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MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL CHARACTERISTICS OF ENDOMETRIAL LAYERS IN WOMEN OF REPRODUCTIVE AGE WITH ENDOMETRIAL HYPERPLASIA WITHOUT ATYPIA

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Immunohistochemical staining may be useful for the differential diagnosis of endometrial hyperplasia (EH) without/with atypia and carcinoma. Several immunohistochemical biomarkers have already been investigated for use as diagnostic adjuncts in the diagnosis and classification of EH and may also predict progression from EH to carcinoma. However, the optimal molecular biomarker would be one that could reliably distinguish between hyperplastic benign with/without risk of recurrence, precancerous (hyperplastic atypical) and malignant endometrium, and indicate/predict transition between these three groups. To date, no candidate has been found to fully fill this role, so the search is ongoing.

Aim. *To study the morphological and immunohistochemically features of the structure of all layers of the endometrium, divided into functional and non-functional zones, which may have an impact on the development of endometrial hyperplasia*

Materials and methods. *The study was performed on endometrial morphological material obtained by diagnostic biopsy from 21 women with abnormal uterine bleeding (AUB) in the gynecological department of the Dnipro Clinical Hospital No. 9 in Dnipro during 2022-2023. The study investigated the expression of the biomarkers ER, PgR, Ki67, CK7, and CK8 in women with endometrial hyperplasia without atypia and secretory endometrium.*

Results. *In women with EH without atypia, the expression of ER in the stroma spontaneously increases, while epithelial cells do not show sensitivity to estrogen. The expression of PgR in the glands spontaneously increases, while the expression of PgR in the stroma is low. This may indicate that stromal cells may be less sensitive to progesterone.*

High expression of Ki67 in endometrial hyperplasia causes active processes of cell proliferation, while low expression of Ki67 in normal endometrium indicates its physiological state. These data can be useful for diagnosis and detection of pathological changes of the endometrium.

SK7 is expressed in epithelial cells, even with increased numbers. Normally, during functional observations of the endometrium, the expression of SK7 in epithelial cells is also observed. The functional zone is a layer of the endometrium that undergoes cyclical changes depending on the menstrual cycle of a woman. In this case, there is a regular renewal of cells expressing CK7, which remains one of the typical markers of epithelial cells.

The analysis of SK7 expression allows us to detect differences in the processes of cell proliferation and differentiation between endometrial hyperplasia without atypia and normal endometrium. These data coincide with the findings of other authors, are important for a deeper identification of pathophysiological mechanisms associated with endometrial hyperplasia, and also include additional markers for the diagnosis and prognosis of this condition.

Conclusion

The study results suggest that the expression of ER, PgR, Ki67, CK7, and CK8 may be associated with the development of EH without atypia. Further studies are needed to confirm these findings and to investigate the role of other biomarkers in the pathogenesis and diagnosis of EH.

Key words: *endometrium, endometrial hyperplasia, endometrial hyperplasia without atypia, immunohistochemistry, prognosis.*

Endometrial hyperplasia (EH) is a pathological increase in the number of cells of the endometrial epithelium, which, in the case of atypical proliferation, is considered a precancerous condition and leads to the development of endometrial carcinoma. A significant role in the differential diagnosis of EH without/with atypia and carcinoma is played by the method of immunohistochemically staining, which was discovered (Albert Coons) in 1941. This method was developed for the detection and localization of tissue antigens through the contact of antibodies associated with a color label

that visualizes the necessary cellular and subcellular structures [1].

In recent years, the method of immunohistochemistry has developed and improved, which made it possible to use it for more accurate and detailed analysis of formalin-fixed, paraffin-embedded histological samples [2].

Nowadays, the method of immunohistochemistry is an important tool for studying biological processes, diagnosing diseases and establishing pathological changes in cells and tissues. The discovery of this method opened the way to new achievements in biomedical research and clinical practice [3,4].

