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THYROID STATUS OF THE OFFSPRINGS OBTAINED FROM FEMALES WITH EXPERIMENTAL HYPOTHYROSIS IN THE DYNAMICS OF POSTNATAL ONTOGENESIS

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ABSTRACT

Thyroid dysfunction remains one of the most pressing problems in the world. Among them, a special place is occupied by hypothyroidism in pregnant women, which, according to various sources, is observed in 2-2.5% of all pregnant women and can manifest itself in subclinical or manifest forms. Hypothyroidism in pregnant women has a harmful effect on the offspring, leading to structural and functional disorganization of the own thyroid system, discoordination of immunogenesis processes, disruption of cell proliferation and differentiation, growth and formation of organs and tissues. The relevance of the problem of hypothyroidism in pregnant women in the practice of doctors of various specialties is undeniable, since due to the lack of thyroid hormones necessary for the normal development and functioning of almost every cell of the human body, serious changes occur in all organs and systems. Therefore, studying the effect of hypothyroidism in pregnant women on the structural and functional characteristics of the offspring's immune system in early postnatal ontogenesis is one of the most important current tasks of medicine.

Key words: hypothyroidism in pregnant women, thyroid, offspring, thyroid hormone, mesenteric lymph nodes.

INTRODUCTION

The main literature data are aimed at studying the influence of thyroid pathology in pregnant women, on the development of the fetus and the early neonatal period in infants, paying little attention to the thyroid status of these infants in the first months of life [1,2.10].This is important because some women of fertile age may have undiagnosed or subclinical endemic goiter. The normal amount of thyroid hormones throughout a person's life is one of the factors necessary for the harmonious functioning of the body. The thyroid gland plays an important role in the complex processes of fetal development: it takes part in ensuring the compensatory and adaptive properties of the fetus in response to changes in external conditions, has a significant impact on the development, growth and differentiation of cells and tissues, and stimulates regeneration processes in tissues. [7,8,12].

Consequently, the study of the thyroid status of infants from mothers with hypothyroidism and its impact on the further health of children is one of the priority areas of pediatric endocrinology and pediatrics.

Among thyroid dysfunctions, a special place is occupied by the so-called “maternal hypothyroidism” (pregnant hypothyroidism or gestational hypothyroidism), which is observed in 2-2.5% of all pregnant women and can manifest itself in subclinical or manifest forms [12, 14]. The relevance of the problem of hypothyroidism in pregnant women in the practice of doctors of various specialties is undoubted, since with a deficiency of thyroid hormones, necessary for the normal development and functioning of almost every cell of the human body, severe changes develop in all organs and systems without exception [5, 6].

The purpose of the study to determine the thyroid status of offspring obtained from females with experimental hypothyroidism in the dynamics of postnatal ontogenesis.

Material and methods. The experiments were carried out on 50 white outbred sexually mature nulliparous female rats weighing 160-180 g, as well as 369 (222 - control group, 147 - experimental group) rat pups obtained from them. All animals were kept under standard vivarium conditions with the same diet.

The study was carried out in two stages. At the first stage, after excluding somatic and infectious diseases, all female rats were divided into two groups: females of the 1st group (experimental - 25) were administered the antithyroid drug Mercazolil at a dose of 0.5 mg per 100 g of body weight daily for 21 days and experimental hypothyroidism was induced. The 2nd group of females (intact – 25) received an equal volume of physiological solution. Animals of both groups were

under observation. It should be noted that 2 weeks after the administration of Mercazolil, the majority of female rats of the 1st group showed a slight decrease in motor activity and appetite, drowsiness, and dulling of the coat. In order to determine the functional state of the thyroid gland, on the 15th and 22nd days of the experiment, the concentration of thyroid-stimulating hormone (TSH) and free thyroxine (T4) was determined in the blood serum of 10 animals from each group. After establishing a persistent decrease in the concentration of free T4, we moved on to the second stage of the experiment: females from both groups were paired with healthy males for fertilization. The onset of pregnancy was monitored by detecting sperm in vaginal smears. After pregnancy, the females were separated from the males and placed in separate cages for further research. During periods of pregnancy and feeding of cubs, females continued to be administered a maintenance dose of the drug at the rate of 0.25 mg per 100 g of weight, i.e. In the rats of the experimental group, the periods of fertilization, pregnancy and lactation took place under conditions of mercazolil-induced hypothyroidism.

