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I.A. Kachailo, O.O. Kuzmina, I.A. Guz, T.O. Kozub'
Kharkiv National Medical University, Kharkiv; [1]V.N. Karazin Kharkiv National University, Kharkiv

MECHANISMS OF ENDOMETRIAL HYPERPLASIA DEVELOPMENT IN WOMEN OF REPRODUCTIVE AGE

e-mail: irina.kachailo79@gmail.com

Data from studies of 88 women were examined during a diagnostic endometrial biopsy for abnormal uterine bleeding or increased endometrial thickness. The patients were between 40 and 55 and divided into the main and control groups. A high expression of estrogen-α receptors and a low expression of progesterone hormones were found, indicating proteins' pro-oncogenicity in patients with complex endometrial hyperplasia. Pathogenetic mechanisms of endometrial hyperplasia were factors of proliferation and apoptosis, which is confirmed by a significant increase in the proliferation marker Ki67 of epithelial cells in complex endometrial hyperplasia in endometrial biopsies and a decrease in the apoptosis marker p53. A differentiated approach to diagnosing endometrial hyperplasia is based on the determination of molecular markers (Ki67, p53), which allows one to predict the course of the hyperplastic process and assess the effectiveness of the treatment.

Key words: endometrial hyperplasia, morphological features, hormonal status, therapeutic tactics, expression of estrogen and progesterone receptors, molecular markers.

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

МЕХАНІЗМИ РОЗВИТКУ ГІПЕРПЛАЗІЇ ЕНДОМЕТРІЮ У ЖІНОК РЕПРОДУКТИВНОГО ВІКУ

Проаналізовано дані досліджень 88 жінок у яких під час діагностичної біопсії ендометрію з приводу аномальних маткових кровотеч або збільшення товщини ендометрію було визначено його структуру. Пацієнтки знаходились у віці від 40 до 55 років та були розподілені на основну та контрольну групи. Було встановлено високу експресію рецепторів естрогену-α та низьку до прогестеронових гормонів, що свідчить про проонкогенність білків у пацієнток зі складної гіперплазією ендометрію. Патогенетичними механізмами гіперплазії ендометрію були фактори проліферації і апоптозу, що підтверджується достовірним підвищенням маркера проліферації Ki67 клітин епітелію при складній гіперплазії ендометрію в біоптатах ендометрію, а також зниженням маркера апоптозу p53. Диференційований підхід до діагностики гіперплазії ендометрію заснований на визначенні молекулярних маркерів (Ki67, p53) дає змогу не тільки прогнозувати перебіг гіперпластичного процесу, а й оцінити ефективність проведеного лікування.

Ключові слова: гіперплазія ендометрію, морфологічні особливості, гормональний статус, лікувальна тактика, експресія рецепторів естрогену і прогестерону, молекулярні маркери.

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 hyperplastic processes (EHP) are one of the essential problems of gynecology, which consists of pathological changes in the uterine mucosa and becomes the background for the development of malignant processes [7]. The endometrium is a hormone-sensitive tissue that is capable of cyclic renewal of the cellular composition in response to the hormonal influence of sex hormones and is also sensitive to the action of estrogens, which cause proliferative changes in progesterone and lead to the development of hyperplasia [1].

Regulators of proliferation and apoptosis are essential in the pathogenesis of endometrial hyperplasia (EH) development. Determining markers of programmed cell death disruption in EHP

contributes to predicting the course of pathological processes, preserving and restoring the generative function of women of reproductive age, and preventing malignancy [9].

Absolute or relative hyperestrogenism and a complex of neuroendocrine, metabolic and immune disorders play a key role in the pathogenesis of EHP. Estrogen receptors in the endometrium stimulate proliferative processes in the uterus and affect the development of EHP. 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 [10].

The degree of expression of endometrial and cystic endometrial hyperplasia depends on the active proliferation of glands and stroma of endometrium. Histological examination reveals an increase in the number of epithelial and stromal elements without structural rearrangement of the endometrium, which is not accompanied by gland enlargement and cyst formation.

