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I.A. Kachailo, I.A. Guz, O.O. Kuzmina
Kharkiv National Medical University, Kharkiv

STATE OF THE HORMONAL PROFILE IN ENDOMETRIAL HYPERPLASIA

e-mail: irina.kachailo79@gmail.com

The research data of 93 patients were analyzed. Patients were divided into three clinical groups depending on the form of endometrial hyperplasia: group 1: with uncomplicated non-atypical endometrial hyperplasia – 53 patients; group 2: with complex non-atypical endometrial hyperplasia – 22 patients; group 3: with simple atypical endometrial hyperplasia – 18 patients. The control group consisted of 20 healthy women. Comparative analysis showed that the level of hormones in the 1st phase of the menstrual cycle was not significantly different between the groups for most indices of luteinizing hormone in group 2 compared to groups 1 and 3 ($p < 0.01$). The study of hormonal status in women of 3 clinical groups showed that, compared to the control group, there was a significantly greater increase in the level of testosterone in blood plasma ($p < 0.05$). Progesterone content in the control group was lower (almost by 5 times) than the control level ($p < 0.001$). The estradiol level in groups 1 and 2 decreased and was three times lower compared to the control group ($p < 0.001$). With simple atypical EH, the concentration of estradiol was sharply increased compared to the control groups, 1 and 2, which confirms the stimulation of the proliferative processes' development in the endometrium.

Key words: endometrial hyperplasia, morphological features, hormonal status.

І.А. Качайло, І.А. Гузь, О.О. Кузьміна

СТАН ГОРМОНАЛЬНОГО ПРОФІЛЮ ПРИ ГІПЕРПЛАСТИЧНИХ ПРОЦЕСАХ ЕНДОМЕТРІЮ

Проаналізовано дані дослідження 93 пацієнток, які були поділені у залежності від форми гіперплазії ендометрію на 3 клінічні групи: 1 група: із простою неатиповою гіперплазією ендометрію – 53 пацієнтки; 2 група: зі складною неатиповою гіперплазією ендометрію – 22 пацієнтки; 3 група: з простою атиповою гіперплазією ендометрію – 18 пацієнток. Контрольну групу становили 20 здорових жінок. Порівняльний аналіз показав, що рівень гормонів у 1 фазу менструального циклу достовірно не відрізнявся між групами за більшістю показників лютеїнізуючого гормону у 2 групі порівняно з 1та 3 ($p < 0,01$). Дослідження гормонального статусу у жінок 3 клінічної групи показало, що порівняно з контрольною групою в плазмі крові спостерігається достовірно значуще підвищення рівня тестостерону ($p < 0,05$). Вміст прогестерону в контрольній групі був значно нижчим (майже в 5 разів) за рівень контролю ($p < 0,001$). Рівень естрадіолу в 1 та 2 групах знижувався і був у 3 рази нижчим порівняно з контрольною групою ($p < 0,001$). При простій атиповій гіперплазії ендометрію концентрація естрадіолу була різко підвищеною у порівнянні з контрольною, 1 та 2 групами, що підтверджує стимуляцію розвитку проліферативних процесів в ендометрії.

Ключові слова: гіперпластичні процеси ендометрію, морфологічні особливості, гормональний статус.

The study is a fragment of the research project "Optimization of clinical, diagnostic and therapeutic approaches to the management of gynecological patients taking into account age and the presence of extragenital pathology", state registration No. 0122U000257.

Endometrial hyperplasia (EH) is a gynecological disease determined by the morphological features of the development of the pathological process and is associated with hormonal disorders [1].

EH develops against absolute or relative hyperestrogenism or lack of progesterone. The causes of hyperestrogenism can be the excessive peripheral conversion of androgens into estrogens during obesity, the presence of hormone-producing structures in the ovary, hyperplasia of the adrenal cortex, liver pathology, pathological or age-related changes in the central regulation of reproductive function that lead

to anovulation, hyperinsulinemia, improper use of hormonal drugs. Hyperplastic changes are one of the forms of proliferative processes, mainly associated with the proliferation of the iron component compared to the stromal component [2].

As a target tissue, the endometrium feels the influence of sex hormones and is extremely sensitive to its structure and function [8].

Metabolic and endocrine disorders play an essential role in the pathogenesis of EH: changes in fat metabolism, metabolism in the pathology of the liver and biliary system and gastrointestinal tract, immunity, and thyroid function. In this regard, obesity, hyperlipidemia, diabetes, arterial hypertension, metabolic syndrome and many other disorders are often noted in patients with EH [3].