147 rat pups were born from females with experimental hypothyroidism, and 222 from intact females. Within 7 days after birth, 6 (2.7%) of 222 rat pups in the control group and 11 (7.5%) of 147 rat pups in the experimental group died

After birth, litters of pups were kept with their mother rats for one month before being transferred to other cages. Rats born from mothers with experimental hypothyroidism made up the experimental group (141 rat pups), and rat pups born from intact rats made up the control group (211 rat pups).

The study used general morphological, morphometric and statistical methods.

3-, 7-, 14-, 21- and 30-day-old experimental and control rat pups were sacrificed in the morning, on an empty stomach, by decapitation under light ether anesthesia. For morphological studies, MDR were fixed in Bouin's solution, then pieces of the organ were dehydrated in alcohols of increasing concentrations and embedded in paraffin. Sections 5-7 μm thick, stained with hematoxylin and eosin, were examined using morphological and morphometric methods.

To carry out morphometric studies, we used the Avtandilov grid and the morphometric computer program Nano Zoomer.

All digital data were processed using the variation statistics method. Calculations and statistical analysis were carried out using a statistical package for Window`s. All data were presented as mean ± standard deviation (SD). The statistical significance of differences between the control and experimental groups was compared using the Student's t test, and P values <0.05 were considered significant

Results and discussion. Taking into account the above, to clarify the functional state of the pituitary-thyroid system of rat pups obtained from females with experimental hypothyroidism on the 1st, 7th, 14th, 21st, 30th and 60th days after birth, the concentrations of the hormones TSH, total T3 and free T4 were studied (Table 3.1) .

The state of the thyroid status of rat pups in the dynamics of early postnatal development (M±m)

Time after birth, days	Total T3, ng/ml (n=8)	Free T_4, ng/ml (n=8)	TTG, мME/l (n=8)
1	1,11±0,038	7,14±0,25	2,07±0,071
7	1,3±0,046***	8,61±0,28**	3,97±0,13***
14	1,60±0,058*	10,57±0,34***	6,45±0,22***
21	1,81±0,062*	12,92±0,40***	7,23±0,24*
30	1,70±0,064	11,47±0,38*	8,32±0,28*

Note: *- differences are significant compared to the previous period, (*-P<0,05; **-P<0,01; ***-P<0,001)

Analysis of the dynamics of changes in the concentration of thyroid hormones in control animals showed their wave-like changes in the process of postnatal development. Thus, the concentration of T3 in the blood serum of one-day-old rat pups in the control group was the lowest compared to all other age groups.In 7-, 14- and 21-day-old rat pups, the concentration of this hormone increased by 23%, 20.5% and 13%, respectively, compared to previous periods of research. In 30-day-old rat pups, the T3 content in the blood decreased by 6% compared to 21-day-old rat pups.

In 60-day-old control animals, the concentration of triiodothyronine was maximum and did not differ significantly from the values in 30-day-old rats.

A similar trend of change was observed when studying the concentration of free T4 during postnatal development. The content of free T4 in the blood serum of newborn rat pups, as well as T3, showed the lowest value compared to other age groups.

In 7-, 14-, and 21-day-old rat pups, an increase in serum T4 concentration was observed by 20.7%, 22.7%, and 14.5%, respectively, compared with the indicators of newborn rat pups.

The T4 content in the blood serum of 30-day-old rat pups was reduced by 5% compared to the values of 21-day-old experimental animals. The T4 concentration was maximum on the 60th day after birth compared to other periods.

The dynamics of changes in the TSH content in the blood serum of rats tended to increase from the first day of birth to 2 months of age. The TSH concentration reached its highest value on the 60th day after birth and increased by 30% compared to the values of 30-day-old animals.

Thus, the concentration of thyroid hormones is the lowest in newborn rat pups; their content increases significantly on days 7-21. It is most significant in 60-day-old rat pups, but does not differ significantly from the previous period of the study.

A study of the influence of gestational hypothyroidism on the formation of the thyroid status of the offspring in postnatal ontogenesis showed that hypothyroidism induced in female rats before pregnancy led to a significant impairment of the thyroid function of their offspring.

Data on the thyroid status of rat pups obtained from females with experimental hypothyroidism in the dynamics of early postnatal development are given in Table 2.

