International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 05, 2020
ISSN: 1475-7192

Endometrial Hyperplasia Possibilities of Diagnostic Clarification

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Abstract--- *The present article is dedicated to the evaluation of histological and immunohistochemical methods in the differential diagnostics of endometrial hyperplasia and its association with chronic endometritis. The study included 350 patients aged 45 – 55 years old. The study entry criteria included abnormal uterine bleeding (85.6%) and/or the presence of sonographic signs of pathological changes in the endometrium (14.4%). Patients underwent endometrial curettage and hysteroscopy with histological examination of endocervical and uterine scrapings. By the results of histological examination, 2 groups were formed: group of comparison (30 patients) included patients that did not have pathological alterations in the endometrium by the results of the morphological examination and the main group (320 patients) included histologically confirmed endometrial hyperplasia. Further, immunohistochemical examination of the obtained endometrial tissue was performed. It was established that it is not always possible to diagnose chronic endometritis with the histological method. This method does not differentiate reactive hyperplasia from benign endometrial hyperplasia. For differential diagnostics of endometrial hyperplasia and its association with chronic endometritis, it is necessary to apply the immunohistochemical method, which will allow for the proper choice of the treatment tactics.*

Keywords--- *Endometrial Hyperplasia, Chronic Endometritis, Combination of Endometrial Hyperplasia and Chronic Endometritis.*

I. INTRODUCTION

Endometrial hyperplasia (EH) is one of the most acute problems in modern gynecology due to its high morbidity rate, lack of response to hormonal therapy, and the possibility of malignant transformation [1]. The chronic inflammatory process that develops in the endometrium in patients with EH can be one of the factors that contribute to the failure of tissue sensitivity to sex steroids. Thus, the study of the pathogenesis of complex EH and chronic endometritis is a new research direction and gives additional grounds to the rationale of the present study.

The diagnostics of endometrial hyperplasia is not complicated. Still, there are some controversial moments. “Gold standard” of the diagnostics of normal and altered endometrium is a histological examination of endometrial samples. There are different types of endometrial pathology and their differentiated diagnostics often causes

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DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

complications. For this reason, one of the most important factors in the correct diagnostics of endometrial hyperplasia is a high qualification of ~~the~~ pathologist [2,3].

Presently, the immunohistochemical method is widely used for the early diagnostics of hyperplastic alterations and precursor of endometrial cancer [4]. The most important immunohistochemical markers for the diagnostics of endometrial hyperplasia include suppressors of tumor growth, markers of proliferative activity and apoptosis as well as the components of extracellular matrix [5,6]. However, the ideal marker that would have a high specificity and sensitivity for the effective differentiated diagnostics of endometrial hyperplasia does not exist, and the accumulation of the knowledge on the application of the proposed diagnostic panels is insufficient.

A new research direction in this field is the study of the pathogenesis of combined endometrial hyperplasia and another significant gynecologic pathology – chronic endometritis [7]. The study of morphological peculiarities of complex endometrial hyperplasia and chronic endometritis, expression of proliferative activity, peculiarities of their vascularization and sclerosing allows the researchers to reveal some new pathogenetic mechanisms in patients with combined uterine pathology [8,9]. This is especially important for the prevention and effective therapy of these pathologic conditions.

II. MATERIALS AND METHODS

The authors conducted a prospective study that included 350 patients that underwent inpatient treatment in the Gynecologic department of the Moscow Municipal Clinical Hospital №5 in 2015-2017.

Women included in the study aged 45 to 55 years old. The average age of the patients was 48.2+2.9 years old. This is explained by the criteria of the patients inclusion to the study and indicates that pathological processes in the endometrium develop primarily during perimenopause.

The indications for the hospitalization were abnormal uterine bleeding (85.6%) and/or sonographic signs of the pathological alterations in the endometrium (14.4%).

The study entry criteria were perimenopause, absence of oncologic diseases, absence of endocrine pathology (diabetes mellitus, hypothyroidism and hyperthyroidism, obesity of II-III degree), absence of inflammatory processes of the pelvic organs, signed an informed consent form for all the required therapeutic and diagnostic procedures.

Patients with endometrial polyps, large myomas and submucosal myomas, and adenomyosis II-III degree were not included in the study.

