NITROSATIVE STATUS IN BENIGN EPITHELIAL OVARIAN CYSTIC TUMORS OF NONENDOMETRIOID ORIGIN

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INTRODUCTION

In the structure of cancer incidence special place are occupied benign tumors of the female genital organs. Ovarian tumors are in second place (6.8%) from of all the female genital tumors. Benign forms are found in 75–80% of true ovarian tumors [7, 9]. Despite the fairly detailed knowledge of ovarian tumors, causes of origin and benign tumors of ovarian cysts remain open. One of the most important areas of biomedical research in this field is to elucidate the molecular mechanisms that regulate cell proliferation and apoptosis. Violation of these processes leads to increased speed and reduced cell growth differentiation characteristic of tumor cells.

ANALYSIS OF THE LITERATURE DATA AND STUDY OBJECTIVE

Recently there has been an avalanche increase in the number of scientific publications on the study of the role of nitric oxide. Three American scientists Robert F. Furchgott, Louis J. Ignarro and Ferid Murad received the 1998 Nobel Prize. The goal of researchers was to study the so-called endothelial vascular relaxation factor (endothelium-derived relaxing factor). An unexpected and important discovery was the fact that this was a factor and nitric oxide (NO) [14].

NO is a biological messenger which is synthesized from L-arginine via nitric oxide synthase (NOS) [15]. Recent literature data show that NO, and NOS can modulate cancer-related events, including nitrozative, oxidative stress, apoptosis, cell cycle, angiogenesis, invasion and metastasis [21].

It were described several forms of NOS. For the vast localization in tissues they taken to provide neuronal (nNOS), endothelial (eNOS) and macrophage (macNOS). The first two types of enzymes are preferably constitutional, and the latter operates as inducible form of NOS (iNOS) [1], and in recent times has changed somewhat classification varieties of NO-synthase including distinguished:

1) NOS type 1 (constitutional-neuronal);
2) NOS type 2 (inducible NO-synthase);
3) NOS-3 type (endothelial-constitutional).

NOS type 1 is found mainly in the structures of the central and peripheral nervous system, constantly expressed under normal and pathological, is involved in the regulation of blood pressure. NOS type 2 (iNOS) is expressed in endothelial cells and macrophages in pathological processes, particularly during inflammation, is involved in the synthesis of pro-inflammatory cytokines tumor necrosis factor α, interleukin 1β. At the same time interleukins-4, 8, 10, platelet-derived growth factor inhibiting iNOS and therefore the synthesis of NO. iNOS is expressed also in the heart at myocardial infarction, myocarditis, heart failure. iNOS was found in hepatocytes, chondrocytes. Constitutive endothelial NOS 3rd type involved in the regulation of vascular tone, expressed not only in vascular endothelium, but also in cardiomyocytes, platelets, endothelium lungs

and kidneys. NOS constantly expressed under normal and pathological conditions [1].

Antiproliferative mechanism of action of NO was studied. Reducing the proliferative capacity of the cells under the influence of NO, possibly due to its ability to inactivate the effect of iron enzymes involved in the synthesis of adenosine triphosphate and DNA replication. It is believed that NO can enhance the cytotoxicity of free radicals, and NO-generating compounds that react free radical oxidation, can produce more cytotoxic compounds – peroxynitrite. Peroxynitrite, one of the most powerful oxidants, can directly or indirectly damage DNA and cause covalent modification of proteins in the cell and thus initsiyuyuvaty apoptosis [3]. NO has both cytotoxicity and cytostatic effect against microorganisms and malignant cells with synthesis of NO, which causes the NO-mediated apoptosis [10, 12].

At the same time, there are conflicting published data on the effect of increased cell proliferation under the influence of NO [8]. NO increases proliferation of normal human fibroblasts and aging. Increased NO production may lead to inhibition of apoptosis and increased cell viability lymphoma Nb2. These effects probably related to the antioxidant properties of NO, which due to its ability to bind to the membrane and intracellular iron complexes, inhibit decomposition of peroxides, intercept free radicals and put out the chain reaction of free radical oxidation. In addition, NO may activate intracellular processes in which enzymes from inactive soluble forms of transition to more active membrane [3].