EHP is a group of pathological processes characterized by the progression of clinical and morphological manifestations – from glandular endometrial hyperplasia (GEH) to atypical precancerous conditions [2].

EH often develops against the background of disorders of various links of the hypothalamic-pituitary-ovarian axis, progesterone deficiency and gonadotropin excess [8].

Steroid hormone receptors are crucial in the development of hormone-dependent hyperplastic diseases of the uterus. The state of the endometrial receptor apparatus in EHP is prognostic in the presence of high estrogen levels and progesterone receptors, and the presence of progesterone receptors in the cytoplasm is an indicator of sensitivity to gestagens [4].

The study of the development factors of the molecular mechanisms of EHP and the search for their correction is one of the main problems of an effective approach to the management of the proliferative activity of the endometrial glands [5, 6].

Endometrial activity is regulated by proliferation factors, namely Ki-67 and the apoptosis marker p53. The Ki-67 gene encodes a nuclear protein that participates in the mitotic division of cells and promotes their proliferative activity. The content of the marker in the unchanged endometrium correlates with the phases of the menstrual cycle: it increases in the proliferation stage, reaching a maximum at the end of the follicular phase, and decreases in the secretion stage. The expression of estrogen (ER) and progesterone (PGR) receptors are interconnected, which indicates the hormonal dependence of the expression of Ki-67 and the apoptosis marker p53 [3].

Summarizing the above, it becomes clear that improving the tumor transformation of tissues is a competent approach to the management tactics of patients with EHP. In connection with this, further study of the pathogenetic mechanisms of the development of this disease is a promising way to reduce the frequency of hyper- and neoplastic processes of the endometrium, which gives this problem an undeniable social significance.

The purpose of the study was to establish the mechanisms of development of disorders of endometrial hyperplasia in women of reproductive age by their morphological and immunohistological changes and to determine the therapeutic tactics of the proposed means.

Material and methods. 88 women were examined during a diagnostic endometrial biopsy for abnormal uterine bleeding or increased endometrial thickness. In addition to a general clinical examination, all patients underwent transvaginal ultrasound (US) and hysteroresectoscopy followed by histological examination (HE) of the endometrium. After receiving the HE results, all the women who were studied were divided into the main and control groups. The main group comprised 68 women aged 40 to 55 (mean age was 47.5±2.8 years). The control group included 20 women of the same age who came to the clinic with uterine bleeding but without EH.

Based on the results of the histological examination, the main group was divided into two groups depending on the morphological features: 1 and 2. Women with simple EH (SEH) in the number of 36 (52.9 %) made up 1 group. Group 2 included 32 (47.1 %) patients with complex endometrial hyperplasia (CEH) signs. In addition, depending on the menstrual cycle phase, each subgroup of women of the main group was divided into two more: in the proliferation phase 1a, 2a and the secretion phase – 1b, 2b. For morphological diagnosis, criteria were used to classify precancerous endometrial changes by B. I. Zheleznov.

The number of patients in the main group was distributed as follows: 20 (55.6 %) women were classified as SEH in the proliferation phase (1a), and 16 (44.4 %) patients were observed in the secretion phase (1b). There were 19 (59.4 %) women in the 2a subgroup with CEH in the proliferation phase and 13 (40.6 %) people in the 2b subgroup in the secretion phase. For comparison, the endometrium was in the proliferative phase in 5 (25.0 %) in the control group and in the secretory phase – in 15 (75.0 %) patients.

EH treatment included two stages: I – uterine curettage to remove the changed endometrium and its subsequent morphological examination, and II – selecting the necessary therapy. Attention was paid to

the state of menstrual and reproductive functions, the presence of pelvic pain, the nature and volume of previously performed surgical interventions and their consequences.