The state of the thyroid status of rat pups obtained from females with experimentally induced hypothyroidism in the dynamics of early postnatal development (M±m)

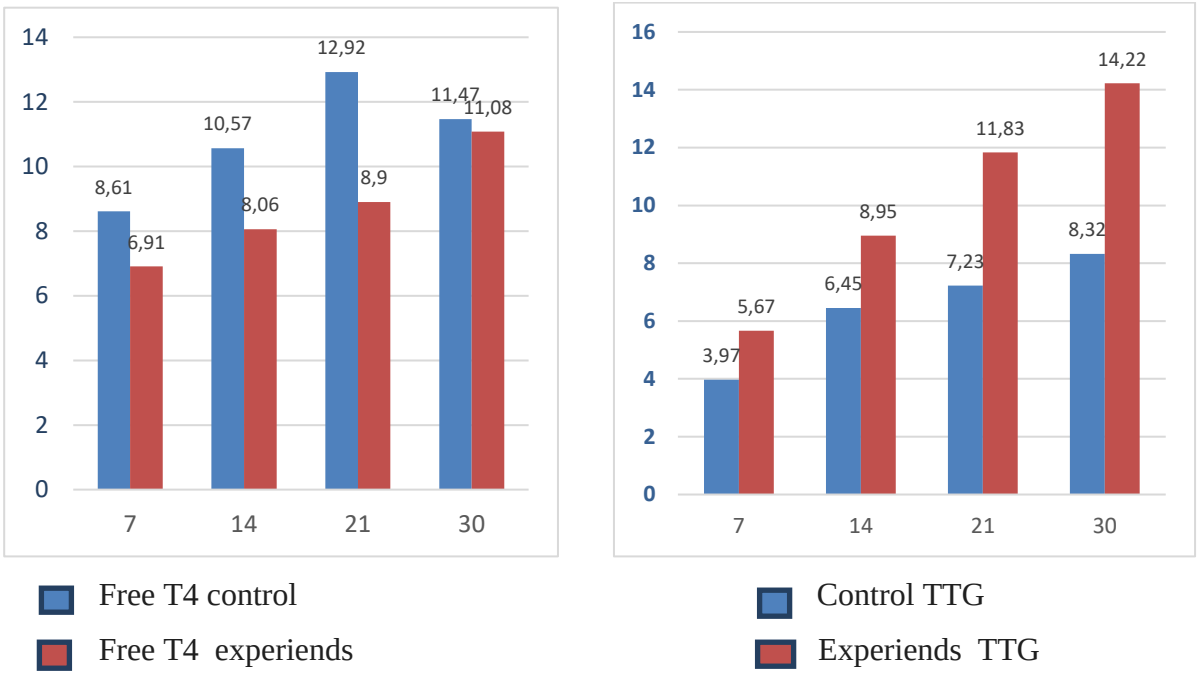
Time after brith, days	Free T_4, ng/ml (n=8)		ТТГ, мМЕ/l (n=8)	
	control	exprerienced	control	exprerienced
1	7,14±0,37	5,64±0,033	2,07±0,10	3,39±0,075
7	8,61±0,42	6,92±0,066	3,97±0,19	5,68±0,14
14	10,57±0,52	8,07±0,16	6,45±0,31	8,96±0,13
21	12,92±0,64	9,18±0,18	7,23±0,35	11,84±0,17
30	11,47±0,56	11,38±0,19	8,32±0,41	14,23±0,18
60	14,62±0,72	10,04±0,12	10,81±0,53	18,82±0,26

Note: *- differences are significant compared to the previous period, P<0.05.

As can be seen from the table, the concentrations of T3 and T4 in the experimental group of animals during all periods of the study were significantly reduced compared to the control. The greatest difference in the concentrations of

T3 and T4 was noted on days 14 and 21 after birth, while the level of hormones in experimental rat pups was more than 1.5-1.6 times lower compared to similar data in the control group.

Dynamics of changes in the concentration of thyroid and thyrotropin hormones in control and experimental rat pups during postnatal development



It should be noted that the decrease in the content of thyroid hormones was accompanied by a significant increase in the concentration of pituitary TSH. In 60-day-old rats, the low level of thyroid hormones remained.

