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RECEPTOR ACTIVITY OF THE EUTOPIC AND ECTOPIC ENDOMETRIUM TO ESTROGEN AND PROGESTERONE MARKERS IN CASE OF ADENOMYOSIS AVAILABLE DURING POSTMENOPAUSE

Abstract. *Objective of the study is to determine ER, PR and AR activity of eutopic and ectopic endometrium in case of adenomyosis available during post-menopause. Materials and methods. 30 cases of adenomyosis have been examined in case of hyperplastic processes in the endometrium and without them in patients aged from 51 to 73 years. Immunohistological examination has been conducted with the purpose to determine the state of receptor apparatus to ER, PR and AR markers. Immunohistological examinations conducted in ectopic foci determined a high mean score of the spread of ER staining of the glandular cells in case of endometrioid adenocarcinoma of the uterus (EACU) and endometrial hyperplasia (EHP) and the stromal cells in the group with EHP. A high mean index of intensity and spread of ER staining of the eutopic endometrium glandular component was found in all the groups. Considerable differences between mean indices of intensity and spread of ER staining of the glandular and stromal cells in adenomyosis foci both between the groups themselves and the examined components are absent ($p>0,05$). An increased level of PR activity was detected respectively to the improvement of differentiation degree of the eutopic endometrium epithelial cells. The comparison of the results of PR activity of the stromal cells and glands of the eutopic and ectopic endometrium did not find any deviations between the examined indices ($p>0,05$). Comparison of the degree of AR expression did not find differences between the groups ($p>0,05$). Conclusions. Adenomyosis during post-menopause period is characterized by prevailed expression level of ER glandular component of the eutopic endometrium over the endometrium in adenomyosis foci in case of EACU and endometrium atrophy available. Increase of ER and PR expression levels occurs respectively to the increase of cellular differentiation degree. Considerable differences by the indices of intensity and staining of PR of the glandular and stromal cells in adenomyosis foci were not found both between the groups themselves and the examined components. Considerable differences by AR expression levels in the eutopic and ectopic endometrium were not found as well. Prospects of further studies: to carry out the analysis of ER, PR and AR expression levels in the ovaries in case adenomyosis available.*

Key words: *adenomyosis; post-menopause; estrogen, progesterone, androgenic receptors.*

Introduction. Endometriosis is benign hormone-dependent inflammatory process associated with structural-functional changes of the female reproductive system, which can be a cause of infertility and disorders in the social, family and economical spheres of life [3, 15]. 176 million of women in the whole world suffer from endometriosis including every 10th one of the reproductive age [15, 16]. In 70-80% of all the

cases endometriosis is manifested by adenomyosis [9, 1, 3]. Women of a reproductive age are mainly affected [15]. At the same time, the disease affects post-menopausal women as well. Occurrence of adenomyosis foci during post-menopausal period is associated with peripheral conversion of androstenediol into estrogen or against the ground of administration of hormonal therapy [15].

Still a considerable progress in investigation of adenomyosis does not enable to formulate completely a clear notion concerning etiopathogenesis of the disease. Metabolic disorders of estrogens are considered to be a leading conception in the development of internal endometriosis [7]. In addition to estrogen and progesterone receptors the variants of their combinations and receptor status of cells are also important [3]. The change of balance of these hormones followed by the development of relative or absolute hyperestrogenemia is the main factor provoking adenomyosis. However, certain scientists state occurrence of endometrioid foci against the ground of hypoestrogenemia and restricted hormonal effect on the heterotopic tissue [6].

16-90% of patients who suffer from internal endometriosis are known to be diagnosed with hyperplastic processes in the endometrium [2]. In recent decades many researchers have indicated the increase of frequency of comorbid (parallel) development of adenomyosis and hyperplastic processes in the endometrium [7, 4].

Investigation of molecular peculiarities of the internal endometriosis foci in combination with other proliferative diseases of the female reproductive system during post-menopausal period is a promising approach, since this group is not completely studied.