The conducted studies showed that the expression of various immunohistochemically markers can affect the development of EH. For this reason, in recent years there has been a growing interest in the study of clinical, imaging, histological and molecular factors that can influence the outcome of therapy [5,6].

Several immunohistochemical biomarkers have already been investigated for use as diagnostic adjuncts in the diagnosis and classification of EH, and may also predict progression from EH to carcinoma [7-10].

But with regard to the diagnosis of EH itself, the optimal molecular biomarker would be one that could reliably differentiate between hyperplastic benign with/without risks of recurrence, precancerous (hyperplastic atypical) and malignant endometrium, as well as indicate/predict the transition between these three groups. To date, no candidate has been found to fully fill this role, so the search is ongoing.

AIM. To study the morphological and immunohistochemically features of the structure of all layers of the endometrium, divided into functional and non-functional zones, which may have an impact on the development of endometrial hyperplasia

MATERIALS AND METHODS

The study was performed on endometrial morphological material obtained by diagnostic biopsy from 21 women with abnormal uterine bleeding in the gynecological department of the Dnipro Clinical Hospital No. 9 in Dnipro during 2022-2023.

The criteria for inclusion in the studied cohort of patients were: the age of women from 32 to 45 years (38.4±2.55), the presence of endometrial hyperplasia without atypia, or secretory changes of the endometrium according to the results of histological examination, the exclusion criteria were: the presence of inflammatory diseases of the pelvic organs , tumor pathology of the uterus and ovaries, endometriosis of the uterus, severe somatic pathology, any form of endocrinopathy and metabolic syndrome. The average body mass index was 27.83±1.96 kg/cm2.

The study included morphological and immunohistochemically research methods. Endometrial tissue was obtained by endometrial curettage, which was performed in women with abnormal uterine bleeding. Primary antibodies to ER (sp1, RTU), PgR (YR85, 1:200), CK 7 (sp1, RTU), CK8 (sp1, RTU), p53 (E247, RTU) and the UltraVision Quanto imaging system (LabVision).

Statistical processing of the obtained results was carried out using the Office 365 A1 for faculty software No. 1003BFFD8C8E8B0D. Arithmetic mean (M) and standard deviation (SD) values were calculated. The non-parametric test χI was used to compare the distribution of features in groups. The difference was considered statistically significant at $p<0.05$ (95% significance level).

RESULTS

Analysis of the expression of the biomarkers ER, PgR, Ki67, CK7 and CK8 in women with endometrial hyperplasia and secretory endometrium is important for understanding the physiological and pathological processes that occur in women (Fig. 1). The expression of these biomarkers can help establish the diagnosis of endometrial hyperplasia and classify it into subtypes depending on the characteristics of the cells and their activity. The expression of these biomarkers may be a prognostic factor, helping to assess the prognosis for patients with endometrial hyperplasia. For example, high expression of ER and PgR may indicate a more favorable prognosis and a more sensitive response to hormone therapy, which may help in planning treatment and monitoring its effectiveness. Ki67 expression is an indicator of cell proliferation and activity. High expression of Ki67 may indicate increased cellular activity and rapid cell division, which may be characteristic of endometrial hyperplasia. While the expression of Ki67 decreases in the secretory phase of the unchanged normal endometrium, but sometimes such increased expression can reveal the presence of active proliferative processes. In addition, the expression of CK7 and CK8 may be associated with an increased number of epithelial cells. They are found in epithelial cells of various organs, including

the endometrium. Studying the expression of these cytokeratins helps reveal the epithelial nature of the cells and to distinguish them from other cells. Thus, analysis of the expression of ER, PgR, Ki67, CK7 and CK8 in endometrial hyperplasia and normal endometrium allows a deeper understanding of the processes of proliferation, differentiation and function of endometrial cells. These data have important diagnostic value for endometrial hyperplasia, the degree of determination of its atypia and the prediction of treatment results (Fig.2).