The biological processes that cause their development lead to the fact that the hormonal tissue cannot only renew the cellular composition cyclically but also to a certain response to the hormonal status at the level of the organism as a whole [9]. Violations of hormonal and immune homeostasis are one of the most critical pathogenetic links in the development and progression of EH.

According to modern concepts, hyperestrogenism is the main, but not the only, factor in developing EH [10]. In addition to increased estrogens, a significant role in developing this pathology is played by violating proliferative processes and cell apoptosis [4]. Cellular and extracellular components also control them at the molecular level [11].

Sex hormones affect the development of malignant processes of the endometrium due to the stimulation of proliferation, which are the main pathological factors of EH [12].

According to modern research, the initiation of EH is possible under the influence of estrogens that enter the body with medications [13]. It has been proven that the long-term use of synthetic estrogens, their metabolites, and selective modulators of estrogen receptors can cause the activation of endometrial cell proliferation [5].

Depending on the degree of changes in the mucous membrane of the uterine body, simple and complex hyperplasia are distinguished, taking into account the presence or absence of cellular atypia. Simple typical hyperplasia is characterized by increased stromal and iron elements, which do not significantly affect the structural rearrangement of the endometrium [14]. In glandular and glandular-cystic EH, the degree of expressiveness of hyperplastic processes and active proliferation of glands and endometrial stroma is accompanied by the formation of cysts. Simple atypical EH differs in that an atypia of glandular cells accompanies it. However, there are no changes in their structure [7]. Complex EH (without atypia) is characterized by a change in the location of the glands, their size and shape, with a decrease in the stromal component, which is often observed in adenomatous EH, which is also characterized by the absence of cellular atypia with a structural change in the tissue [6].

Despite research aimed at studying the pathogenesis of EH, several issues related to hormonal changes, diagnosis, treatment and prognosis of this pathology remain unsolved. EH constitutes a major medical and social problem due to long-term recurrence and a high risk of malignant transformation [1]. Changes in the hormonal status of women with EH made it necessary to carry out these studies.

The purpose of the study was to determine changes in the hormonal status during the development of hyperplastic processes in the endometrium.

Material and methods. The research data of 93 patients were analyzed. Patients were divided into 3 clinical groups depending on the form of endometrial hyperplasia: group 1: with simple non-atypical EH – 53 patients; group 2: with complex non-atypical EH – 22 patients; group 3: with simple atypical EH – 18 patients. The control group consisted of 20 healthy women.

When analyzing somatic pathology in the groups of examined women, no statistically significant differences were found ($p>0.05$). Concomitant extragenital pathology was found in all patients, and it is important to note that some of them had a combination of several extragenital diseases.

All patients underwent a laboratory examination, including determination of blood group and Rh factor, serological reactions to HIV, viral hepatitis B and C, syphilis, general clinical and biochemical blood examination, coagulogram, general urinalysis, microscopic examination of secretions from the genitourinary organs, cytology cervix.

The diagnosis of EH was verified based on the clinical picture, the data from an ultrasound examination of the pelvic organs, hysteroscopy, and the morphological picture of scrapings from the uterine cavity after diagnostic scraping.

To determine the thickness of the endometrium, ultrasound diagnostics was carried out using the Aloka 88B-1700 device (Japan) with the function of color mapping and pulse-wave dopplerometry. Ultrasound examination was performed on days 5–9 of the menstrual cycle. Ultrasound criteria for

endometrial hyperplasia were considered endometrial thickness of more than 7 mm in the 1st phase and more than 15–16 mm in the second phase of the menstrual cycle.

Hysteroscopy was performed with the help of endoscopic equipment from the company "Karl Storz" (Germany). The study was performed under intravenous anesthesia. During the hysteroscopy, all the walls of the uterine cavity, the area of the fallopian tubes and the cervical canal were examined. The condition of the mucous membrane of the uterus (thickness and correspondence to the day of the menstrual cycle) and the presence of pathological formations of the endometrium were evaluated. At the end of the study, biopsy material of the endometrium and endocervix was taken, after which a control hysteroscopy was performed. Histological examination of the endometrium was performed according to the standard method of serial sections.

Indices of hormones in blood plasma were performed using diagnostic tests (10-3700 – manufacturer BCM Diagnostics USA). The concentration of testosterone, progesterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol and prolactin was determined.

Statistical data processing was performed using the Statistica 10 application software packages. All obtained data were prepared using MicroSoft Excel software. The level of statistical significance was set at $p < 0.05$.

Results of the study and their discussion. Every month, changes in the endometrium occur in a woman's body, which is related to the phases of the menstrual cycle and its structure, depending on the hormonal background. The endometrium responds to hormones and undergoes regular menstrual cycles throughout a woman's reproductive years. A complex orchestra of hormones controls each menstrual cycle. During the menstrual cycle, the endometrium prepares for a possible pregnancy, becoming thicker and saturated with blood vessels. However, in some situations, the endometrium is exposed to long-term hormone exposure. This leads to increased growth and crowding of the endometrium of the gland and can lead to hyperplasia.