Objective: to determine receptor activity of eutopic and ectopic endometrium to the markers of estrogen, progesterone and androgen in case of adenomyosis available during post-menopause.

Materials and methods. The material for the study was surgical material (extracted uteri) from 30 patients (51-73 years of age) with adenomyosis in case of comorbid pathology (endometrioid adenocarcinoma of the uterus (EACU) and endometrial hyperplasia (EHP)) or without it, who were treated in the Center of Restoration and Reconstructive Medicine (University Clinic) of Odessa National Medical University. The selection criteria were the following: amenorrhea over 12 months (post-menopause) and confirmed clinical diagnosis of adenomyosis. The patients were divided into three groups: the first one included 10 women with adenomyosis and simple non-atypical hyperplasia of the endometrium; the second group – 10 women with adenomyosis and

adenocarcinoma of the uterus; the third group (control one) – 10 women with adenomyosis and age changes.

The fragments of the material to be examined were fixed in 10 % neutral formalin with pH 7.0 during 24 hours at the temperature of 37 °C. Then the specimens were processed according to the common unified methods. Immunohistochemical reaction was performed with the use of monoclonal mouse antibodies of estrogen-receptor alpha (ER, clone EP1), progesterone (PR) and androgen antibodies (AR). Expression of estrogen, progesterone and androgen markers was assessed by the numerical score system of the continuous staining method to determine ER- and PR-status (Allred D. C. et al., 1998) (Table 1)[14].

Table 1

Numerical score system to assess continuous staining

Intensity(I)	Spread of staining (Π)
0 = none	(0) – none of stained cells
1 = weak	(1) – stained cells less than 1/100
2 = intermediate	(2) – number of stained cells from 1/100 to 1/10
3 = strong	(3) – number of stained cells from 1/10 to 1/3
	(4) – number of stained cells from 1/3 to 2/3
	(5) – number of stained cells over 2/3

General statistical analysis was made by means of standard methods of mathematical-statistical processing with the use of software MS Office Excel. Means values (M) and error of mean values (m) were estimated. To compare parametric data the method of paired Student criterion was used, probability was determined with p<0,05.

Results. As a result of the immunohistochemical examination conducted on 30 women of a post-menopause period suffering from adenomyosis with and without hyperplastic processes in the endometrium, we have drawn the conclusions concerning the levels of receptor activity of eutopic and ectopic endometrium to the markers of estrogen, progesterone and androgen.

Discussion. Immunohistochemical (IHC) examination determined high mean score of the spread of ER staining of the glandular cells in the

ectopic foci in case of EACU and EHP available, $3,14 \pm 0,6$ and $4,14 \pm 0,5$ respectively (Fig. 1). A similar tendency is characteristic for the stroma of endometrioid heterotropy in the group with EHP. Low indices of ER staining intensity of the stromal component of adenomyosis foci were determined in case of EACU ($0,71 \pm 0,31$) concerning other groups and epithelial cells of ectopic foci in the group itself. A lower level of ER expression of the glandular component of the endometrioid heterotropy was found in case of endometrium atrophy than in case of EHP ($p < 0,05$) (Table 2). Single scientific works are indicative of prevailed receptor activity of the epithelial cells over the stromal ones in adenomyosis foci, where the groups of the study included mainly women of reproductive and pre-menopausal age [11, 13].

