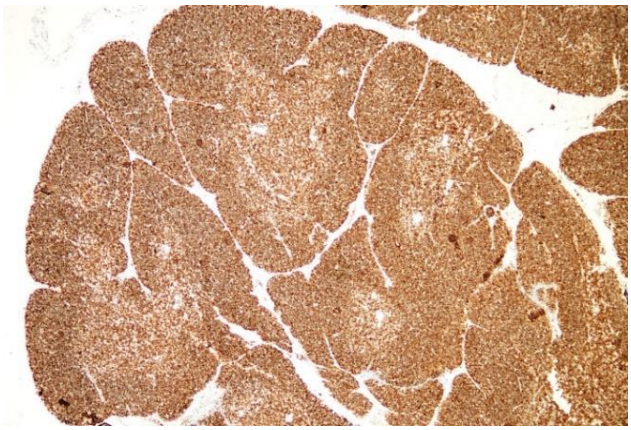

Figure 4. Thymus of a 21 day old rat pup: (A) treated with CD3 monoclonal antibodies. Paraffin cut. Magnification x 130; (B) treated with CD20 monoclonal antibodies. Paraffin cut. Magnification x 200; (C) treated with CD3 monoclonal antibodies. Paraffin cut. Magnification x 130

For the brain zone of the thymus lobules of newborn rat pups, which corresponded to one third of the thymus lobule, a reduced number of lymphocytes was characteristic, between which were located as separate reticular epithelial cells with increased cytoplasm oxyphilia, macrophages and monocyte-like cells, Hassal's thymic bodies were sometimes found.

In the research of the anthropometric data of rat pups obtained from females with chronic toxic hepatitis, a developmental delay was found, expressed in a decrease in body weight on days 1-7 after birth, as well as a decrease in the body length of animals and the thymus mass of rat pups from birth and up to 21 days after birth, as well as in the developmental delay of rat pups (see Table 1).

Table 1.

Influence of toxic maternal hepatitis on some anthropometric parameters and thymus mass in rat pups in the dynamics of early postnatal ontogenesis (X±Sx)

Age animals	**Gr. of animals**	**Исследуемые параметры**			
		Rat weight, g	Rat body length, mm	The absolute weight of the thymus, g.	Relative mass of thymus (x10-2)
Day 1	C	5,6±0,11	27,1±0,47	10,2±0,26	1,82±0,049
	E	**5,1±0,10**	**23,9±0,41**	**8,3±0,23**	1,82±0,047
Day 3	C	6,0±0,16	33,0±0,57	18,1±0,35	3,05±0,016
	E	**5,3±0,15**	**27,1±0,32**	**16,0±0,36**	**2,92±0,011**
Day 7	C	8,9±0,17	51,5±0,55	26,4±0,43	2,97±0,065
	E	**8,1±0,14**	**36,4±0,39**	**22,9±0,41**	**2,82±0,065**
Day 15	C	18,6±0,34	51,5±0,55	78,5±0,61	4,2±0,067
	E	18,9±0,21	**41,5±0,52**	**71,8±0,53**	**3,8±0,047**
Day 21	C	29,1±0,47	55,2±0,86	132,9±1,08	4,58±0,083
	E	26,8±0,50	**47,6±0,82**	**119,6±1,27**	**4,51±0,065**
Day 30	C	45,3±0,50	57,6±0,93	221,0±1,89	4,89±0,078
	E	42,7±0,90	51,6±1,24	181,6±1,80	5,29±0,170

Note: 1. conditional abbreviations Gr.g-x - group of animals, C - control, E - experienced;
2. Bold type indicates the values where the differences are significant relative to the previous period at P<0.05.

The thymus of offspring from the experimental group of animals - females with chronic heliotritis hepatitis was characterized by a peculiar dynamics of structural and functional changes.

The thymus of newborn rats, an experimental group of animals that developed against the background of toxic hepatitis of the mother, was distinguished by pronounced structural changes in the processes of differentiation of the thymus into the cortical and medulla, in favor of the medulla, which was quite clearly expressed in newborn rats. In the dynamics of early postnatal development, there is a decrease in the area of the lobules occupied by the cortical zone from 3 days after birth to 15 days of development, against this background, an increase in the proportion of the brain zone and the area occupied by the connective tissue was noted. Along with this, it should be noted an increase in the number and size of Hassall's bodies from 3 days to 30 days of postnatal development (see Table. 2, Fig. 2). Also, when viewing preparations in the cortical zone of the thymus of rat pups of the experimental group, a significant decrease in the density of cellular distribution was determined, and not only in the subcapsular zone, an increase in the number of destructive lymphocytes and macrophages with heterophagosomes in the form of dense inclusions, apparently, which is a sign of increased thymocytolysis. The severity of the described changes decreased only by the 30th day of postnatal ontogenesis.

Table 2.

