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BENEFITS OF MENOPAUSAL HORMONE THERAPY IN COMBINATION WITH L-THYROXINE IN WOMEN WITH HYPOTHYROIDISM.

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The Summary. Efficiency of menopausal hormone therapy (MHR) in the complex with Levothiroxin has been studied. The research was conducted among women with climacteric syndrome, who have the background of an endemic craw with hypothyroidism. At purpose of combine therapy positive influence on a hormonal and lipid range has been noted.

Keywords: menopausal hormonal therapy, the complicated menopause, hypothyroidism, Levothiroxin's therapy.

Introduction. In perimenopause, within the framework of the hormonal continuum, drugs for menopausal hormone therapy are replaced by drugs for menopausal hormone therapy. At the initial stage, the idea of using female sex hormone preparations after the loss of reproductive function belonged to gynecologists and was aimed at correcting the menopausal syndrome. As a result of epidemiological studies, a decrease in the risk of CVD in women against the background of menopausal hormone therapy was established, and the possibility of its use for the prevention of coronary heart disease and hypertension interested cardiologists [1,3]. Over the past 15 years, about ten large randomized clinical trials have been conducted, during which data were obtained on both the positive and negative effects of estrogen and estrogen-progestogen therapy. There is also a direct correlation between the initiation of therapy and its effectiveness. The protective effects of MHT are more pronounced if therapy is initiated at the first manifestations of menopausal syndrome. Taking into account the features and genesis of the pathological course of the "transitional" period, the use of MHT in perimenopause is pathogenetically justified and scientifically proven [2, 4].

The period of perimenopause itself is also characterized by an increase in the frequency of thyroid pathology: 40% of women have thyroid nodules and

hypothyroidism, which, however, never takes the form of myxedema [8, 9]. Considering that some types of MHT (in particular, estrogens) increase the total content of thyroxine (T4) along with an increase in tyroliberin, MHT with estrogens and progestogens in hypothyroidism is not contraindicated [10-12].

The purpose of the study. Study the clinical effect of MHT in combination with L-thyroxine with an assessment of the effect of the therapy on the general condition, lipid and hormonal spectrum of the blood of women with menopausal syndrome, developed against the background of endemic goiter with hypothyroidism.

Materials and methods. We examined 86 women with menopausal syndrome. The main group consisted of 46 patients with menopausal syndrome and endemic goiter with hypothyroidism. The comparison group with her was formed by 40 women with menopausal syndrome without thyroid pathology.

The severity of menopausal syndrome was assessed by the Kupperman menopausal index. Thorough clinical and laboratory studies were also provided.

The size of the thyroid gland and its structure were evaluated using ultrasound examination.

To study the state of the pituitary-ovarian system, the content of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), progesterone (P), free testosterone (Tf) was determined by method of enzyme immunoassay. The functional state of the thyroid gland was assessed by the content of thyroid-stimulating hormone (TSH) in the blood serum, free fraction of thyroid hormones – triiodothyronine (T3f), thyroxine (T4f). Hormonal studies were carried out in the laboratory of functional diagnostics using standard Human kits on the Stat fax machine. Venous blood sampling was performed on the 6th-7th day of the menstrual cycle in the presence of menstruation, in the morning hours before meals before treatment and after treatment, which allowed us to assess the combined estrogen-progestogenic effect on the studied parameters of the hormonal spectrum of blood.

To study the lipid profile, blood lipid spectrum parameters were determined: cholesterol (Ch), triglycerides (TG), high, low and very low density lipoproteins (HDL, LDL, VLDL) – studied on the Cypress Diagnostics analyzer (Belgium) using special standard techniques and an electrophoresis system followed by computer processing in the laboratory of functional diagnostics.

Statistical analysis of the data obtained was carried out using standard software packages Statistica for Windows 6.0, Microsoft Exel. The arithmetic mean (M), arithmetic mean error (m), frequency (M±m) were analyzed. The probability of error was assessed according to the Student's criterion.