Examination of ER activity of the glandular component of the eutopic endometrium presented high mean score of intensity and spread of staining in all 3 groups (Fig. 2) (Table 2). The results of the study of ER expression of the eutopic endometrium are indicative of the absence of considerable differences in the levels of receptor activity depending on comorbid pathology ($p > 0,05$), which agrees partially with conclusions of certain scientists. According to the evidence of certain sources endometrium in case of simple EHP is characterized by a high level of estrogen activity with its gradual decrease in case of combined EHP and EACU [17]. There is an opposite opinion: decreased expression of steroid receptors occurs in the direction of the increased differentiation of cells, the highest indices are found in case of EACU respectively [14, 17]. Assessment of the results of ER activity of the eutopic and ectopic endometrium showed that the 2nd and 3rd groups of women are characterized by higher levels of estrogen expression of the epithelial cells in the eutopic endometrium than in adenomyosis foci (Fig. 3). Such differences are not

peculiar for the stromal component ($p > 0,05$). The data of certain studies indicate that ER activity is lower in endometrioid heterotropy than in eutopic endometrium [9-11]. However, there are opposite opinions concerning prevailing expression of steroid hormones in the foci of internal endometriosis than in eutopic endometrium [11]. Higher estrogen activity of eutopic endometrium concerning ectopic one in the group with atrophy is explained by insufficient amount of ER associated with decrease of their expression in endometrioid heterotropy [9, 17].

Analysis of the activity level of progesterone receptors found a considerable part of stained

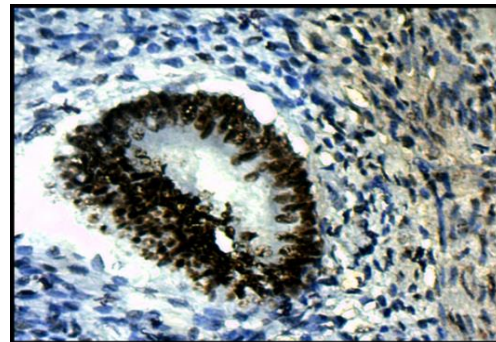


Fig. 1. Adenomyosis focus against the ground of simple non-atypical EHP of a 56-year-old woman. Estimation for glands – 3+++ in 100%; for stroma – 2++ in 60%. IHC reaction with antibodies to estrogen. x400.

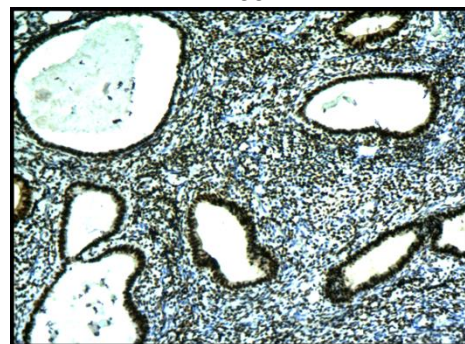


Fig. 2. Simple form of endometrial hyperplasia without atypical form in a 73-year-old woman. Estimation for glands – 3+++ y 100%; for stroma – 3+++ y 70%. IHC reaction with antibodies to estrogen. x400.

Table 2

Mean indices of intensity (I) and spread (Π) of staining of ER-receptors in eutopic and ectopic endometrium (M±m, score)

Component	Eutopic endometrium				Ectopic endometrium			
	Glandular		Stromal		Glandular		Stromal	
Index	I	Π	I	Π	I	Π	I	Π
I (n=10)	2,67±0,37	4,5±0,55	2,33±0,37	4,17±0,72	2,14±0,37	4,14±0,5	1,86±0,28	3,57±0,46
II (n=10)	2,56±0,19	4,56±0,26	1,25±0,44	2,63±0,75	1,71±0,31	3,14±0,6	0,71±0,31	2,0±0,85
III (n=10)	2,67±0,41	4,67±0,41	1,67±0,41	3,0±0,71	1,11±0,28	1,78±0,58	1,78±0,24	3,11±0,51