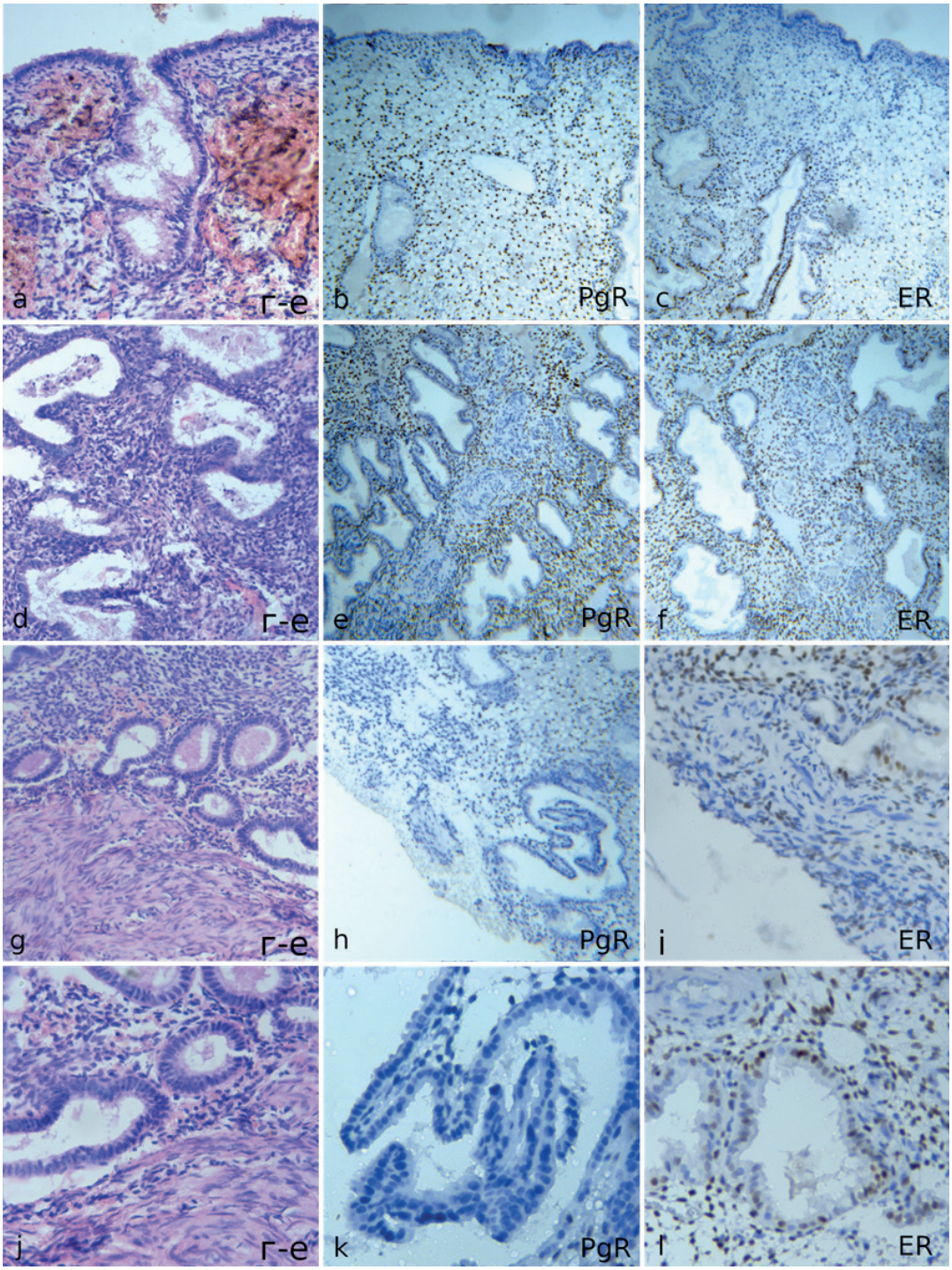

Fig. 1. Endometrial hyperplasia without atypia. (a, b, c) – the surface (compact) layer of the zona compacta (Ч100); (d, e, f) – the middle (spongy) layer of the zona spongiosa (Ч400); (g, h, i) – deep (basal) layer of the zona basalis (Ч400); (a, d, g,) – uniform membrane-cytoplasmic staining with SC8 marker in all layers of the endometrium, IGH method with Mayer's hematoxylin; (b, e, h) – cluster membrane staining with CK7 marker, which decreases from the superficial to the basal layer, IHC method with Mayer's hematoxylin; (c, f, i); intranuclear reaction with the proliferation marker Ki-67, the number of which increases from the superficial to the basal layer, IHC method with Mayer's hematoxylin

