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Clinical characteristics of women with endometrial hyperplasia on the background of thyroid dysfunction

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The objective: **to define the specificities of clinical characteristics in women of reproductive age with endometrial hyperplasia associated with hypothyroidism.**
Materials and methods**. There were 180 women with endometrial hyperplasia under our supervision. In 120 women, the pathology of endometrium was associated with newly diagnosed hypothyroidism. The patients with the thyroid dysfunctions were divided into the following groups: asymptomatic persons – 48 cases; symptomatic ones – 45 women; compensated patients with mild symptoms – 27 individuals. The control group consisted of 60 patients with endometrial hyperplasia without thyroid pathology.**
The data of the somatic and gynecological anamnesis, the concentration of sex hormones and thyroid hormones, the results of histological examination of the endometrium were analyzed in all the women.
Results**. The following data were found: the age of women with hyperprolactinemia without thyroid pathology is younger than the age of those with hyperprolactinemia and thyroid pathology; hypothyroidism in women with endometrial hyperplasia is contingent on frequently growing body weight, but not obesity; the most common concomitant pathology in women with endometrial hyperplasia and hypothyroidism was mastopathy which was diagnosed almost in every third patient.**
The frequency of such endocrine pathologies as polycystic ovary syndrome and hyperprolactinemia in women with endometrial hyperplasia has almost increased twice in the presence of hypothyrosis. In case of endometrial hyperplasia and hypothyrosis there was a significant decrease of estradiol concentration with a preserved level of gonadotropic hormones (luteinizing hormone and follicle-stimulating hormone), and the lowest values were defined in women with symptomatic hypothyroidism. Chronic endometritis, the detection rate of which does not depend on thyroid dysfunction, was diagnosed in 61.5 % patients with endometrial hyperplasia.
Conclusions**. Thyroid dysfunction is involved in the mechanisms of development of hyperplastic processes of the endometrium, which is the basis for screening the functional state of the thyroid gland in women with endometrial pathology.**
Keywords: *endometrial hyperplasia, hypothyroidism, thyroid gland, hormones, morphology.*

Клінічна характеристика жінок з гіперплазією ендометрія на тлі дисфункції щитоподібної залози

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Мета дослідження: визначення особливостей клінічних характеристик у жінок репродуктивного віку з гіперпластичними процесами ендометрія на тлі дисфункції щитоподібної залози.
Матеріали та методи. Під спостереженням перебували 180 жінок із гіперпластичними процесами ендометрія. У 120 жінок патологія ендометрія була асоційована з вперше виявленим гіпотиреозом (основна група). Пацієнтки з порушеннями функції щитоподібної залози були розподілені на підгрупи: безсимптомні – 48 спостережень; симптоматичні – 45 спостережень; компенсовані слабко вираженою симптоматикою – 27 спостережень. До контрольної групи увійшли 60 жінок з гіперпластичними процесами ендометрія без патології щитоподібної залози.
У всіх жінок аналізували дані соматичного та гінекологічного анамнезу, концентрації статевих гормонів та гормонів щитоподібної залози, результати гістологічного дослідження ендометрія.
Результати. За даними дослідження виявлено такі ознаки: вік жінок із гіперпролактинемією без патології щитоподібної залози менший за вік жінок із гіперпролактинемією та патологією щитоподібної залози; гіпотиреоз у жінок з гіперпластичними процесами ендометрія зумовлений збільшенням маси тіла, але не ожирінням; найпоширенішою супутньою патологією у жінок з гіперпластичними процесами ендометрія на тлі гіпотиреозу була мастопатія, яка діагностована у кожної третьої пацієнтки.
Частота таких ендокринних патологій, як синдром полікістозних яєчників і гіперпролактинемія, у жінок з гіперпластичними процесами ендометрія зросла вдвічі за наявності гіпотиреозу. При гіперпластичних процесах ендометрія на тлі гіпотиреозу відзначено достовірне зниження концентрації естрадіолу при збереженому рівні гонадотропних гормонів (лютеїнізуючий та фолікулостимулювальний гормони), а найнижчі показники визначені у жінок із маніфестним гіпотиреозом. Хронічний ендометрит, частота виявлення якого не залежить від дисфункції щитоподібної залози, діагностували у 61,5% жінок з гіперпластичними процесами ендометрія.
Висновки. Тиреоїдна дисфункція бере участь у механізмах розвитку гіперпластичних процесів ендометрія, що є підставою для скринінгу функціонального стану щитоподібної залози у жінок із патологією ендометрія.
Ключові слова: *гіперплазія ендометрія, гіпотиреоз, щитоподібна залоза, гормони, морфологія.*

