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A DIFFERENTIATED APPROACH TO THE MANAGEMENT OF PATIENTS WITH HYPERPLASTIC DISEASES OF THE UTERUS COMPLICATED BY ABNORMAL UTERINE BLEEDING

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Abstract

The purpose: to justify a differentiated approach to the management of patients with hyperplastic uterine diseases complicated by abnormal uterine bleeding (AUB) based on the study of the morpho-functional features of the endo- and myometrium. It has been shown that PgR expression is low in patients with combined lesions of the endometrium and myometrium complicated by AMC. The degree of PgR expression has a strong negative correlation with pathological changes of the endometrial-myometrial junction (r=-0.71), which made it possible to consider these criteria in the creation of a differentiated algorithm for the management of patients taking into account clinical and morphological pathogenetic variants of the disease. The use of differentiated approaches to the treatment of patients with combined hyperplastic processes of the uterus, taking into account the clinical and morphological features of the disease, made it possible to reduce the number of recurrences of AMC and achieve a long-term clinical effect in comparison with traditional treatment.

Key words: endometrial hyperplasia; uterine myoma; adenomyosis; menstrual dysfunction; abnormal uterine bleeding; diagnosis; treatment.

The combined pathology of the endometrium and myometrium is observed in 40-55% of premenopausal women, while 40% of women with uterine fibroids, adenomyosis, and 80% of women with endometrial hyperplasia (EH) develop abnormal uterine bleeding (AUB) [1].

AUB is one of the main reasons for hospitalization of women in gynecological hospitals, it is an indication for 2/3 of all hysterectomies, which can cause additional complications. Therefore, it is important to search for effective therapeutic approaches to reduce the frequency of surgical interventions [2, 3].

The frequency of EH relapses and menstrual dysfunction against the background of combined endometrial and myometrial hyperproliferative pathology after hormonal treatment remains quite high. Given the increased risk of malignancy in premenopause, the issue of early diagnosis and individualized treatment does not lose its relevance [1-4].

In clinical practice, insufficient attention is paid to the evaluation of immunohistochemical features (phenotypes) of hyperproliferative uterine diseases (HUD) [5]. This complicates the choice of optimal treatment and increases the likelihood of developing complications and relapses of AUB.

In conditions of limited access to modern molecular genetic technologies, when determining the phenotype, priority is given to general clinical research methods, as well as to the application of pathomorphological and immunohistochemical methods in vivo [8, 9]. However, the assessment of the connection of different phenotypes with the occurrence of AMC and the selection of optimal treatment strategies is still an unsolved scientific task.

The purpose of the study is to justify a differentiated approach to the management of patients with hyperplastic diseases of the uterus, complicated by abnormal uterine bleeding, based on the study of the morpho-functional features of the endometrium and myometrium.

Research materials and methods. At the first, retrospective stage, an analysis of 343 case histories of patients with combined HUD with AUB and 107 case histories of patients with HUD without AUB was performed, and the most significant risk factors of AUB in such patients were determined.

At the second, prospective stage, 60 women with combined hyperplastic diseases of the endometrium and myometrium were examined, including 30 (1, the main group) with AUB, and 30 (2, comparison group) – without AUB. As a control, 30 practically healthy women of the same age who underwent a routine examination were examined.

Exclusion criteria were: atypical hyperplasia and endometrial cancer, inflammatory diseases, postmenopause, presence of submucous uterine fibroids, large uterine fibroids, multiple fibroids, coagulopathy.

All patients underwent a comprehensive examination, which included clinical and paraclinical research methods, in accordance with the orders of the Ministry of Health of Ukraine No. 676 dated 12.31.2004 "On the approval of clinical protocols for obstetric and gynecological care", as well as No. 353 dated 04.13.2016 "Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care. Abnormal uterine bleeding" and No. 869 dated 05.05.2021 "On the approval of the Unified clinical protocol of primary, secondary (specialized), tertiary (highly specialized) medical care "Endometrial hyperplasia" [10-12]. The intensity of AUB was determined according to Janssen (1995) and Magnay (2014) [13], the intensity of menstrual bleeding - according to the Mansfield-Voda-Jorgensen Menstrual Bleeding Scale [14]. Ultrasound examination was performed on a Toshiba Aplio 500 device (Japan) using convex (working frequency 2.0-5 MHz) and transvaginal 7.5 MHz sensor [18].