If NO production there for a long period of time, the excessive production of NO may lead to mutations and ultimately – to cancer [16, 20]. In addition to increased metastatic potential of tumor cells by mutations in the DNA NO production by tumor cells promotes angiogenesis, essential process for tumor growth and support [11, 13].

Several studies have shown the important role of NO in ovarian physiology. It is shown that NO is synthesized locally ovaries and may play a role in the development of follicles, ovulation and luteal formation [18]. Data on changes in the content derived NO and NOS activity in benign ovarian tumor during virtually absent, which led to goals and objectives of our study.

Study aim – to explore the features of nitrozative status in benign epithelial cystic ovarian tumors of nonendometriod origin.

MATERIALS AND METHODS

The study involved 220 patients of reproductive age: 40 patients with follicular ovarian cysts (group F), 60 – with serous cystadenomas (group S), 60 – with mucinous cystadenomas (group M), 30 – with cystadenocarcinomas nonendometrioid origin (group C) and 30 conditionally healthy physical and gynecological patients in the control group (group K).

Criteria for inclusion in the study of reproductive age; histologically confirmed diagnosis of follicular cysts, serous cystadenomas, mucinous cystadenomas, cystadenocarcinomas nonendometrioid origin. Exclusion criteria: tilting breaks and cystic formations; previous hormonal drugs the day before surgery; endometriosis; metastasis of primary tumors of different origin; previous chemotherapy.

It were studied the stable NO metabolites in biological fluids such as blood and peripheral intracystic liquid. Aseptically peripheral blood was removed before the operation, intracystic fluid - during operation by aspiration. The collected fluid was centrifuged, stored at t = -70 °C to study. Intracystic samples of fluid from the blood impurities were excluded from the study.

To determine concentrations of stable metabolites of NO (NO_2^- + NO_3^- = NO_x) in biological fluids used the method by VA Metelskaya, NG Humanova [6]. This method is based on the recovery of NO_3^- to NO_2^- vanadium chloride (III), followed by determination of nitrite using Hrissa reagent (a solution of sulfanilamide and N-naftyletylendiamine dihydrochloride in 30% glacial acetic acid) as color image reagent (giving crimson color in the presence of NO liquids). To 0.2 ml of the sample studied fill up 0.4 ml of ethanol for deproteinizated, centrifuged for 20 minutes at 3000 rotations per minute. Next to each well microplate reader was added to 80 ml of the supernatant, 80 ml of vanadium chloride and 80 ml reagent Hrissa. Measurements were made at immunosorbent analyzer Stat Fax 3200 (microplate reader) (Awareness technology Inc. Palm City, FL 34990, USA). Results are expressed in mcmol/l.

Determination of serum tumor markers CA 125, CA 19-9, HE-4 was carried out by immunochemical detection of e electrochemiluminescent method using standard reagents Roche Diagnostics (Switzerland) analyzer "Sobas®6000 analyzer series" (USA).

Operating specimens were fixed in 10% formalin before pouring in paraffin. Sections were stained with hematoxylin and eosin were reviewed and selected by a pathologist for immunohistochemical analysis. Selected deparafinized, rehydrated sections were heated in a microwave oven in 0.01 M citrate buffer (pH 6.0) for 30 minutes. The activity of endogenous peroxidase blocked with 3% hydrogen peroxide for 10 minutes, then washed with saline, phosphate buffered. Sections were incubated overnight at 4 °C with anti-iNOS rabbit polyclonal antibodies (NOS2 C-19: sc-649, Santa Cruz Biotechnology, Germany). As used conjugate avidin-biotin peroxidase solution (Dako Cytomation LSAB and system-HRP, Denmark). The signal was visualized using diaminobenzidine (Dako Cytomation Liquid DAB and substrate Chromogen System, Dako, Denmark). Sections were contrasted Harris hematoxylin, dehydratated, purified and studied morphometric. As a positive control was used a sample of skin with chronic granulomatous inflammation. The intensity of expression was assessed semiquantitative: the absence of expression – "-" with weak expression – "±", with normal expression – "+" (corresponding to the control value), with increased expression (increased density of positive areas 30-50%) – "++", while overexpression (increase positive half sections) – "+++" [17].