After the examination that included clinical-laboratory and sonographic methods (transabdominal, transvaginal pelvic ultrasound, doppler color flow mapping), all ~~the~~ patients underwent uterine curritage under the control of hysteroscopy. Hysteroscopy was performed for all the patients for the diagnostics of the causes of uterine bleeding and for the control of uterine curritage. «Karl Storz» (Germany) hysteroscopes were used for the procedure and sterile isotonic saline solution (ml) was used as the cavity expanding medium by the standard method. Depending on the results of the histologic study of the scrubs from the cervical canal and uterine cavity, the patients were divided into two groups after the first examination.

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

The group of comparison included 30 patients that did not have any pathological changes in the endometrium revealed during the morphological study. The main group included 320 patients with the histologically confirmed endometrial hyperplasia. Patients from the main and comparison groups primarily complained of long-term uterine bleeding (more than 7 days) during the period – 50.6% and 51.0%, respectively. Besides, in the main group, 45.9% of patients reported excessive menstrual bleeding and the duration of the period disturbances was more than 1.5 years on average. In the group of comparison, menorrhagia was observed not so often (in 22.9% of cases), and the majority of women (77.3%) had a normal menstrual cycle.

At the final stage, after the complex immunohistochemical study, three main groups of patients were formed: Group I – 130 patients with endometrial hyperplasia, Group II – 70 patients with endometrial hyperplasia combined with chronic endometritis, Group III – 48 patients with chronic endometritis and reactive endometrial hyperplasia.

Morphological studies were performed in Moscow municipal center of pathological studies at the Municipal Clinical Hospital №5 and the Department of pathological anatomy at the Moscow State University of Medicine and Dentistry

(Head of the Department is Zairatiyants O.V.). The materials for the morphological study were endometrial samples obtained during uterine curettage.

The complex morphological study included histological and immunohistochemical methods.

Histological Method. The obtained material was fixed in 10% neutral buffered formalin and waxed in paraffin blocks according to a standard method. The histological sections 4-5 μm obtained with microtome “Leica” (Germany) (not less than 2 sections from each block) were hematoxylin and eosin stained. The sections were studied and photographed with “Leica DM LB” microscope (Germany) and digital camera “Olympus” (Japan). The authors used the morphological classification of endometrial hyperplasia (WHO, 2014) based on two main categories of its changes: endometrial hyperplasia (benign, without atypia, EH) and endometrial (endometrioid) intraepithelial neoplasia/atypical hyperplasia (EIN).

For the immunomorphological study, the immunoperoxidase method with specific monoclonal antibodies to vascular endothelial growth factor (VEGF, clone of G153-694), transforming growth factor –β-1 (TGFβ1), and fibronectin was used.

The expression of lysyl oxidase (LOX) was evaluated with immunohistochemical method that was performed with specific monoclonal antibodies to lysyl oxidase on paraffin sections. The authors used lysates of the obtained tissue material that was probed by a standard procedure. The samples of lysates were stored at –20 to – 80°C for 4 days in sterile conditions. The samples were frozen and thawed only once. After the thawing, the samples were mixed thoroughly. The samples with an elevated level of lipids and with signs of bacterial contamination were not used. The study of the samples was performed in the Shemyakin–Ovchinnikov Institute of bioorganic chemistry RAS (Head of the Institute is Shakhparonov M.I.).

Statistical analysis of the obtained results was performed by the calculation of the mean (M), standard deviation (σ), standard error of the mean (m), standard deviation (S). Further, a comparison of the parametric variants based on Student t-test (t) and calculation of the significant coefficient (p) was performed. For the evaluation of the significance of differences between the mean values, the following formula was used:

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

$$p = \frac{M_1 - M_2}{\sqrt{m_1^2 + m_2^2}}$$

where M – mean value, m – standard error of the mean. The difference was statistically significant at $p < 0.01$ and $p < 0.05$; $t \geq 2$

III. RESULTS

The results of the histological study showed that in some cases, in patients with EH, unevenly spread cystic-expanded glands of different size that are typical for hyperplasia are revealed. The glandular epithelium was proliferative, without signs of atypia. Sclerosis and lympho-macrophagic infiltration of the stroma with the inclusion of plasmocytes and leucocytes were observed.

In other observations, the histological picture was different. Unlike in other cases of EH, small monomorphic glands prevailed and only single glands were cystic-expanded. Diffuse lympho-macrophagic infiltration of the stroma with focal lymphoid follicles with light centers was observed. The expressed sclerosis of the stroma with the formation of periglandular lesions and the sclerosis of vascular walls not typical for other known forms of endometrial hyperplasia were revealed.