Detected cases of EH were classified according to the WHO (2014) classification adopted by the International Society of Gynecological Pathologists, which divides hyperplasia into two groups: atypical hyperplasia and atypical hyperplasia [15]. Immunohistochemical studies were performed using monoclonal antibodies (Dako, clones ERα, PgR 636, Ki-67 MIB-1, Denmark) [19]. The FIGO PALM-COEIN classification was used to assess the clinical manifestations and etiology of AMC [16].

The treatment was carried out according to the protocol approved by the order of the Ministry of Health of Ukraine dated December 31. 2004 No. 676, unified clinical protocols (orders of the Ministry of Health of Ukraine No. 353 dated 04.13.2016 and No. 869 dated 05.05.2021) [10-12] and international recommendations (RCOG, 2016) [17] by using progestins (dydrogesterone 10 mg continuously for 6 months or the use of LNG-IUD (52 mg, 20 μg/24h)), or performed hysteroscopic interventions in the scope of endometrial resection or hysterectomy.

The choice of treatment method for AMC was determined according to the degree of expression in the endometrium of α-receptors for estrogens (ERα), receptors for progesterone (PgR) and Ki-67 protein, the presence of structural changes in the endometrial-myometrial junction (EMJ), as well as the state of carbohydrate - lipid metabolism.

The study was performed in accordance with international recommendations aimed at protecting the rights and safety of patients, including the Declaration of Helsinki and the Belmont Report, recommendations of the Council of International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonization (ICH) of Good

Clinical Practice (GCP) [20]. All participants of the prospective stage of the study signed an informed consent.

At all stages of the statistical analysis, the standard functions of the MS Excel software package were used to prepare primary tables of conjugation and grouping of features [21]. Determination of criterion values and basic calculations were carried out using statistical packages of the STATISTICA 13.0 program (TIBCO, USA) [22]. Parametric and non-parametric methods of dispersion and correlation analysis were used. The null hypothesis was accepted at p=0.05.

Research results and their discussion. During the analysis of medical documentation (the first stage of the study), EH (43.3%), adenomyosis (26.7%), endometrial polyps (10.6%), uterine fibroids (19.4%) were diagnosed in patients with AUB. In the vast majority of examined patients (93.3%), cases of comorbid lesions prevailed. The frequency of metabolic syndrome (according to body mass index, lipidogram assessment, and glycemia level) in the examined patients was 24.5%, 39.4% of the patients had signs of type IIb dyslipidemia, and in the vast majority of cases these features were not taken into account when appointment of pharmacotherapy.

The main risk factors for AUB in patients with combined endometrial and myometrial pathology were age over 40 years (OR 2.3; 95% CI (1.3-4.1)), body mass index (BMI) greater than 30 kg/m^2 (OR 3.5; 95% CI (2.0-6.0)), presence of metabolic syndrome (OR 1.8; 95% CI (1.0-3.9)), arterial hypertension (OR 3.0; 95% CI (1.9-2.5)), concomitant adenomyosis (OR 3.0; 95% CI (1.5-5.8)), uterine myoma (OR 3.1; 95% CI (1, 3-7.5)), frequent scraping of the uterine cavity (OR 3.0; 95% CI (1.6-5.6)), pelvic inflammatory disease in history (OR 1.6; 95% CI (0 .8-3.1)), uterine scar (OR 0.8; 95% CI (0.5-1.1)), etc.

After hysteroscopy, removal and assessment of the state of the endometrium, progestins were used for the purpose of treatment in 74.3% of cases, COCs - in 12.8%. Operative treatment was performed in 12.8% of cases (hysterectomy or hysteroscopic endometrial ablation). Catamnetic observation of 82 patients showed that during 6-12 months, the phenomena of AUB persistence in the form of "bleeding" were observed in 22 (26.8%) women, in 13 (15.9%) patients, phenomena of EH persistence were observed, including in 2 patients (2.4%) progressed to atypical GE during the observation period.

At the second stage of the study (prospective), the average age of the examined women had no significant differences and amounted to (42.1±0.5) years. The average age of onset of menarche was (12.8±0.3) years. Heavy menstrual bleeding was noted in 12 (40.0%)

patients of group 1. In the vast majority of women in group 1 (17 or 56.7%), the duration of menstrual disorders was more than 5 years.