Studies conducted in recent years have significantly expanded the understanding of such a fairly common hormone-dependent disease as endometrial hyperplasia (EHP). In the structure of gynecological pathology, the frequency of EH is 15–40% [1, 2]. Often, EH is combined with thyroid diseases, which requires a attentive approach to diagnosis and treatment [3]. EHP in women of reproductive age is a potential cause of reduced fertility and a risk factor for cancer [4]. EHP is based on a violation of coordination between glandular and stromal components of endometrium due to a violation of the action of steroid hormones at the subcellular level [5, 6].

At the present stage, the problem of endometrial hyperplasia (EHP) against the background of thyroid dysfunction has become particularly important due to an increase in the frequency of combined pathological processes [7]. In women of early and late fertile age, the formation of EHP in more than 50% is combined with diseases of the thyroid gland. In women of reproductive age suffering from hypothyroidism, glandular EHP is detected in 55% of cases [2, 8, 9].

To date, the etiology, pathogenesis, clinic, diagnosis and treatment of endometrial hyperplasia against the background of thyroid dysfunction remain definitively unresolved and debatable [18]. The solution of these problems will be facilitated by determining the clinical and anamnestic characteristics of patients with EHP against the background of hypothyroidism.

The aim of the study was to determine the clinical characteristics of women of reproductive age with EHP against the background of thyroid dysfunction.

MATERIALS AND METHODS

We observed 180 women with EHP. In 120 patients, endometrial pathology was associated with hypothyroidism (the main group). Patients with thyroid dysfunction were divided into subgroups depending on the severity of hypothyroidism: subclinical – 48 cases; manifest – 45 cases; compensated with mild symptoms – 27 cases. The control group consisted of 60 patients with EHP without thyroid pathology.

Inclusion criteria: reproductive age, primary hypothyroidism, established morphological diagnosis of EHP without atypia. Exclusion criteria: decompensated hypothyroidism; secondary or tertiary hypothyroidism.

The classification adopted by the International Society of gynecologists and pathomorphologists was used to verify the diagnosis of EHP [2]. Hysteroscopy was performed for the morphological diagnosis of EHP.

To verify the diagnosis of hypothyroidism, the level of Thyroid-Stimulating Hormone (TSH) and free thyroxine (free T4) in the blood serum of women was determined. Hypothyroidism involves having high TSH levels. Increased TSH concentration and decreased free T4 indicated manifest hypothyroidism. Subclinical hypothyroidism corresponded to an increase in TSH in the case of normal freeT4 concentrations.

Hormonal status was determined based on TSH and free T4 levels of prolactin (PRL), luteinizing hormoneb(LH), follicle-stimulating hormone (FSH), estradiol (E2), progesterone (P), dehydroepiandrosterone sulfate (DHEA-S), testosterone, 17-OH progesterone.

Statistical calculations were performed in Excel with the determination of the arithmetic mean (M) and standard deviation (m). The reliability of differences was determined using the TTEST function.

RESEARCH RESULTS AND THEIR DISCUSSION

The clinical characteristics of the examined groups were based on the determination of age characteristics, mass-growth parameters, and anamnestic data. The average age of women in the study groups had no significant differences and was 34.7±4.4 years ($p<0.05$). For the entire population of patients with hypothyroidism, the average age was 35.1±5.9 years. In the control group, this indicator was 35.2±3.8 years, which had no significant differences ($p<0.05$). Almost every third woman with hypothyroidism (32.4%) was in the age range of 25-30 years, while in the control group patients under the age of 30 were noted only in 15% of cases – less than 2 times. This fact allows us to conclude that thyroid pathology can cause an increase in the frequency of EHP at a young age.

