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Possibility of Neoplastic Transformation of Ovarian Endometriosis

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Abstract--- The aim of the study: *was to investigate the features of neoplastic endothelial transformation in the foci of ovarian endometriosis (OE).*

Materials and Methods: *Histologic and immunohistochemical methods were used for the study of 78 and 35 cases of OE, respectively, and 8 cases of adenocarcinomas. The authors used antibodies to Ki-67, Bcl-2, p53 and nuclear hepatocytes factor 1 beta (HNF-1β).*

Results: *Epithelial walls of endometrial cysts had syncytial papillary changes (39.7%), metaplasia with hobnail-like cells (15.4%), atypia of epithelium with fluctuation of the expression of Ki-67 and Bcl-2 from low to relatively high (41.0%), and with the expression of p53 that tended to increase. The expression of HNF-1β in lesions without atypia was revealed in 56.3% of cases, and in lesions with atypia – in 94.7%, and was identified only in clear cell adenocarcinomas.*

Conclusion: *hyperexpression of HNF-1β suggested adaptive character and histogenetic association of OE with clear cell ovarian tumors.*

Keywords--- *Ovarian Endometriosis, Epithelial Atypia of Ovarian Endometriosis, Nuclear Hepatocytes Factor 1 Beta (HNF-1β), Clear Cell Ovarian Adenocarcinoma.*

I. INTRODUCTION

Endometriosis is one of the relevant diseases in modern gynecology. It is a multifactor condition that is associated with hyperplasia of tissue, that is similar by morphological and functional properties to the endometrium, beyond the uterus. This condition has some characteristics of a malignant process: the presence of local and remote lesions, the ability of cells to migration, invasions with further damage of target organs [1,2].

Presently, the histogenesis of ovarian endometriosis (OE) and endometriosis-associated tumors provokes disputes. The risk of the development of malignant ovarian neoplasms in patients with OE is increased by 2.5 times [3]. In 12.1% of cases, OE contained foci of epithelial metaplasia with lesions of endometriosis, in 9.4% - hyperplasia, in 5.9% - atypia, and in 4.1% - ovarian cancer was diagnosed [4]. According to the data of other authors, the rate of occurrence of foci of epithelial atypia in OE lesions reached 35-80% [5].

Ovarian cancer is a heterogenic group of tumors in terms of morphological and molecular-biological properties. Serous tumors are characterized by the mutation of p53, mucinous tumors – by the mutation of K-ras, and

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endometrial – β-catenin and PTEN. The specific immunohistochemical (IHC) marker of clear cell ovarian tumors, that is primarily associated with OE, is a nuclear hepatocytes factor 1 beta (HNF-1beta or HNF-1β). Other ovarian and endometrial tumors do not express HNF-1β [6,7,8]. HNF-1β – is a protein that belongs to a superfamily of transcription factors that binds with DNA as a homo- or heterodimer that is normally involved in the embryogenesis of pancreas and nephron. Mutations in the gene encoding this transcription factor were revealed in patients with kidney cystic disease, some types of diabetes mellitus, and some tumors (ovarian, endometrial, prostate, and renal). HNF-1β plays an important role in the protective mechanisms of cells from oxidative stress and inhibits apoptosis interacting with the inhibitor of apoptosis Bcl-2 [6,7,8]. It was shown that hyperexpression of HNF-1β in clear cell tumors creates the basis for their resistance to chemotherapy. The role of HNF-1B in the mechanism of neoplastic epithelial transformation in OE lesions was also discussed. Its expression was revealed in the epithelium of 40% of endometrial ovarian cysts and was often observed in patients with epithelial atypia of endometrioid lesions [6,7,8,9,10,11].

The aim of the present study was to investigate morphological and molecular-biological features that indicate the possibility of neoplastic epithelial transformation in the OE lesions for the reduction of the recurrence of OE and preservation of the fertility in women of reproductive age.

II. MATERIALS AND METHODS

The authors used archive materials of Eramishantseva state clinical hospital and Bachrushinykh state clinical hospital for 2014-2016 to analyze medical histories of 147 patients of reproductive age that were diagnosed with ovarian endometriosis or recurrent ovarian endometriosis. Patients were aged 18-45 with the prevailing range of 27-35 years old. The average age of patients was 32.1 years old.