The patients of groups 1 and 2 underwent hysteroscopy and morphological confirmation of EH. In group 1, cases of a combination of EH, polyps and adenomyosis prevailed (56.7%), EH, adenomyosis and uterine myoma (36.7%). In patients of group 2, respectively, the combination of EH and adenomyosis was observed in 4 (13.3%), EH and endometrial polyps – in 26.7%, EH and intramural uterine myoma – in 53.3%, EH, adenomyosis and uterine myoma – in 6.7% of women.

The total score for DEER was (13.2±0.4) points in patients of group 1, (9.1±0.2) points in group 2, and (7.3±0.7) points in the control group. At the same time, in most cases in group 1 (62.0%) the EMJ had structural changes in the form of a discontinuous, cystic structure, and was involved in the pathological process. Cystic areas of EMJ were present in 3 (9.7%) cases, hyperechoic points – in 5 (16.1%), hyperechoic lines – in 4 (12.9%) cases. EMJ changes were combined with other ultrasound signs of adenomyosis.

When determining the degree of expression of ERα, PgR and Ki-67, phenotypic features were revealed (Fig. 1). The level of PgR expression in group 1 was low, in contrast to patients in group 2. This corresponds to our previously established phenotypes [5]. The presence of correlations of medium strength between the values of the atherogenicity coefficient and the expression of ERα (r=0.51) and Ki-67 protein (r=0.59), as well as between the expression of ERα and body fat mass (r=0.62). The risk of malignancy in the examined women was (D>1.0 - D=1.4±0.1).

Three main classes of clinically significant phenotypes of patients with HUD and AUB were determined, which differed in the expression of endometrial receptors, namely:

1. Low level of expression of ERα, PgR and Ki-67.

2. Low degree of expression of PgR for any degree of expression of ERα and Ki-67.

3. Moderate or high degree of expression of PgR at any degree of expression of ERα and Ki-67.

Thus, the presence of different immunohistochemical phenotypes made it possible to differentiate the tactics of patient management, taking into account that the response to progestagen therapy may be different in different patients, depending on the actual sensitivity of the target tissue to hormones.

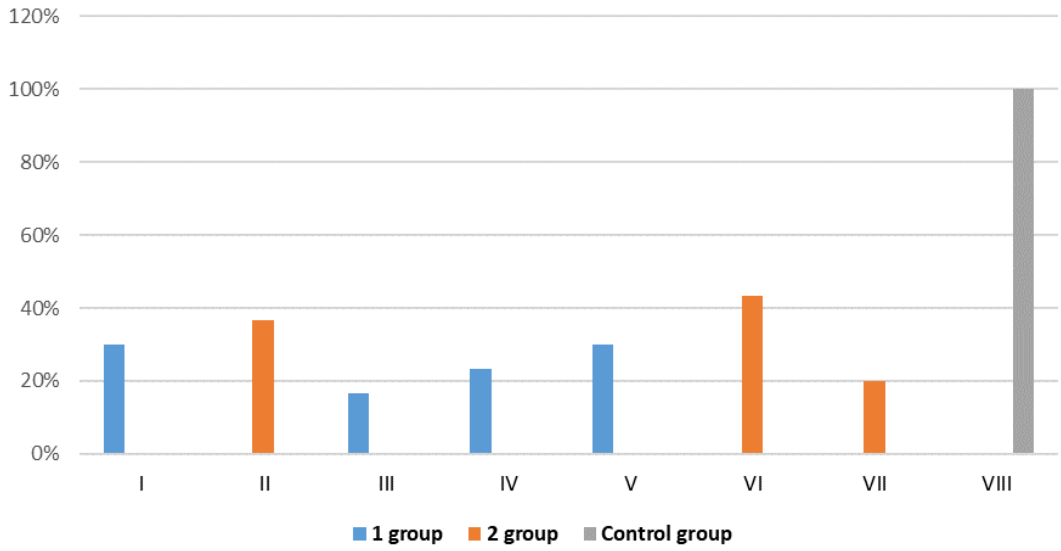

Fig. 1. Phenotypic features of the endometrium in the examined patients: I - low level of expression of ERα, PgR and Ki-67; II - moderate degree of expression of ERα, low degree of expression of PgR and Ki-67; III - moderate degree of expression of ERα and Ki-67, low degree of expression of PgR. IV - high degree of expression of ERα, low degree of expression of PgR and Ki-67; V - high degree of expression of ERα, low degree of expression of PgR, moderate degree of expression of Ki-67; VI - high level of ERα expression, moderate level of PgR expression, low level of Ki-67 expression; VII - high degree of expression of ERα and PgR, moderate degree of expression of Ki-67; VIII - Moderate degree of expression of ERα and PgR, low degree of expression of Ki-67.