The main complaint of 38 patients (27.3%) was bleeding from the genital tract. The nature of bloody secretions differed, from one-time smearing to repeated moderate and abundant.

The study of hormonal status in women of 3 clinical groups showed that, compared to the control group, there was a slight but significantly greater increase in the level of testosterone in blood plasma ($p < 0.05$).

Progesterone content in the control group was lower (almost 5 times) than the control level ($p < 0.001$). However, the estradiol concentration in groups 1 and 2 varied and was three times lower compared to the control group ($p < 0.001$).

In group 3, with simple atypical EH, the estradiol concentration is sharply increased compared to the control groups 1 and 2, confirming the stimulation of proliferative processes in the endometrium.

Table 1

Plasma hormone levels in the examined women

Indices of hormone levels	Groups of women			
	Control, n = 20, M±m	Clinical 1, n = 53, M±m	Clinical 2, n = 22, M±m	Clinical 3, n = 18, M±m
Testosterone (nmol/L)	1.3±0.2	2.5±0.42 *	3.4±0.22 *	4.8±0.12 **
Progesterone (nmol/L)	42.2±1.8	8.8±0.97***	7.7±0.55***	6.6±0.35***
T3 (nmol/L)	1.9±0.7	1.8±0.28	1.4±0.13	1.6±0.11
T4 (nmol/L)	92.9±5.6	84.0±6.21	83.6±5.42	84.0±6.21
TSH (mIU/L)	1.7±0.4	1.6±0.29	1.7±0.12	1.2±0.21
FSH (mIU/L)	5.9±0.6	10.8±1.05 *	15.1±1.32 **	18.2±2.02 *
LH (mIU/L)	5.5±0.6	6.10±0.57	12.1±0.41***	7.4±0.41
Estradiol (pmol/L)	512.0±21.6	151.0±18.2***	137.8±13.22***	607.2±24.11***
Prolactin (mIU/L)	376.7±30.4	414.5±31.5	433.8± 41.2	464.3±55.2

In all clinical observation groups, FSH concentration was significantly higher (10.8±1.05, 15.1±1.32, 18.2±2.02) compared to the control group (4.89±0.65), which is probably because EH develops against the background of hyperestrogenism.

Other analyzed indices do not reach statistically significant values ($p < 0.05$).

The described data indicate that with simple atypical EH, proliferative processes in the endometrium can occur against the background of hyposecretion of estrogens against the background of progesterone deficiency (group 1). In women of clinical groups 1 and 2, practically similar dynamics are observed in the indices of hormonal status.

Testosterone content is significantly higher in clinical groups 1, 2 and 3 than in controls ($p < 0.05$).

In the 2nd observation group, against the background of increased FSH ($p < 0.01$), the content of concentration and LH significantly increased ($p < 0.05$). At the same time, progesterone significantly decreases in all clinical observation groups compared to control ($p<0.001$) and occurs against the background of reduced estradiol content in groups 1 and 2 ($p<0.001$).

In the group of women with simple atypical EH, the analyzed indices show a slightly different picture compared to the control group's data. Thus, the testosterone content significantly exceeds the control index ($p < 0.05$). A significant decrease in progesterone ($p<0.001$) and an increase in FSH ($p<0.001$) are noted against the background of increased estradiol content ($p<0.05$). LH, prolactin, and thyroid hormone content do not reach significant changes ($p>0.05$).

The given data show that with simple atypical EH, proliferative processes in the endometrium can occur against the background of hyposecretion of estrogens but with progesterone deficiency.

The endometrium is a hormone-sensitive tissue that has the ability not only to cyclical renewal of almost the entire cellular composition but also to a specific response to all changes in hormones, cytokines, adhesion molecules, growth factors, biogenic amines and other biologically active substances at the level of the whole organism. This interaction is ensured by a complex network of intercellular and intracellular signalling pathways, in which all the above molecules act paracrine, autocrine or endocrine.