Medical histories were used for the evaluation of the patients' complains that were divided into 3 groups (pelvic pain, infertility, menstrual disorder). The authors studied gynecologic and somatic anamnesis of patients with earlier diagnosed OE and performed surgical treatment, processed the results of laboratory assays (including the levels of oncomarkers and AMH), defined the main consistencies in the description of ultrasound examinations of pelvic organs that were done before the surgical treatment in the specified hospitals.

After the resection of ovaries for OE in the studied group of patients, 147 histological specimens were obtained that provided 78 fragments of ovarian tissue for further detailed examination. Besides, the study included 8 ovarian adenocarcinomas (2 cases of clear cell, 2 cases of highly differentiated serous, 2 cases of endometrial and 2 cases of mucinous adenocarcinomas). Patients with adenocarcinomas did not have OE revealed in the anamnesis and in the obtained operational specimens.

Histological studies and the studies of the obtained specimens were performed with a standard method of fixation in 10% neutral solution of formalin, waxing, and preparation of 3 μm thick paraffin sections by a rotor microtome HM355S ("Thermo Scientific", Germany) that were placed on glass slides with further hematoxylin and eosin staining. The study of the specimens confirmed and specified pathohistological diagnosis, revealed the endometrioid lesions in the ovarian tissue along with endometrial cyst, and sampled the blocks for immunohistochemical (IHC) study. The diagnosis OE was confirmed based on generally accepted morphological

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criteria: presence of epithelial lining in the cyst and/or adenous structures that consist of endometrial type cells (taking into account reactive, regenerative, dystrophic, metaplastic alterations and atypia), presence of endometrial stroma and macrophages with hemosiderin in the infiltrate and/or cyst lumen [12,13,14].

The immunohistochemical method was used for the study of 35 cases with OE (with 4 mono- and polyclonal antibodies) and 8 cases with ovarian adenocarcinomas (only with polyclonal antibodies to HNF-1β). Primary antibodies used were antibodies to the marker of proliferating cells, nuclear protein Ki-67 (monoclonal antibody, clone MIB-1, DAKO, Norway, 1:150 dilution), to the inhibitor of apoptosis Bcl-2 (monoclonal antibody, clone of 124, Cell Marque, USA, 1:250 dilution), to oncoprotein p53 (monoclonal antibody, clone of DO7, Cell Marque, USA, in a ready-to-use dilution), to the protein of superfamily of transcription factors, nuclear hepatocytes factor 1 beta (HNF-1B, polyclonal antibody, GeneTex, USA, 1:200 dilution).

The reactions were performed simultaneously for all the material to obtain the comparable data according to the method of Shi et al and the protocols to mono- and polyclonal antibodies provided by the manufacturers [15,16]. For the visualization of the reactions, the authors used a test system with universal secondary antibodies labeled with chromogen (3,3'-diaminobenzidine) Histophine ("Nichirei Corp.", Japan). For the evaluation of IHC reaction, the method of Histochemical score (H-score) [17] was used taking into account the quantity and intensity of cellular nuclei (Ki-67, p53, HNF-1B) and cytoplasm (Bcl-2) staining: up to 80 - low, 80-140 – moderate, 141-300 – significant expression. The calculation was performed for 100 epithelial cells in 3 random fields of vision at the magnification of x400. Statistical data were processed with MS Office Excel and Statistica for Windows 10.0. The data were presented as mean ± standard deviation (M ± σ). Mann-Whitney non-parametric analysis was used. The critical level was significant at 0.05.

Further, patients with OE underwent inpatient observation for the control of the effectiveness of the surgical treatment or correction of the therapy after the histological study for the reduction of the risk of a possible recurrence of endometriosis in order to preserve the fertility of patients of the reproductive age. The authors evaluated the levels of oncomarkers (CA-125, CA-19-9, CA-72-4, CA-15-3) and AMH along with ultrasound imaging of pelvic organs in 6 months and in 1 year after the surgical treatment. Besides, patients received agonists of gonadotropin-releasing hormone (a-GnRH) for 3 months. If patients did not wish to realize their reproductive function, they received progestins for 6 months.

III. RESULTS

In 73.5% of cases, the studied patients complained about infertility (43.54% of cases), pelvic pains (36.73% of cases), and menstrual disorder (14.97% of cases).

