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MORPHOFUNCTIONAL TRANSFORMATIONS DURING THE THYROID MORPHOGENESIS OF THE WISTAR RATS OFFSPRING AFTER INTRAUTERINE DEXAMETHASONE EXPOSURE

Fedosieieva O.V. ✉, Bushman V.S., Necheporenko A.G. Morphofunctional transformations during the morphogenesis of the thyroid gland of the offspring of Wistar rats after intrauterine exposure to dexamethasone. Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine.

ABSTRACT. Background. In recent years, the prevalence of thyroid pathologies of various origins among children in the world has reached a significantly high level. The use of glucocorticoids during pregnancy remains a debatable issue in obstetrics today, as they can both positively and negatively affect the processes of organ morphogenesis and be the cause of pathological conditions in the postnatal period. **Objective**: to establish the features of morphofunctional transformations during the morphogenesis of the thyroid gland of the offspring of rats at an early age in normal and after intrauterine action of dexamethasone. **Methods.** 108 thyroid glands of rats of 3 experimental groups were microscopically examined using histological and immunohistochemical methods, followed by statistical processing of the obtained results. **Results.** Against the background of high levels of total follicular thyrocytes per 1 day of life in animals that received prenatal dexamethasone, cytoplasmic expression of TgAb was expressed, which correlated with the indicators of nuclear and cytoplasmic Fox-1 expression. From the 7th to the 11th day, a decrease in the total number of thyrocytes per unit area was observed due to the accumulation of colloid in the follicles, an increase in Fox-1 cytoplasmic expression and a decrease in nuclear expression, against the background of increased proliferative activity. By day 21, Fox-1 cytoplasmic and nuclear expression were almost identical. There was a decrease in the intensity of TgAb expression in the cytoplasm of thyrocytes and its expression in the colloid, a decrease in the number of Ki-67 positive thyrocytes per conditional unit area compared with the previous observation period. **Conclusion.** It was found that prenatal exposure of dexamethasone causes the offspring accelerate the development of morphological structures of the thyroid gland, but functionally they are in a state of stress of both the synthesizing apparatus and the process of hormone excretion, which is expressed in the imbalance of immunohistochemical expression of Fox-1 and TgAb. Such thyrocytes with signs of disturbances in synthetic activity desquamate into the lumen of the follicles, while on the 11th day we compensatory increase in the proliferative activity of the thyroid epithelium.

Key words: thyroglobulin, thyroid gland, rats, dexamethasone, parenchymal organs, immunohistochemistry.

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Background

The thyroid gland is important for the normal functioning of the body, and is the largest endocrine organ, which among the endocrine glands developed as the first in the process of embryogenesis. Pathology of the thyroid gland over the past 20 years has been ranked first positions among endocrine diseases of children in Ukraine and all over the world, and it forms the picture of the prevalence of all endocrine diseases, as it occupies a total of 58.0% of their structure, mainly due to disorders of organ morphogenesis and immune neuro-endocrine imbalance [1,

2]. The action of thyroid hormones is variously directed at all metabolic processes, functions of many organs and tissues, including fetal development, growth processes and tissue differentiation [3, 4, 5].

The thyroid gland has a high sensitivity to exogenous and endogenous influences and the ability to morphologically rearrange tissue [6, 7]. In clinical practice, synthetic glucocorticoids such as dexamethasone are used to accelerate fetal maturation in pregnant women at risk of preterm birth [8, 9, 10]. Antenatally glucocorticoids mimic the effects of endogenous elevation of plasma cortisol, which is usually observed in the fetus, close to the date of birth [11]. In humans and other mammals, a surge of cortisol in the body causes structural and functional changes in the tissues of the fetus, preparing it for childbirth and extrauterine life [12, 13, 14].

The question of the use of glucocorticoids during pregnancy remains a debatable issue in obstetrics today, because they can both positively and negatively affect the processes of organ morphogenesis and be the cause of pathological conditions in the postnatal period. It is known that the entry of cortisol from mother to fetus through the placenta is controlled by enzymes produced by the latter. However, synthetic glucocorticoids, such as dexamethasone, can freely cross the blood-placental barrier and cause changes in postnatal immunity and disease in the future [15, 16]. Despite the large number of studies on the effects of glucocorticoids on the fetus, there is almost no data on the prenatal effect of glucocorticoids on the processes of morphogenesis of the thyroid gland in the postnatal period. Therefore, the question of prenatal influence of dexamethasone on the processes of morphogenesis of the thyroid gland in the postnatal period of life is morphologically unresolved, and needs further scientific clarification, which is an extremely important experimental basis for improving the management of newborns and children by neonatologists, pediatricians, pediatricians.