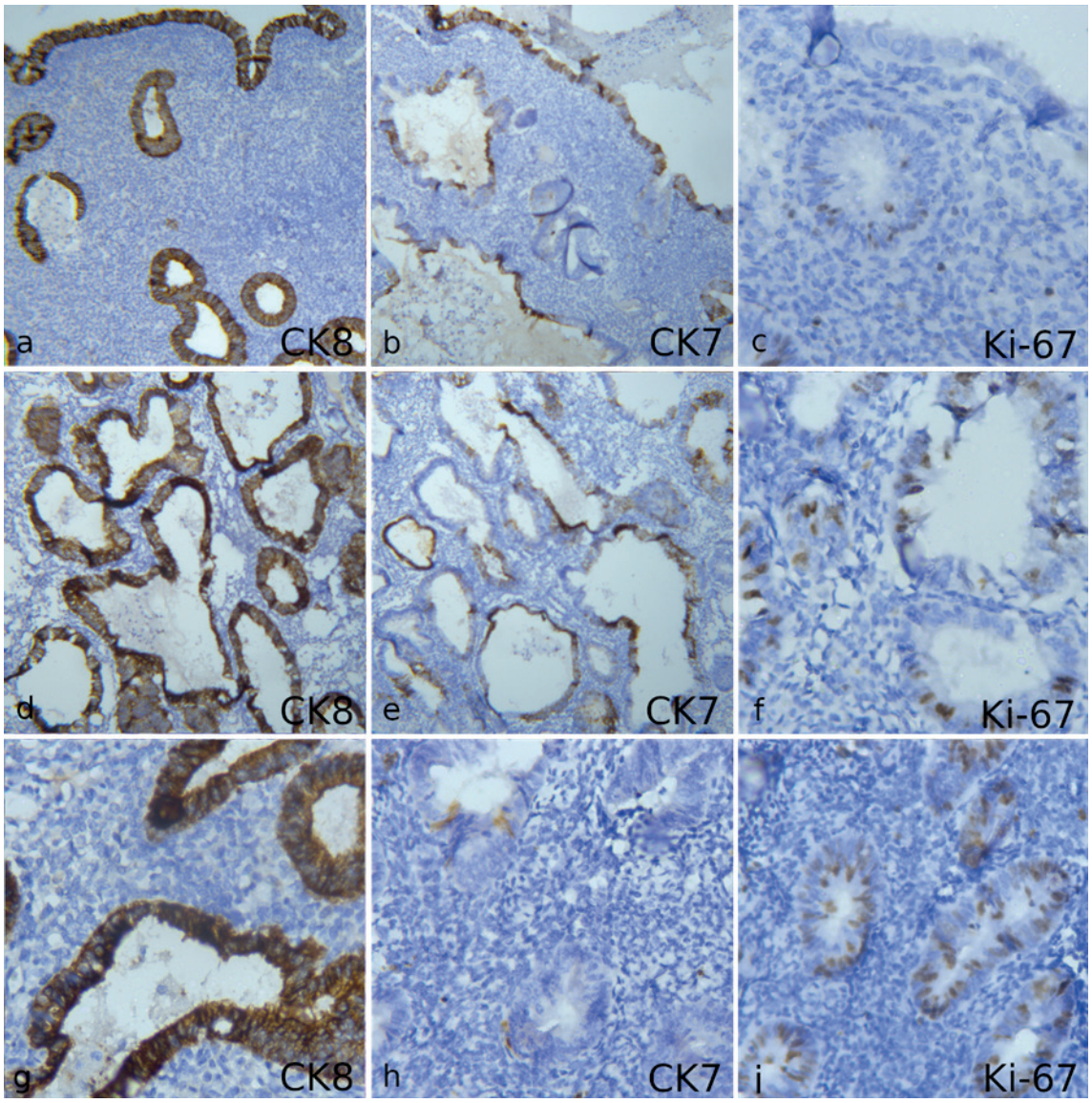

Fig. 2. Endometrial hyperplasia without atypia. (a, b, c) – the surface (compact) layer of the zona compacta (Ч100); (d, e, f) – the middle (spongy) layer of the zona spongiosa (Ч400); (g, h, i) – deep (basal) layer of the zona basalis (Ч400); (a, d, g,) – uniform membrane-cytoplasmic staining with SC8 marker in all layers of the endometrium, IGH method with Mayer's hematoxylin; (b, e, h) – cluster membrane staining with CK7 marker, which decreases from the superficial to the basal layer, IHC method with Mayer's hematoxylin; (c, f, i); intranuclear reaction with the proliferation marker Ki-67, the number of which increases from the superficial to the basal layer, IHC method with Mayer's hematoxylin

DISCUSSION OF RESEARCH RESULTS

Expression (ER) in different layers of the endometrium in EH without atypia manifested itself in the following way. In the basal and functional layers of the endometrium with EH without atypia, the expression of ER in the stroma spontaneously increases (100.00%); that is, no expression of ER was detected in the epithelial cells (0.00%). This may indicate that the stroma actively responds to the hormonal signal of estrogen, while epithelial cells do not show sensitivity to estrogen. In the secretory endometrium, ER expression in the stroma spontaneously increases (71.43%), compared to ER expression in epithelial cells (28.57%).

This may indicate that the stroma reflects the hormonal signal of estrogen and may be active during the secretion phase. On the other hand, epithelial cells may be less sensitive to estrogen, which is characteristic of a normal menstrual cycle. The results of the analysis show that ER expression can be seen in different types of endometrium. The high expression of ER in the stroma may be associated with the active effect of estrogen on

