

## Research Article

# Essential Hypertension after Radiation Exposure

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- Chernobyl accident
- Pregnant women
- I-131
- Primary (Essential) hypertension

**Abstract**

The proportion of primary hypertension in women who, at different stages of pregnancy, received irradiation of the thyroid gland (TG) due to the incorporation of radioactive iodine (I-131) as a result of the accident at the Chernobyl nuclear power plant, is about 40% of the whole cardiovascular pathology. The main group for the study included 221 women, the control group included 40 women. The increase in the incidence of this pathology began immediately after the accident, i.e. after 1986. Three decades later, it has no tendency to reach a plateau. In the dynamics of the annual incidence of essential hypertension during the 30 years following the accident, three maximums can be distinguished: in 2003, 2009, and 2014. These data cannot be associated with the detection of pathology as a result of clinical examination, since in the group of non-irradiated pregnant women, identical in age, social status and place of residence, only one case of primary hypertension was recorded during the same period of time. A dose dependence was found in the induction of essential hypertension among women from the main group. This disease occurred during the formation of the absorbed dose by thyroid gland due to radioiodine in the range of 50-100 mGy and more than 160 mGy. The obtained data can be explained by the instability of specific genes of thyroid cells of the organism of pregnant women after the incorporation of I-131, which are capable of being responsible for the synthesis of thyroid hormones, and so in other functions, which will be reflected in the subsequent appearance of hypertension.

**ABBREVIATIONS**

**TG:** Thyroid Gland; **CVS:** Cardiovascular System; **TSH:** Thyroid Stimulating Hormone

**INTRODUCTION**

Based on the available sources, there are currently abundant data on stochastic consequences of radiation exposure. These include leukemias, malignant neoplasms of various localizations, and, first of all, thyroid cancer [1]. The latter pathology is caused by the release of a mixture of iodine radionuclides into the environment during radiation accidents, which are an obligatory product of Uranium decay in the reactor core [2]. As a result of the Chernobyl accident, the first stochastic consequence in Belarus, Ukraine, and the Russian Federation was thyroid cancer rate increase in children [3]. One of the most probable reasons for this phenomenon was a high absorbed dose by thyroid gland formed in children due to radioactive iodine [4]. Currently, an increased incidence of thyroid cancer is noted in adults who were from 0 to 18 years old at the time of the accident [5].

At the same time, other types of pathology, that are not of oncological nature, have been studied extremely insufficiently. It is only known that in persons whose professional activity is associated with sources of ionizing radiation high doses of radiation can lead to the appearance of general somatic pathology and, first of all, cardiovascular diseases [6]. There are very few

data on effects of low-intensity radiation levels of the order of tens and hundreds of mGy or mSv.

In previous studies on women who were irradiated with radioactive iodine (I-131) being at various stages of pregnancy (in April-May 1986, i.e. at the time of the accident at the Chernobyl nuclear power plant), an increase in cardiovascular pathology was subsequently discovered [7,8]. The maximum incidence of all types of cardiovascular pathology in those women is in 2011. In the morbidity structure, primary hypertension prevailed. Other types of pathology were much less common. This morbidity pattern was in sharp contrast to the incidence of cardiovascular disease in women who had not received radioactive iodine exposure during the pregnancy. Primary hypertension was almost not registered in them, however, hypertensive heart disease (I11) (45.1%) prevailed.

The obtained data require a more detailed assessment, in connection with which in the present study we investigated the incidence of primary (essential) hypertension (I10) in the described group of women.

**MATERIALS AND METHODS**

The study consisted of women who lived in the Stolin district of the Brest region, through which a radioactive cloud passed on the night of April 26, 1986, contaminating it with radionuclides ejected from the damaged 4th block of the Chernobyl nuclear

power plant. That cloud contained a large amount of radioactive iodine, and so the population of this area was subjected to the so-called “iodine” strike. The necessary protective measures were not taken, and that is why radioactive iodine, primarily I-131, entered organisms of residents through their lungs, and then through digestive systems with food, and it has been accumulated in their thyroid glands, thereby forming an absorbed dose for this organ.

The study cohort included 221 women for whom an information in the State register of persons affected by the Chernobyl accident was available. This group of women was designated as the main one. The absorbed thyroid dose ranged from 48 to 246 mGy. 32 women (14.5%) were in the first trimester of pregnancy, 91 women (41.2%) were in the second trimester, and 60 women (27.1%) were in the third trimester. For 38 women (17.2%), there were no data on the gestational age.