In 10.20% of cases, patients had earlier surgical treatment for OE in the anamnesis. In 1.4% of patients, there was a repeated surgery treatment for recurrent OE. Time from primary surgical treatment for OE to the recurrence that was resolved after the treatment at Eramishantseva and Bakhrushinykh hospitals was 0.25 years (3 months) in 1 patient, 1 year in 3 patients, 2 years in 3 patients, 3 years in 1 patient, 4 years in 4 patients, 5 years in 1 patient, 6 years in 1 patient, and 8 years in 1 patient. In 1.4% cases, the time from primary recurrence with surgical treatment to the next recurrence with surgical treatment before the application to Eramishantseva and Bakhrushinykh hospitals

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was 4 months and 72 months, respectively. Further, only in 17.65% of cases, hormonal pharmacotherapy was indicated.

Aggravated gynecological and somatic anamnesis in the studied patients was observed in 48.3% and 51.7% of cases, respectively. The most widespread diseases were uterine cervix ectopia (44.44%), chronic salpingo-oophoritis (26.39%), uterine myoma (22.22%), adenomyosis (22.22%), as well as gastrointestinal tract (71.05%), cardiovascular (21.05%), and respiratory (11.84%) diseases.

Before the acceptance to Bakhrushinykh and Eramishantseva hospitals for surgical treatment, all the studied patients underwent a complete laboratory and instrumental examination at local maternity welfare centers. The evaluation of the level of oncomarkers, such as CA-19-9, CA-125, CA-72-4, HE4, CEA, performed before the acceptance to the mentioned hospitals is presented in Table 1.

Table 1: Characteristics of Diagnostic on co-markers in Patients Prior to Surgery

Oncomarker (OM)	**Normal range (U/ml)**	**№ of patients assessed**	**Variation (U/ml)**	**№ of patients with increased OM levels (%)**	**Mean levels for increased values**
CA-125	0-35	74 (50.34%)	2-273	36 (48.65%)	77.90±8.35
CA-19-9	0-37	51 (34.69%)	0.6-136	6 (11.76%)	80.53±12.37
CA 72-4	0-8.2	7 (4.76%)	1.69-35.9	4 (57.14%)	19.72±6.47
CA 15-3	0-31.4	16 (10.88%)	1-19.99	-	-
HE-4	0-140	7 (4.76%)	15.6-68.45	-	-
CEA	0-4.9	18 (12.24)	0.3-1.87	-	-

The level of AMH was checked in 2.04% of cases and all the values prior to surgery remained within the reference range.

Ultrasound examination of pelvic organs prior to surgery for OE showed primarily a one-chamber unilateral neoplasm 3 to 6 cm (85.03% of cases) with anechoic structure (59.18% of cases) with fine content (59.18% of cases). In all the cases, the capsule walls were distinct and even, and only in 6.80% of cases, the walls induration was observed. The description of the neoplasm's blood supply was described only in 6.80% of cases, and in all the described protocols, the neoplasm was avascular. Adhesive process in pelvic organs was described only in 6.80% of cases. The presence of retrocervical endometriosis was mentioned only in 1.36% of cases. Thus, according to the classification of endometrial ovarian cysts (Adamyan, 1992, 1998), the majority of the abovementioned descriptions corresponded to II-III stages of the disease [18].

In 82.99% of cases, unilateral laparoscopic ovarian resection was performed within the affected tissues. In 12.24% of cases, bilateral resection was performed. In 68.71% of cases, the coagulation of endometrioid lesions of different localization was performed. In 1.36% of cases, the resection of retrocervical endometriosis was performed. And in 60.54% of cases, adhesiolysis was performed.

Further observation of patients with OE and control of the levels of AMH and oncomarkers (CA-125, CA-19-9, CA-72-4, CA-15-3) revealed that all the parameters were within the reference values. Ultrasound examination of pelvic organs showed that there was an insignificant decrease in the volume of the ovary resected earlier. However,

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the follicle apparatus was well visualized. In 6.80% of cases, the development of an adhesive process of I-II stage was registered in the area of the operated adnexa.

It should be noted that during the general observation of the patients and the indicated treatment, there were no cases of OE recurrence registered, which indicated the adequate volume of the performed treatment and properly chosen individual pharmacotherapy for endometriosis. In 22.72% of cases, within a year of the observation, patients with earlier diagnosed infertility had a spontaneous progressing pregnancy registered during an ultrasound examination.

