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Clinical and diagnostic evidence of benign endometrial pathology in postmenopausal patients

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The objective: **to study clinical and diagnostic features of the benign endometrial conditions in the postmenopausal women.**
***Materials and method*. 64 postmenopausal patients with various severity of postmenopausal vaginal bleeding were examined. All patients underwent clinical, radiological, laboratory and histological examinations, reproductive history data and body mass index indicators were evaluated. Of them 33 persons were diagnosed with complex endometrial hyperplasia without atypia, 16 women – endometrial polyp and 15 women – hyperplasia with atypia.**
Routine gynecological examination including abdominal and pelvic examination following transvaginal ultrasound examination for the determination of the uterine and ovarian volume as well, as the endometrial thickness were conducted. Patients included in the study underwent computer tomography and magnetic resonance imaging as indicated.
All patients with endometrial pathology underwent endometrial biopsy by standard dilatation and curettage or Pipelle-biopsy with histological examination of the obtained material. The concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-S), estradiol, estrone, progesterone, prolactin, and testosterone were determined in blood serum.
***Results*. It was confirmed that in 87,5% of cases endometrial hyperplasia manifested with vaginal bleeding. Endometrial thickness in examined persons ranged from 14.1±1.6 mm in patients with atypical endometrial hyperplasia to 21.3±4.8 mm in patients with complex endometrial hyperplasia without atypia.**
The study of blood levels of hormones found that postmenopausal patients with endometrial hyperplasia have lower FSH concentration, LH/FSH ratio, estradiol, testosterone levels, with significantly high values of prolactin, DHEA-S and estrone. During the postmenopausal period, hyperplasia was developed in 10% of cases by the presence of bleeding, and 86.2% of cases by the presence of blood spotting.
***Conclusions*. The study suggests that high body mass index, numerous artificial abortions, high blood levels of estrone, DHEA-S and prolactin as well as increased thickness of endometrium influence the frequency of endometrial hyperplasia in postmenopausal women.**
Keywords: *postmenopausal period, endometrial hyperplasia, endometrial polyp, body mass index.*

Клініко-діагностичні ознаки доброякісної патології ендометрія у пацієнток у постменопаузі

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Мета дослідження: вивчення клініко-діагностичних особливостей доброякісних захворювань ендометрія у жінок у постменопаузі.
Матеріали та методи. Обстежено 64 жінки у постменопаузі з різним ступенем тяжкості постменопаузальних вагінальних кровотеч. У всіх пацієнток проведено клінічне, рентгенологічне, лабораторне та гістологічне дослідження ендометрія, оцінювали дані репродуктивного анамнезу та показники індексу маси тіла. З них у 33 жінок діагностовано комплексну гіперплазію ендометрія без атипії, у 16 – поліп ендометрія і у 15 жінок – гіперплазію з атипією. Проводили рутинне гінекологічне обстеження, що включало огляд органів черевної порожнини і малого таза, трансвагінальне ультразвукове обстеження для визначення об'єму матки та яєчників, а також товщини ендометрія. Пацієнткам, включеним до дослідження, за показаннями виконували комп'ютерну та магнітно-резонансну томографію. Усім жінкам із патологією ендометрія проводили біопсію ендометрія стандартним методом дилатації та вишкрібання або Pipelle-біопсію з подальшим гістологічним дослідженням отриманого матеріалу. У сироватці крові визначали концентрації фолікулостимулювального гормону (ФСГ), лютеїнізуючого гормону (ЛГ), дегідроепіандростеронсульфату (ДГЕА-С), естрадіолу, естрону, прогестерону, пролактину і тестостерону.
Результати. Підтверджено, що у 87,5% випадків гіперплазія ендометрія проявляється вагінальними кровотечами. Товщина ендометрія в обстежених коливалася від 14,1±1,6 мм у пацієнток з атиповою гіперплазією ендометрія до 21,3±4,8 мм у пацієнток з комплексною гіперплазією ендометрія без атипії.
Дослідження гормонального фону крові продемонструвало, що у пацієнток з гіперплазією ендометрія у постменопаузі знижені рівень ФСГ, співвідношення ЛГ/ФСГ, концентрація естрадіолу, тестостерону за достовірно високих значень пролактину, ДГЕА-С та естрону. У постменопаузальний період гіперплазія розвивалася у 10% випадків за наявності кровотеч, а у 86,2% випадків відзначено незначні кров'янисті виділення.
Висновки. Результати дослідження свідчать про те, що високий індекс маси тіла, численні штучні аборти, високі рівні естрону, ДГЕА-С і пролактину у крові, а також збільшена товщина ендометрія впливають на частоту розвитку гіперплазії ендометрія у жінок у постменопаузальний період.
Ключові слова: *постменопаузальний період, гіперплазія ендометрія, поліпи ендометрія, індекс маси тіла.*

