

ROLE OF OXIDATIVE PROTEIN DESTRUCTION PRODUCTS IN THE EXTERNAL GENITAL ENDOMETRIOSIS PATHOGENESIS AND PROGRESSION

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External genital endometriosis is characterized by high prevalence. Despite unquestionable role of oxidative stress in the development of endometriosis, its features associated with the disease progression are poorly understood. The study aimed to assess the role of oxidative protein modification (OPM) products in the disease progression. A total of 28 women with the established and histologically verified diagnosis of endometriosis took part in the study. The subjects were stratified into group 1 (stage II–III, $n = 10$) and group 2 (stage IV, $n = 18$) based on the disease stage in accordance with the American Association of Gynecologic Laparoscopists (AAGL) classification. The content of OPM products in the ectopic endometrium homogenate was determined by spectrophotometry. The following indicators were significantly higher in patients of group 2, than in patients of group 1: the total OPM product content ($p = 0.040$), basic aldehyde-dinitrophenylhydrazones ($p = 0.039$), and the total amount of ketone-dinitrophenylhydrazones ($p = 0.024$). Furthermore, women of group 2 showed significantly lower reserve-adaptative potential values, than patients of group 1 ($p = 0.045$). We found a positive correlation between the disease severity and the content of OPM products showing intergroup differences (R between 0.397 and 0.443, $p < 0.05$), along with the negative correlation with the reserve-adaptative potential ($R = -0.388$, $p = 0.042$) based on the correlation analysis results. According to the data obtained, the oxidative stress activity in endometriosis foci was correlated with the disease severity. Furthermore, accumulation of OPM products and depletion of the tissue adaptive capacity are typical.

Keywords: endometriosis, oxidative stress, oxidative protein modification, advanced external genital endometriosis, endometriosis markers

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Compliance with ethical standards: the study was approved by the Ethics Committee of the South Ural State Medical University (protocol No. 2 dated 05 May 2025). All subjects submitted the informed consent to take part in the study.

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РОЛЬ ПРОДУКТОВ ОКИСЛИТЕЛЬНОЙ ДЕСТРУКЦИИ БЕЛКОВ В ПАТОГЕНЕЗЕ И ПРОГРЕССИРОВАНИИ НАРУЖНОГО ГЕНИТАЛЬНОГО ЭНДОМЕТРИОЗА

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Для наружного генитального эндометриоза характерна высокая распространенность. Несмотря на несомненную роль окислительного стресса в развитии эндометриоза, его особенности при прогрессировании заболевания недостаточно изучены. Цель проведенного исследования — оценить роль продуктов окислительной модификации белков (ОМБ) в прогрессировании заболевания. В исследовании приняли участие 28 женщин с установленным и гистологически подтвержденным диагнозом наружного генитального эндометриоза. В зависимости от стадии заболевания по классификации Американской ассоциации гинекологов-лапароскопистов (AAGL) участниц распределили в группы 1 (II–III стадия, $n = 10$) и 2 (IV стадия, $n = 18$). В гомогенате эктопического эндометрия определяли содержание продуктов ОМБ методом спектрофотометрии. У пациенток группы 2 следующие показатели были статистически значимо выше, чем у женщин из группы 1: суммарное содержание продуктов ОМБ ($p = 0,040$), альдегид-динитрофенилгидразоны основного характера ($p = 0,039$) и общее количество кетон-динитрофенилгидразонов ($p = 0,024$). Также у женщин из группы 2 выявили статистически значимо более низкое значение резервно-адаптационного потенциала, чем у пациенток из группы 1 ($p = 0,045$). По результатам корреляционного анализа обнаружена прямая корреляционная связь между тяжестью заболевания и содержанием продуктов ОМБ, имеющих межгрупповые различия (R от 0,397 до 0,443, $p < 0,05$), а также обратную корреляционную связь с резервно-адаптационным потенциалом ($R = -0,388$, $p = 0,042$). В соответствии с полученными данными активность окислительного стресса в очагах эндометриоза коррелировала с тяжестью заболевания. При этом характерны накопление продуктов ОМБ и истощение адаптационных резервов ткани.