Each woman gave informed consent for diagnostic curettage of the uterine cavity and necessary treatment. The management of patients with EHP is coordinated by order of the Ministry of Health of Ukraine dated 05.05.2021 No. 869 "On the approval of the Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care "Endometrial hyperplasia".

All women underwent hysteroscopy or fractional curettage of the uterine mucosa, followed by histological examination of scrapings. To clarify the diagnosis, we performed hardware hysteroscopy with the help of a rigid 7 mm hysteroscope, Karl Storz (Germany), under intravenous anaesthesia after previously dilating the cervical canal to 7.5 mm.

Histological examination of the endometrium was performed according to the standard method of serial sections.

Before the diagnostic removal of the endometrium from the uterine cavity, each patient underwent a general clinical and gynecological examination.

Pelvic ultrasound was performed on all patients on days 5–8 of the menstrual cycle and, if necessary, to clarify the diagnosis on days 21–24. All patients underwent transvaginal ultrasound of the pelvic organs using the TOSHIBA Xario (Japan) device to assess the condition of the uterus and pelvic organs. During the ultrasound, the state and size of the uterus were studied, and the structure of the myometrium was evaluated. The study of M-echo made it possible to evaluate the thickness of the endometrium, its echomorphology and echogenicity.

In 45 patients of the main group with various types of EHP and 12 women of the control group, an immunohistochemical study (IHCS) was performed with the determination of steroid hormone receptors (ER-α and PGR) and markers of proliferative activity –protein Ki-67 and apoptosis p53.

Monoclonal antibodies (DAKO) using the double antibody immunoperoxidase method were used to assess the expression of ER-α and PGR receptors. Proliferation markers Ki-67 and p-53 were performed by counting the number of stained nuclei per 100 cells in 3 fields of view. The result was expressed as a percentage and evaluated according to the accepted scale: 1) 0–20 % – low proliferative activity; 2) 21–50 % – moderate proliferative activity; 3) 51–100 % – high proliferative activity.

Statistical data processing was done using standard computer programs on a personal computer using Microsoft Excel spreadsheets and Statistica for Windows v. 10.0, StatSoft Inc. (USA). For each characteristic, the arithmetic mean (M), mean square deviation, standard error of the mean (m), and Student's test value (t) were taken into account. All quantitative data were processed using variational statistics.

Results of the study and their discussion. Clinical and statistical characteristics of the main group of patients with EH confirm their high frequency of gynecological and extragenital morbidity.

In women of the main group, chronic salpingo-oophoritis was observed in 35.3 % ($p<0.01$), benign cystic formations of the ovaries – in 21.4 % ($p<0.01$), polycystic ovary syndrome – in 6.7 % ($p> 0.05$), uterine leiomyoma – in 38.8 % ($p<0.01$), endometriosis – in 9.2 % ($p<0.05$). The above-mentioned gynecological diseases were not observed among patients of the control group.

During the analysis of the menstrual function of the studied women, it was found that the age of menarche was higher in EH – 13.5±0.1 versus 12.4±0.1 years in the control group ($p<0.02$).

Many infectious and viral diseases were observed among patients with EH.

During the study of reproductive history, it was established that 13.8 % ($p<0.05$) of patients in the main group had primary infertility and 16.3 % ($p<0.01$) – had secondary infertility.

Attention is drawn to the large number of artificial abortions in the anamnesis in patients of the main group (44.7 % versus 27.6 %) in the control group. Among patients of the main group, this parameter was 2.5±0.1; among patients of the control group, it was 5.2 times less±0.3 ($p<0.01$).

32.8 % of patients with EH used an intrauterine device (IUD), while more than half of the patients had an intrauterine spiral in the uterine cavity for more than 5 years. Among patients in the control group, only 4.7 % chose this method of preventing unwanted pregnancy.

Even though diseases of the organs of the reproductive system were found in more than 49.6 % of all examined subjects of the main group, patients with CEH suffered from diseases of the mammary gland 3.7 times more often ($p <0.05$) than patients with SEH.