The **aim** of the work is to establish the features of morphogenesis of the thyroid gland of rats in the milk period of postnatal ontogeny in normal and after intrauterine action of dexamethasone.

Material and methods

The study involved the thyroid glands of 108 white laboratory Wistar rats from 1 to 21 days of age. The animals were obtained from the vivarium of PE "Biomodelservice" in Kyiv.Rats were kept in a vivarium in acrylic cages with a volume of 300 cm3 for 4-5 animals each and free access to water on a standard diet. Before and during the experiment, the rats were in the same conditions: in the vivarium at t 20-25 ° C, humidity not more than 50%, the volume of air exchange (extraction-inflow) 8:10, in the light mode day and night. The animals were healthy in behavior and general condition. The conditions of care for animals complied with the norms of the "International Recommendations for Medical and Biological Research with the Use of Animals". The work also followed the rules and regulations established by the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 18.03.86) and the Law of Ukraine "On Protection of Animals from Cruelty" (from 21.02.2006 № 3447-IV, edition of 09.12.2015, grounds 766-19).

Animals were divided into 3 groups, 6 animals in each group: Group I - intact rats; Group II - control - animals which, on the 18th day of the dated pregnancy transuterine, transdermal, subcutaneously in the interscapular area was injected with 0.9% saline in the amount of 0.05 ml; III - experimental group - animals, which during laparotomy, by intrauterine, transdermal subcutaneous injection in the interscapular area was injected with a solution of dexamethasone at a dose of 0.05 ml at a dilution of 1:40 intrauterinely on the 18th day of pregnancy (Ukrainian patent №112288) . In the experimental subgroups used the allowable, generally accepted number of animals for statistical processing and obtaining reliable results 6 animals.

Thyroid gland with tracheal area was removed on 1, 3, 7, 11, 14, 21 days of life, fixed in 10% solution of neutral buffered formalin during the day. The objects were filled into paraffin blocks by the conventional method. Histological sections with a thickness of 4 μm were stained with hematoxylin and eosin for observation light microscopy and morphometry, histochemically with azan to determine the density of the colloid. The number of cells was counted in histological sections in a standardized field of view of the microscope at magnification x40 (number of cells per 40,000 μm2) followed by calculation of cell density per 1 mm^2.

For immunohistochemical study used monoclonal antibodies ki-67 (Ki-67), Thyroglobulin Antibody (2H11), Fox-1 Antibody (A-12) Santa Cruz Biotechnology Inc. using the method of indirect staining with conjugated HRP murine IgG-binding proteins, m-IgGκ BP-HRP (Santa Cruz Biotechnology Inc.), followed by incubation in a substrate of peroxidase and a mixture of chromogen DAB-3-diaminobenzidine tetrachloride, staining nuclei by Mayer hematoxilin, hemp dyeing enlightenment and balm.

The result was regarded as positive in the precipitation of chromogen salts in the form of a specific reaction (nuclear, cytoplasmic reaction depending on the location of the antigen). he intensity of benzidine label deposition was evaluated by photographic digital morphometry using Image J in each case in 5 standardized microscope space with a magnification of 400 (lens x40, eyepiece x10), where the intensity of marker expression was determined and quantified in conventional units of optical density negative reaction - 0-20; low level of expression - 21-50; moderate level of expression - 51-100; high level of expression - more than 100. The cell composition of

immunopositive cells was calculated using a visual method accounting of morphological structures in a standardized microscope space at magnification x40 (number of cells per 40000 μm2), followed by calculation of cell density per 1 mm2.

A set of morphometric studies was performed by microscope Carl Zeiss Primo Star equipped with the Axiocam digital microphoto attachment using program complex Zeiss Zen 2011. Statistical processing of the results was performed in the program "STATISTICA® for Windows 6.0" (StatSoft Inc., USA, license № AXXR712D833214FAN5). Hypothesis about the normality of the distribution of the studied indicators were checked by the Shapiro-Wilk test. Calculated the median lower and the upper quartile, the data were presented as Me (Q1; Q3). Significance of the difference between the frequency of positive immunohistochemical reaction in 2 groups was tested by the criterion of χ^2. For all types of analysis differences were considered significant at $p < 0,05$.