The next stage of the study was performed with the immunohistochemical method. The observation in Group I revealed single dispersed plasmocytes in the stroma that produced primarily IgM. In Group II, minor foci of plasmocytes were observed that expressed both IgM and IgG.

In Group III, the plasmocytes level was significantly elevated and diffuse plasmocytic infiltration of the endometrial stroma was observed, wherein plasmocytes that expressed IgG prevailed. Such infiltrates were typical only in this group of observation.

Immunomorphological study of the growth factors (VEGF and TGFβ1) revealed different levels of their accumulation in patients with different variants of hyperplastic processes. The expression of VEGF was significantly lower in glandular epithelium and stroma ($p<0.05$) in patients with EH in comparison with an unaltered epithelium at the phase of proliferation.

In Group II, the expression of VEGF in the epithelium did not differ statistically from other types of hyperplasia but, in the stroma, the expression of VEGF was significantly and statistically higher (1.5+0.06). Probably, the overexpression of VEGF in the stroma is the result of the inflammatory process and enhances the angiogenesis (Table 2).

Table 1: Degree of Plasmocytes Infiltration (scored 0-3) in the Endometrial stroma in the Test Subgroups

Parameter	Endometrium, proliferation phase, n = 15	EH n = 15	Combination of EH and chronic endometritis n = 19	Combination of the signs of chronic endometritis and reactive endometrial hyperplasia n =18
Plasmocytes with IgM	0	0	1	3
Plasmocytes with IgG	0	0	2	3

Note: plasmocyte count is expressed in cells (0 – single cells, 1 – small focal infiltrates, 3 – expressed diffusive infiltration). Score (0-3).

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

Table 2: Expression of VEGF in the test Subgroups

Parameter	Endometrium, phase of proliferation = 30	EH n = 80	Combination of EH and chronic endometritis n =40	Combination of the signs of chronic endometritis and reactive endometrial hyperplasia n =40
Glandular epithelium	2.2±0.09	1.8±0.03 *	1.9±0.07	2.1±0.10 **
Stromal cells	0.8±0.07	0.6±0.04	1.5±0.06*	1.8±0.12 *, **

Note: *- significance of difference ($p<0.05$) in comparison with the control group, ** - in comparison with EH subgroup

In patients with chronic endometritis complicated with reactive endometrial hyperplasia (Group III), the expression of VEGF in the stroma was significantly higher than in the control observations (1.8+0.12 and 0.8+0.07, respectively) and in patients with EH (0.6+0.4 and 0.6+0.9).

The expression of $TGF_{\beta 1}$ was significantly higher in the glandular epithelium in patients with EH (0.9+0.05) ($p<0.05$) in comparison with unaltered endometrium at the stage of proliferation (0.3+0.2). In the stroma, the expression of $TGF_{\beta 1}$ was two times higher in patients with EH (0.5+0.03). Different observations in patients with all types of hyperplasia and different samples of the endometrium revealed that its expression significantly varied. In the subgroup of patients with EH complicated with chronic endometritis, the expression of $TGF_{\beta 1}$ in the epithelium (1.3+0.06) and stroma (1.4+0.04) was significantly higher than in patients with EH that was not complicated with chronic inflammation (Table 3).

Table 3: Expression of $TGF_{\beta 1}$ in the Test Subgroups

Parameter	Endometrium, phase of proliferation = 30	EH n = 60	Combination of EH and chronic endometritis n = 40	Combination of the signs of chronic endometritis and reactive endometrial hyperplasia n = 40
Glandular epithelium	0.3±0.02	0.9±0.05 *	1.3±0.06 *,**	0.3±0.06 **
Stromal cells	0.2±0.01	0.5±0.03 *	1.4±0.04 *,**	1.6±0.03 *, **

Note: *- significance of difference ($p<0.05$) in comparison with the control group, ** - in comparison with EH subgroup

In patients with chronic endometritis complicated with reactive endometrial hyperplasia, the expression of $TGF_{\beta 1}$ in glandular epithelium was similar to the group of comparison but significantly lower (0.3+0.06) than in the observations of different types of hyperplasia. This confirms the secondary character of hyperplastic alterations in this subgroup. In the stroma, it was significantly and statistically higher (1.6+0.03) than in the control. In patients with EH, it was close to the observations with simple hyperplasia and complicated development of chronic

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

endometritis. A high level of expression of $TGF_{\beta 1}$ in patients with chronic inflammatory processes in the endometrium was associated with the progression of sclerosis in the endometrial stroma.