The mucous membrane of the uterine body with SEH was characterized by numerous, unevenly distributed glands of various shapes and sizes, including cystically enlarged ones, in some areas with weak folds in the direction of the lumen of the glands. In contrast to CEH, the presence of SEH was observed. This condition is characterized by profound violations of the structure and architecture of the endometrium, which are caused by the growth of elements of the mucous membrane over its entire surface.

In the structure of extragenital pathology among the patients of the main group, vegetative-vascular dystonia took first place, registered in 31.6 % of women in the main group against 6.8 % of women in the control group. 18.4 % of women in the main group had chronic diseases of the digestive tract, while only 4.8 % were in the control group.

The study revealed that, according to the pelvis ultrasound diagnostics, no pathology of the ovaries was detected in all the examined women. Endometrial thickness (mean m-echo) in patients of the main group was 13.8±1.7 mm, and in women from the control group, 5.6±1.2 mm ($p < 0.05$).

During IHCS, it was determined that, compared to controls, the expression of estrogen receptors in the endometrium and stroma was significantly higher in EH patients. In SEH 1a – 139.6±18.5, 1b – 141±11.2 (endometrium, $p <0.001$); 1a – 122.7±12.3, 1b – 126.1±8.1 (stroma, $p <0.001$). With CEH 2a – 155.4±12.5, 2b – 151.8±13.4 (endometrium, $p <0.001$); 2a – 132.5±9.3, 2b – 134.6±11.4 (stroma, $p <0.001$).

In patients with CEH, the expression of progesterone receptors was weaker in the stroma and epithelium of the glands compared to the control group, which implies a low effectiveness of hormonal therapy in this category of patients. A particularly weak expression was observed in women of subgroup 2b when uterine curettage was performed on the 21st–23rd day of the menstrual cycle (Table 1).

The conducted IHCS studies deepened our understanding of the pathogenesis of EH. In particular, high expression of ER-α receptors and low PGR hormones were established, indicating proteins' pro-oncogenicity in patients with CEH. These data confirm the high risk of developing oncological transformation of the endometrium in CEH and the impracticality of hormonal therapy in this category of patients. Markers of EHP development make it possible to predict the development of neoplastic changes and make it necessary to conduct this study.

Table 1

Steroid hormone receptors in patients with endometrial hyperplasia

Steroid hormone receptors	Control n=20	SEH		CEH	
		Stages of development (proliferation (P), secretion (S)			
		Subgroup 1A P (20)	Subgroup 1B S (16)	Subgroup 2A P (19)	Subgroup 2B S (13)
Er-α endometrium	119±10.51	139.6±18.5 ***	141±11.2 ***	155.4±12.5 ***	151.8±13.4 ***
ER-α stroma	102±7.5	122.7±12.3 ***	126.1±8.1 ***	132.5±9.3 ***	134. ***6±11.4
PGR endometrium	94.1±7.8	92.3±6.2	95.1±6.0	95.5±4.8	91.2±4.4
PGR stroma	105±7.8	103.7±9.34	111.1±5.5	113.3±7.6 *	92.4±3.5

Note: differences with the control are significant * – ($p<0.01$), * * * – ($p<0.001$).

Table 2 shows data on the expression of biomolecular markers in the endometrium during the stages of proliferation and secretion in SEH and CEH.

Table 2

Molecular markers in unchanged endometrium and hyperplasia in the stage of proliferation and secretion

Parameter	Control (unchanged endometrium)		SEH		CEH	
			Subgroup 1A	Subgroup 1B	Subgroup 2A	Subgroup 2B
	Stages of development (proliferation (P) %, secretion (S) %					
	P (5)	S (15)	P (20)	S (16)	P (19)	S (13)
	8.4±1.1	6.9±0.6				
Proliferation marker expression			Ki-67			
			10.8±0.4*	12.7±0.8*	15.3±2.2*	23.4±08*
			P-53			
			9.4±0.3*	8.8±1.8	11.6±1.8*	7.9±0.8

* $p <0.05$ significance of differences relative to the control group.