The duration of the postmenopausal period currently has a fairly wide range (varies from 30 to 50 years), which is associated with an increase in the average life expectancy of women. This, in turn, contributes to a significant increase in the incidence of different pathological processes including benign and malignant tumors of genital organs.

Hyperplastic processes developing in the female reproductive organs have become an urgent problem of modern healthcare. The structure of hyperplastic processes is correlated with their frequency, so, it varies between 3–29%, of which 20-30% undergo malignization. Study of the epidemiology of endometrial hyperplasia (EH) reveals that women who were diagnosed with hyperplasia without atypia were in the range of 50–54 years. Hyperplasia with atypia is most common in the age group of 60–64 years, and the disease was quite rare below the age of 30 years [1–3]. In the morbidity structure of women with malignant neoplasms, endometrial cancer (EC) ranks II in the age group of 55–69 years old and III in the age group of 40–54 years old.

The incidence of endometrial cancer is related to age: every 5 years it increases 2–3 times, the majority of patients (about 76%) are women aged 50–60 years. In the postmenopausal period the frequency of endometrial carcinoma, in both women with simple and women with complex endometrial hyperplasia, increases up to 23%. The main cause of endometrial hyperplasia is the incidence of relative hyperestrogenia on the background of progesterone insufficiency or absolute hyperestrogenia as a consequence of increased estrogen secretion. The abnormal gland-to-stroma ratio is caused by the irregular growth of the endometrium and is followed by a spectrum of pathological changes in the endometrial tissue. It leads to the development of varying degrees of histopathological complexity and atypical features in the cells and nuclei. Without adequate treatment, endometrial hyperplasia may develop into endometrial cancer [4–7].

As in earlier forms of hormone replacement therapy, the majority of EH cases occur in the presence of chronic exposure to estrogen unopposed by progesterone [8]. Additionally, the overproduction of estrogen by fat cells contributes to the increased risk of EH and endometrial cancer in obese women as well [9, 10]. Higher EH risk is also associated with diabetes, hypertension, and obesity [11–14]. In addition to rising estrogen levels, obesity may result in chronic inflammation that can encourage hyperplasia and cancer development [8]. In comparison to women with no obesity, obese women (body mass index [BMI] >30 kg/m^2) presented a nearly 4-fold rise in the incidence of atypical EH. Moreover, women who have a BMI of 40 kg/m^2 demonstrated a 23-fold increased risk of EH without atypia and a 13-fold increased risk of EH with atypia [15].

The most common clinical manifestation of the EH in the postmenopausal period is uterine bleeding. Sometimes the only clinical finding of EH is increased thickness of endometrium more than 4 cm revealed during routine ultrasound examination. Among the two-thirds of postmenopausal women visiting gynecologic office, the abnormal vaginal bleeding is the presenting clinical symptom. Approximately 10% of postmenopausal women have episodes of vaginal bleeding in the anamnesis. [16–18]. However, the incidence of postmenopausal bleeding (PMB) may decrease with age. With the onset of menopause, bleeding is reported in approximately 40% of women per year, but 3 years after menopause, PMB decreases to 4% per year [19–22].

Any postmenopausal woman with vaginal bleeding should be promptly and appropriately evaluated through a comprehensive clinical examination and diagnostic studies, including endometrial biopsy and imaging. Management of PMB depends on the etiology of the disease [22–25].

The objective: to study clinical and diagnostic features of the benign endometrial conditions in the postmenopausal women.

MATERIALS AND METHODS

This investigation was a prospective observational study. A total of 64 postmenopausal women with benign endometrial pathology were observed in the Educational-Surgical Clinic of Azerbaijan Medical University (Department of Obstetrics and Gynecology I) in the period of 2020–2023. The patients underwent detailed history taking, clinical examination, and transvaginal scan for uterine and ovarian volume. Based on clinical, histological findings it was confirmed that of 64 patients 33 (51,6%) were diagnosed with complex endometrial hyperplasia without atypia, 15 (23,4%) with EH with atypia, and 16 (25%) patients were diagnosed with endometrial polyp.