The expression of fibronectin was minimal and evenly expressed in patients with unaltered endometrium at the phase of proliferation and in patients with EH. However, in patients with EH complicated with chronic endometritis or patients with chronic endometritis and reactive endometrial hyperplasia, the expression of fibronectin sharply increased, especially, in the foci of sclerosis (Figure 1, 2).

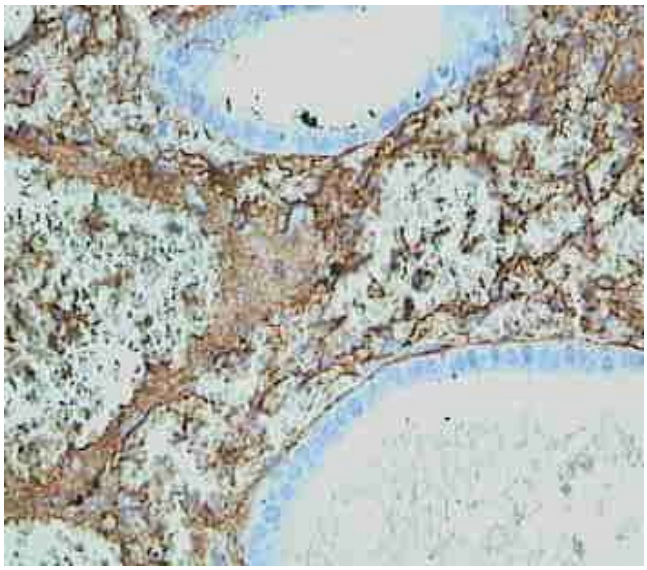

Figure 1: Expression of fibronectin I Patients with EH in Combination with Chronic Endometritis

Expressed and inconsistent expression of fibronectin in the stroma. Indirect immunoperoxidase method with antibodies to fibronectin, x400

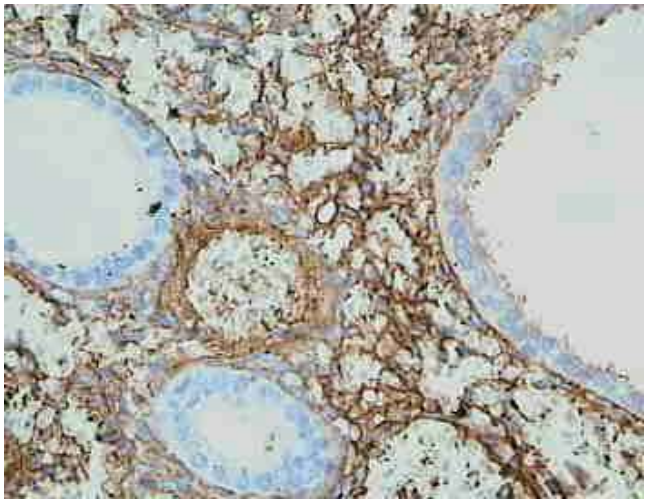

Figure 2: Chronic Endometritis with Reactive Endometrial Hyperplasia

Expressed and inconsistent expression of fibronectin in the stroma. Indirect immunoperoxidase method with antibodies to fibronectin, x400

DOI: 10.37200/IJPR/V24I5/PR2020189
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The study of LOX revealed that there was no significant difference in the number of cells that contained LOX between an unaltered endometrium at the stage of proliferation and EH. The number of these cells was 18 to 49 in the field of vision of the microscope in the area of 0.0384 mm^2. The authors did not reveal a significant difference between the endometrium at the stage of proliferation (37+3) and EH (37+4) and the production and accumulation of LOX ($p>0.05$).

In patients with EH combined with chronic endometritis, the cytoplasmatic expression of LOX was higher than in patients with EH. It should be noted that there was a tendency towards the enhancement of the expression of LOX in patients with combined EH and chronic endometritis (46+4) in comparison with EH ($p>0,05$). LOX containing cells were found not only in the stromal component but also in the glandular one (Table 4).