The results of the histochemical study showed that out of 78 histologically studied samples of tissues with OE, 43 samples (55.1%) contained from 1 to 4 endometrioid lesions in the area of the resected fragment of the ovary with endometrial cyst (represented by epithelial and stromal components) in the cyst wall and in the remote areas.

78 studied samples of epithelial walls of endometrial cysts and/or other endometrioid lesions contained microfoci or larger areas with syncytial papillary regenerative (hyperplastic) alterations (31 samples, 39.7%), metaplasia with hobnail-like cells (12 samples, 15.4%), focal hyperplasia (papillary, adenous-solid, with foci of squamous metaplasia and atypia of epithelium) (3 samples, 3.9%).

In 32 samples (41.0%), atypia of epithelium was revealed, wherein 27 samples (34.6%) were characterized by "regenerative/dystrophic" atypia [12,13,14] that developed due to an expressed dystrophy of epitheliocytes combined with inter-epithelial leukocytes and inflammatory infiltration of the adjoining stroma of the endometriosis focus. In 5 samples (6.4%), these alterations were not revealed and true "neoplastic" atypia was diagnosed. In 2 samples (1.3%), a wall of endometrial cyst contained a small focus of mucinous borderline tumor.

The histochemical study included 35 cases of OE and 8 ovarian adenocarcinomas. The results of the tests are presented in Table 2.

Table 2: Results of Immunohistochemical Analysis of Endometrioid Lesions and Ovarian Adenocarcinomas (M±σ)

Parameter	**Endometriosis (lesions without atypia) n=35[1]**	**Endometriosis (lesions with atypia) n=32[1]**	**Clear cell adenocarcinoma n=2[1]**	**Serous adenocarcinoma (high grade) n=2[1]**	**Endometrioid adenocarcinoma n=2[1]**	**Mucinous adenocarcinoma n=2[1]**
Ki-67	27±14	79±11[3]	-[2]	-	-	-
p53	12±10	16±12	-[2]	-	-	-
Bcl-2	43±11	121±27[3]	-[2]	-	-	-
HNF-1B	62±17	188±13[3]	195±29[3]	Very few	Very few	Very few

Note: [1]n=35 – the number of cases where only foci without atypia were identified in endometrioid lesions (only in 3 cases out of 35, no endometrioid lesions with foci of epithelium with atypia were found); n=32 – the number of cases where 1 or more foci with atypia, along with foci without atypia, were found in endometrioid lesions; [2]not assessed; [3]$p<0.05$ compared to endometrioid lesions without atypia.

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Thus, great variability of the expression in the epithelium of OE lesions was observed in the proliferative activity of Ki-67. Its level varied from low to relatively high, primarily in the foci with regenerative/dystrophic and true atypia of epithelium, where the expression of other studied antigens was also more significant. The expression of the oncomarker p53 was low but it tended to increase in the foci with regenerative/dystrophic and true atypia of epithelium (statistically insignificant, though). The level of the expression of the inhibitor of apoptosis Bcl-2 was different but it was primarily elevated in the foci with regenerative/dystrophic and true atypia of epithelium.

It should be noted that unlike the foci with atypia, the foci with syncytial papillary regenerative (hyperplastic) alterations with metaplasia with hobnail-like cells and focal hyperplasia (papillary, adenous-solid, with foci of squamous metaplasia) did not differ by the expression of Ki-67, p53, and Bcl-2 from the unaltered epithelium of the endometrioid type.

The expression of a specific factor of transcription of clear cell ovarian and endometrial tumors HNF-1β was revealed in the nuclei of epithelial cells in the majority of endometrioid lesions (77.1%) of all the studied cases. It was observed in the nuclei of a part of epitheliocytes of endometrioid cysts as well as in the epithelium of other endometrioid lesions (revealed in the cyst walls and in remote ovarian tissue) regardless of the presence of metaplastic or hyperplastic alterations in the epithelium. In 35 cases, the count of endometrioid lesions different by the morphology showed that in 16 cases, there were no foci of atypia, and in 9 of them (56.3%), the expression of HNF-1β was observed. The nuclei of epithelial cells in endometrioid lesions with foci of atypia (regenerative/dystrophic or true), revealed in 32 cases out of 19, expressed HNF-1β in 94.7% of cases of such lesions (18 cases). There was no expression of HNF-1β in a mucinous borderline tumor revealed in the endometrioid cyst wall in 1 case. There were no differences (histologic, molecular-biologic) in endometrioid lesions in patients with recurrent OE.