As can be seen from fig. 1, in group 1 of patients, phenotypes with a high degree of ERα expression and a low degree of PgR expression prevailed (Figs. 2-4). These features were accompanied by morpho-functional changes of EMJ, presence of concomitant adenomyosis. The negative correlation between the morphofunctional changes of EMJ and the degree of PgR expression was strong (r=-0.71), which is consistent with the data on the lower sensitivity to progestagen therapy in patients with adenomyosis [4].

According to the results of our research, we proposed an algorithm for the comprehensive examination and management of patients with combined hyperproliferative diseases of the uterus, which includes the study of the degree of expression of PgR, ERα and the proliferation protein Ki-67 in the endometrium, the state of carbohydrate-lipid metabolism and the presence of structural changes of the EMJ (Fig. 5).

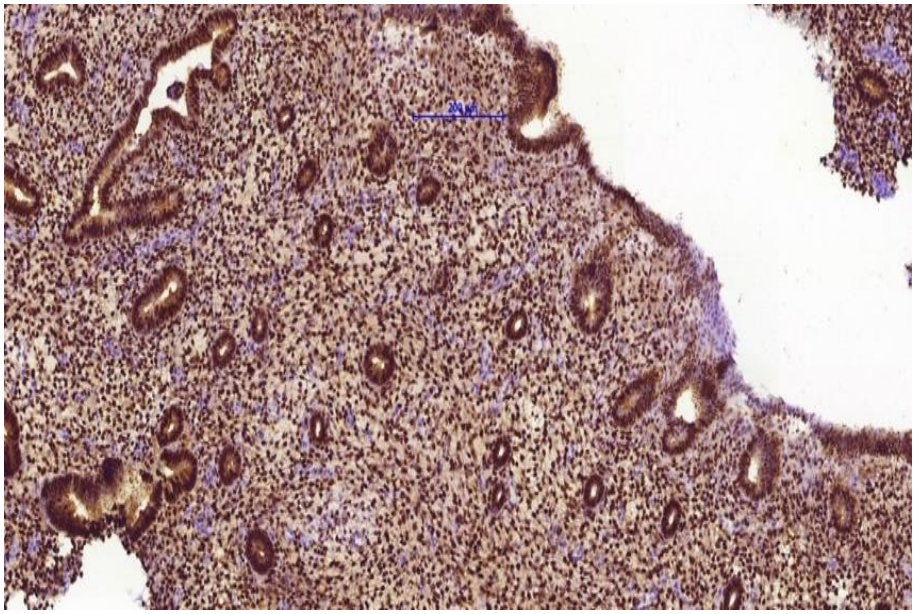

Fig. 2. A 40-year-old woman with AUB before treatment. Low level of PgR expression in the endometrium. Streptavidin peroxidase reaction. × 100.