Table 4: Expression of LOX in Patients with Different Types of Endometrial Hyperplasia

(Number of Cells with Positive Reaction in the Field of Vision of the Microscope in the Area of 0.0384 mm^2)

	Range of values	**M+σ**
Phase of proliferation	37-44	37+3
EH	18-49	37+4
Combination of the signs of EH and chronic endometritis	45-64	48+4
Chronic endometritis and reactive endometrial hyperplasia	40-59	42+4

IV. DISCUSSION

The histological study performed by two independent pathologists revealed some difficulties in the morphological differential diagnostics of combined signs of EH and chronic endometritis [10,11].

Expressed reactive inflammatory infiltration in response to endometrial hyperplasia foci of ischemic necrosis can lead to the development of focal or diffuse alterations that are similar to those observed during acute endometritis [12]. In some observations, the severity of inflammatory process significantly prevailed over the alterations associated with endometrial hyperplasia and the samples preserved differential diagnostic signs of these pathological processes.

Progressive reactive inflammation in some observations can become a prevailing pathological process. In patients with persistent inflammation or its relapse, sclerotic alterations of the stroma get enhanced and in combination with lympho-macrophagic infiltration lead to the development of the clinical picture similar to chronic endometritis [13].

Difficulties in the morphological differential diagnostics are caused by the combination of signs of EH and chronic endometritis. In patients with EH, the expression of chronic inflammatory alterations can lead to a diagnostic mistake. Such signs of chronic endometritis as lympho-macrophagic infiltration with the inclusion of plasmocytes and leukocytes, sclerosis of stromal component, and formation of lymphoid follicles do not provide precise differentiation of what pathologic process is primary – hyperplasia or endometritis [14,15].

In some cases, there were observations that were morphologically similar to both EH and chronic endometritis. Their histological signs were the same as for EH but with the prevalence of monomorphic by the size and shape

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

glands in combination with the generally accepted criteria for the morphological diagnostics for chronic endometritis: lympho-macrophagic infiltration with a high level of plasmocytes, formation of lymphoid follicles with light centers, expressed periglandular sclerosis, and vascular walls sclerosis.

In the unaltered endometrium at the stage of proliferation and in cases with EH, the number of plasmocytes that produce IgM and IgG was insignificant (Table 1). Acute reactive inflammation in cases with EH was associated with focal aggregation of plasmocytes that express both IgM and IgG. Such inflammatory alterations should be treated as secondary (reactive) acute endometritis in patients with EH (taking into account the results of the morphological study).

Thus, the observations that combined histological signs of EH and chronic endometritis should be divided into two subgroups. In Subgroup I, there were small, primarily focal aggregates of plasmocytes that expressed IgM and IgG, and the increase in their total number was observed. Taking into account the results of the histological study (absence of significant differences from other cases of EH, excluding the signs of moderately expressed chronic inflammation), it can be concluded that, in such patients, EH was complicated with the development of reactive inflammation that acquired the signs of chronic endometritis with time. Thus, EH complicated with chronic endometritis was diagnosed.

In Subgroup II, there was an increase in the number of plasmocytes. An expressed diffusive plasmocytic infiltration of the endometrial stroma was observed and plasmocytes that expressed IgG prevailed in the infiltrate. In these observations, the histological study revealed expressed periglandular sclerosis of the stroma and monomorphic type of single cystic-expanded glands. Plasmocytes producing IgG indicate secondary immune response typical for chronic inflammation. Plasmocytic infiltration is the main diagnostic morphological sign of chronic endometritis. All these observations indicate chronic endometritis and the alterations in the glands similar to EH are reactive epithelial alterations. Epithelial hyperplastic reactive alterations were well-studied in patients with chronic inflammation of different localization. Thus, Subgroup II patients were diagnosed with chronic endometritis with reactive endometrial hyperplasia.

Further immunomorphological studies of molecular-biological profile in these two subgroups confirmed the correctness of the observations division and allowed the authors to propose their pathogenesis and prognosis.

The observed high expression of VEGF and $TGF_{\beta 1}$ in the observation groups II and III could be caused by the inflammatory process. It contributes to the further activation of the processes of angiogenesis and sclerosing in the endometrium and cannot exclude secondary character of hyperplastic alterations in the studied groups.

For the first time, the authors revealed the expression of the matrix extracellular component - lysyl oxidase (LOX). The observed tendency towards the increase in the expression of LOX in patients with EH combined with chronic endometritis indicate the progression of the processes of hypoxia and ischemia in the presence of chronic inflammation and, thus, it can become an unfavorable factor for the development of endometrial intraepithelial neoplasia. The obtained data confirmed the involvement of LOX in the cellular-matrix interaction [16,17]. High expression of fibronectin, especially in the foci of sclerosis, also indicates the factors of the development and

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

progressing of pathological processes in the endometrium in patients with EH in combination with chronic endometritis.