stromal cells, which may be involved in its functional characteristics. On the other hand, the absence of ER expression in epithelial cells may be specific for EH without atypia, which may indicate changes in cellular regulation and endometrial functions in that condition $p<0.05$ indicates statistical significance of differences between groups. From the above data, it is clear that the expression of progesterone receptors (PgR) also differs in different endometrial spheres and depends on the endometrium. With EH without atypia in the basal and functional layers of the endometrium, with EH without atypia, the expression of PgR in the glands spontaneously increases (85.71%), which may indicate the activity of progesterone receptors in epithelial cells. In the stroma of the endometrium, the expression of PgR is low (14.29%). This may indicate that stromal cells may be less sensitive to progesterone. With secretory endometrium, the expression of PgR in the glands spontaneously increases (100.00%), which makes it possible to detect the proactivity of progesterone receptors in epithelial cells. At the same time, the expression of PgR in the stroma is low (14.29%), which may be related to the fact that stromal cells are less sensitive to progesterone.

The obtained results confirmed that the expression of PgR can be changed in different types of endometrium. High expression of PgR in glands with EH without atypia and secretory endometrium may be associated with the proactivity of progesterone receptors in epithelial cells, which is characteristic of the functionally active layer of the endometrium. On the contrary, low expression of PgR in the stroma may indicate a lower sensitivity of stromal cells to progesterone compared to epithelial cells of the functional layer. The value of $p < 0.05$ indicates the static significance of the values between the groups, which will confirm the statistical weight of the obtained results.