The influence of toxic hepatitis of the mother on the development of structural and functional zones and Thymus Gassall's bodies in rat pups in the dynamics of early postnatal ontogenesis (X±Sx)

Days of postnatal development	Gr. of animals	Thymus lobule zones			Hassall's bodies (abs. units)
		Cortical	Brain	Connected tissue	
		relative units	relative units	relative units	
Day 1	C	66,01±0,77	29,70±0,46	3,87±0,08	0,20±0,13
	E	69,55±0,45	27,15±0,40	**4,20±0,05**	0,60±0,16
Day 3	C	67,63±0,65	28,39±0,49	4,00±0,09	1,10±0,10
	E	**63,43±0,55**	**32,20±0,55**	**4,32±0,07**	**2,90±0,23**
Day 7	C	80,46±0,78	15,61±0,69	4,90±0,16	6,60±0,37
	E	**74,30±0,34**	**19,3±0,54**	**6,40±0,09**	**9,40±0,40**
Day 15	C	71,46±0,97	26,3±0,62	4,20±0,20	7,20±0,47
	E	**66,9±0,43**	**30,01±0,46**	**5,60±0,10**	**10,60±0,67**
Day 21	C	70,60±0,89	26,80±0,61	4,60±0,22	11,5±0,66
	E	**65,68±0,49**	**29,30±0,37**	**5,88±0,09**	**14,80±0,32**
Day 30	C	72,09±0,82	25,90±0,66	3,85±0,08	18,60±0,56

	E	71,46±0,48	27,79±0,39	**4,80±0,11**	**23,02±1,02**

When conducting cytometric researches of the thymus of rat pups in the dynamics of early postnatal ontogenesis, we counted the cells, taking into account the division of thymus lobules into three zones: cortical, cortico-medullary and cerebral zones.

Cytometry of the cortical zone of the thymus of rat pups revealed a decrease in the average number of small and medium lymphocytes starting from the 1st day (232.6±6.58 and 208.4±4.54 in the control and experimental groups, respectively) and up to 15 days of age (262.0±5.59 and 227.2±6.00), the number of lymphoblasts from birth up to 15 days of age, as well as a decrease in the total number of cells on the 1st and 3rd days (334.3±7 .23 and 293.2±5.60) and (349.9±6.55 and 272.0±6.66) and a decrease in the total number of mitotically dividing cells in the cortical zone (0.44±0.009 and 0.39± 0.009, as well as 0.44±0.009 and 0.40±0.016, respectively). Then, starting from the 7th day and up to the 30th day of postnatal development in rat pups, a significant increase in mitotically dividing cells of the thymic cortical zone was already observed.

In the cortico-medullary zone of the thymus of rat pups from females with toxic hepatitis, an increase in the average number of lymphoblasts was noted starting from the 1st day up to 30 days after birth (65.4±1.13 and 61.4±1.02, as well as 57 .5±1.07 and 66.2±1.04 on the 1st day and 30th day after birth, respectively), as well as monocyte-like cells and macrophages. When studying the average number of reticulocytes in this zone, their increase from 1 to 7 days of age was observed (15.7±0.35 and 12.4±0.52, as well as 19.5±0.32 and 22.3±0 .89 respectively). In addition, the thymus corticomedullary zone was characterized by an increase in mitotically dividing cells from the 1st to the 15th day of age.

For the brain zone of the thymus of rat pups of the experimental group of animals, a decrease in the average number of small and medium-sized lymphocytes was characteristic, starting from the 3rd day and up to 21 days after birth (110.30±3.13 and 85.60±2.92, as well as 119 0±3.26 and 101.5±2.16 in control and experimental animals on the 1st and 21st days after birth, respectively), while on the 1st and 3rd days after birth, a decrease in the mean number of lymphoblasts (0.5±0.025 and 0.4±0.022, as well as 0.75±0.016 and 0.45±0.019, respectively), and then from 7 to 30 days of age, a significant increase in their average number was observed (1, 21±0.038 and 2.23±0.082, as well as 0.3±0.06 and 0.8±0.07 on days 7 and 30, respectively). Along with this, on the 7th and 15th days there was also an increase in the number of reticular cells (60.32±1.00 and 65.30±0.78, as well as 58.40±1.19 and 64.60±0.84 per 7 and 15 days, respectively), in all periods of development there is a significant increase in monocytes and macrophages, and an increase in the number of cells in the mitosis stage from day 7 to day 30 (0.52±0.019 and 0.75±0.051 on day 7 and 0 ,26 ± 0.015 and 0.40 ± 0.019 on the 30th day of development), it should also be noted that in 3-day-old experimental rat pups in the cerebral zone of the thymus lobules, a decrease in the total number of cells (0.26 ± 0.015 and 0.40 ±0.019 in the control and in the experiment, respectively).

