BRITISH MEDICAL JOURNAL

British Medical Journal

Volume 2, No.6, November 2022

Internet address: http://ejournals.id/index.php/bmj
E-mail: info@ejournals.id
Published by British Medical Journal
Issued Bimonthly
3 knoll drive. London. N14 5LU United Kingdom
+44 7542 987055

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FEATURES OF PHYSICAL DEVELOPMENT AND FORMATION OF THE ENDOCRINE STATUS OF THE OFFSPRING OBTAINED UNDER CONDITIONS OF EXPERIMENTAL HYPOTHYROIDISM IN FEMALES

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Abstract: This article is devoted to the identification of features of physical development and formation of the endocrine status of male rats obtained under conditions of experimental hypothyroidism of pregnant females.

Hypothyroidism in female rats was induced by oral administration of the anti-thyroid drug Mercazolil at the rate of 0,5 mg per 100 g of body weight for 21 days. After establishing a steady decrease in the concentration of free thyroxine in the blood serum, the females were fertilized by healthy males. During periods of pregnancy and lactation, females continued to receive a maintenance dose of the drug. We assessed the physical development and formation of the endocrine status of offspring obtained from females with experimental hypothyroidism.

It has been established that maternal hypothyroidism leads to a delay in physical development and a pronounced imbalance of the pituitary - thyroid - testicular system in their offspring.

Keywords: hypothyroidism of pregnant females, offspring, postnatal ontogenesis, physical development, pituitary - thyroid system, pituitary - testicular system.

The endocrine system is a collection of interconnected structures performing certain functions. The formation, development and functioning of organs begin even during fetal development and continue until physiological maturity; however, under the influence of endo- and exogenous factors, disturbances can occur not only in the functioning of the endocrine glands, but throughout the whole body, which further negatively affects the reproduction of the offspring [3, 5, 6, 7].

One of the causes of perinatal pathology, including the birth of physiologically immature offspring, is extragenital maternal diseases, among which the pathology of the thyroid gland is of particular importance. Among the pathologies of the thyroid gland, a special place is occupied by the so-called "maternal hypothyroidism" (hypothyroidism of pregnant females or gestational hypothyroidism), which in recent years has attracted more and more attention of researchers, since with a deficiency of thyroid hormones necessary for the normal development and functioning of almost every cell of the human body, major changes may occur in all organs and systems without exception [12, 14]. According to the literature, children from mothers suffering from hypothyroidism lag behind in physical development, often have anomalies of the central nervous system [15, 16], are predisposed to the development of infectious diseases as well as being prone to sexual dysfunctions. It has been established that even subclinical forms of thyroid pathology in the mother can have an extremely unfavorable effect on the condition of the fetus and the newborn [17].

Despite the widespread increase in the number of thyroid hypofunctions, the effect of maternal hypothyroidism on the physical development and hormonal status of the offspring in the dynamics of postnatal ontogenesis has been studied extremely insufficiently.

The purpose of the study is to elucidate the features of physical development and the

formation of the endocrine status of rat pups obtained under conditions of experimental hypothyroidism of pregnant females.

Material and Methods. Hypothyroidism in female rats was induced by administering per os anti-thyroid drug Mercazolil at the rate of 0,5 mg per 100 g of body weight for 21 days (experimental group). After establishing a steady decrease in the concentration of free thyroid hormones (T4 and T3), females were fertilized by healthy males. During periods of pregnancy and lactation, females continued to receive a maintenance dose of the drug at the rate of 0,25 mg per 100 g of body weight. The control group of females received an equal volume of sterile saline.

Physiological maturity of the offspring in the control and experimental groups was assessed by the number of live born fetuses, the number of litter, the survival rates of animals during early postnatal ontogenesis (the first 7 days after birth), the dynamics of body weight growth. The following factors were also taken into account in each litter: opening of the palpebral fissures, detachment of the auricles, the appearance of a primary and secondary coat, eruption of incisors, descent of the testicles into the scrotum.

The hormonal status was studied in 14-, 21-, 30-, and 60-day-old rat pups obtained from healthy females and females with experimental hypothyroidism. After killing rat pups, blood was collected in dry sterile test tubes without anticoagulants, and the resulting blood serum was used to determine the concentration of hormones. Thyroxine (T4), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone in blood serum were determined by enzyme immunoassay using special kits from the company - Human (Germany) and a spectrophotometer - Single ? (Germany).

All digital data were processed by the method of variation statistics. The calculation and statistical analysis were carried out using the statistical package for Windows□. All data were presented as mean ë standard deviation (SD). The statistical significance of differences between the control and experimental groups was compared using the t-test, and P values < 0.05 were considered significant.