We included 40 women in the control group from the same district of the Brest region who lived in identical conditions, but whose pregnancy occurred later, i.e. in 1987. By this time, I-131 disintegrated almost completely and therefore, at the time of pregnancy, absorbed doses by their thyroid glands had not been formed. However, the same living conditions in the contaminated area of the district formed a general exposure in the surveyed women, which was practically the same in the main and in the control groups. The age of women in the control group at the time of the accident was 16-35 years. There were 4 women (10%) in the first trimester of pregnancy, 10 women (25%) were in the second trimester, and 16 women (40%) were in the third trimester. There were no data on gestational period for 10 women (25%).

Among the main group, primary hypertension was diagnosed in 86 women who were in the age of 17 – 44 years (mean value 27 years). The range of absorbed doses by the thyroid was within 48-193 mGy (mean value 83 mGy). There were 15 women (17.5%) in the first trimester of pregnancy, 35 (41%) in the second trimester, and 22 women (25.5%) in the third trimester. There were no data on the trimester of pregnancy for 14 women (16.3%).

The absorbed doses by the thyroid gland due to I-131 were calculated by the head of the laboratory for the reconstruction of radiation doses for the population of the State Research Center of the Federal Medical Biophysical Center named after A.I. Burnazyan, Federal biomedical agency (FMBA) of Russia, Doctor of Technical Sciences, Shinkarev S.M. Doses were calculated using a semi-empirical 2004 iteration model. In addition, for some cases, the doses absorbed by the thyroid gland were determined based on the data of radiometric, so-called “direct” measurements of the exposure dose rate over the area of this organ, carried out from April 26 to June 30, 1986 [9].

The total doses (1986-2016) occurred due to the living in the contaminated area were calculated using the RESRAD-ONSITE software, version 7.2 (Environmental Science Division of Argonne National Laboratory, USA). The density of the surface activity of the soil of the Stolin district for Cesium-137 was provided by the State Institution “Republican Center for Hydrometeorology,

Control of Radioactive Contamination and Environmental Monitoring”.

The morbidity data were obtained from the State Register of Persons Affected by the Chernobyl Accident. The work took into account only the primary morbidity.

Statistical data processing was carried out using the applied computer programs Statistics 10.0 (StatSoft.Inc, USA) and SigmaPlot 12.5 (Systat Software Inc., Germany).

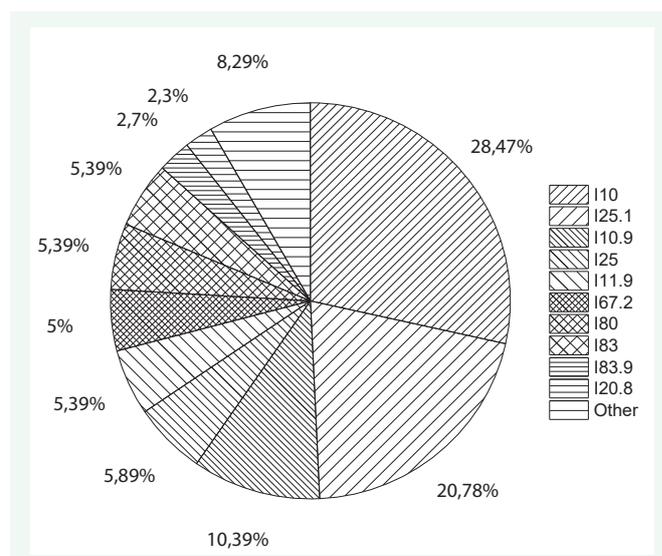
This study was approved by the Ethics Commission of the Belarusian Association of Physicians (10.12.2020).

## RESULTS

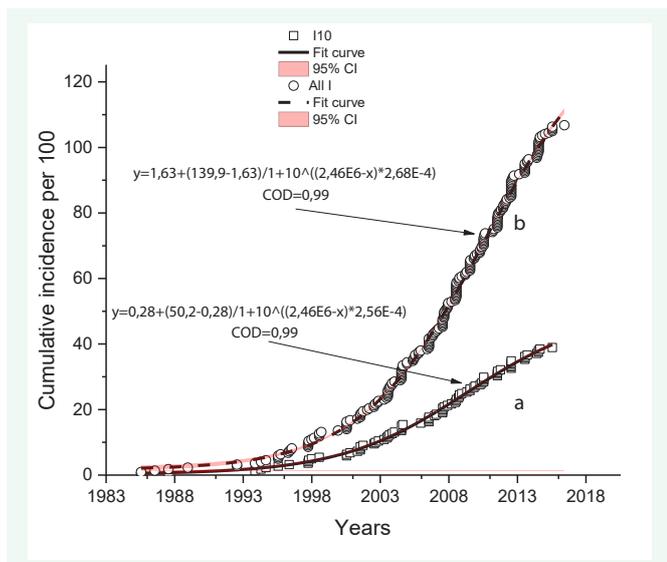
Figure 1 shows the structure of diseases of the cardiovascular system (CVS) for 1986-2016 in a cohort of women whose TG incorporated radioactive iodine (I-131) during pregnancy. The greatest contribution to the total pathology was made by essential (primary) hypertension (I10 - 28.5% and I10.9 - 10.4%). Atherosclerotic heart disease was approximately two times less common (I25.1 - 20.8%). Chronic ischemic disease (I25) and hypertensive heart disease (with predominant heart damage) without (congestive) heart failure (I11.9) 5.9% and 5.4%, respectively, occurred in that group of women at the same frequency. Other types of pathology, like various forms of angina pectoris and vascular diseases, were significantly less pronounced.