Thus, experimentally induced hypothyroidism in females revealed a significant inhibition of the synthesis and secretion of thyroid hormones, despite the high concentration of pituitary thyroid-stimulating hormone in the offspring during all periods of postnatal development.

Conclusions:

The results obtained allow us to conclude that experimental hypothyroidism in females, caused before pregnancy and continuing during lactation, leads to disruption of the development of thyroid function in the offspring at all times of postnatal ontogenesis and the development of primary hypothyroidism in them, which is expressed in a decrease in the concentration of thyroid hormones and an increase in thyroid-stimulating hormones. At the same time, despite the increased level of thyroid-stimulating hormone, hypothyroidism in rat pups persisted until puberty.

REFERENCES

1. Azizova F.Kh., Yuldasheva M.T., Azizova P.Kh. Study of morphological and morphometric changes in the thymus during experimental hypothyroidism in the prepubertal period of ontogenesis // Journal of Biomedicine and Practice. – 2021. – vol. 6., No. 3. – P.139-146.

2. Andersen S.L, Olsen J, Laurberg P. Foetal programming by maternal thyroid disease/Clin Endocrinol (Oxf). 2015 Dec;83(6):751-8. doi: 10.1111/cen.12744. Epub 2015 Mar 13.

3. Jaeger M., Netea-Maier R. Thyrotrophin and thyroxine support immune homeostasis in humans//Biology, Medicine, Published 17 January 2021.

4. Grace Mengqin Ge, Miriam T.Y. Leung, Kenneth K.C.Man et all. Maternal thyroid dysfunction during pregnancy and the risk of adverse outcomes in the offspring: a systematic review and meta-analysis//J.Clin. Endocrinol. Metab. - 2020 Dec. 1;105(12):555.

5. Anne H. van der Spek, Eric Fliers and Anita Boelen. Thyroid hormone metabolism in innate immune cells// Journal of Endocrinology.- 2017, V.236. - R67–R81

6. Leah M. Thornton Hampton, Miranda G. Finch, Christopher J. Martyniuk, Barney J. Venables. Developmental thyroid disruption causes long-term impacts on immune cell function and transcriptional responses to pathogen in a small fish model//Scientific Reports volume 11, Article number: 14496 (2021).

7. Madaminova G.I., Azizova F.Kh., Ishandzhanova S.Kh., Azizova P.Kh. Features of physical development and formation of the endocrine status of the offspring obtained under conditions of experimental hypothyroidism in females// British Medical Journal. Great Britain, 2022. Volume 2, № 6. – P. 47–53.

8. María C.O., Henny H., Karen B. et.all. Imprinting of maternal thyroid hormones in the offspring//International Reviews Of Immunology.-2017.- 36(1):1-16.

9. María del Mar Montesinos, Claudia Gabriela Pellizas. Thyroid Hormone Action on Innate Immunity// Front. Endocrinol., 04 June 2019, Volume 10. https://doi.org/10.3389/fendo.2019.00350

10. Moog N.K., Entringer S. Influence of maternal thyroid hormones during gestation on fetal brain development// Neuroscience. - 2017 Feb.7. - 342:68–100.

11. Moreno-Reyes R., Glinoer D., Van Oyen H., Vandevijvere S. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. I Clin EndocrinolMetab. 2013;98(9):3694-701. doi: 10.1210/jc.2013-2149.

12. Pakkila F., Männistö T., Surcel HM., Ruokonen A. et all. Maternal thyroid dysfunction during pregnancy and thyroid function of her child in adolescence/J. Clin. Endocrinol. Metab. 2013 Mar;98(3):965-72.

13. Sawyer Huget-Penner, Denice S. Feig Maternal thyroid disease and its effects on the fetus and perinatal outcomes// Prenatal Diagnosis.- First published: 17 March 2020.- https://doi.org/10.1002/pd.5684

14. Zhang C, Yang X, Zhang Y, Guo F, Yang S, Peeters RP, Korevaar TIM, Fan J, Huang HF.J. Association Between Maternal Thyroid Hormones and Birth Weight at Early and Late Pregnancy// J Clin Endocrinol Metab. 2019 Dec 1;104(12):5853-5863.

15. Zhang F., Chen J. [et al.] Subclinical hypothyroidism in pregnant rats impaired learning and memory of their offspring by promoting the p75NTR signal pathway // Endocrine Connections. –2018 (7), – P. 688-697.