Results and discussion

The morphological structure of the thyroid gland of newborn rats 1-3 days of life of all studied groups was represented by glandular parenchyma and connective tissue stroma with blood and lymphatic vessels and nerves. The study of thyroid micropreparations of animals experimentally prenatally exposed to dexamethasone revealed that the gland of animals of the first day of life was slightly more excited: the number of resorption vacuoles in the colloid, which was dense in total, increased. In the interfollicular intervals there were more follicles of colloidal type with ki-67-positive cells. At this age, there is a large number of light thyrocytes in the wall of the follicles, it is ki-67-positive of the cell. The axis of proliferation is oriented parallel to the basement membrane of the follicle. If in the preparations of the thyroid gland of intact animals it was easy to find epithelial proliferative cell clusters, then in the glands of this period the animals of the experimental group they were almost absent. The expression of antibodies to thyroglobulin (TgAb) in the thyroid gland of animals of intact and control groups is moderate and is visualized in the cytoplasm of thyrocytes, in hollow follicles - in colloid. In the thyroid glands of animals of the experimental group TgAb-expression in the colloid of hollow follicles is not uniform and has a foamy appearance, due to the large number of resorption vacuoles, while in most follicular thyrocytes cytoplasmic expression of TgAb is not immunohistochemically detected, a bright cytoplasmic reaction with Fox-1 antibodies was observed (pic.2). Immunohistochemically Fox-1 positive cytoplasmic expression in most thyrocytes was present throughout the cytoplasm, occasionally in the apical part of thyrocytes, which indicated the intensive rapid development of the protein-synthesizing apparatus.The pattern of distribution of immunohistochemical Fox-1 positive reaction in thyrocytes of thyroid follicles of control and intact groups was mosaic and was visualized mainly in thyrocytes of peripheral follicles, and there was both nuclear and cytoplasmic positive reaction with Fox. Comparing the results of immunohistochemical studies with Fox-1 antibodies between groups, it should be noted that prenatal administration of dexamethasone affects the intensification of differentiation not only structural units - follicles, but also a specific synthetic intracellular apparatus of thyrocytes, because when mRNA matures, coronary maturation are connected thanks to Fox -1.

On the 7th day of postnatal life, the structure of the gland changed in the direction of increasing the manifestations of the process of blocking the excretion of thyroid hormones, but the synthesis and excretion of components into the follicle cavity was preserved. Follicles enlarged throughout the body, and large subcapsular follicles were even slightly deformed due to the appearance of intussusception directed into the cavity of the follicles. At the sites of intussusception, the shape of the cells was cubic and single prismatic, they visualized ki-67-positive cells, resorption vacuoles were absent, their number was much smaller compared to the thyroid glands of intact and control animals. One week after birth, the thyroid glands of experimental animals exposed to dexamethasone showed a decrease in the area of the thyroid epithelium. This is due to the fact that the height of the cells of the follicular epithelium becomes smaller, the cubic and flat shape of thyrocytes predominates, prismatic cells are rare, mainly in small follicles. There was a 1.6 fold increase in the area of the colloid compared to the control due to an increase in the number of large and medium-sized follicles containing dense, dense colloid and desquamated cells, with no colloid vacuolation. In control animals, the expression of TgAb is not uniform throughout the follicle cavity, intense parietal in the area of resorption vacuoles. The cytoplasmic TgAb reaction is weak, visualized in single follicular thyrocytes in the apical part of the cells. Intense cytoplasmic and moderately intense colloidal TgAb+ expression was observed in experimental animals (Fig. 1).

Moreover, in the flattened thyrocytes of overstretched follicles, the expression of Fox-1 was present only in the apical part. Due to the mosaic location of follicles with flattened thyroid epithelium throughout the parenchyma of the gland, examination microscopy revealed locations of follicles with reduced Fox-1 expressive activity (Pic.1), indicating a decrease in the content of synthetic organelles in such cells and reorganization of hormone-producing processes (Fig. 2).

On the 11-21th day of postnatal life, large follicles with flattened thyrocytes, desquamated cells, and dense colloid without resorption vacuoles were subcapsularly visualized in the thyroid glands of animals prenatally exposed to dexamethasone. In the

part of the follicles lined with cubic thyrocytes, the colloid was absent. The number of microfollicles became smaller, and the proportion of proliferating ki-67-positive cells in the wall of the follicles decreased insignificantly compared to the previous period, but compared to the control of proliferating cells was less.