Consideration of the morbidity in the comparison group showed that essential hypertension was recorded only once during the same period of time (2% of all cases).

At the next stage, it was necessary to find out the dynamics of the incidence of primary hypertension (Figure 2). It is clearly seen that this pathology began to be registered in the Stolin district immediately after 1986, and its dynamics is expressed as an S-shaped curve. The growth of this pathology continues. For comparison, the figure shows the morbidity data for the



**Figure 1** The structure of morbidity in a cohort of women who received exposure to radioactive iodine during pregnancy.



**Figure 2** Cumulative incidence of irradiated women pregnant in 1986 with primary hypertension (a) and all types of cardiovascular pathology (b) for 1986-2016.

same period of time for all types of cardiovascular pathology. The nature of this curve has the same appearance, but the steepness of the curve is much more pronounced, which is quite understandable.

Evaluating these data, it should be recalled that in the sample of non-irradiated women in whom pregnancy occurred later during the same period of time, only one case of essential hypertension was detected.

During the analysis of the annual incidence of all types of cardiovascular pathology in women who were irradiated with radioactive iodine during pregnancy, the maximum incidence was revealed in 2011 with a mild peak in 2004 [8]. The study of the annual dynamics of registration of essential hypertension in the same group of women showed the presence of 3 pronounced morbidity peaks. The first peak was in 2003. The second, most pronounced peak was in 2009, and the third was in 2014 (Figure 3).

It is not possible to compare these data with the incidence of this pathology among women who did not receive radiation exposure during pregnancy, since among the sample we took, only one case of this pathology was registered at the end of 2000.

Study of the dose-dependent cumulative incidence of essential hypertension among women exposed to I-131 during pregnancy showed selectivity for the induction of this disease (Figure 4). Most often, this disease was caused by absorbed doses by the TG in the range of 48 - 102 mGy. This situation took place in 87% of cases. And only in 13% of cases, primary hypertension was induced by doses of more than 160 mGy.

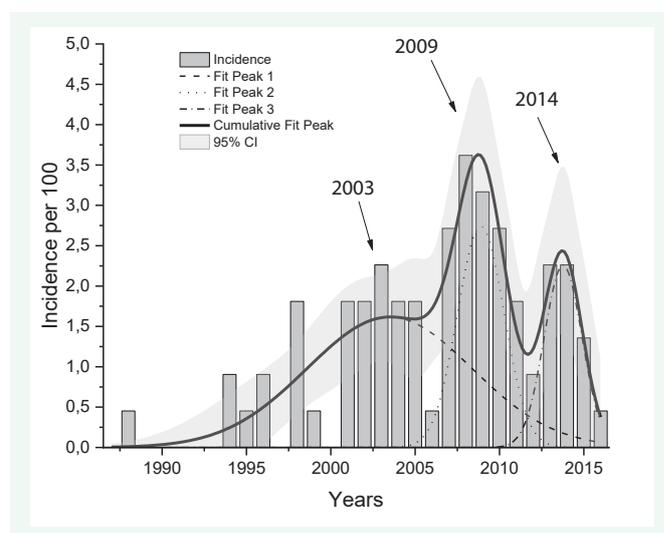
To establish the maximum values of absorbed doses that can cause an increase in the incidence of primary hypertension more accurately, the same data were subjected to a computer search for peaks. The diagram of morbidity versus dose dependence clearly shows two peaks (Figure 5). The first of them, that is

wide, corresponds to the absorbed dose by the thyroid gland in the region of 63 mGy. The second peak, that is much narrow one, is in the region of the absorbed dose equal to 160 mGy.