In recent years, great importance has been attached to the processes of apoptosis, which plays a leading role in the functioning of the female reproductive system. During the menstrual cycle, endometrial cell death by apoptosis and their regeneration occur in a strictly regulated sequence and depend on the stage of the cycle. Identifying markers of programmed cell death disruption at the stage of endometrial hyperplasia can make it possible to predict the adverse course of the disease and choose the optimal individual treatment tactics aimed at preserving and restoring generative function in women of reproductive age and preventing malignancy. Endometrial hyperplasia and atrophy can consistently replace each other depending on changes in hormonal relationships in the reproductive system. It is believed that proliferatively active estrogens are the main factor causing endometrial hyperproliferation, which progresses to simple or complex endometrial hyperplasia in the absence of progesterone. Increased levels of follicle-stimulating and luteinizing hormones have a stimulating effect on the function of the ovaries, which corresponds to the increased production of estrogens, which are not compensated by the action of progesterone. The risk of developing hyperplastic diseases of the endometrium and myometrium increases significantly against the background of disturbances in the receptor and proliferative state of the endometrium. It is possible that in the development of hyperplastic and tumour diseases, an important role is played not only by the increase in the processes of cell proliferation but also by the violation of the mechanisms of programmed cell death. It is accompanied by the accumulation of defective cells or cells with excess proliferation and impaired expression of receptors for steroid hormones – estrogens and progesterone, an increase in the frequency of cytogenetic abnormalities in the endometrium, uterine fibroids, which correlate with such peripheral blood lymphocytes. The consequence of this is the combination of hyperplasia with diseases of the female genital organs.

Endometrial hyperplasia is a pathological condition in which the lining of the uterus grows excessively. Endometrial hyperplasia is especially dangerous because, occurring without any clinical manifestations in the early stages in young women, it leads to infertility in the future, and in perimenopausal women, it creates all the conditions for the transformation of healthy endometrial cells into malignant ones. The etiology and pathogenesis of various types of hyperplasia are considered from the point of view of the development of neuro-humoral pathologies. Expected changes in the state of the endometrium are directly related to the reproductive system, which is regulated by the neuroendocrine system. That is why all the factors that lead to hyperplasia first show their effect at the neuro-humoral level.

The leading role in etiopathogenesis is excessive estrogen stimulation, combined with insufficient production of progesterone, hormone-independent proliferation, inflammatory processes, reduced apoptosis, pathological neoangiogenesis and impaired immune status in the endometrium. Endometrial damage is an intermediate link in the entire chain of pathological processes in the body.

Risk factors for the development of endometrial hyperplasia: a woman's age, autoimmune disorders, diseases of the liver and gall bladder, pathology of the adrenal glands, diabetes, lack of pregnancy, early menarche, late menopause, obesity, smoking, long-term use of certain hormonal drugs, hereditary predisposition. Clinical manifestations of endometrial hyperplasia largely depend on the age of the patient, specific etiology and the presence of concomitant diseases. Signs of endometrial hyperplasia are mainly manifested by a violation of menstrual function and metabolic processes.

The main reason for the occurrence of EH and tumors in hormone-dependent tissues is a violation of the normal rhythm of the production of estrogen and progesterone content. The development of

pathological processes of cell proliferation in EH occurs in connection with the activation of three signalling cascades: steroid hormones, epidermal growth factors and cytokines [7].

Long-term stimulation of proliferative processes in hormone-dependent tissues occurs under absolute or relative insufficiency of steroid hormones, which are antagonists of estrogens, androgens, glucocorticoids, mainly progesterone [3, 9]. Patients have a long and continuous effect of estradiol, which leads to a progesterone deficiency state.

Suppose the function of the LH-producing pituitary remains unchanged. In that case, the function of the FSH-producing cells is at a high level, which should lead to the emergence of many follicles, which, on the other hand, are stimulated by physiological concentrations of prolactin [4, 8].

In addition, it can be assumed that not estrogens themselves, but modulators of their action, which are various hormones, growth factors, lipid mediators, cytokines, and biogenic amines, cause the development of pathological effects of estrogens on the uterus, which lead to the development of malignant tumours.

Conclusion

Despite the improvement of diagnostic, therapeutic and surgical methods, the problem of treating hyperplastic processes of the endometrium is relevant. The complexity and heterogeneity of the pathogenesis of the disease, the variety of interpretations of its individual links, and the ambiguity of tactical approaches create certain difficulties in choosing the pathogenetic rationale for treatment, especially hormonal therapy. Hyperplastic processes of the endometrium are an actual problem, which is caused by the peculiarities of the etiopathogenesis and clinical manifestation of the disease, a decrease in reproductive potential, a high frequency of relapses, a limitation of the possibilities of conservative treatment of this pathology in women due to concomitant extragenital diseases and a high risk of malignancy. Disturbance of the balance in the "estrogen-progesterone" system leads to inhibition of the processes of structural reconstruction of the preparation of endometrial cells for the action of progestogens. With an insufficient concentration of estradiol in the endometrium cells, changes occur that can support the constant proliferation of the epithelium and ensure the formation of endometrial hyperplasia and, subsequently, its malignancy.

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