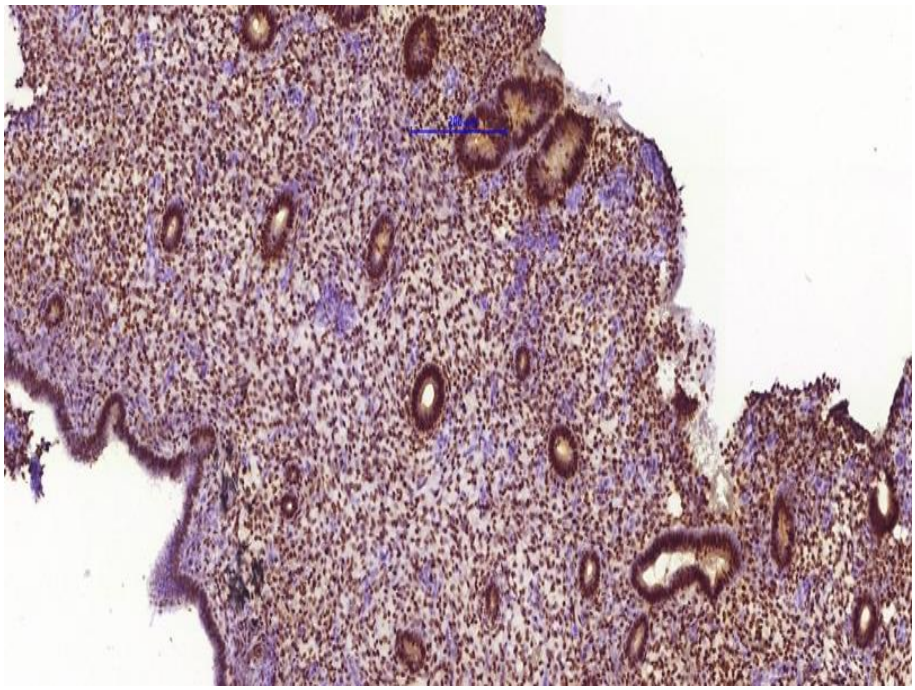

Fig. 3. A 42-year-old woman with AUB before treatment. A high degree of ERα expression in the endometrium. Streptavidin peroxidase reaction. ×100.

Patients of group 1 (9 women) with a low degree of PgR expression, who probably will not have a response to drug therapy, given the presence of concomitant hyperproliferative diseases (adenomyosis, uterine fibroids), were prescribed surgical treatment (endometrial resection or hysterectomy, as indicated). The rest of the patients of group 1 (21 women) were treated with an intrauterine system with levonorgestrel (52 mg, 24 μg/day), taking into

account the presence of structural changes of the EMJ (concomitant adenomyosis, uterine myoma). We prescribed dydrogesterone as a metabolically neutral progestogen that has a minimal effect on carbohydrate and lipid metabolism to the patients of the second group, without AUB, without EMJ pathology, with a high degree of ERα PgR expression (30 women).

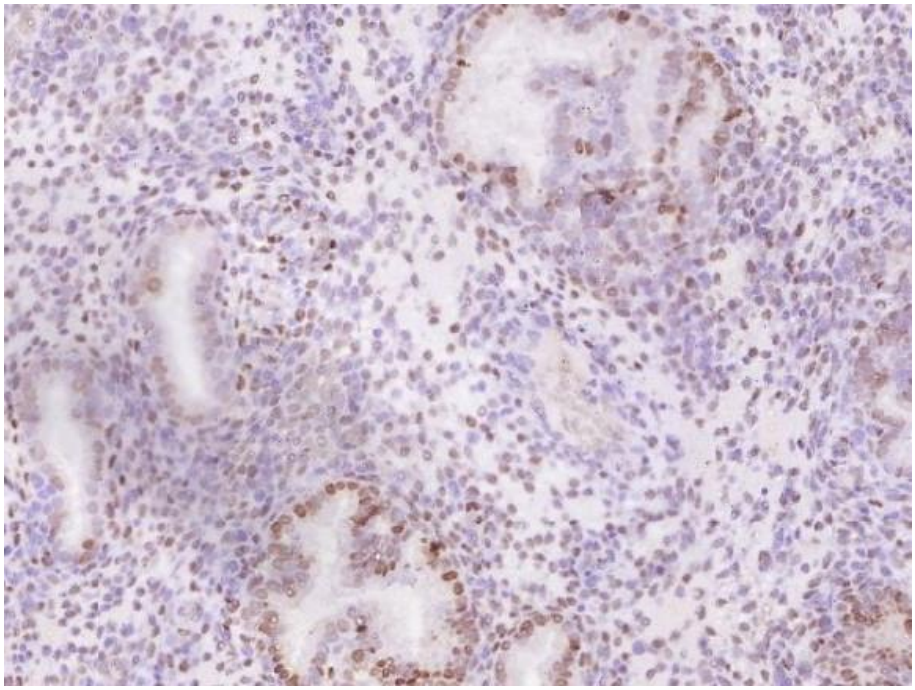

Fig. 4 A 43-year-old woman with AMC. A low level of expression of Ki-67 in cells of the stroma of the endometrium, a moderate level of expression of Ki-67 in the glandular epithelium. Streptavidin peroxidase reaction. × 400.

In patients of both groups, after treatment, ERα expression, as well as Ki-67 protein expression decreased by up to 30% in the glands and up to 15% in the stroma, which can contribute to the prevention of EH recurrence in premenopause (Figs. 6-8).