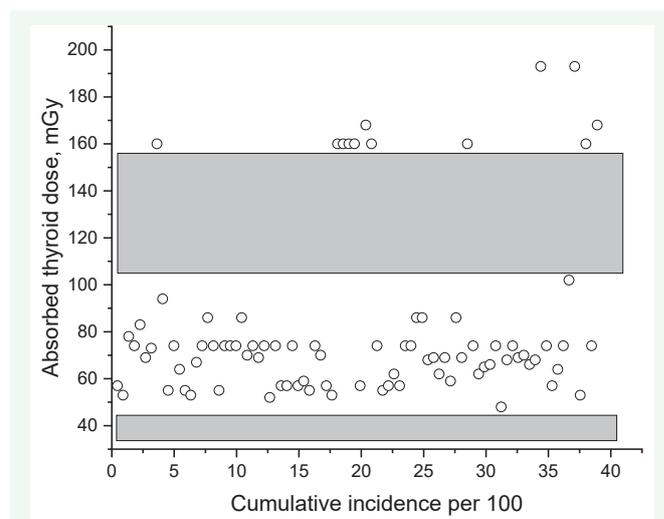
There is no significant difference between the time of the onset of hypertension for women with low doses absorbed by the thyroid (40-70 mGy) and those with high doses (higher than 120 mGy). It is likely that the fact of the irradiation during the pregnancy together with other yet unknown confounders, and not the exact absorbed dose by the thyroid, is responsible of the time of the onset of hypertension.

**DISCUSSION**

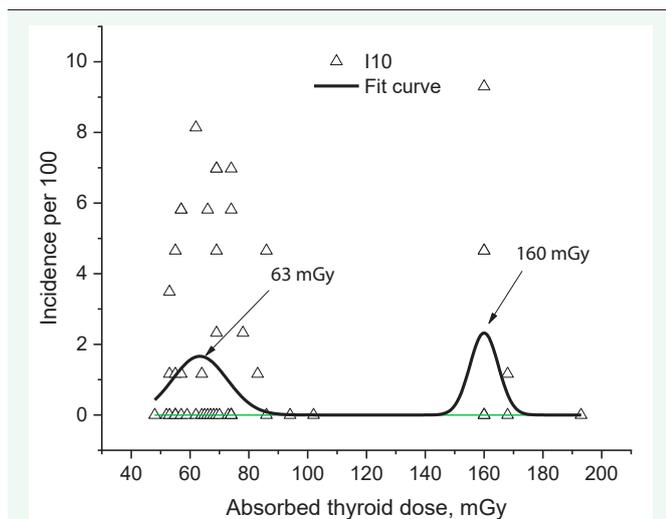
Differences in the structure of the incidence of primary hypertension among irradiated and non-irradiated women may indirectly indicate the role of the radiation factor in the occurrence



**Figure 3** The incidence of primary hypertension (I10) in pregnant women from 1986 to 2016, who were irradiated with I-131 as a result of the Chernobyl accident.



**Figure 4** Cumulative incidence of primary hypertension depending on the dose received by the thyroid gland among women exposed to radioactive iodine during pregnancy.



**Figure 5** Dose dependence of the incidence of primary hypertension in the group of pregnant women.

of this pathology, that was expressed in the accumulation of I-131 in TG. This factor is dominant, since the social status of the main and control groups of women, as well as their living conditions in the territory of the same region contaminated by Cesium radionuclides, are almost identical. However, more information is needed on the pathology-inducing factor. The increase in the incidence of essential hypertension in the main group began to be recorded immediately after the accident (Figure 2). The dynamics of the incidence of hypertension resembles the cumulative incidence of all types of cardiovascular pathology. However, the fact of its further growth without reaching a plateau is especially alarming.

The analysis of annual morbidity and its comparison with similar data concerning other types of cardiovascular pathology is of undoubted interest. Primary hypertension is characterized by a more complex pattern of the initial detection of this pathology, which is characterized by three peaks: 17, 23 and 28 years after the Chernobyl accident. It is very difficult to explain this fact by the detectability of pathology in the process of clinical examination of the population, since both exposed and non-irradiated women participate in it, among the latter only one case of essential hypertension was identified in 30 years after the Chernobyl accident. Nevertheless, the first rise in incidence can be explained by the onset of menopause in women. Since the average age of women in the main group in April 1986 was 27 years old, so they were about 44 years old at the time indicated above. This is the age of menopause. During this period, the level of estrogens in the body of women decreases. Estrogens are known to carry a protective function preventing the pathology of CVS. At the age of menopause, numerous complaints of a different nature appear, including an increase in blood pressure along with other symptoms, which makes them turn to specialists.