Thus, for the differential diagnostics in cases complicated for the histological verification of the diagnosis, not only clinical-laboratory data but also the results of a complex immunomorphological study should be used.

The histological study does not always provide precise diagnostics of chronic endometritis. In cases when there is an incomplete clinical picture of the inflammatory process in the uterine mucosa, the immunohistochemical study should be performed for the evaluation of not only the levels of plasmocytes but also other markers like VEGF, $TGF_{\beta 1,}$ LOX, fibronectin [18].

Besides, reactive endometrial hyperplasia is similar histologically to EH, so it is impossible to perform differentiated diagnostics of these pathological conditions basing only on the morphological study. Reactive endometrial hyperplasia can be confused with EH and patients receive hormonal therapy which turns to be ineffective. These difficulties in the morphological differential diagnostics indicate the feasibility of obligatory performance of immunohistological study for the identification of endometrial pathology.

The issue of mutual influence of hyperplasia and inflammation, in particular, on the prognosis of the development of neoplastic alterations, also attracts the authors' interest. It cannot be excluded that these two pathological processes have inter stimulating influence.

Thus, the chronic inflammatory process enhances intercellular and stromal- parenchymatous disorders that are present in endometrial hyperplastic processes or promote their development. This leads to the activation of the processes of sclerosing, neoangiogenesis, and hypoxia that enhance the proliferative activity of glandular epithelium and, especially, the stroma of hyperplastic endometrium and, thus, creates optimum conditions for the development and progressing of tumor processes. The complex immunohistochemical study provided grounds for the feasibility of its application in the diagnostics of different pathological processes in the endometrium, which allows for the timely and correct choice of the therapy for patients with endometrial hyperplastic processes.

Clinical significance of our study is in the optimization of therapeutic tactics for patients with endometrial hyperplastic processes and prevention of the recurrence of this disease [19,20]. Timely diagnostics of chronic endometritis that accompanies hyperplastic process allows the specialists to choose correct tactics of the treatment and apply differential approach to the therapy.

V. CONCLUSION

1. The performed histological study revealed that the group of observation with a combination of the signs of EH and chronic endometritis is inconsistent and includes cases with EH complicated with chronic endometritis and observations of chronic endometritis with reactive endometrial hyperplasia. Often, differential diagnostics between these conditions is impossible without immunohistochemical study.
2. In cases with different variants of endometrial hyperplastic processes, there was a different expression and accumulation of VEGF, $TGF_{\beta 1,}$ LOX, and fibronectin. In patients with accompanying inflammatory process in the endometrial tissue, the authors revealed significant disturbances not only in the angioarchitectonics of

DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

the endometrial tissue but also intensive processes of sclerosing that are associated with the accumulation of the products of extracellular matrix and promote hypoxia in the endometrium.

3. In cases when EH is combined with chronic endometritis or in cases when chronic endometritis is combined with reactive hyperplasia resulted from the long-term impact of a pathological factor (inflammation) in the endometrium, expressed cellular and cellular-matrix disbalance was observed. In these conditions, even in cases with low proliferative activity, optimum conditions for EH recurrence and further tumor transformation are created.

This confirms the presence of disturbances in the structure of the extracellular matrix and promotes the development and progressing of pathological processes in the endometrium. Timely diagnostics of chronic endometritis that accompanies endometrial hyperplastic process has a high clinical and practical value because it allows the specialists to choose correct tactics of the treatment and apply a differential approach to the therapy.

VI. AUTHOR'S CONTRIBUTION

Each other made a significant contribution to the manuscript preparation:

Sergey A. Levakov – study concept preparation; Nataliya A. Sheshukhova – immunohistological study of the samples; discussion of the obtained results and manuscript writing; Elizaveta A. Obukhova – selection of patients and histological study of the endometrial tissue.

ACKNOWLEDGEMENTS

Morphological study was performed in Moscow Clinical Hospital №5 and the Department of pathologic anatomy at the Moscow State University of Medicine and Stomatology. The evaluation of the expression of lysyl oxidase (LOX) was performed in the Institute of bioorganic chemistry of RAS.

Conflict of Interests. The authors declare no conflict of interests.

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DOI: 10.37200/IJPR/V24I5/PR2020189
Received: 12 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020