The observation period of the results of differentiated application of conservative therapy in female patients was 12 months. In order to control the effectiveness of the treatment, a Papel biopsy of the endometrium was performed after 6 months and, if necessary, after 12 months. Phenomena of persistence of AUB in the form of "bleeding" were observed in 3 patients (10.0±5.4%) vs. 22 (26.8±4.9%) with traditional treatment, without taking into account the morphofunctional phenotype of the disease ($p<0.05$).

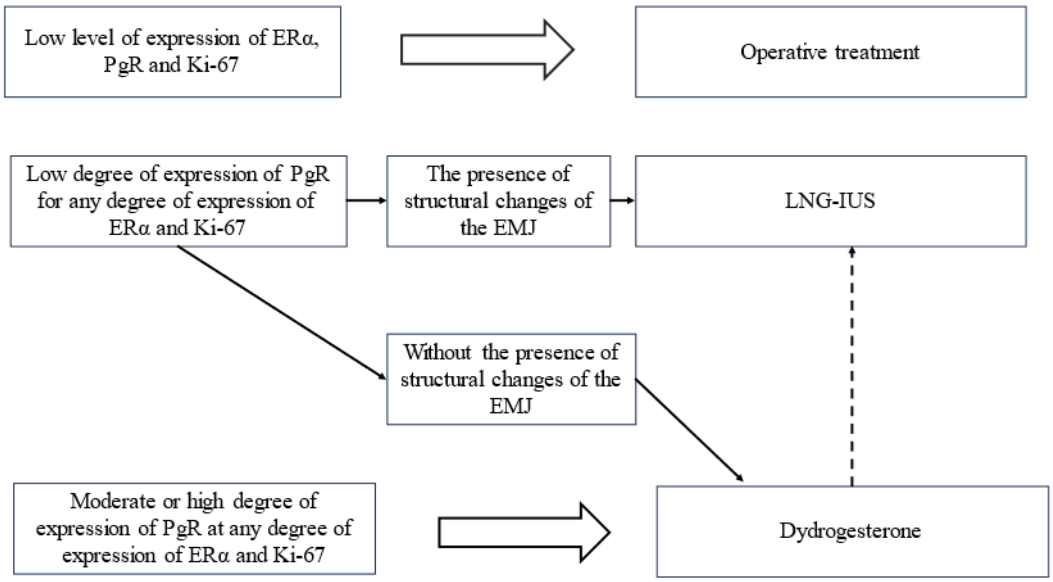

Fig. 5. Algorithm for choosing a treatment method for patients with GE and AMC depending on the morpho-functional features of the state of the endo- and myometrium.

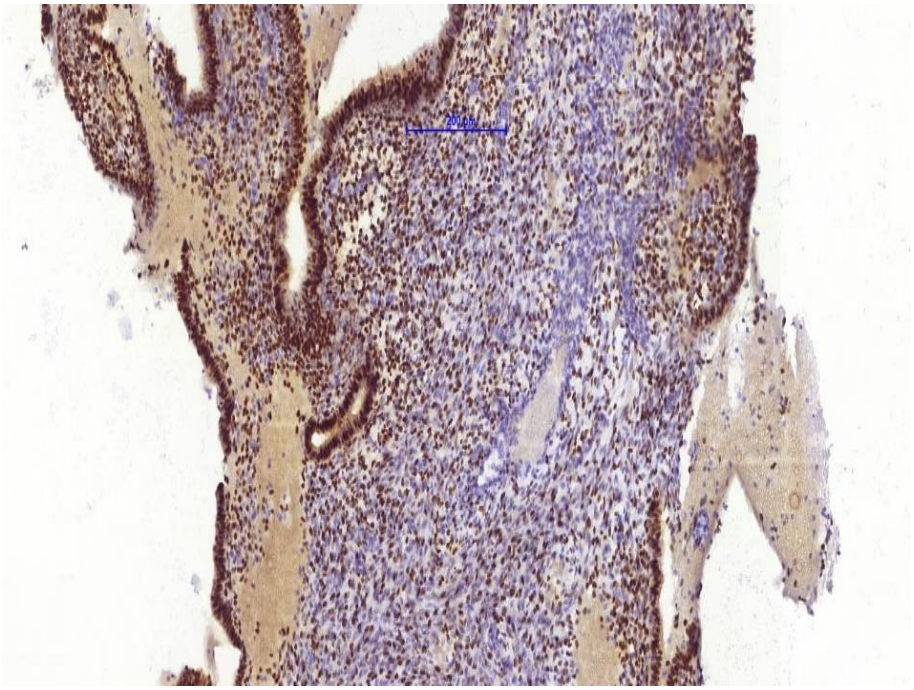

Fig. 6. A 43-year-old woman with AUB (group 1). A moderate level of ERα expression after treatment. Streptavidin peroxidase reaction. ×100.