Results and Discussion. At present, there is enough data indicating the important role of general physiological constants of laboratory animals, taking into account their sex and age characteristics, in assessing the effect of maternal extragenital pathology on the degree of their physiological maturity [1, 9, 13]. Based on this, we analyzed the physiological development of the offspring of female rats with experimental hypothyroidism.

The study showed that in the offspring of female rats with hypothyroidism, the number of newborns in the litter decreased, so if in the control group the average number of rat pups in the litter was 8,9ë0,6, then in the experimental group this indicator was significantly reduced and equal to 6,4ë0,4. In a comparative analysis of litters by sex, a decrease in the proportion of males in animals of the experimental group was noted; the ratio of females and males in the litter in the control and experimental groups were 52,8:47,2 and 59,4:40,6, respectively.

In addition, the offspring of female rats with experimental hypothyroidism showed a decrease in viability. Thus, it was found that the proportion of surviving rat pups to the fourteenth day of postnatal development in the experimental group was 91%, against 97,3% in the control.

According to modern concepts [1, 8], a decrease in the dynamics of weight gain in an animal during the early postnatal period is one of the signs of physiological immaturity. According to our data, in animals of the experimental group, there was a slowdown in the accumulation of body weight after birth compared with the control. The dynamics of studying the daily weight gain of rat pups showed that in the first 2 weeks after birth,

the daily weight gain in rat pups of the control group was 0,98ë0,06 g, while in animals from females with experimental hypothyroidism this indicator was 0,87ë0,03 g. In the period from the 15th to the 30th day after birth, in rat pups of the control and experimental groups, the increase in body weight were 1,49ë0,05 g and 1,39ë0,04 g, and in the period from the 30th to the 60th day 1,40ë0,04 and 1,27ë0,07 g, respectively.

Thus, the daily increase in body weight of the animals of the experimental group in the period of postnatal development was significantly less than in rat pups obtained from healthy females.

An analysis of the timing of the onset of certain stages of physical development of experimental animals made it possible to conclude that in rat pups of the experimental group, some signs of physical development are delayed, namely, descent of the testicles into the scrotum, eruption of incisors, opening of the eyes, covering the body with secondary wool. These features lagged behind the control by 3.7, 1.2, 1.7, 1.0 days, respectively. Meanwhile, detachment of the ear, bodies with primary wool practically corresponded to physiological norms and did not differ significantly from the indicators of the comparison group.

Thus, analyzing the data obtained, we can conclude that physiologically immature offspring are born in female rats with experimental hypothyroidism, which reflects the decrease in the number of newborns in litters, the decrease in the number of surviving rat pups, the decrease in the number of males, and the delay in the accumulation of body weight after birth as well as longer preservation of signs of immaturity compared with the control group.

Throughout a person's life, a normal level of thyroid hormones is necessary for the harmonious functioning of the body. The thyroid gland plays an important role in the complexprocesses of intrauterine development: it partici pates in the implementation of compensatory-adaptive reactions of the fetus when environmental conditions change, thyroid hormones affect growth and ossification processes as well as the formation of the central nervous system of the fetus [16,19].

Considering the above, the next stage of our study was to determine the formation of the hormonal status of rat pups born from healthy females and from females with experimental hypothyroidism.

In the thyroid gland, thyroxine (T4) is synthesized, which then, under the action of deiodinase enzymes, is converted into triiodothyronine (T3), a more active form.

On the basis of studies of total triiodothyronine (T3), free thyroxine (T4) and thyroid-stimulating hormone (TSH) in the blood, the thyroid status of the offspring was established in the dynamics of postnatal ontogenesis.

An analysis of the dynamics of thyroid hormones showed a wave-like nature of changes in their content in the dynamics of postnatal development. So, in 1-day-old newborn rat pups of the control group, the concentration of total T3 in the blood serum was the lowest compared to all other age groups. In 7-, 14-, and 21-day-old rat pups, there was a significant increase in the concentration of this hormone by 23%, 20,5%, and 13%, respectively, compared with the previous periods of the study. On the 30th day, an insignificant decrease in the concentration of T3 was noted in comparison with the 21-day-old rat pups. 60-day-old rat pups had the highest content of triiodothyronine. However, no significant differences were found between 30-day-old control and experimental offspring.

The same trend of changes in the dynamics of postnatal ontogenesis was found in the study of free T4. The content of free T4 in newborns, as well as T3, was the lowest compared to all other age groups. By the 7th, 14th, and 21st days of life, the level of T4 in rat pups became significantly higher by 20,7%, 22,7%, and 14,5%, respectively,

compared with the previous observation periods. In 30-day-old rat pups, an insignificant decrease in T4 concentration was noted compared to 21-day-old animals. On the 60th day of postnatal life, this indicator was the highest compared to all other age periods.