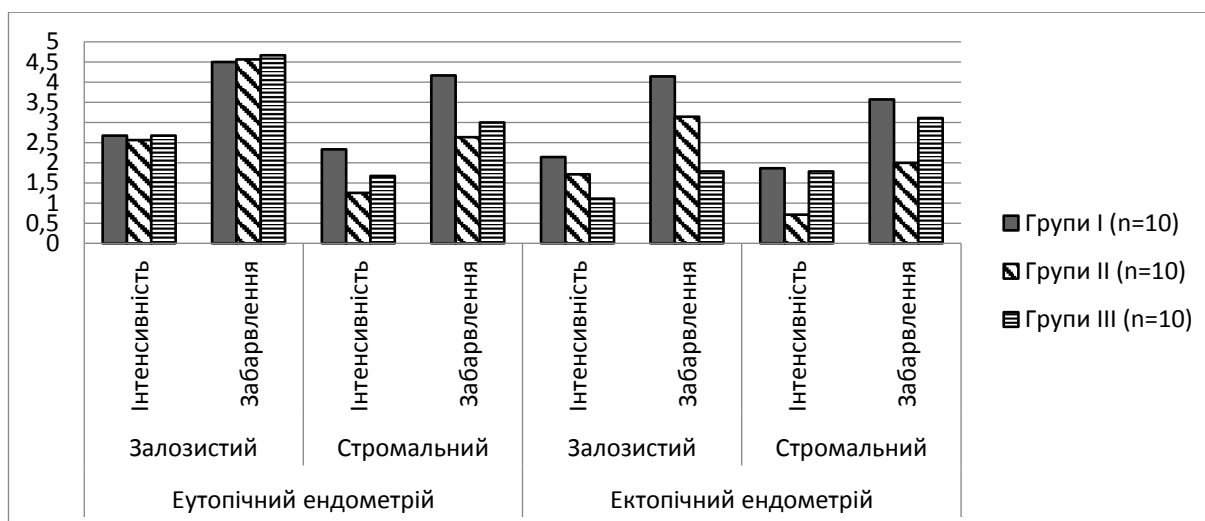


Fig. 3. Mean indices of intensity and staining of ER-receptors in eutopic and ectopic endometrium ($M \pm m$, score).

cells of the glandular and stromal components of eutopic endometrium (Fig. 4). Similar to the cases with ER expression simple non-atypical EHP is characterized by the highest score of intensity – «3» and spread of staining of the epithelial cells – «5» and their decrease in case of complex atypical EHP. The group with EACU is characterized by an increased level of receptor PR activity respectively to the improvement of EACU differentiation degree. The glandular component of low differentiated EACU had minimal score in intensity and spread of staining, stroma according to the given criteria was estimated as “0” in some cases. The mentioned indices in the group were the highest for high-differentiated EACU. The obtained results partially correspond with conclusions of other scientists: the highest degree of PR activity with simple EHP, and the lowest – with complex EHP and EACU [8, 17]. In I and II groups stromal component obtained rather high score by the level of spread of cellular staining – mostly «4» and «5», and as a result mean indices are $4,6 \pm 0,27$ and $4,56 \pm 0,36$ respectively. Analysis of the glandular and stromal components of endometrium by the level of intensity and staining did not find considerable differences ($p > 0,05$) (Table 3), which contradicts the opinion of certain scientists concerning the fact that the number of PR is bigger in the stromal cells irrespective of endometrial state [8]. Considerable difference between mean indices of the degree of intensity and spread of staining of glandular and stromal cells in the internal endometriosis foci (Fig. 5) was not found between the groups themselves and between the examined components ($p > 0,05$) (Table 3).

Results of comparison of PR activity of the stromal cells and glands of eutopic and ectopic endometrium did not find considerable deviations between the examined indices ($p > 0,05$) (Fig. 6), which contradicts statements of other researchers concerning relatively lower level of PR expression in adenomyosis foci than in eutopic endometrium [7, 11]. There is an opposite opinion as well: the components of endometrioid

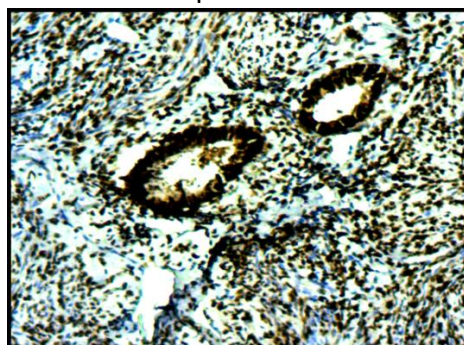


Fig. 4. Endometrioid carcinoma of endometrium G1 in a 70-year-old woman. Estimation for glands – 3+++ y 100%; for stroma – 3+++ in 70%. IHC reaction with antibodies to progesterone. x400.