The expression of HNF-1β, evaluated in different adenocarcinomas, was revealed only in clear cell adenocarcinomas. These tumors were characterized by a significant expression of this marker by the nuclei of the majority of tumor cells. In other adenocarcinomas, only nuclei of single tumor cells had a low or moderate expression of HNF-1β.

IV. DISCUSSION

The results of the present study confirmed a high rate of the development of histological and molecular-biologic alterations in endometrioid lesions that indicated an elevated risk of neoplastic transformation. Endometrioid lesions with histological signs of atypia of epithelium (regenerative/dystrophic atypia in 34.6% of cases and true atypia in 6.4%) had an increased expression of the marker of proliferation of Ki-67, inhibitor of apoptosis Bcl-2, and specific factor of transcription of clear cell ovarian tumors HNF-1β, and there was a tendency to hyperexpression of oncomarker p53. There were no differences revealed in the elevated expression of all the studied antigens in the foci of regenerative/dystrophic and true atypia. Probably, this is associated with high subjectivity in its histological differentiation. There were no generally accepted morphological criteria of their difference. The lack or presence of inflammatory infiltrate (inter-epithelial leukocytes, lymphocytes) and dystrophic alterations cannot be an objective marker [12,13,14]. There were no peculiarities revealed in endometrioid lesions in patients with recurrent OE either.

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There were differences revealed in the expression of Ki-67 and Bcl-2 in the foci with atypia of epithelium and without it, which explains the reason why the hyperexpression was revealed in some studies and was not revealed in other studies. Besides, the levels of these markers in the endometrium and endometrioid lesions changed depending on the phase of the menstrual cycle [19].

The study showed that the epithelium of endometrioid lesions, regardless of the features of its atypia, was characterized by the hyperexpression of the specific factor of transcription of clear cell ovarian and endometrial tumors HNF-1β, which was observed in 56.3% of lesions without the foci of atypia and in 94.7% of the foci with atypia. This proves the hypothesis that the hyperexpression of HNF-1β in the epithelium of endometrioid lesions is widely widespread and has an adaptive character [6,7,8]. Histogenetic association between OE and clear cell ovarian tumors, that have an expression of HNF-1β as a diagnostic marker, was also confirmed.

V. CONCLUSION

Further molecular-biological and genetic studies on ovarian endometriosis should be conducted. They will contribute to the understanding of its association with ovarian tumors and the establishment of the origin of endometriosis. The obtained data will allow the doctors to identify risk groups of women of the reproductive age by the possible development of neoplastic process and to perform thorough monitoring of this cohort of patients with the further required volume of surgical treatment.

REFERENCES

[1] Jiang Q.Y., Wu R.J. Growth mechanisms of endometriotic cells in implanted places: A review. *Gynecol Endocrinol* 2012; 28:562–67. doi: 10.3109/09513590.2011.650662. Epub 2012 Feb 2.

[2] Levakov S.A., Gromova T.A., Kedrova A.G., Sheshukova N.A.. Endometriosis-associated ovarian cancer. 2016, №4, v. 12, 47-51.

[3] Pearce C.L., Templeman C., Rossing M.A., Lee A., Near A.M., Webb P.M., et al.. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *LANCET* 0ncol 2012:13-385. doi: 10.1016/S1470-2045(11)70404-1. Epub 2012 Feb 22.

[4] Krawczyk N., Banys-Paluchowski M., Schmidt D., Ulrich U., Fehm T.. Endometriosis-associated Malignancy. *Geburtshilfe Frauenheilkd.* 2016 Feb; 76(2): 176–181.doi: 10.1055/s-0035-1558239.

[5] Yu H.C., Lin C.Y., Chang W.C., Shen B.J., Chang W.P., Chuang C.M. et al.. Increased association between endometriosis and endometrial cancer: a nationwide population-based retrospective cohort study. *Int J Gynecol Cancer.* 2015 Mar;25(3):447-52. doi: 10.1097/IGC.0000000000000384.