Taking into account the presence in patients of the main group of endemic goiter with hypothyroidism, the atherogenic effect of which is generally recognized, the oral cyclic (biphasic) hormonal agent Femoston 1/10 was chosen as a drug for MHT for patients of both groups. The reason for this was a number of factors. The estrogenic component in the drug is an analogue of natural estradiol, the effectiveness of which in terms of reducing the atherogenic potential of the blood is recognized by all authors, and, most importantly, this estrogen does not increase blood triglycerides, unlike conjugated estrogens. The oral route of administration of estrogens, in contrast to parenteral forms, has a pronounced beneficial effect on lipid metabolism due to the effect during the primary passage in the liver [7]. The cyclic regimen of administration in combination with the gestagenic component of the drug helps to prevent the development of hyperplastic processes in the endometrium in women of perimenopausal age. Progestogen didrogesterone in the composition of the drug belongs to the progesterone class and, unlike norsteroid derivatives, has a synergic effect with estrogens on plasma lipoprotein metabolism [13].

Taking into account the presence of hypothyroidism in the patients of the main group of endemic goiter, the complex of therapy for them included L-thyroxine 25-50 mcg, with an increase in the dose by 25 mcg every 4 weeks (up to 100-200 mcg) for 6 months.

Research results. The average age of patients in the examined groups was 47.5 + 4.01 years in the main group, 48.9 + 5.11 years in the comparison group. The age range was 40-54 years, the duration of postmenopause in both groups did not exceed 2 years.

Based on the data, in the group of women with a functionally complete thyroid gland, a more favorable course of menopausal syndrome was noted than in the group of women with hypothyroidism. Thus, the mild severity of endemic goiter according to menopausal index in the group of women with a functionally complete thyroid gland was noted in 28%, while in women with hypothyroidism this indicator was 16%.

In 55% of women with a functionally complete thyroid gland, the course of endemic goiter was noted to be of moderate severity. In the group of women with hypothyroidism, the average severity of endemic goiter is lower – 49.5%. However, severe endemic goiter in women with hypothyroidism is observed more than 2 times more often – 34.5% versus 17% in the group of women with a functionally complete thyroid gland.

When studying the dynamics of hormonal levels in the pituitary-ovarian and thyroid systems, we established the dependence of the severity of endemic goiter on fluctuations in hormone levels. Thus, the TSH level increased accordingly to the severity of the disease, and with hypothyroidism it was significantly higher compared to the indicators with a full-fledged thyroid gland.

According to the results, the level of thyroid-stimulating hormone fluctuated depending on the functional state of the thyroid gland and the severity of endemic goiter. Thus, there was a significantly high TSH index with a combination of hypothyroidism and severe forms of endemic goiter (moderate and severe degrees). Whereas thyroid hormone levels were not found to depend on the severity of endemic goiter. As follows from the data obtained, the course of menopausal syndrome significantly worsened with an increase in TSH levels. This trend is observed in the group of women with endemic goiter, a significantly high level of tyrotropin directly correlated with moderate and severe menopausal syndrome. If with a mild degree of

menopausal syndrome with thyroid hypofunction, the TSH level was 3.86±0.33 (mME/L), then with moderate and severe menopausal syndrome, the TSH indicators were 4.73±0.17 and 6.64±0.27 (mME/L), respectively, and were significantly higher. This is confirmed by our clinical data on a more severe course of the menopausal period in thyroid disease.

When studying the hormonal profile of the pituitary-ovarian system, we attempted to identify whether there is a natural relationship between changes in the level of gonadotropins and the severity of menopausal syndrome. The levels of gonadotropins and estradiol by severity of menopausal syndrome, shown in the table, showed no dependence of the severity of menopausal syndrome on fluctuations in the level of FSH, the same trend was noted with respect to the level of estradiol. As for the level of LH, it significantly decreased with increasing severity of menopausal syndrome. This is confirmed by the results with unchanged thyroid status: the LH level was 40.73±2.2 (IU/L) with severe menopausal syndrome, with moderate severity – 51.94± 3.23 (IU/L) and 59.6±2.01 (IU/L) – with mild. In the group of women with hypothyroidism, the level of LH decreased even more significantly. Thus, with a mild degree of menopausal syndrome, the LH index was 57.2 ±3.23 (IU/l). In moderate and severe menopausal syndrome, LH levels were 48.9±3.16 (IU/L) and 38.78±2.01 (IU/L), respectively, with a significant difference between the indicators.