The results of immunohistochemical studies using CD3 antibodies - markers of T- and CD20 antibodies - markers of B-lymphocytes in the thymus of rat pups of the control group of animals revealed a certain dynamics of changes in the ratio of these cells during early postnatal ontogenesis. It should be noted that already in newborn rat pups there was a well-pronounced expression of T-lymphocytes over the entire area of the thymus lobule, with the only difference being the density of the antigen detected in the cells, which increased in parallel with the increase in the period of development of postnatal ontogenesis (see Fig. 3).. At the same time, somewhat

different results, different from the data of other researchers, were obtained by us in the study of B-lymphocytes. Characteristic immunohistochemical staining was observed in a very small amount and only in the connective tissue trabeculae separating the thymus lobules, and even on the 7th day after birth in very small amounts inside the lobules in the area of the perivascular spaces. In the dynamics of postnatal development, a slight increase in B-lymphocyte cells was observed in the thymus of rat pups on days 21–30 after birth (see Fig. 4).

In the thymus of rat pups born from females with CTH, immunohistochemical studies for the presence of T- and B-lymphocytes in the dynamics of early postnatal ontogenesis revealed significant changes relative to control parameters. In rat pups, starting from the 7th day, the most pronounced decrease in the number of CD3+ - T-lymphocytes with a densely expressed antigen was observed in the cortical zone of the thymus lobules by more than 12% compared with the indicator in the control group of animals, and progression of this process was noted up to 30s. days after birth. It is noteworthy that against this background, a significant increase, up to 8%, in the number of cells of the B-lymphocyte series is revealed and not only in the perivascular connective tissue, but also in the parenchymal part of the brain zone of the thymus lobules, among monocyte-like cells, macrophages and reticuloepithelial cells.

When analyzing the results obtained, it should be taken into account that chronic heliothrine intoxication leads to the occurrence of toxic hepatitis, which generally tends to progress, i.e. is a model of aggressive chronic hepatitis [1, 3]. With active forms of hepatitis, changes in the immune status occur, in particular, there are profound changes in the T- and B-systems of immunity and there is an increase in the titer of immunoglobulins of various classes, an increase in the gamma fraction of globulins, which is the criteria for assessing the activity of the developing pathological process. Moreover, in cases where the process becomes chronic, against the background of a slight decrease in T-helpers, the number of T-suppressors (killers) is significantly reduced, which contributes to the formation of anti-hepatic antibodies and activation of the pathological process with the inclusion of an autoimmune mechanism [5, 11, 20].

Without a doubt, the mother's liver pathology, and first of all, a violation of the detoxification function, as well as autoimmune reactions occurring in the mother's body, cannot but affect the development of the thymus of the offspring, which has a special histological structure, including the connective tissue stroma, epithelium and lymphoid parenchyma. It is known that these components are in continuous interaction and are under the control of microenvironment cells and bioactive components secreted by them, which determines the functional activity of the central organ of the immune system responsible for T-cell immunity [6, 10, 13]. Thereby, we established morphometric changes in the thymus of offspring from females with CTH in the form of a decrease in the area occupied by the cortical zone, due to an increase in the proportion of the brain zone and connective tissue stroma. A decrease in the number of small and medium-sized lymphocytes in the cortical zone, the number of lymphoblasts and mitotically dividing cells in the early periods of postnatal ontogenesis, followed by an increase in the average number of mitotically dividing cells in week-old rats until the 30th day of development. Conversely, the cortico-medullary zone was characterized by an increase in the average number of mitotic cells, an increase in the number of reticulocytes and cells of the monocyte-macrophage series, and Hassall's bodies are most likely signs of accidental involution of the thymus, most likely associated with transplacental and transmammary effects of hepato- and other toxins on rat pups [5, 9, 12, 14, 15]. While the reaction of the brain zone of the thymus is most likely due to the T-suppressor and autoimmune effects of the mother's body on the

developing offspring. The progression of changes starting from days 7–15 seems to be due to a gradual increase in the "volume of antigenic stimulation" after childbirth and the subsequent transition of the pups to a mixed diet [11, 17].

CONCLUSION

1. Maternal CTG has a negative effect on the fertility of sexually mature females: only 84% of the females were pregnant after mating and in 64% of the animals the pregnancy ended in a successful delivery, there was an increase in postnatal mortality up to 39.6% (6.2% in the control).

2. In the offspring of females with CTH, there was a decrease in the average number of pups in the litter, a decrease in the average weight of pups up to 7 days, as well as growth retardation, a decrease in the absolute and relative weight of the thymus up to 21 days after birth.

3. Morpho-, cytometric and immunohistochemical studies indicate that in the thymus gland of offspring from females with CTG there are signs of developmental delay, hyperplasia, violation of the ratio of the areas of the cortical and brain zones of the thymus lobules, an increase in Hassal's bodies and cytometric changes characteristic of the accidental involution of the thymus with signs of suppression T-cell system of immunity.

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