Ключевые слова: эндометриоз, окислительный стресс, окислительная модификация белков, распространенный наружный генитальный эндометриоз, маркеры эндометриоза

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Endometriosis is one of the most common diseases in women of childbearing age. The development of endometriotic foci is associated with repeated episodes of intra-abdominal bleeding. The associated local oxidative stress represents one of pathogenetic factors of endometriosis progression [1, 2]. The complexity of assessing reactive oxygen species in this disorder results in the need to test oxidative stress products [3]. Alteration of cellular functions occurs under exposure to oxidative stress products, specifically protein modification (OPM) products. The OPM products play a role of inflammatory mediators in various chronic disorders. Due to the structure stability, OPM products can be used to assess the oxidative stress severity in endometriosis. Elevated levels of OPM products in blood serum, peritoneal and follicular fluid of patients with external genital endometriosis had been previously determined [3–5]. However, since endometriotic foci represent the basic pathological unit of endometriosis, investigation of the disease process features in the ectopic endometrium is crucial the study of pathogenesis and identification of endometriosis markers [6].

The study aimed to assess the role of oxidative protein destruction products in the advanced external genital endometriosis pathogenesis and progression.

METHODS

The study was conducted at the Department of Gynecology of the Chelyabinsk Regional Clinical Hospital between February 3, 2025 and December 15, 2025. Inclusion criteria: female sex, age 18–45 years, the diagnosis of advanced external genital endometriosis established based on the therapeutic and diagnostic laparoscopy results, availability of the signed informed consent. Exclusion criteria: pregnancy, breastfeeding, systemic glucocorticosteroid therapy, hormone therapy for endometriosis within 3 months before enrollment, precancerous condition of the cervix or cervical cancer, endometrial hyperplasia, endometrial polyps, submucous fibroids in the uterine body or hybrid fibroids in the uterine body with the cavity deformity, inflammatory diseases of the pelvic organs; type 1 and 2 diabetes mellitus, subcompensated or decompensated thyroid disorders, endogenous hypercortisolism, hyperparathyroidism, acromegaly, autoimmune rheumatic diseases, malignant neoplasms.

A total of 28 patients (average age 31.8 ± 6.9 years) post therapeutic and diagnostic laparoscopy were enrolled. Assessment of the external genital endometriosis stage according to the American Association of Gynecologic Laparoscopists (AAGL) classification based on laparoscopy results was performed in all women [7]: stages II, III, IV were determined in 5 (17.85%), 5 (17.85%), and 18 (64.3%) patients, respectively. The study participants were divided into two groups based on the external genital endometriosis severity according to the AAGL scale considering severity and the risk of surgery [8]. The study participants stage II and III external genital endometriosis according to the AAGL classification were included in group 1 ($n = 10$), and patients with stage IV disease were included in group 2 ($n = 18$). Women of groups 1 and 2 had comparable age structure and chronic pain severity assessed using the visual analogue scale (VAS) ($p > 0.05$). The diagnosis of endometriosis was histologically verified in all patients.

Enucleation of ovarian cysts, excision of endometrioid heterotopia and endometrioid infiltration were performed in patients during the therapeutic and diagnostic laparoscopy. To obtain the ectopic endometrium homogenates, fragments of the cyst capsules, ectopic foci and endometrioid infiltration were collected using the non-energy “cold” scissors. The

ectopic endometrium was homogenized with the 0.9% sodium chloride solution for 3 min at a temperature of 4°C (1 : 10). The OPM product content in the ectopic endometrium homogenate was determined using the SF-56 spectrophotometer (LOMO-Spectrum, Russia) based on the reaction between protein carbonyl derivatives and 2,4-dinitrophenylhydrazine with subsequent registration of the early and late OPM products (aldehyde-dinitrophenylhydrazones (ADNPH) and ketone-dinitrophenylhydrazones (KDNPH), respectively) in the UV and visible ranges [9]. The oxidized protein carbonyl derivatives were registered in the UV range (products of neutral origin): ADNPH — 230, 254, 270, 280, and 356 nm; KDNPH — 363 and 370 nm; in the visible range (products of basic origin): ADNPH — 428 and 430 nm; KDNPH — 434, 524, 530, and 535 nm. The results were expressed in optical density units per mass of protein (AU/mg). To assess the metal-induced OPM, oxidation of proteins by the hydroxyl radical $\text{OH}\cdot$ in the Fenton reaction was activated using the reaction mixture containing the FeSO_4 (10 mM), hydrogen peroxide (0.3 mM) and EDTA (10 mM) solutions prepared ex tempore. The reserve-adaptive potential (RAP) was calculated as a ratio of the results of measuring the products of spontaneous protein oxidation to that of measuring the induced protein oxidation, taking the results of measuring the induced protein oxidation as 100%.