The dose characteristic of the appearance of this pathology is of great interest in the presented data. There is no doubt that the cause of subsequent hypertension in women may be a combination of two factors: pregnancy and thyroid irradiation. At the same time, there are ranges of absorbed doses by the TG,

which can be associated with the development of this pathology. The first of them is located in the range of rather small doses, equal to 48-102 mGy, and the second is for more than 160 mGy. At doses absorbed by the TG of up to 45 mGy, as well as in the range from 100 to 160 mGy, primary hypertension does not subsequently develop. These data can, with a certain degree of confidence, indicate the involvement of some functions of the TG as a result of exposure to radioactive iodine. Pregnancy can also play a role in these mechanisms.

These data are confirmed by the peak dependence of the incidence of essential hypertension on the absorbed dose by the TG of pregnant women. As shown in Figure 5, there are two peaks of morbidity: in the area of 60 and 160 mGy.

Earlier, studies on the action of I-131 showed that more than two dozen genes expressed in TG change their activity in response to radiation [10]. A number of genes (Pax8, Sic5a5, Tg, Tpo), which play an important role in the functioning of the TG, the synthesis of thyroid hormones, and the effect on the metabolism of peripheral cells, are down regulated by small doses of radiation caused by I-131 and change their activity with the increase of radiation exposure. There are other examples. Thus, the mentioned gene Sic5a5 under conditions of different activity of I-131 exhibits biphasicity: at low and medium radioiodine activities, it is down regulated to a greater extent than in intermediate ones, and at high activities, on the contrary, it is up regulated [10]. From this point of view, the above data on the existence of two peaks in the increase of the incidence of primary hypertension among pregnant women who were irradiated with radioactive iodine in April-May 1986 can be explained. In women, various absorbed doses were formed, which could be responsible for the change in the expression of genes and the appearance of two peaks. And the TG, in turn, plays an important role in the functioning of CVS due to the production of its hormones [11].

At the same time, it is known that irradiation induces instability of the cell genome [12]. Its instability is a persistent functional state that leads to a violation of genetic control and is the most important factor in the development of subsequent pathology. These changes can be fixed in the body of pregnant women, and therefore we observe these effects many years after the Chernobyl accident.

It is known that certain periods of pregnancy are associated with complex changes in the pituitary-thyroid system of women [13]. In different trimesters of pregnancy, many biochemical parameters change, including the levels of T4, T3, TSH, etc. So at the end of the first trimester of pregnancy (at 10 weeks), the TSH level drops to minimum values, and then, as the gestation period increases (by week 20) its level returns to the normal value [14]. Accordingly, the level of T4 will change in the woman's body. For the formation of T4, trans membrane transport of iodide (I<sup>-</sup>) is required. In these processes, expression of Sic5a5 / NIS, Tg and other genes may be necessary [10]. On the background of a decrease in the TSH level, an insufficient level of trans membrane iodide transfer will negatively affect the state of the thyroid system of a woman and a fetus and, due to the mentioned instability of the genome, may serve as the reason for the subsequent appearance of non-oncological pathology.

Obviously, the features of the development of general somatic effects over long periods of time after radiation exposure differ significantly from the stochastic effects, which are characterized by the lack of a threshold and a gradual increase in morbidity according to one model or another. In the data we have described, we are talking about a separate organ – the TG, which in many respects is the “conductor” in the body and regulates many functions, including the activity of the CVS. However, it should be borne in mind that the mechanisms proposed by us can be inherent only in pregnant women, due to the fact that this physiological state is characterized by the tension of many body systems, including endocrine system, and can be the cause of genome instability under radiation exposure.

## CONCLUSION

Essential hypertension (I10) during the next three decades after radiation exposure has an incidence of almost 40% among all cardiovascular diseases in women who were exposed to radioactive iodine (I-131) during pregnancy. In the comparison group for the same period of time, there are only isolated cases of essential hypertension. The growth of this pathology began immediately after the Chernobyl accident and has no tendency to reach a plateau. Three peaks of the incidence of essential hypertension are observed: 17, 23 and 28 years after exposure. The first of them can be explained by the onset of menopause. In the incidence of primary hypertension over the next 30 years after Chernobyl disaster, dose dependence is revealed. The incidence of this pathology noticeably increases in the range of absorbed doses by the TG from radioactive iodine of 40-100 mGy and more than 160 mGy. The obtained data can be explained by the instability of specific genes of thyroid cells of the body of pregnant women after the incorporation of I-131, that are responsible for the synthesis of thyroid hormones and other functions, that resulted in the onset of hypertension.

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