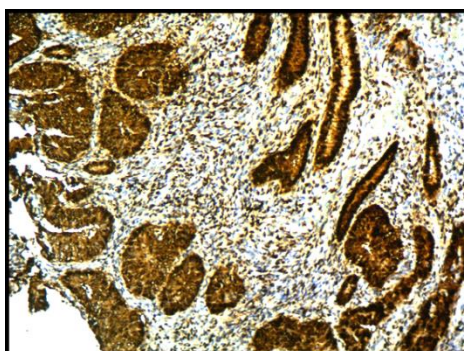


Fig. 5. Adenomyosis focus against the ground of simple non-atypical EHP in a 60-year-old woman. Estimation for glands – 3+++ y 100%; for stroma – 3+++ y 70%. IHC reaction with antibodies to progesterone. x400.

heterotropy have higher PR activity than eutopic endometrium [11].

Analysis of indices of intensity and spread of AR staining showed low score – «0» and «1» mainly (Fig. 7, 8). Comparison of the degree of AR expression did not find considerable differences between the groups of patients examined

($p > 0,05$) (Fig.9) (Table 4), which corresponds to the conclusions of other scientists [7]. However, certain scientists draw attention to the available differences of internal endometriosis foci by the level of receptor expression of steroid hormones, and androgenic in particular, from the surrounding endometrium [5].

Table 3

Mean indices of intensity (I) and spread (Π) of staining of PR-receptors in eutopic and ectopic endometrium (M±m, score)

Component	Eutopic endometrium				Ectopic endometrium			
	Glandular		Stromal		Glandular		Stromal	
Index	I	Π	I	Π	I	Π	I	Π
I (n=10)	2,4±0,27	4,6±0,27	2,8±0,22	4,2±0,42	2,25±0,55	3,75±1,09	2,0±0,47	4,25±0,55
II (n=10)	2,56±0,26	4,56±0,36	2,67±0,35	4,0±0,56	2,2±0,65	3,6±1,1	2,0±0,61	3,4±1,04
III (n=10)	2,67±0,41	4,33±0,82	2,0±0,71	3,33±0,82	2,25±0,33	4,0±0,49	2,63±0,2	4,38±0,2

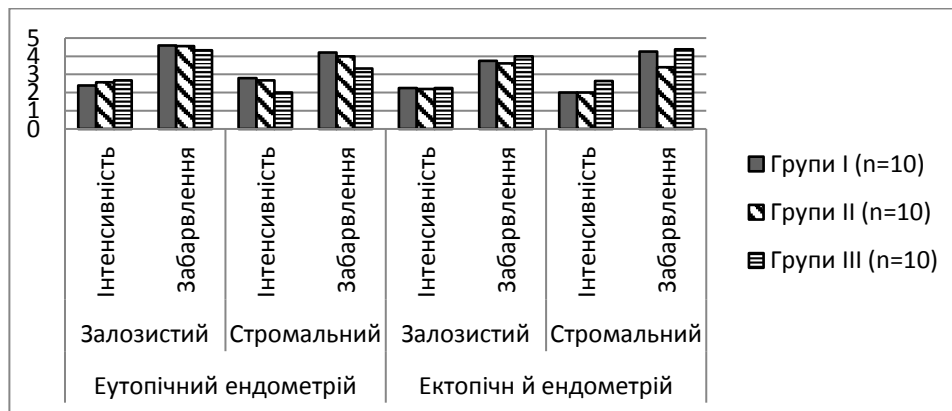


Fig. 6. Mean indices of intensity and staining of PR-receptors in eutopic and ectopic endometrium (M±m, score).