The results of the study indicate a high proliferative activity of endometrial cells in women with CEH, who had a significant increase in the Ki-67 proliferation marker from 15.2±2.2 % to 23.4±08 % ($p <0.05$), while in SEH, this index was significantly lower and practically did not differ from the control group (from 8.8±0.4 % to 6.7±0.8 %, $p <0.05$) of epithelial cells).

P53 protein expression in patients with CEH was significantly lower than in endometrial biopsies compared to women with SEH. The apoptosis marker p53 in CEH was significantly reduced (from 11.6±1.8* to 7.9±0.8 %, ($p <0.05$)) relative to women with SEH (respectively from 9.4±0.3 to 8.8±1.8 %, $p <0.05$).

We proposed an algorithm for examining patients with hyperplastic processes, which is based on verifying the morphological diagnosis using immunohistochemical criteria: the presence/absence of expression of steroid hormone receptors, Ki-67 proteins, and the apoptosis marker p53. In addition to the generally recognized classical pathogenetic mechanisms of the development of EHP, one of the main

reasons can be confidently called the predominance of proliferation processes over apoptosis against the background of the changed receptor status of the endometrium, especially in women with CEH.

An attempt to comprehensively influence the specified pathophysiological mechanisms makes it possible to significantly increase the effectiveness of treatment of EHP and reduce the risk of recurrence and progression of the proliferative process.

Thus, the possible molecular and cellular pathogenetic mechanisms of SEH may be factors of proliferation and apoptosis, which is confirmed by a significant increase in the proliferation marker Ki-67 of epithelial cells in CEH in endometrial biopsies, as well as a decrease in the apoptosis marker p53.

A differentiated approach to diagnosing EHP is based on the determination of molecular markers (Ki67, p53), which makes it possible not only to predict the course of the hyperplastic process but also to assess the effectiveness of the treatment.

The developed complex of clinical and laboratory studies (including IHCS) can be used to identify groups at risk of recurrence of hyperplastic processes and possible malignancy of the endometrium and to prescribe surgical treatment to patients in a timely manner.

Considering the above studies, it is appropriate to consider the hyperplastic process as successive stages of the formation of the pathological process of hyperproliferation of the endometrium.

The long-term use of contraceptives, which leads to the development of a chronic inflammatory process and damage to the receptor apparatus of the endometrium, is a risk factor for the development of EH [11].

Summarizing the study, we proposed an algorithm for examining patients with hyperplastic processes. This algorithm is based on verifying the morphological diagnosis using immunohistochemical criteria: the presence/absence of expression of steroid hormone receptors, Ki-67 proteins, and the apoptosis marker p53 [8]. The p53 protein balances proliferation and programmed cell death (apoptosis). It is the product of the TP53 tumor suppressor gene and is expressed in all body systems [3]. In addition to the recognized pathogenetic criteria for the development of EH, one of the main reasons can be confidently called the predominance of proliferation processes over apoptosis against the background of the changed receptor status of the endometrium in women with CEH [10].

Conclusion

The study's results indicate a high proliferative activity of cells in EH, confirmed by a significant increase in the proliferation marker Ki67 of epithelial cells in endometrial biopsies and a decrease in the apoptosis marker p53.

High expression of ER-α receptors and low levels of PGR hormones indicate the pro-oncogenicity of proteins in patients with CEH, which confirms the high risk of developing oncological transformation of the endometrium in CEH and the impracticality of hormone therapy in this category of patients. Markers of EH development make it possible to predict the development of neoplastic changes and make it necessary to conduct this study.

A differentiated approach to the diagnosis of EH, based on IHCS with the determination of molecular markers, makes it possible not only to predict the course of the hyperplastic process but also to promptly prescribe the necessary treatment to patients.