It should be noted the change in the LH/FSH index, which also influenced the severity of manifestations of pathological menopause. The LH/FSH index decreased with increasing severity of menopausal syndrome: from 0.88 to 0.64 with an unchanged thyroid gland and from 0.70 to 0.57 with hypothyroidism.

The results obtained allow us to conclude about the influence of the functional state of the thyroid gland on the thyroid-stimulating and gonadotropic activity of the pituitary gland. The clinical symptoms of pathological menopause in women with thyroid hypofunction are associated with the severity of thyroid insufficiency, as well as with the LH/FSH index. A decrease in the LH/FSH index and a high thyrotropin index are risk factors for the development of severe forms of menopausal syndrome.

When analyzing the effect of therapy on the hormonal and lipid spectrum of the blood of women of the examined groups, it was possible to identify the following. There was a significant decrease in gonadotropins (FSH, LH, PRL, TSH) to the levels characteristic of the premenopausal period. In patients with endemic goiter and hypothyroidism, a significant decrease in TSH to the upper limit of the age norm was found.

T3 and T4 levels increased both in women of the main and in patients of the comparison group (within the age norm), and in women with endemic goiter and hypothyroidism, T3 and T4 indicators reached normal ($p < 0.05$).

In a significant decrease in TSH and an increase in the levels of hormones T3 and T4 in the patients of the main group, we assume a positive effect of L-thyroxine, which they received. There was a significant increase in estradiol and a tendency to increase progesterone in women of both groups.

Thus, we have established a pronounced positive effect of complex therapy on the level of pituitary, ovarian and thyroid hormones in perimenopausal women both with and without thyroid dysfunction. The beneficial effect of complex therapy with MHT was also noted on the blood lipid profile in patients of the comparison group, and in combination with L-thyroxine and on the impaired lipid metabolism of women with hypothyroidism.

The positive effect was expressed in a decrease in the levels of cholesterol (Ch), triglycerides (TG) due to a decrease in the concentration of low density lipoproteins (LDL) and a tendency to increase high density lipoproteins (HDL).

Conclusions. Thus, the corresponding indicators of hormones and lipid profile were found in women with physiological menopause without functional pathology of the thyroid gland. Women with menopausal complications and a functionally complete thyroid gland have moderate hyperlipidemia. As for women with menopausal disorders for hypothyroidism, according to the indicators of the lipid profile, it is possible to state pronounced hyperlipidemia with a high degree of probability of atherosclerosis. When studying the indicators of lipid metabolism depending on the

menopausal syndrome, it was found that in women with CS, the indicators of total cholesterol and triglycerides significantly exceeded those in the groups of subjects with the physiological course of menopause. In women with menopausal syndrome, there was a tendency to increase the levels of atherogenic LDL and VLDL fractions, and more pronounced in subjects with hypothyroidism. HDL levels were significantly lower in the groups of women with complicated menopause, regardless of the functional state of the thyroid gland.

It is well known that the prognostic sign of the risk of atherosclerosis and cardiovascular complications is not so much the absolute values of the concentration of lipid fractions, as the ratio of atherogenic and anti-atherogenic fractions to each other. This is an indicator of the atherogenicity index, which was significantly higher in women with menopausal syndrome.

The decision to take hormonal drugs in connection with the onset of menopause or refusal from them is probably one of the most important decisions that a woman has to make, especially in the presence of concomitant endocrine pathology. The available MHT preparations differ both in effectiveness and safety. The most acceptable for MHT in perimenopausal women is estrogen, a progestogenic drug that includes only analogues of natural female sex hormones - 17–estradiol and metabolically neutral didrogesterone, which has the most favorable spectrum of action on the cardiovascular system and has the lowest risk of developing metabolic disorders and cancer of the reproductive system.

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