Routine gynecological check-up including abdominal and pelvic examination following transvaginal ultrasound (TVU) by Medison Accuvix A30 Ultrasound System (Samsung, South Korea) with the frequency of transducer 2-6.5 MHz for the determination of the uterine and ovarian volume as well, as the endometrial thickness were conducted. Patients included in the study underwent computed tomography (CT) and magnetic resonance imaging (MRI) as indicated. The indicators of follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-S), estradiol (E2), estrone (E1), progesterone (P), prolactin (Prl) and testosterone (T) in the blood serum were determined by immune essay method (ELISA) with the set of test system «DRG Diagnostics» (Germany).

In addition, in our study the level of CA-125 (CA-125 tumor marker, Cancer Antigen–125) was determined in venous blood by electrochemiluminescent immunoassay (ECLIA) method. The concentration of marker was determined on a Cobas e 411 immunochemical analyzer using the CA125 kits from Roche Diagnostics (GmbH).

Endometrial biopsy using standard dilatation and curettage or Pipelle-biopsy with further histological examination of the material obtained in the proses was performed in all patients with endometrial pathology.

For statistical processing of data obtained during the study, methods of variation, dispersion, discriminant and ROC analysis were used. All calculations were carried out in the SPSS-26 statistical package.

RESULTS AND DISCUSSION

When analyzing the age of patients with endometrial hyperplastic processes (EPH), it was revealed that the average age was 58.9±0.9 (43–73) years. The average duration of menopause was 11.3±0.7 (4–26) years. In patients with EPH, the average weight was 81.6±1.8 (52–122) kg,

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Table 1

Frequency of PMB in patients with benign endometrial hyperplasia

			Histological findings			Total
			Complex hyperplasiya	Endometrial polyp	Hyperplasiya with atypia	
Bleeding	No	Count	7	1	0	8
		%	21,2	6,2	0,0	12,5
	Yes	Count	26	15	15	56
		%	78,8	93,8	100,0	87,5
Total		Count	33	16	15	64
		%	100,0	100,0	100,0	100,0

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5,004	2	,082
Likelihood Ratio	6,640	2	,036
Linear-by-Linear Association	4,254	1	,039
N of Valid Cases	64		

the average height was 160±0.8 (148–78) cm. When calculating body mass index, it was found that this indicator fluctuates within 19–49 kg/m^2 (the average body mass index was 31.9±0.8 kg/m^2). Based on the data obtained, it was revealed that obesity of varying degrees of severity predominated in patients with EHP.

As a comparison group 20 women in postmenopausal period without EHP were included in the study to compare the hormonal levels. The women of this group had uncomplicated postmenopausal period, they were characterized by the similar average age (52.4±0.6 (47–70) years), duration of menopause (10.4±0.5 (6–22) years), mean weight (79.9±1.3 (55–117) kg), height (163±0.6 (150–173) cm), mean BMI (30.7±0.9 (20–44) kg/m^2).

It was revealed through research that 85.5% of women had a record of high frequency childbirth (the period between childbirths less than 2 years), of which 100% of women had induced abortions. In this group of patients, the incidence of infertility was 5.2%. Having a history of episodes of recurrent endometrial hyperplasia during the reproductive period, which is a result of hormonal imbalance, is crucial for postmenopausal patients with hyperplastic processes. This pathology of the reproductive period was found in the anamnesis of every fifth patient from this group.

Objective examination and analysis of the complaints revealed that the women with EHP had the episodes of bleeding and bloody discharge from the genital tract. It was established in 87,5% of cases, so, these results are specific for hyperplastic proses (Table 1) [29].

According to the results of our study, endometrial hyperplasia recurred in 28 (43.1%) patients. This category of patients had a history of cyclic and acyclic bleeding during the reproductive period, as well as bloody discharge in the postmenopausal period, which was the reason for curettage of the endometrium for diagnostic and therapeutic purposes.

When studying the frequency of gynecological surgical interventions in women with EHP, conservative myomectomy was detected in 3 (4.6%) patients, tubectomy due to tubal pregnancy – in 1 (1.5%) patient, cystectomy – in 4 (62%) patients.

It should be noted that out of 64 patients with EHP, 12 (18.5%) experienced relapses of endometrial hyperplasia during the reproductive period, which required scraping of the uterine cavity for diagnostic and therapeutic purposes. Subsequently, this group of women received hormonal treatment.