The resulting preparations were investigated using a light microscope.

Statistical analysis of the data was performed using Excel.

RESULTS AND DISCUSSION

Age of examined patients with serous cystadenomas has averaged 30.10 ± 0.51 years, with mucinous cystadenomas – 30.17 ± 0.47, with follicular cysts – 30.43 ± 0.57, with cystadenocarcinomas – 31.57 ± 31.57, in control group – 30.00 ± 0.45 and probably did not differ between groups.

The average diameter of cystic formations was the largest in the mucinous cystadenomas (11.97 ± 0.81 cm) and cystadenocarcinomas (9.90 ± 0.94 cm). In serous cystadenomas it amounted to 9.06 ± 0.60 cm, with follicular cysts 7.19 ± 0.26 cm.

Analysis of oncomarkers examined patients showed, as expected, their largest concentration in the presence cystadenocarcinomas (Table 1). In patients with follicular cysts, serous and mucinous cystadenomas the levels of oncomarkers were within reference values.

Study of NO_x levels in biological fluids of examined patients revealed the likely reduction of serum neutral NO metabolites in the cystadenocarcinomas (23.1 ± 0.6 mmol/l), serous (24.2 ± 0.3 mmol/l) and mucinous (23.9 ± 0.4 mmol/l) cystadenomas in comparison with follicular cysts (25.2 ± 0.3 mmol/l) and control (26.2 ± 0.2 mmol/l) (Figure 1). Differences intracystic NO_x concentrations in mucinous, serous ystadenomas and follicular cysts were statistically significant, but small. At the same time the level of NO_x in intracystic contents of cystadenocarcinomas exceeded that of the follicular cysts in 1.96 times ($p < 0.01$), in serous cystadenomas in 1.99 times ($p < 0.01$) and mucinous cystadenomas in 1.79 times ($p < 0,01$) (Table 2, Figure 2 i 3).

TABLE 1. LEVELS OF SERUM ONCOMARKERS IN EXAMINED PATIENTS

Formations' histostructure	CA 125, U/ml		CA 19-9, U/ml		HE-4, pmol/l	
	M ± m	min – max	M ± m	min – max	M ± m	min – max
Follicular cysts, n=40	$7.32 \pm 1.13^{k, m, c}$	3.20 – 29.35	$8.77 \pm 1.25^{k, s, m, c}$	12.56 – 32.31	$28.84 \pm 2.12^{k, s, m, c}$	15.33 – 38.62
Serous cystadenomas, n=60	$24.99 \pm 1.77^{k, m, c}$	3.21 – 50.50	$22.90 \pm 1.80^{k, f, m, c}$	14.32 – 34.11	$45.17 \pm 1.57^{k, f, m, c}$	33.64 – 54.22
Mucinous cystadenomas, n=60	$17.13 \pm 1.10^{k, f, s, c}$	7.69 – 33.21	$28.82 \pm 1.90^{k, f, s, c}$	14.45 – 34.79	$43.05 \pm 2.06^{k, f, s, c}$	32.00 – 50.68
Ovarian cystadenocarcinomas, n=30	$137.98 \pm 3.80^{k, f, s, m}$	32.78 – 677.52	$51.16 \pm 2.36^{k, f, s, m}$	26.61 – 92.33	$101.16 \pm 3.32^{k, f, s, m}$	78.35 – 198.11
Control group, n=30	$6.47 \pm 0.88^{f, s, m, c}$	0.51 – 13.56	$11.29 \pm 0.97^{f, s, m, c}$	4.33 – 17.88	$14.96 \pm 0.45^{f, s, m, c}$	8.92 – 45.17
Normative data	0 – 35		0 – 37		0 – 70	

$^{f, s, m, c, k}$ significant difference with groups of women with follicular cysts, with serous cystadenomas, with mucinous cystadenomas, with cystadenocarcinomas, with control group, $p < 0.05$