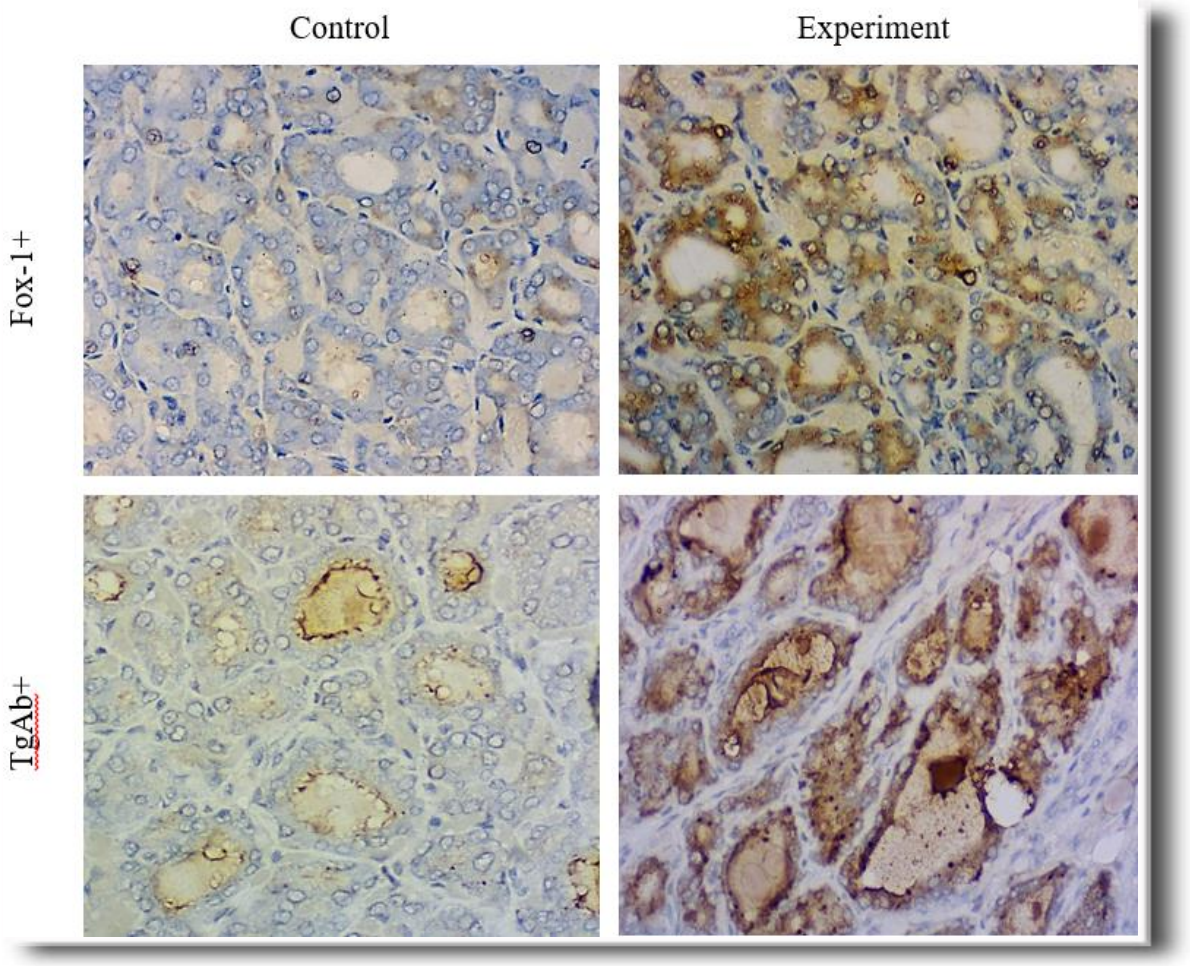

Fig. 1. Comparative visualization of immunohistochemical changes in the thyroid gland of rats on 7th life`s day. Immunoperoxidase method. ×400.