The data obtained by determining the level of hormones of the hypothalamic-pituitary-ovarian system are reflected in Table 2.

Table 2

Indicators of hormone levels in patients with EHP in the postmenopausal period

Indicators	Patients with EHP (n=64)	Women in postmenopausal period without EHP (n=20)	P-value
FSH, mIU/ml	38,7±4,2 (3,65-79,62)	54,24±2,4	< 0.05
LH, mIU/ml	23,9±2,7 (4,44–49,01)	21,92±1,92	> 0.05
LH/FSH	0,681±0,06 (0,33–2,15)	0,40±0,03	< 0.05
Prl, ng/ml	802,9±191,7 (4,27–2229)	116,86±3,95	< 0.05
DHEA-S, ng/ml	121,8±22,5 (15,67–545,8)	1,3±0,03	< 0.05
E1, ng/ml	122,2±8,2 (40,2–200,9)	9,5±0,52	< 0.05
E2, ng/ml	16,7±3,4 (0,4–69,29)	40,4±2,1	< 0.05
P, ng/ml	0,67±0,374 (0,04–10,05)	0,54±0,09	> 0.05
T total ng/ml	0,2±0,01 (0,02–0,64)	1,81±0,005	< 0.05

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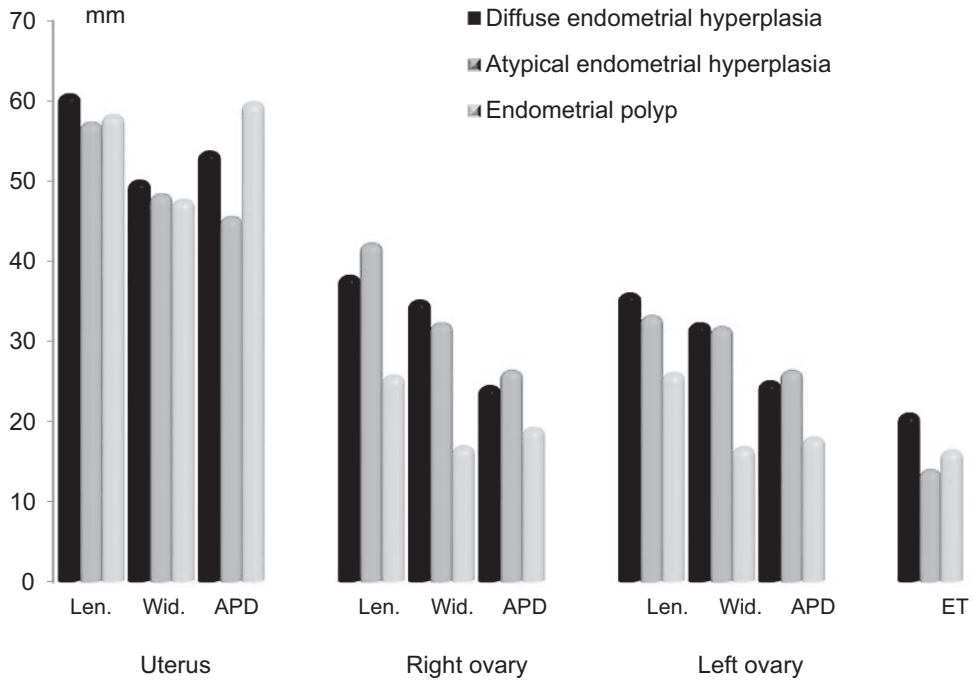

Results of echographic study in focal and diffuse endometrial hyperplasia

Notes: Len – length; Wid – width; APD – anterior-posterior diameter; ET – endometrial thickness.

The results presented in the table indicate that postmenopausal patients with EHP are characterized by lower levels of estradiol, FSH, LH/FSH ratio, testosterone, but with significantly higher values of estrone, DHEA-S and prolactin [29].

Determination of the tumor marker CA-125 revealed an increase in its level to 51.9±13.2 (17–262) IU/ml.

It should be emphasized that these data demonstrate significant fluctuations in CA-125 during the postmenopausal period in the presence of EH. This suggests that changes in the level of CA-125 during EH in postmenopausal women do not have diagnostic value for this pathology; accordingly, they require further instrumental studies to confirm the diagnosis.