Statistical analysis was conducted using the jamovi, version 2.7.17 software (J. Love, D. Dropmann, R. Selker, Australia). Since the indicators assessed were non-normally distributed, numerical values of those were presented as Me (Q25; Q75), and significance of differences was assessed using the Mann–Whitney test. The correlation analysis involving the use of the Spearman's rank correlation coefficient (R) was conducted to determine correlations between indicators. The differences were considered significant at $p < 0.05$.

RESULTS

The resulting values of oxidative protein modification product content and RAP in the ectopic endometrium homogenates of patients with advanced external genital endometriosis are provided in Table.

The OPM product content assessment in the spontaneous detection mode revealed significantly higher total OPM product content ($p = 0.040$), basic ADNPH, neutral KDNPH, and total KDNPH amount in patients of group 2, than in patients of group 1. The total neutral ADNPH content, total amounts of basic ADNPH and KDNPH in patients of groups 1 and 2 were comparable. No significant differences in the content of various OPM products between patients of group 1 and women of group 2 were revealed in the metal-catalyzed detection mode.

Five significant correlations between the external genital endometriosis severity and the OPM product content in the spontaneous detection mode were identified based on the correlation analysis results. Among those four were positive correlations of the external genital endometriosis stage with the total content of OPM products, basic ADNPH, total amounts of KDNPH and neutral KDNPH. The fifth correlation identified was a negative correlation of RAP with the external genital endometriosis severity. The Spearman's rank correlation coefficient values and significance levels of the significant correlations identified are provided in the Figure.

DISCUSSION

The increase in the OPM product content of the ectopic endometrium homogenate suggests the oxidative stress

Table. Oxidative protein modification indicators in the ectopic endometrium homogenates of patients with advanced external genital endometriosis

Indicators	Group 1 (n = 10)	Group 2 (n = 18)	p
Spontaneous detection mode			
S OPM, AU/mg of protein	46.3 [30.8; 52.8]	68.7 [50.3; 116]	0.04
S ADNPH, AU/mg of protein	41.5 [27.8; 49.3]	62.1 [42.5; 103]	0.08
S ADNPH vis, AU/mg of protein	1.83 [1.02; 3.07]	4.84 [3.45; 5.95]	0.039
S ADNPH UV, AU/mg of protein	38.6 [26.6; 47.7]	58.2 [36.2; 96.6]	0.109
S KDNPH, AU/mg of protein	3.59 [2.86; 5.15]	7.49 [6.45; 11.0]	0.024
S KDNPH vis, AU/mg of protein	0.192 [0.071; 0.367]	0.45 [0.332; 0.784]	0.076
S KDNPH UV, AU/mg of protein	3.4 [2.79; 4.79]	6.98 [5.81; 10.6]	0.021
Metal-catalyzed detection mode			
S OPM, AU/mg of protein	361 [246; 469]	322 [224; 469]	0.796
S ADNPH, AU/mg of protein	286 [182; 389]	266 [182; 389]	0.832
S ADNPH, vis, AU/mg of protein	55.0 [37.7; 71.9]	42.1 [33.8; 60.5]	0.464
S ADNPH, UV, AU/mg of protein	226 [164; 315]	226 [152; 330]	0.906
S KDNPH, AU/mg of protein	69 [44.7; 86.6]	53.7 [41.3; 80.9]	0.524
S KDNPH, vis, AU/mg of protein	5.87 [3.81; 7.6]	4.19 [3.6; 6.43]	0.436
S KDNPH, UV, AU/mg of protein	63.2 [40.9; 79]	49.5 [38.2; 75.1]	0.524
Estimates			
RAP, %	85.6 [78.1; 91]	74.8 [71.1; 84.1]	0.045