Table 4

Mean indices of intensity (I) and spread (Π) of staining of AR-receptors in eutopic and ectopic endometrium (M±m, score)

Component	Eutopic endometrium				Ectopic endometrium			
	Glandular		Stromal		Glandular		Stromal	
Component	I	Π	I	Π	I	Π	I	Π
I (n=10)	0,29±0,2	0,43±0,32	0,57±0,22	0,71±0,31	0,25±0,17	0,25±0,17	0,85±0,13	0,85±0,13
II (n=10)	1±0	1,33±0,23	1±0	1,17±0,18	0,4±0,27	0,8±0,55	0,8±0,42	0,8±0,42
III (n=10)	0,2±0,22	0,2±0,22	0,4±0,27	0,4±0,27	0,5±0,24	0,83±0,52	0,5±0,24	0,5±0,24

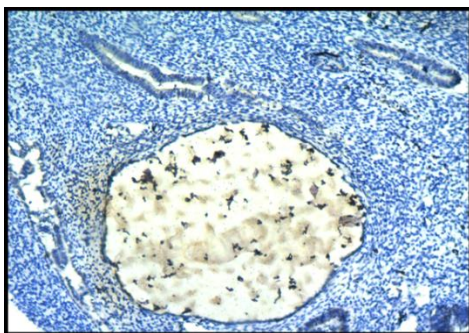


Fig. 7. Age changes (endometrial atrophy) in a 68-year-old woman. Estimation for glands – 1+ in 5%; for stroma – 1+ in 0,5%. IHC reaction with antibodies to androgen. x400.

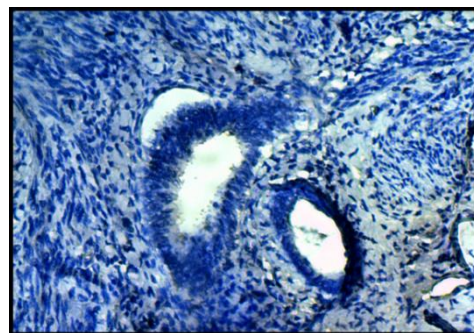


Fig. 8. Adenomyosis focus against the ground of endometrial atrophy in a 68-year-old woman. Estimation for glands – 0 in 100%; for stroma – 0 in 100%. IHC reaction with antibodies to androgen. x400.



Fig. 9. Mean indices of intensity and staining of AR-receptors in eutopic and ectopic endometrium ($M \pm m$, score).

The difference in opinions concerning immunohistochemical peculiarities of one and the same pathological process can be explained by the presence of comorbid pathology of endometrium (hyperplastic processes of endometrium) and age changes of our patients (post-menopause). Prevalent majority of studies associated with adenomyosis refer to women of a reproductive age and pre-menopausal period without available comorbid pathology of endometrium.

Conclusions. The following immunohistochemical peculiarities were found to be characteristic for adenomyosis during post-menopausal period:

1. Prevalent level of ER expression of the glandular component of eutopic endometrium over the endometrium of adenomyosis foci in case of EACU available and endometrial atrophy. A low level of ER expression in the stromal cells in comparison with the glandular ones both in the foci of endometrioid heterotropy and eutopic endometrium in case of EACU.

2. Increase of levels of ER and PR expression in accordance to the increase of cellular differentiation level.

3. Considerable differences by the indices of intensity and staining of PR of the glandular and stromal cells in adenomyosis foci between the groups and between the examined components are not found.

4. Considerable differences by the levels of AR expression in eutopic and ectopic endometrium are not found.

Prospects of further studies: to carry out the analysis of ER, PR and AR expression levels in the ovaries in case adenomyosis available.

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