Analysis of Ki67 biomarker expression in endometrial hyperplasia without atypia and in normal secretory endometrium allows studying the level of cell proliferation in the conditions and identifying possible differences. In EH without atypia, an increased level of Ki67 expression is found. The biomarker Ki67 is an indicator of cell proliferation and cell division activity. Increased expression of Ki67 correlates with increased proliferation of endometrial cells in a proper state. This may be due to increased endometrial screening after menstruation and a disturbance in the balance of cell proliferation and apoptosis. In normal secretory endometrium, expression of Ki67 usually decreases during the secretory phase of the menstrual cycle. This is due to the fact that cell proliferation in this state is limited and occurs in accordance with processes such as the preparation of the endometrium for the implantation of a fertilized egg. In a normal state, the endometrium goes through different phases of the cycle, and the expression of Ki67 corresponds to the level of proliferation according to the phases of the menstrual cycle.

Thus, analysis of Ki67 expression allows us to detect a difference in cell proliferation between endometrial hyperplasia without atypia and normal secretory endometrium. High expression of Ki67 in endometrial hyperplasia causes active processes of cell proliferation, while low expression of Ki67 in normal endometrium indicates its physiological state. These data can be useful for diagnosis and detection of pathological changes of the endometrium. SC7 (cytokeratin 7) is a protein that belongs to the family of cytokeratins, which include intermediate filaments in the cellular cytoskeleton. Cytokeratins are important structural proteins that cause mechanical injury and damage to the cytoskeleton. CK7 is typical for epithelial cells, in particular, it is found in cells of some epithelial tissues, such as the epithelium of the lungs, liver, kidneys, and gall bladder.

CK7 (cytokeratin 7) is a protein that belongs to the family of cytokeratins, which include intermediate filaments in the cellular cytoskeleton. Cytokeratins are important structural proteins that cause mechanical injury and damage to the cytoskeleton. CK7 is typical of epithelial cells; in particular, it is found in the cells of some epithelial tissues, such as the epithelium of the lung, liver, kidney, gall bladder, and endometrium. The role of SK7 includes what can be considered a marker for the detection and characterization of different types of cancer tumors. For example, CK7 expression may aid in tumor differentiation, progression, and metastasis. In endometrial hyperplasia and in normal conditions, SK7 is expressed in endometrial epithelial cells. SK7 expression refers to the typical characteristics of epithelial cells and can be used for the differential diagnosis of endometrial hyperplasia and normal endometrium. In endometrial hyperplasia, which is a precancerous condition, there is an increase in the number of endometrial epithelial cells. SK7 is found in epithelial cells, even with increased numbers. Normally, during functional observations

of the endometrium, the expression of SK7 in epithelial cells is also observed. The functional zone is a layer of the endometrium that undergoes cyclical changes depending on the menstrual cycle of a woman. In this case, there is a regular renewal of cells expressing CK7, which remains one of the typical markers of epithelial cells. The basal layer of the endometrium responds weakly to estrogen stimulation and is insensitive to progesterone, which is clearly visible in an immunohistochemical study with markers for estrogen and progesterone receptors. In endometrial hyperplasia and in normal conditions, CK7 continues to be expressed in the basal osseous endometrium. This suggests that even with increased cellular activity and changes in tissue architecture, typical epithelial cells with the presence of SK7 are present in the basal cells. It is also important to note that SK7 is also expressed in functioning endometrial disease, both in hyperplasia and normal. CK7 expression is a characteristic feature of epithet 1. Endometrial hyperplasia without atypia: in the basal dimension of the endometrium with hyperplasia, CK7 is expressed in all samples (100%), which is a massive increase in the number of epithelial cells. At the same time, the functional state of SC7 is also observed in all cases (100%), of which 71.43% have high expression, and 28.57% have a decrease. This can be an observation of structural changes in the endometrium, which are carried out through the processes of cell proliferation and differentiation, which are characteristic of this phase of the menstrual cycle. D B In the secretory endometrium, in its basal layer, SK7 expression was also observed in all samples (100%). In the manifestation of SK7, it was also observed in all samples (100%), in 85.71% of manifestations, and in 14.29% - high. Such an indicator can cause a higher level of cell proliferation during the functional examination of the normal endometrium compared to hyperplasia without atypia. Thus, the analysis of SK7 expression allows us to detect differences in the processes of cell proliferation and differentiation between endometrial hyperplasia without atypia and normal endometrium. These data coincide with the findings of other authors, are important for a deeper identification of pathophysiological mechanisms associated with endometrial hyperplasia, and also include additional markers for the diagnosis and prognosis of this condition [2].