Ultrasound examination of the pelvic organs using TVU was performed in all women with EH included in the study. According to the objectives of the study, the size of the uterus and ovaries was determined, and the thickness of the endometrium was measured. It was found that these patients had an increase in the size of the uterus and ovaries. In addition, we revealed a significant increase in endometrial thickness. These results had been a reason for a morphological study of endometrial scraping to confirm the diagnosis. Along with this, an increase in ovarian size was detected, which was nonspecific for women with a long period of postmenopause (Figure).

As seen from the diagram, the uterine size, endometrial thickness, and the size of both ovaries increased in diffuse endometrial hyperplasia (33 patients (51,6%)). In atypical endometrial hyperplasia (in 15 patients (23,4%)) the similar situation is observed. However, we found that atypical EH has a slight decrease in endometrial thickness compared with diffuse endometrial hyperplasia.

According to the results of an ultrasound examination of the uterus, women with endometrial polyps (16 of 64 (25%)) had an increase in the length, anteroposterior size and thickness of the endometrium. The width of the uterus in this group of patients was close to that of women with diffuse endometrial hyperplasia.

An increase in endometrial thickness, being the most specific echographic indicator for EH during the postmenopausal period, fluctuated from 14.1±1.6 mm in women with atypical endometrial hyperplasia to 21.3±4.8 mm in patients with diffuse endometrial hyperplasia, which may be the basis for morphological research. The same indicator in patients with endometrial polyps was 16,5±1.3 mm.

It should be noted that an echographic examination, revealing the presence of an increase in the thickness of the endometrium, does not make it possible to differentiate endometrial hyperplastic processes from endometrial cancer. In our opinion, this reduces the diagnostic value of the research method and dictates the need for immediate diagnostic curettage and biopsy of the endometrium, followed by histological examination of the material obtained during the biopsy.

According to the latest researches, it has been determined that in the development of endometrial hyperplasia in the postmenopausal period, a significant role is played by relative and absolute hyperestrogenia [23–25]. Hormonal changes in the female body on the background of ovarian hypofunction are predisposing factors to the development of endometrial cancer, manifested by the presence of bloody discharge of varying intensity. But, it should be taken into account, that in postmenopause EH tends to be asymptomatic. According to radiological findings, it was established that the frequency of asymptomatic complex endometrial hyperplasia is about 27.6%. The

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frequency of asymptomatic endometrial polyps averages 70.3%. The frequency of adenocarcinoma is within 1%, asymptomatic fibroids 0.5% [26, 27].

The frequency of bleeding, which is the primary clinical manifestation of pathology of the uterus and endometrium during the postmenopausal period, is 28.6%. Against the background of bleeding of varying intensity, endometrial polyp is diagnosed in 42.8%, and diffuse endometrial hyperplasia in 28.6% of cases [26, 28].

The diagnosis of EH is currently carried out according to subjective complaints, mandatory histological verification of endometrial sample and ultrasound data. Nevertheless, due to the lack of data on their positive effect in the diagnosis of proliferative changes in the endometrium, the regular use of computed tomography and magnetic resonance imaging is not recommended. The lack of specific clinical manifestations for each of the nosological units of endometrial pathology further complicates diagnosis.

Additionally, the significance and efficacy of transvaginal ultrasound in randomly determining endometrial thickness of more than 4 mm in asymptomatic postmenopausal women is subjected to controversial questions. According to multiple studies, it was discovered that in women with an M-echo of more than 4 mm without postmenopausal bleeding, according to the findings of a histological examination of an endometrial biopsy, atypical hyperplasia, endometrial cancer and endometrial polyp were determined in majority of cases [27].

CONCLUSIONS

The present study examined risk factors that play a key role in the occurrence of postmenopausal endometrial hyperplastic processes. This pathology of the reproductive period was found in the anamnesis of every fifth patient from this group. During the postmenopausal period, hyperplasia was developed in 10% of cases by the presence of bleeding, and 86.2% of cases by the presence of spotting.

Based on morphological, functional and clinical research methods, the fact that diffuse endometrial hyperplasia predominated in 52.3% of women was confirmed. With approximately equal frequency, the presence of focal endometrial hyperplasia (24.5%) and atypical hyperplasia (23.0%) was observed. The BMI of patients with EH in the postmenopausal period was 31.9±0.8 kg/m^2 in our study. Therefore, high risk factors for EH in the postmenopausal period are the presence of recurrent episodes of endometrial hyperplasia during the reproductive period, obesity and generally the state of being overweight of varying severity, as well as a record of a vast number of induced abortions.

There is no conflict of interest.

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