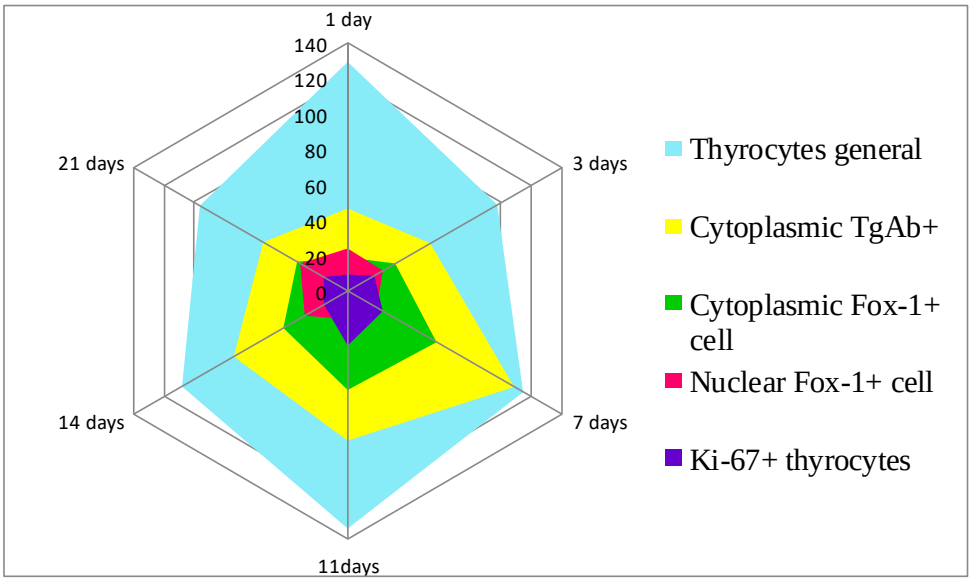

Fig. 2. Dynamics of quantitative distribution of immunohistochemical markers expression in thyroid gland against the background of the total number of thyrocytes per unit area after prenatal dexamethasone exposure.

The number of light thyrocytes increased compared to the previous term and groups of intact and control, indicating the differentiation of cells into active hormone-producing. cytoplasm of thyrocytes, in hollow follicles - in colloid. In the thyroid glands of animals of the experimental group TgAb expression in the colloid of hollow follicles is not uniform and has a foamy appearance, due to the large number of resorption vacuoles, while in most follicular thyrocytes cytoplasmic expression of TgAb is not immunohistochemically detected. In the thyroid glands of animals of the experimental group TgAb-expression in the colloid of hollow follicles is not uniform and has a foamy appearance, due to the large number of resorption vacuoles, while in most follicular thyrocytes cytoplasmic expression of TgAb immunohistochemically is not detected. In extrafollicular proliferating thyrocytes there was a bright perinuclear and cytoplasmic Fox-1 positive reaction (Fig.2). This histological picture was throughout the parenchyma of the thyroid gland. In cubic thyrocytes of follicles of colloidal type of Fox-1 secretion, the expression was brightly visualized in the cytoplasm of cells, which is characteristic of the intensification of protein-synthetic processes and intracellular proliferation of synthetic organelles of thyrocytes. At the same time, in the thyroid gland of rats of intact and control groups there was a bright positive cytoplasmic and nuclear expression of Fox-1 antibodies in most follicular thyrocytes.

Conclusion

It was found that prenatal exposure of dexamethasone causes the offspring accelerate the development of morphological structures of the thyroid gland, but functionally they are in a state of stress of both the synthesizing apparatus and the process of hormone excretion, which is expressed in the imbalance of immunohistochemical expression of Fox-1 and TgAb. Such thyrocytes with signs of disturbances in synthetic activity desquamate into the lumen of the follicles, while on the 11th day we compensatory increase in the proliferative activity of the thyroid epithelium.

Prospects for further research

It is planned to continue the study features of TgAb, Fox-1, Ki-67, TTF, p53 expression changes in thyroid gland rat`s offspring after prenatal dexamethasone exposure until puberty.

Sources of financing

This study is a part of the research work of Zaporizhzhia State Medical University " Immunomorphological features of internal organs under the action of endogenous and exogenous factors on the body" (state registration № 0118U004250).

Conflicts of interest

All authors declare no conflicts of interest in this paper.

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Федосєєва О.В., Бушман В.С., Нечепоренко А.Г. Морфофункціональні перетворення у ході морфогенезу щитоподібної залози потомства щурів лінії Wistar після внутрішньоутробного впливу дексаметазону.