In the functional layer of the endometrium with EH, SK7 expression was observed in all cases (100%), but of them, 71.43% had high expression, and 28.57% - low expression. This may be due to structural changes in the endometrium, which are carried out by the processes of cell proliferation. Examination of the secretory endometrium showed that CK7 expression was also observed in all samples (100%). In the manifestations of CK7, it is also observed in all samples (100%), and in 85.71% it was average, and in 14.29% it was high. Such an indicator can cause a higher level of cell proliferation during the functional examination of a normal endometrium compared to EH without atypia. Thus, the analysis of CK7 expression allows us to detect differences in the processes of cell proliferation and differentiation between endometrial hyperplasia without atypia and normal endometrium. These data are important for the deeper identification of pathophysiological mechanisms associated with endometrial hyperplasia, and also include additional markers for the diagnosis and prognosis of this condition.

Analysis of the expression of the biomarkers ER, PgR, Ki67, CK7 and CK8 in women with endometrial hyperplasia and secretory endometrium is important for understanding the physiological and pathological processes that occur in women. The expression of these biomarkers can help establish the diagnosis of endometrial hyperplasia and classify it into subtypes depending on the characteristics of the cells and their activity. The expression of these biomarkers may be a prognostic factor, helping to assess the prognosis for patients with endometrial hyperplasia. For example, high expression of ER and PgR may indicate a more favorable prognosis and a more sensitive response to hormone therapy, which may help in planning treatment and monitoring its effectiveness. Ki67 expression is an indicator of cell proliferation and activity. High expression of Ki67 may indicate increased cellular activity and rapid cell division, which may be characteristic of endometrial hyperplasia. While the expression of Ki67 decreases in the secretory phase of the unchanged normal endometrium, but sometimes such increased expression can reveal the presence of active proliferative processes. In addition, the expression of SC7 and SC8 may be associated with an increased number of epithelial cells. They are found in epithelial cells of various organs, including the endometrium. Studying the expression of these cytokeratins helps reveal the epithelial nature of

the cells and to distinguish them from other cells. Thus, analysis of the expression of ER, PgR, Ki67, CK7 and CK8 in endometrial hyperplasia and normal endometrium allows a deeper understanding of the processes of proliferation, differentiation, and function of endometrial cells. These data have important diagnostic value for endometrial hyperplasia, the degree of determination of its atypia and the prediction of treatment results.

CONCLUSION

Analysis of the expression of steroid hormone receptors in different layers of the endometrium of the secretory phase and endometrium with hyperplasia without atypia found a statistically significant difference only in the expression of ER of all layers (surface, functional and basal) with the advantage of the number of samples with high expression of ER in the stroma of samples of endometrial hyperplasia without atypia ($p<0.05$), on the other hand, such a difference was not found for PgR, despite the trend of a decrease in the basal parts of the endometrium with hyperplasia without atypia and secretory endometrium in the percentage of PgR positive immunoreactivity cells to the complete absence in the epithelium of the glands.

The proliferative activity of endometrial cells according to the Ki-67 marker increased from superficial to basal parts and showed a statistically significant difference between endometrial hyperplasia samples without atypia and secretory endometrium.

Cytokeratin markers CK8 and CK7 showed a significant difference in expression between themselves: SC8 remained at a constant level of expression, regardless of the depth of the endometrial glands - revealed an organ-specific expression for the endometrium, while SC7, on the contrary, was most expressed in the luminal highly differentiated epithelial of the surface layers and was lost in the basal/stem cells of the deep layers of the endometrium, but a statistically significant difference between secretory endometrium and endometrial hyperplasia without atypia was not found.