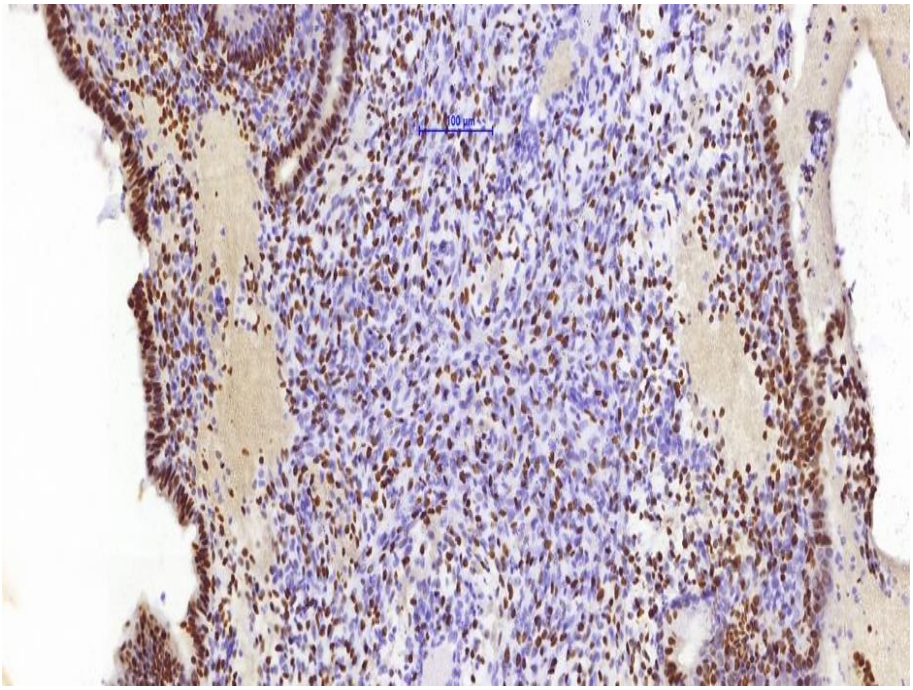

Fig. 7. Woman 38 years old (group 2). Expression of PgR in the endometrium after treatment. Streptavidin peroxidase reaction. × 200.

