

lek. Justyna Milczarek-Banach

„Mała tarczyca” jako czynnik predykcyjny występowania niedoczynności tarczycy o etiologii innej niż autoimmunizacyjna u kobiet w wieku rozrodczym – ocena wpływu bisfenolu A i jego analogów.

**Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne**

Promotor: dr hab. n. med. Piotr Miśkiewicz

Klinika Chorób Wewnętrznych i Endokrynologii
Warszawski Uniwersytet Medyczny



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3. "Small thyroid gland" as a predictive factor for a non – autoimmune hypothyroidism in women of reproductive age – evaluation of the influence of bisphenol A and its analogs – Summary

Hypothyroidism is a group of clinical symptoms caused by a deficiency of thyroxine (T4) and the resulting insufficient action of triiodothyronine in the cells of the organism, leading to a generalized slowdown of metabolic processes. The most common cause of primary hypothyroidism in adults is chronic autoimmune thyroiditis. Other factors include: postoperative hypothyroidism, radioiodine treatment, drug-induced hypothyroidism. A separate group consists of people who do not have the presence of anti-thyroid antibodies or other known causes of hypothyroidism. It seems that one of the possible causes of hypothyroidism in this group is that the volume of the thyroid gland is small ("small thyroid gland"). Ultrasound examination (USG) of the thyroid gland shows normal, homogeneous echogenicity. In contrast in autoimmune thyroiditis, the thyroid is hypoechoic and heterogeneous. One of the probable causes leading to the development of hypothyroidism are endocrine disruptors, including bisphenols. Their widespread occurrence creates a risk of hypothyroidism in people without aggravating factors (such as autoimmune thyroiditis). In women of childbearing age hypothyroidism has a negative impact on fertility, pregnancy and the health of the offspring. Therefore, it is important to be aware of the presence of any factors, apart from autoimmune thyroiditis, that may have a negative impact on thyroid function. Early diagnosis and appropriate treatment are extremely important in this group, especially in women planning pregnancy or being pregnant.

The studies carried out as part of this doctoral dissertation were aimed at: (i) analyzing the relationship between the thyroid volume and laboratory parameters of thyroid function in women of reproductive age without autoimmune thyroiditis, (ii) an attempt to determine the lower limit of the normal thyroid volume - defining the term "small thyroid gland", (iii) determining the frequency of "small thyroid gland" and hypothyroidism in women of reproductive age without autoimmune thyroiditis, (iv) analyzing of the relationship between exposure to bisphenol A (BPA) and its 10 analogues (BPS, BPC, BPE, BPF, BPG, BPM, BPP, BPZ, BPFL, BPBP) and the function and volume of the thyroid gland, (v) summarizing of current knowledge on the impact of BPA and its analogues on the thyroid gland.

This doctoral dissertation includes the series of three thematically consistent articles, describing the problem of the presence of "small thyroid gland" in women of

reproductive age without autoimmune thyroiditis and the influence of BPA and its analogues on the development of hypothyroidism.

The first study investigated the relationship between the volume of the thyroid gland and thyrotropin (TSH). An attempt was also made to determine the lower limit of the thyroid volume in women of reproductive age without autoimmune thyroiditis - defining the term "small thyroid gland". In addition, the prevalence of "small thyroid gland" and hypothyroidism in young women without autoimmune thyroiditis is presented. There was a negative correlation between the volume of the thyroid gland and TSH. Thyroid volume <9 ml was found to be a statistically significant predictor of TSH >2.5 μ IU/ml in young women without autoimmune thyroiditis. "Small thyroid gland" concerned about 40% of the examined women. This means that the "small thyroid gland" is a fairly common problem in young women and the ultrasound of the thyroid gland before planned pregnancy is a valuable additional tool in the diagnosis of women particularly at risk of developing hypothyroidism in pregnancy. This study is so far the only one that has attempted to determine the lower limit of normal thyroid volume in a group of women of reproductive age without autoimmune thyroiditis. Depending on the accepted standards, the incidence of elevated TSH in women of reproductive age without autoimmune thyroiditis was 29% (for TSH >2.5 μ IU/ml) and 4% (for TSH >4.2 μ IU/ml).

In the second study there was analyzed the relationship between the volume and function of the thyroid gland and exposure to BPA and its analogues. There are many widespread environmental factors that can lead to a reduction in the volume of the thyroid gland and, consequently, to the development of hypothyroidism in young women. It has been shown that low-volume thyroid glands are more common in women exposed to BPC. BPC exposure is also associated with a more frequent increase in TSH >2.5 μ IU/ml. There was no association between exposure to BPA or other analogues and the volume and function of the thyroid gland. Most probably, the significant influence of BPC as the only one of the tested BPA analogues is due to the unique chemical structure of BPC that most resembles T4. This is the first study that comprehensively analyzed the effect of BPA and its analogues on the function and volume of the thyroid gland in non-pregnant women of reproductive age.

The third study summarizes the current knowledge about the influence of BPA and its analogues on the thyroid gland. The results of research on BPA and its analogues on the volume and function of the thyroid gland are contradictory and dependent on the study design and methods used. It is likely that BPA analogues have a more damaging effect on the thyroid gland than BPA itself.

In conclusion, the "small thyroid gland" unrelated to autoimmune thyroiditis is one of the possible causes of hypothyroidism. Endocrine disruptors have a potential negative impact on the thyroid gland and may lead to the development of hypothyroidism. The conducted study showed such an effect of BPC, one of the BPA analogues. Endocrine disruptors, including BPA and its analogues, are common in the human environment and contact with them is unavoidable. The scale of the phenomenon may intensify despite pro-ecological activities. The presence of untreated hypothyroidism in pregnant women is associated with the risk of complications for the mother and the fetus. There are no universal recommendations regarding the management of a woman planning pregnancy or being pregnant. They differ depending on the country, endocrinology and gynecology societies, and the update of recommendations. On the basis of the presented studies, it seems that the determination of TSH proposed by some societies only in the group with an increased risk of hypothyroidism (e.g. with autoimmune diseases) does not detect hypothyroidism caused by the action of endocrine disruptors. Apart from the obligatory, routine TSH measurement, it is worth considering the thyroid USG examination in women planning pregnancy or being pregnant. Diagnosis of "small thyroid gland" when planning pregnancy may be associated with an increased risk of hypothyroidism creating the need to monitor TSH during the planned pregnancy.