There were no significant differences in average body mass index (BMI) values between groups of women with hypothyroidism ($p>0.05$). For all examined women with thyroid pathology, the average BMI value was 23.7±3.5, which almost did not differ from the data in the control group – 23.5±2.6 ($p>0.05$).

Based on the above data, there is no link between obesity and hypothyroidism. However, the following fact attracts attention. Overweight among women with hypothyroidism was observed in 25.8%, while in the control group this indicator was 11.7%. Obesity of I and II degrees occurred in isolated cases, which did not allow us to come to certain conclusions. The results show that hypothyroidism in women is associated with overweight, but not obesity.

The opinions of modern authors on this issue are contradictory. Thus, according to some researchers, women have pronounced associations of obesity with manifest and subclinical hypothyroidism [11]. According to the above results, in the case of hypothyroidism, there was a high prevalence of metabolic syndrome (41.6%) and abdominal obesity (45%) ($p<0.05$) [5, 16]. According to other studies, 54% of women with primary hypothyroidism were overweight, but not obese [12]. The data obtained by us correspond to this point of view of modern researchers.

Such close attention to the weight and height characteristics of the women studied is due to the fact that overweight and obesity are among the risk factors for EHP. Obese women (BMI > 30 kg/m^2) showed a 4-fold increase in the incidence of atypical EHP. Among women with a BMI of 40 kg/m^2, a 13-fold increased risk of EHP with atypia was found [13].

We studied the territorial stay and social status of the women, which is due to the influence of ecological and geographical zones on the functional state of the thyroid gland [14, 15]. Most of the women in the clinical and control groups were urban residents. Among patients with hypothyroidism, residents of the city accounted for 65.6%, and the control group – 73%.

In our opinion, the fact that more than 2/3 of all women surveyed lived in the city is not due to etiological factors, but to the greater availability of specialized medical care in the city.

The number of women engaged in physical and intellectual work was similar in all groups. The predominance of women engaged in intellectual work is indicated. This feature was characteristic of both all clinical groups of women suffering from hypothyroidism and the control group. Among all women with hypothyroidism, intellectual labor specialists accounted for 54%, and in the control group – 50%.

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Other researchers note that the risk of developing GPE is higher in women engaged in intellectual work associated with stress factors [1, 16].

The somatic status of the studied groups of women was studied. Mastopathy was most common among extragenital pathology in the examined women (30.3%). However, in the control group, this pathology was 15%, which is twice as rare as in women with EHP on the background of thyroid dysfunction ($p<0.05$).

Varicose veins were also often observed in the examined women with EHP on the background of thyroid dysfunction (16.5%). In the control group, vascular pathology was detected in 10% of cases. Cholelithiasis and diabetes mellitus occurred in isolated cases in both study groups and did not have a statistically significant difference.

The data obtained on the incidence of mastopathy among women in the main group can be compared with the results of other researchers. A sharp increase in breast pathology in women with EHP against the background of hypothyroidism is also noted by modern authors [17, 18]. Moreover, mastopathy is considered a multifactorial pathology, the main causes of which are thyroid dysfunction – 27%, hyperprolactinemia – 27%, ovarian dysfunction – 46% [19].

Attention is drawn to the incidence of polycystic ovary syndrome (PCOS) and hyperprolactinemia (HPRL) among women in the main group compared to the control group: PCOS in the presence of thyroid dysfunction was 19.9%, HPRL – 22.4% versus 10% and 8.3%, respectively, in the control group.

Our study coincides with the results of a study by other authors: among 137 women with PCOS, 21.9% were diagnosed with hypothyroidism [20]. This proves the close association of thyroid dysfunction with impaired neuroendocrine regulation in the hypothalamic-pituitary-ovarian system.