Note: p — significance based on the Mann–Whitney test; S — total OPM product content; ADNPH — aldehyde-dinitrophenylhydrazones; KDNPH — ketone-dinitrophenylhydrazones; UV — UV range; vis — visible range; AU/mg — OPM product content in optical density units per mass of protein.

involvement in the external genital endometriosis pathogenesis. The increase in the total OPM product content in the spontaneous detection mode can be associated with the important role of mitochondria in the development of oxidative stress specifically in endometriosis foci. To date, the increase in the number of mitochondria in the ectopic endometrium cells has been confirmed, along with the presence of such structural alterations of mitochondria, as elongation, increase in the number and density of cristae. Such alterations result in the increased bioenergetic activity of mitochondria in endometriosis foci, increased production of reactive oxygen species and acidification of the medium [10]. It has been found that the synthesis of matrix NO synthase is increased in the endometrium of patients with external genital endometriosis [11, 12], which results in the increased nitrogen oxide (II) generation. Consequently, the ADNPH and KDNPH content in the spontaneous OPM detection mode is increased.

The elevated OPM product levels in endometrial homogenates can be associated with the oxidative stress caused by the increase in the levels of free and accumulated iron in endometrial stromal cells [4–6].

There are two pathways of free iron formation in peritoneal fluid associated with the menstrual blood reflux: it is formed during destruction of hemoglobin by heme oxygenase-1 and toxic heme formation during phagocytosis of erythrocytes by the attracted peritoneal macrophages. Free peritoneal iron takes part in the Fenton reaction and leads to free radical formation. The attracted peritoneal macrophages, in turn, stimulate migration to endometriosis foci of other immune cells, together with which they actively produce ROS, further increasing the oxidative stress activity [12–15]. Accumulation of OPM proteins in peritoneal fluid also stimulates oxidative metabolism of neutrophils and monocytes, thereby contributing to the more intense ROS production [4].

The decreased synthesis of iron-regulatory proteins 1 and 2 in endometriosis foci has been determined [16, 17], which

leads to accumulation of iron and activation of iron-dependent oxidation. This results in the death of some endometrioid cells, release of cytokines, vascular endothelial growth factor (VEGF), and re-activation of proliferation, adhesion, and angiogenesis in endometriotic foci [14, 18–20].

The increase in the total amount of KDNPH in the spontaneous detection mode and in the KDNPH amount in the UV range suggests the prolonged oxidative stress in patients with stage IV endometriosis according to the AAGL classification [9]. The long-term exposure to OPM products, in turn, reduces the levels of E-cadherin responsible for inhibition of invasion, increases the expression of the p-ERK and p-P38 genes in the MAPK pathway and contributes to proliferation of cells in endometriosis foci [21].

Despite the lack of significant differences in the OPM product content in the metal-catalyzed detection mode, the RAP decrease in stage IV advanced external genital endometriosis suggests the decrease in the ectopic endometrial cell adaptation to oxidative stress with the endometrioid process progression. In such a case, the increase in oxidative stress activity can result in the cell damage and, therefore, NF-κB signaling pathway activation. The NF-κB pathway activation can lead to the increased synthesis of interleukins IL-2, IL-10, IL-27 and VEGF, which would enhance the endometrioid cell growth, proliferation and their invasion of the surrounding tissues [11, 12, 22].

CONCLUSIONS

The oxidative stress activity in external genital endometriosis is correlated to the disease severity, which is confirmed by the increase in the total content of OPM products, basic ADNPH, total amounts of KDNPH and neutral KDNPH in the spontaneous detection mode, as well as the RAP decrease. The increase in the amounts of OPM products can result from changes in the function of mitochondria in the ectopic endometrial cells, the