The dynamics of changes in the concentration of thyroid stimulating hormone (TSH) in the blood serum of rat pups in the period from their birth to two months of age tended to increase, and the highest TSH concentration was detected on the 60th day after the birth of rat pups, which exceeded the values of 30-day-old animals by 30%.

Thus, in newborn rat pups, the lowest concentration of thyroid hormones was noted; on days 7-21 and 60 after birth, the concentration increased significantly. The lowest concentration of thyroid and thyroid-stimulating hormones in newborns, apparently, is associated with the insufficiently formed pituitary - thyroid system and, accordingly, with insufficient functional activity of the thyroid gland. An increase in the concentration of T3, T4 and TSH in the early period of postnatal ontogenesis (7-21 days) may be associated with an increase in the proliferative activity of cells, intensive growth and development of organs and systems, with a change in the nature of nutrition, the transition to definitive nutrition, which is consistent with the data of Kuzminova A.S. et al. (2019). The increased content of thyroid hormones in the early postnatal period indicates their important role in the regulation of growth and development of the organism. The increased formation of thyroid and thyroid-stimulating hormones in the body of two-month-old rat pups can be explained by puberty and functional restructuring of their body.

Studies conducted to examine the effect of gestational hypothyroidism on the formation of the thyroid status of offspring in postnatal ontogenesis showed that experimentally induced hypothyroidism in females before pregnancy led to a significant impairment of the thyroid function of their offspring. The concentrations of T3 and T4 in the experimental group in 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 the 14th and 21st days after birth, when the level of hormones in the experimental rat pups was more than 1,3-1,4 times lower than in the control group, while the decrease in the content of thyroid hormones was accompanied by an increase in the concentration of pituitary TSH.

In 60-day-old rats, the low level of thyroid hormones remained, and the content of free T4 in the experimental animals was 1,5 times lower than in the control, which indicates a deep suppression of the hormone-producing function of the thyroid gland. In response to this, by negative feedback mechanisms, the concentration of pituitary TSH increased by 1,7 times, which can be considered as a compensatory reaction of the endocrine system in response to the blockade of thyroid function.

The results obtained allow us to conclude that experimental hypothyroidism in females caused before pregnancy leads to the dysfunction of the thyroid gland of their offspring in the form of primary hypothyroidism, which manifests itself with a decrease in the concentration of thyroid and an increase in thyroid-stimulating hormones. At the same time, despite the elevated level of thyroid-stimulating hormone, hypothyroidism in rat pups persists until adulthood.

It is known that thyroid hormones have a significant impact on the regulation of the process of spermatogenesis [10, 18, 20]. Due to negative feedback mechanisms, the level of thyroid hormones affects the content of thyroid-stimulating hormone of the pituitary gland, and it, in turn, can affect the liberins or statins of the nuclei of the hypothalamus. As a result, the entire hypothalamic-pituitary- thyroid - gonadal system may change [2, 4, 11].

Taking into account the above, to determine the functional state of the pituitary -

testicular system of rats obtained from females with experimental hypothyroidism on the 60th day after birth (upon reaching puberty to exclude the effect of age-related changes in the testicles on the results of the study), the concentrations of gonadotropic hormones and testosterone were determined.

Data on the study of the level of gonadotropic and sex hormones showed that in experimental animals obtained from females with experimental hypothyroidism, the content of luteotropic and follicle-stimulating hormones decreased by 2-3 times compared with the control. As a result of this, in experimental animals, a 3-4 fold decrease in the content of testosterone in the blood serum was noted.

Thus, the results of the study showed that experimental hypothyroidism induced in females before pregnancy led to a significant imbalance of the pituitary - thyroid and pituitary - testicular systems in the body of the offspring, which is accompanied by a decrease in the concentration of thyroid, gonadotropic, sex hormones and an adaptive increase in the content of thyroid-stimulating hormone.

Conclusions:

1.In female rats with experimental hypothyroidism, physiologically immature offspring are born, which is reflected in a decrease in the number of rat pups (especially male pups) in litters, a decrease in the number of surviving rat pups, a slowdown in the accumulation of body weight after birth, and a longer preservation of signs of immaturity compared to the control group.

2.During the period growth and puberty in rats, the function of the thyroid gland increases, which is expressed by an increase in the level of thyroid hormones in the blood serum.

3.Experimental hypothyroidism induced in females before pregnancy leads to a significant imbalance of the pituitary - thyroid and pituitary - testicular systems in the offspring.

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