РЕФЕРАТ. Актуальність. В останні роки розповсюдженість патологій щитоподібної залози різного ґенезу серед дитячого населення світу сягнула значно високого рівня. Дискусійним питанням в акушерстві на сьогодні залишається питання використання глюкокортикоїдів під час вагітності, адже вони можуть як позитивно, так і негативно впливати на процеси морфогенезу органів та бути причиною виникнення патологічних станів у післянатальному періоді. **Мета:** встановлення особливостей морфофункціональних перетворень в ході морфогенезу щитоподібної залози потомства щурів у ранньому віці в нормі та після внутрішньоутробної дії дексаметазону. **Методи.** Мікроскопічно досліджено 108 щитоподібних залоз щурів 3 експериментальних груп із застосуванням гістологічних та імуногістохімічних методів, з подальшою статистичною обробкою отриманих результатів. **Результати.** На тлі високих показників загальної кількості фолікулярних тироцитів на 1 добу життя у тварин, які пренатального отримали дексаметазонб була виражена цитоплазматична експресія TgAb, що корелювало з показниками нуклеарної та цитоплазматичної Fox-1 експресії. З 7-го по 11-й день встановлено зниження загальної кількості тироцитів на умовну одиницю площі за рахунок накопичення колоїду у фолікулах, зростання Fox-1 цитоплазматичної експресії та зниження нуклеарної експресії, на тлі збільшення проліферативної активності. До 21 доби показники Fox-1 цитоплазматичної та нуклеарної експресії були майже тотожними. Відбувалося зменшення інтенсивності експресії TgAb в цитоплазмі тироцитів та вираженость її у колоїді, зменшення кількості Ki-67 позитивних тироцитів на умовну одиницю площі у порівнянні з попереднім строком спостереженням. **Підсумок.** Встановлено, що пренатальне введення дексаметазону викликає у потомства прискорення розвитку морфологічних структур щитоподібної залози, але функціонально вони знаходяться у стані напруги як синтезуючого апарату так і процесу виведення гормонів, що виражається у дисбалансі імуногістохімічних показників експресії Fox-1 та TgAb. Такі тироцити з ознаками порушень у синтетичній діяльності десквамують у просвіт фолікулів, натомість на 11 добу компенсаторно бачимо зростання проліферативної активності тиреоїдного епітелію.

Ключові слова: тироглобулін, щитоподібна залоза, щури, дексаметазон, паренхіматозні органи, імуногістохімія.

Федосеева О.В., Бушман В.С., Нечепоренко А.Г. Морфофункциональные преобразования в ходе морфогенеза щитовидной железы потомства крыс линии Wistar после внутриутробного воздействия дексаметазона.

РЕФЕРАТ. Актуальность. В последние годы распространенность патологий щитовидной железы различного генеза среди детского населения мира достигла значительно высокого уровня. Дискуссионным вопросом в акушерстве сегодня остается вопрос использования глюкокортикоидов во время беременности, ведь они могут как положительно, так и отрицательно влиять на процессы морфогенеза органов и быть причиной возникновения патологических состояний в післянатальному периоде. **Цель**: установление особенностей морфофункциональных преобразований в ходе морфогенеза щитовидной железы потомства крыс в раннем возрасте в норме и после внутриутробной действия дексаметазона. **Методы.** Микроскопически исследовано 108 щитовидной железы крыс 3 экспериментальных групп с применением гистологических и иммуногистохимических методов, с последующей статистической обработкой полученных результатов. **Результаты**. На фоне высоких показателей общего количества фолликулярных тироцитив на 1 сутки жизни у животных, пренатального получили дексаметазонб была выражена цито-

плазматическая экспрессия TgAb, что коррелировало с показателями нуклеарной и цитоплазматической Fox-1 экспрессии. С 7-го по 11-й день установлено снижение общего количества тироцитив на условную единицу площади за счет накопления коллоида в фолликулах, рост Fox-1 цитоплазматической экспрессии и снижение нуклеарной экспрессии, на фоне увеличения пролиферативной активности. До 21 суток показатели Fox-1 цитоплазматической и нуклеарной экспрессии были почти тождественными. Происходило уменьшение интенсивности экспрессии TgAb в цитоплазме тироцитив и выраженности ее в коллоиде, уменьшение количества Ki-67 позитивных тироцитив на условную единицу площади по сравнению с предыдущим сроком наблюдения. **Заключение**. Установлено, что пренатальное введение дексаметазона вызывает у потомства ускорения развития морфологических структур щитовидной железы, но функционально они находятся в состоянии напряжения как синтезирующего аппарата так и процесса вывода гормонов, выражается в дисбалансе иммуногистохимических показателей экспрессии Fox-1 и TgAb. Такие тироциты с признаками нарушений в синтетической деятельности десквамуют в просвет фолликулов, но на 11 сутки компенсаторно видим рост пролиферативной активности тиреоидного эпителия.

Ключевые слова: тироглобулин, щитовидная железа, крысы, дексаметазон, паренхиматозные органы, иммуногистохимия.