The prevalence of HPRL in subclinical hypothyroidism was 20.4%. At the same time, no correlation was established between serum TSH and PRL levels [21]. In contrast to this statement, it is reported that elevated PRL levels in hypothyroidism were detected with almost identical frequency in 18% of cases, but there was a positive correlation between TSH and PRL levels [18, 22].

Some authors found a combination of hyperprolactinemia and subclinical hypothyroidism in 40% of patients [2, 23], and subclinical hypothyroidism was found in all patients with PCOS and hyperprolactinemia [17, 24].

In our studies, hypothyroidism causes a two-fold increase in the incidence of PCOS and HPRL. The classic explanation for this phenomenon is that a reduced level of thyroid hormones causes excessive production of tyroliberin (according to the feedback principle), which leads to an increase in the secretion of not only TSH, but also PRL [2, 25]. It should also be noted that chronic anovulation (with PCOS, elevated PRL levels) associated with elevated estrogen levels is a risk factor for EHP [26].

We evaluated the hormonal status of women with EHP against the background of hypothyroidism and patients in the control group. When comparing the concentration of 17-OH progesterone among the studied women of the main (0.56±0.19 ng/mL) and control (0.55±0.18 ng/mL) groups, no statistically significant differences were found ($p>0.05$). Also, there were no statistically significant differences between the main and control groups when assessing the concentration of the hormones DHEA-S, testosterone and progesterone.

Noteworthy are the dynamics of changes in estradiol levels in women with HPE on the background of hypothyroidism (65.3±21.8 pg/ml) compared to the control group (54.9±22.1 pg/mL), which has statistically significant differences ($p<0.05$). The lowest concentration of the hormone was observed in women with manifest hypothyroidism, the highest levels of estradiol were observed in patients with subclinical hypothyroidism. LH and FSH concentrations corresponded to the standard values in the main and control groups.

The isolated decrease in estradiol levels, which is not accompanied by changes in LH and FSH concentrations, can be explained by the results of subsequent studies. With hypothyroidism in women, the activity of metabolic clearance of androstenedione and estrone decreases, which is accompanied by an increase in their peripheral aromatization. At the same time, the activity of sex hormone-binding globulin decreases in plasma, which contributes to a decrease in the concentration of total estradiol [16]. In turn, a decrease in the activity of peripheral estrogen metabolism causes the formation of less active fractions that are not able to maintain the feedback principle in the regulation of gonadotropins, but the levels of the latter remain normal [13].

The analysis of the reproductive health of the examined women was carried out. According to the results of our study, a high miscarriage rate of 20.8% was found among women in the main group, which is 7 times higher than this indicator in the control group of 3.3% ($p<0.05$). Also, the rate of undeveloped pregnancy in women with thyroid dysfunction was observed in 9.1% of women, which is 5.4 times higher than this indicator of the control group of 1.7% ($p<0.05$).

This fact confirms that thyroid pathology with impaired thyroid function, in particular subclinical hypothyroidism, has an adverse effect on the processes of embryogenesis, placentation and gestation, which worsens the results of pregnancy [5, 19].

According to the results of other studies, it was also noted that non-developing pregnancy, especially repeated pregnancy, occurs against the background of thyroopathy, since every fourth patient has thyroid pathology, mainly hypothyroidism 80%. Hypothyroidism can be recognized as a risk factor for non-developing pregnancies. The risk of developing a non-developing pregnancy against the background of subclinical hypothyroidism is 2.48, and for repeated cases 2.15 [1, 22].

Assessing the nature and frequency of concomitant gynecological pathology in the examined women, statistically significant differences in groups were revealed ($p<0.05$). Gynecological history is burdened in 51.5% of women in the main group, while in the control group only 28.2%. In the examined women, chronic inflammatory diseases of the genitals occurred in 30.7% of the main and 21.6% of the control group; cervical pathology – in 19.1% and 10% and ovarian cysts – in 11.6% and 6.6%, uterine fibroids -10% and 5%, respectively. Infertility in the Anamnesis was observed in patients of the main group 1.5 times more often than in the control group.