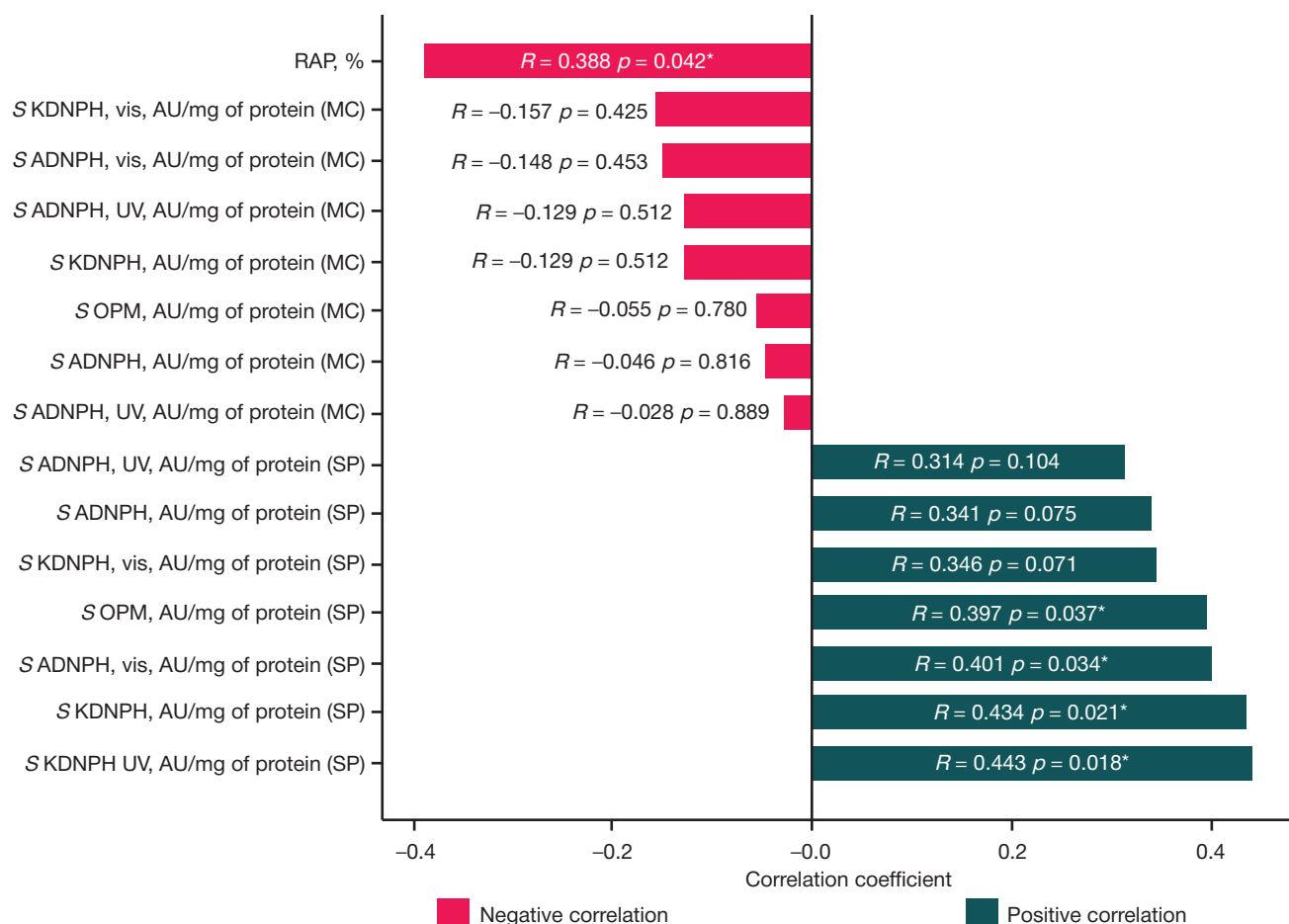


Fig. Correlations between the oxidative protein modification indicators of the ectopic endometrium homogenate and the advanced external genital endometriosis severity according to the AAGL classification. S — total OPM product content; ADNPH — aldehyde-dinitrophenylhydrazones; KDNPH — ketone-dinitrophenylhydrazones; UV — UV range; vis — visible range; AU/mg — OPM product content in optical density units per mass of protein; MC — metal-catalyzed detection mode; SP — spontaneous detection mode; R — Spearman's rank correlation coefficient; p — significance level; * — significant correlations

increased synthesis of nitrogen oxide (II) and iron accumulation in endometriosis foci, as well as accumulation of free iron in the abdominal cavity. The redox status features identified in

endometriosis foci can be used as a potential serum marker of external genital endometriosis. Further research is necessary to test this hypothesis.

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