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РЕЗЮМЕ

МОРФОЛОГІЧНА ТА ІМУНОГІСТОХІМІЧНА ХАРАКТЕРИСТИКА ШАРІВ ЕНДОМЕТРІЯ У ЖІНОК РЕПРОДУКТИВНОГО ВІКУ З ГІПЕРПЛАЗІЄЮ ЕНДОМЕТРІЮ БЕЗ АТИПІЇ

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Імуногістохімічне фарбування може бути корисним для диференціальної діагностики гіперплазії ендометрію (ГЕ) без/з атипією та карциномою. Кілька імуногістохімічних біомаркерів вже було досліджено для використання як діагностичних допоміжних засобів у діагностиці та класифікації ГЕ, а також вони можуть передбачати прогресування від ГЕ до карциноми. Однак, оптимальним молекулярним біомаркером був би такий, який міг би надійно розрізнити доброякісну гіперплазію. з/без ризику рецидиву, передраковий (гіперпластичний атиповий) і злоякісний ендометрій, а також вказати/передбачити перехід між цими трьома групами. На сьогоднішній день не знайдено жодного кандидата, який би повністю зайняв цю посаду, тому пошуки тривають.

Мета. Вивчити морфологічні та імуногістохімічні особливості будови всіх шарів ендометрію, розділених на функціональні та нефункціональні зони, які можуть впливати на розвиток гіперплазії ендометрія.

Матеріали та методи. Дослідження проводили на морфологічному матеріалі ендометрію, отриманому методом діагностичної біопсії 21 жінки з аномальною матковою кровотечею у гінекологічному відділенні Дніпровської клінічної лікарні №9 м. Дніпра протягом 2022-2023 років. У дослідженні досліджували експресію біомаркерів ER, PgR, Ki67, CK7 і CK8 у жінок з гіперплазією ендометрія без атипії та секреторного ендометрію.

Результати дослідження. У жінок з ГЕ без атипії спонтанно підвищується експресія ЕР у стромі, тоді як епітеліальні клітини не виявляють чутливості до естрогену. Експресія PgR в залозах спонтанно зростає, тоді як експресія PgR в стромі низька. Це може означати, що стромальні клітини можуть бути менш чутливими до прогестерону.

Висока експресія Ki67 при гіперплазії ендометрію викликає активні процеси клітинної проліферації, а низька експресія Ki67 в нормальному ендометрії свідчить про його фізіологічний стан. Ці дані можуть бути корисні для діагностики та виявлення патологічних змін ендометрія.

SK7 експресується в епітеліальних клітинах навіть у збільшеній кількості. У нормі під час функціональних спостережень за ендометрієм також спостерігається експресія SK7 в епітеліальних клітинах. Функціональна зона - це шар ендометрію, який зазнає циклічні зміни в залежності від менструального циклу жінки. При цьому відбувається регулярне оновлення клітин, що експресують CK7, який залишається одним із типових маркерів епітеліальних клітин.

Аналіз експресії SK7 дозволяє виявити відмінності в процесах клітинної проліферації та диференціації між гіперплазією ендометрію без атипії та нормальним ендометрієм. Ці дані збігаються з висновками інших авторів, важливі для глибшої ідентифікації патофізіологічних механізмів, асоційованих з гіперплазією ендометрію, а також містять додаткові маркери для діагностики та прогнозу цього стану.

Висновок

Результати дослідження свідчать про те, що експресія ER, PgR, Ki67, CK7 і CK8 може бути пов'язана з розвитком ГЕ без атипії. Потрібні подальші дослідження, щоб підтвердити ці висновки та дослідити роль інших біомаркерів у патогенезі та діагностиці ГЕ.

Ключові слова: ендометрій, гіперплазія ендометрія, гіперплазія ендометрія без атипії, імуногістохімія, прогноз.