Morphological characteristics of endometrial pathology of the examined groups of women were carried out by us. According to the results of histological examination, simple endometrial hyperplasia prevailed in both the main and control groups. No significant differences were found between the

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groups (p>0.05). In women with thyroid dysfunction, simple hyperplasia was diagnosed in 61.4%, in the control group – in 64.7%. This fact allows us to conclude that thyroid dysfunction contributes to an increase in the frequency of EHP, but does not affect its morphological structure.

The next feature identified when considering the morphological characteristics of EHP is the frequency and structure of detection of endometrial polyps. No statistically significant differences were found in the groups, polyps were observed with almost the same frequency up to 23%, and glandular polyps predominated in morphological structure in all groups (about 74%).

When analyzing the results of histological examination of women with EHP, there is a high frequency of detection of signs of chronic endometritis. Among women of the main group with thyroid dysfunction, 59.7% were diagnosed with chronic endometrium. A similar pattern was observed in women with EHP without thyroid dysfunction: histologically verified chronic endometritis 63% of cases. The present data allow us to conclude that more than half of the cases have chronic endometritis among women with EHP; the frequency of diagnosis of chronic endometritis among women with and without hypothyroidism is comparable (60% vs. 63%), which indicates, in our opinion, that there is no influence of thyroid pathology on endometrial inflammatory processes.

In the works of other researchers, similar results are given. Thus, among 119 patients with a morphologically verified diagnosis of EHP chronic endometritis was detected in 57 women, that is, the association of EHP and chronic endometritis was in almost half of the cases. In context, it should be emphasized that, according to some authors, chronic endometritis is important in the emergence of EHP. Most researchers consider chronic inflammation as a favorable factor for the further development of hyperplastic and neoplastic diseases. However, the molecular mechanisms contributing to the disruption of tissue and cellular homeostasis with the occurrence of hyperplastic changes during a long-term local inflammatory response in the endometrium are poorly understood [27].

It is reported that in chronic endometritis there is a decrease in the expression of estrogens in the endometrial epithelium and overexpression of progesterone receptors in the stroma, which is due to the manifestation of a compensatory reaction of endometrial tissue. As a result, the damaged endometrial mucosa becomes thinner and does not respond to hormonal stimuli. Hormone-dependent disorders were found to be affected by hormone secretion at the level of target organs in the form of «thin» endometrium, polyposis, and EHP [13, 23].

In EHP and chronic endometritis, high proliferative activity of the glandular stroma (Ki-67), high expression of transforming growth factor- (TGF-) and vascular endothelial growth factor (VEGF) were noted, which contributes to the activation of neoangiogenesis processes and disruption in the extracellular matrix. Inflammation potentiates the proliferative activity of the epithelium and stroma of the hyperplastic endometrium and creates favorable conditions for atypical cell transformation [2]. Our research proves the need to include anti-inflammatory and antibacterial therapy in the complex of therapeutic measures in the case of EHP.

CONCLUSIONS

Thus, the results of the clinical characteristics of the examined women allowed us to establish the following features:

- the age of women with EHP suffering from hypothyroidism was younger than that among women without thyroid dysfunction;
- hypothyroidism in women with EHP is associated with increased body weight, but not obesity;
- the most common concomitant pathology for women with EHP against the background of hypothyroidism is mastopathy, which is diagnosed in almost every third patient;
- the frequency of such endocrine pathologies as PCOS and HPRL among women with EHP increased almost twice in the presence of hypothyroidism;
- with EHP on the background of hypothyroidism, a significant decrease in estradiol concentrations was noted with a preserved level of gonadotropic hormones (LH and FSH), and the lowest values were determined among women with manifest hypothyroidism;
- in 61.5% of women with EHP, chronic endometritis was detected, the frequency of which does not depend on thyroid dysfunction.

In our opinion, the specified features indicate the participation of thyroid dysfunction in the mechanisms of the development of EHP. The last circumstance is the basis for screening the functional state of the thyroid gland among women with endometrial pathology.

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