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O.I. Koval, O.A. Kaniura
Bogomolets National Medical University, Kyiv

ORGANIZATION OF DENTAL CARE FOR UKRAINIAN CHILDREN DURING MARTIAL LAW

e-mail: Okoval78@ukr.net

The war changed the lives of Ukrainians and presented them with new challenges. Not all children can receive proper medical, including dental care, at their place of residence due to constant shelling and systematic destruction of critical infrastructure. The humanitarian disaster has increased the risk factors for the growth of dental morbidity among children. This sets new tasks for the children's dental service to organize the provision of dental care to children under martial law in Ukraine. We have analyzed the dental care experience of children in Ukraine during martial law. We studied the organization and provision of medical and advisory assistance, including to children of Internally Displaced Persons; training in oral hygiene for children with disabilities, children of Internally Displaced Persons, low-income families, etc.; sanitary and educational work on the dental health of children among parents. Also, we access the Organization of Emergency Medical Care for children of Ukraine who were forced to cross the border, as well as the Organization of Humanitarian Assistance of medical direction directly to children (personal hygiene products, etc.) and medical institutions. In martial law, the priority is the choice of conditions for rehabilitating the oral cavity under general anesthesia, for the smooth operation of which strategic reserves of material and technical support are necessary.

Key words: martial law, dental sanitation, children, general anesthesia, humanitarian aid.

О.І. Коваль, О.А. Канюра

ОРГАНІЗАЦІЯ СТОМАТОЛОГІЧНОЇ ДОПОМОГИ ДІТЯМ УКРАЇНИ В ПЕРІОД ДІЇ ВОЄННОГО СТАНУ

Війна змінила життя українців та поставила їх перед новими викликами. Не всі діти можуть отримати належну медичну, в тому числі стоматологічну допомогу за місцем проживання внаслідок постійних обстрілів та системного руйнування критичної інфраструктури. Гуманітарна катастрофа посилила фактори ризику зростання стоматологічної захворюваності серед дітей. Це ставить нові завдання перед дитячою стоматологічною службою щодо організації надання стоматологічної допомоги дітям в умовах дії Воєнного стану в Україні. Нами проведено аналіз досвіду стоматологічної допомоги дітям України в період дії Воєнного стану, а саме: організації та надання лікувально-консультативної допомоги, в тому числі і дітям внутрішньо переміщених осіб; навчання гігієні порожнини рота дітей з інвалідністю, дітей внутрішньо переміщених осіб, малозабезпечених сімей, тощо; санітарно-просвітницької роботи щодо стоматологічного здоров'я дітей серед батьків; організації надання невідкладної медичної допомоги дітям України, які були вимушені перетнути кордон а також організації гуманітарної допомоги медичного направлення безпосередньо дітям (засоби індивідуальної гігієни, тощо) та медичним закладам. За результатами досліджень: в реаліях Воєнного стану пріоритетним є вибір умов проведення санації порожнини рота під загальним знеболенням, для безперебійної роботи якого необхідні стратегічні запаси матеріально-технічного забезпечення.

Ключові слова: воєнний стан, стоматологічна санація, діти, загальне знеболення, гуманітарна допомога.

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The war changed the lives of Ukrainians and presented them with new challenges. Active military operations in the southeastern regions of our country and constant shelling of several border regions forced a large number of the population to leave their places of permanent residence. The Annual Report of the Commissioner for Human Rights of the Verkhovna Rada of Ukraine (2022) states that almost 70 % of Ukrainian children were forced to leave their homes and move within the country or abroad. Children were most affected in the Donetsk, Kharkiv, Kyiv, Mykolaiv, Zaporizhzhia, Kherson, Chernihiv, Luhansk and Dnipropetrovsk regions. Not all children can receive proper medical, including dental care, at their place of residence due to constant shelling and systematic destruction of critical infrastructure [8]. The humanitarian disaster has increased the risk factors for the growth of dental morbidity among children. This