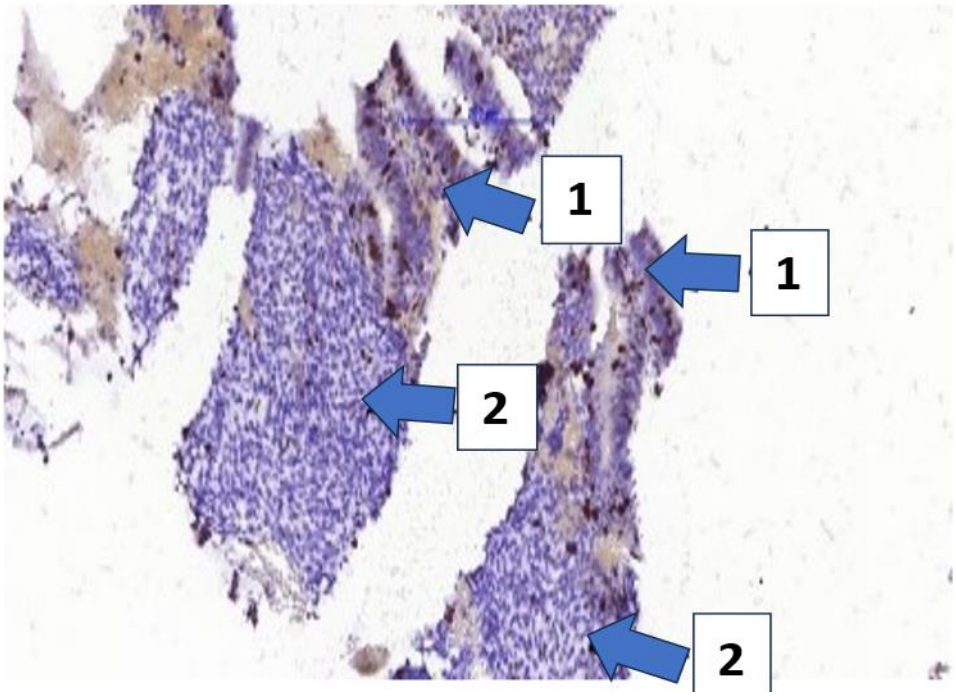

Fig. 8. Woman 47 years old (group 1). Expression of Ki-67 in the functional layer of the endometrium after the treatment (1 - glands, 2 - stroma).
Streptavidin peroxidase reaction. ×400.

Persistence and progression of EH in the prospective study after 6-12 months in both groups was not detected, while in the retrospective group with conventional treatment for 6 months. 13 (15.9%) of observation showed persistence of EH for 6-12 months, including 2 patients (2.4%) during which the disease progressed to atypical hyperplasia.

Thus, the application of a differentiated approach to the management and treatment of patients with HUD, taking into account the clinical and morphological characteristics of the endo- and myometrium, made it possible to reduce the number of recurrences of AUB, avoid the persistence and progression of EH in comparison with traditional treatment.

Conclusions:

1. The main risk factors for AMC in patients with combined endo- and myometrial pathology were age over 40 years (OR 2.3; 95% CI (1.3-4.1)), body mass index more than 30 kg/m^2 (OR 3.5; 95% CI (2.0-6.0)), presence of metabolic syndrome (OR 1.8; 95% CI (1.0-3.9)), arterial hypertension (OR 3.0; 95% CI (1.9-2.5)), concomitant adenomyosis (OR 3.0; 95% CI (1.5-5.8)), uterine myoma (OR 3.1; 95% CI (1.3-7.5)), frequent scraping of the uterine cavity (OR 3.0; 95% CI (1.6-5.6)), pelvic inflammatory disease in history (OR 1.6; 95% CI (0.8-3.1)), uterine scar (OR 0.8; 95% CI (0.5; 1.1)), etc.

2. Three main classes of clinically significant phenotypes of patients with HUD and AUB were determined, which differed in the expression of endometrial receptors, namely: 1) low level of expression of ERα, PgR and Ki-67; 2) low level of PgR expression at any level of ERα and Ki-67 expression, 3) moderate or high level of PgR expression at any level of ERα and Ki-67 expression. In patients with combined lesions of the endometrium and myometrium complicated by AUB (group 1), the expression of PgR is low, in contrast to group 2 (combined hyperplastic processes of the uterus without AUB). Correlations of medium strength were established between the values of the atherogenicity coefficient and the expression of estrogen receptors (r=0.51) and Ki-67 protein (r=0.59), as well as with body fat mass (r=0.62 for ERα). The risk of malignancy in the examined women was (D>1.0 - D=1.4±0.1). The degree of PgR expression has a strong negative correlation with pathological changes of the endometrial-myometrial junction (r=-0.71), which made it possible to consider these criteria in the creation of a differentiated patient management algorithm.

3. The use of differentiated approaches to the treatment of patients with combined hyperplastic processes of the uterus, taking into account the clinical and morphological features of the disease, made it possible to reduce the number of AUB persistence from 22 (26.8±4.9%) to (10.0±5.4%) in the form of "bleeding" ($p<0.05$), to prevent the persistence and progression of endometrial hyperplasia in comparison with traditional treatment.

Authors' contribution:

All authors note an equal contribution to the conception, writing and approval of the article. The authors have read and approved the published version of the manuscript.

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Institutional Review Board Statement A positive decision of the commission on bioethics of the Odessa National medical university (protocol N 72 dated 04.03.2023) was received to conduct the study, the main moral and ethical principles of the Helsinki Declaration of the World Medical Association for Biomedical Research were observed.

Informed Consent Statement

Written informed consent for the processing of personal data and their further use was obtained from the patients participating in the study.

Data Availability Statement

All information is publicly available, data on a specific patient can be obtained upon request from the leading author

Conflicts of Interest

The authors declare no conflict of interest

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