[6] Amano Y., Mandai M., Yamaguchi K., Matsumura N., Kharma B., Baba T. et al.. Metabolic alterations caused by HNF1β expression in ovarian clear cell carcinoma contribute to cell survival. *Oncotarget.* 2015;22;6(28):26002-17. doi: 10.18632/oncotarget.4692.

[7] Mandai M., Amano Y., Yamaguchi K., Matsumura N., Baba T., Konishi I.. Ovarian clear cell carcinoma meets metabolism; HNF-1β confers survival benefits through the Warburg effect and ROS reduction. *Oncotarget.* 2015;13;6(31):30704-14. doi: 10.18632/oncotarget.5228.

[8] Suzuki E., Kajita S., Takahashi H., Matsumoto T., Tsuruta T., Saegusa M.. Transcriptional upregulation of HNF-1β by NF-κB in ovarian clear cell carcinoma modulates susceptibility to apoptosis through alteration in bcl-2 expression. *Lab Invest.* 2015;95(8):962-72. doi: 10.1038/labinvest.2015.73. Epub 2015 Jun 1.

[9] DeLair D., Han G., Irving J.A., Leung S., Ewanowich C.A., Longacre T.A. et al.. HNF-1β in ovarian carcinomas with serous and clear cell change. *Int J Gynecol Pathol.* 2013;32(6):541-6. doi: 10.1097/PGP.0b013e318273fd07.

[10] Hoang L.N., Han G., McConechy M., Lau S., Chow C., Gilks C.B. et al.. Immunohistochemical characterization of prototypical endometrial clear cell carcinoma-diagnostic utility of HNF-1β and oestrogen receptor. *Histopathology.* 2014;64(4):585-96. doi: 10.1111/his.12286. Epub 2013 Dec 7.

DOI: 10.37200/IJPR/V24I5/PR2020182
Received: 10 Mar 2020 | Revised: 28 Mar 2020 | Accepted: 06 Apr 2020

[11] Kao Y.C., Lin M.C., Lin W.C., Jeng Y.M., Mao T.L.. Utility of hepatocyte nuclear factor-1β as a diagnostic marker in ovarian carcinomas with clear cells. *Histopathology.* 2012;61(5):760-8. doi: 10.1111/j.1365-2559.2012.04267.x. Epub 2012 Jul 2.

[12] Kurman R.J., Ellenson H., Ronnett L., Brigitte M. (Eds.). Blaustein's Pathology of the Female Genital Tract. *6th Ed.*, 2011.

[13] Kurman RJ, Carcanglu ML, Herrington CS, Young RH, eds. WHO Classification of Tumours of female reproductive Organs. *4th ed. Lyon: WHO Press;* 2014.

[14] Zaino, R., Carinelli,S.G., Ellenson, L.H.. Tumours of the uterine corpus: epithelial tumours and precursors. *WHO Press*, Lyon; 2014: 125–126.

[15] Brinkmann V., Abu Abed U., Goosmann C., Zychlinsky A.. Immunodetection of NETs in Paraffin-Embedded Tissue. *Front Immunol.* 2016 Nov 22;7:513. eCollection 2016.

[16] Mojiri A., Stoletov K., Carrillo M.A., Willetts L., Jain S., Godbout R. et al.. Functional assessment of von Willebrand factor expression by cancer cells of non-endothelial origin. *Oncotarget.* 2017 Feb 21;8(8):13015-13029. doi: 10.18632/oncotarget.14273.

[17] Cohen D.A., Dabbs D.J., Cooper K.L., Amin M., Jones T.E., Jones M.W. et al.. Interobserver Agreement Among Pathologists for Semiquantitative Hormone Receptor Scoring in Breast Carcinoma. *Am J Clin Pathol* (2012) 138 (6): 796-802. doi: 10.1309/AJCP6DKRND5CKVDD.

[18] Clinical recommendations. Endometriosis: diagnostics, treatment, and rehabilitation. – M., 2013, p. 1-15.

[19] Zajrat'janc O.V., Adamjan L.V., Andreeva E.N. et al. Molecular-biological peculiarities of ectopic endometrium in patients with genital endometriosis. *Archives of Pathology.* 2010. №5. p.6-12.

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