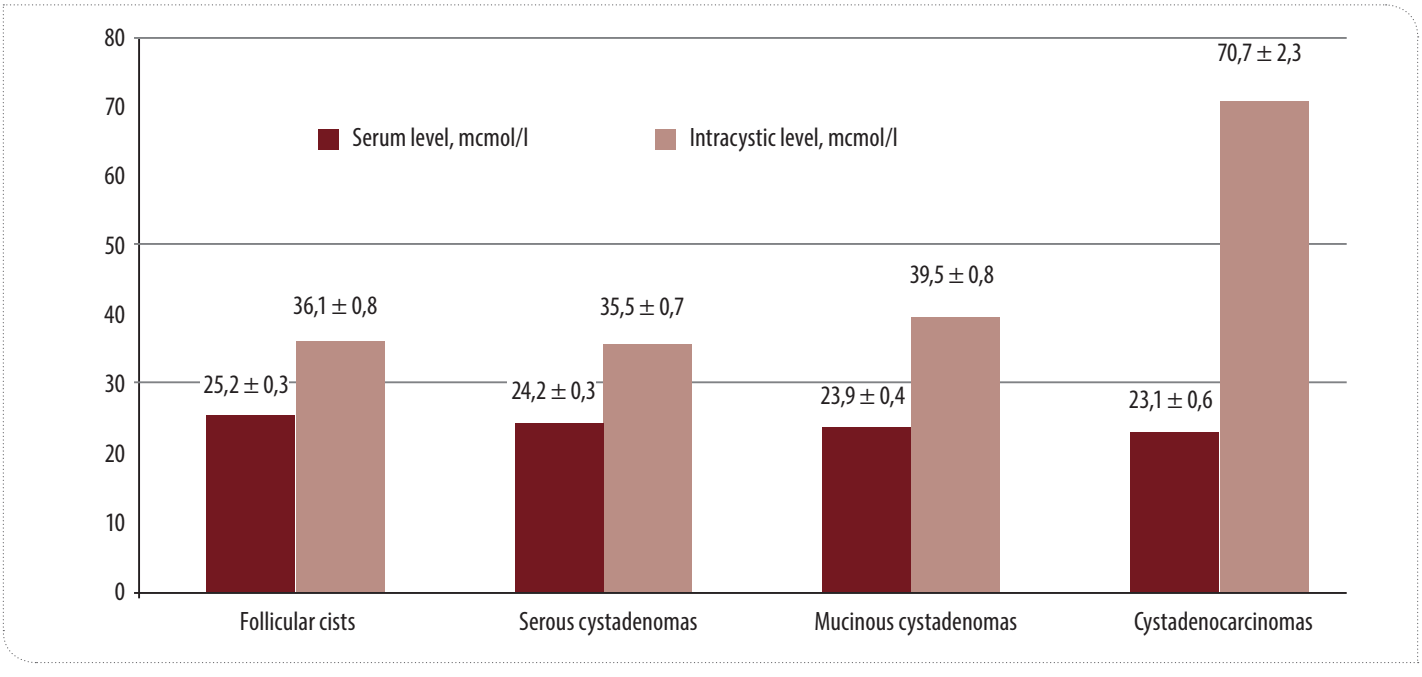

FIGURE 1. THE AVERAGE NO_x LEVEL IN BIOLOGICAL FLUIDS OF PATIENTS (mMol/l)

TABLE 2. THE INTENSITY OF iNOS IMMUNOHISTOCHEMICAL STAINING IN THE WALLS REMOVED FORMATIONS, n (%)

Formations' histostructure	The weak intensity of iNOS expression (+/- or +)	Increased intensity of iNOS expression (++ or +++)
Follicular cysts, n = 40	28 (70.00)^{c}	12 (30.00)^{c}
Serous cystadenomas, n = 60	43 (71.67)^{c}	17 (28.33)^{c}
Mucinous cystadenomas, n = 60	41 (68.33)^{c}	19 (31.67)^{c}
Ovarian cystadenocarcinomas, n = 30	3 (10.00)$^{f, s, m}$	27 (90.00)$^{f, s, m}$

$^{f, s, m, c, k}$ significant difference with groups of women with follicular cysts, with serous cystadenomas, with mucinous cystadenomas, with cystadenocarcinomas, with control group, $p < 0.05$

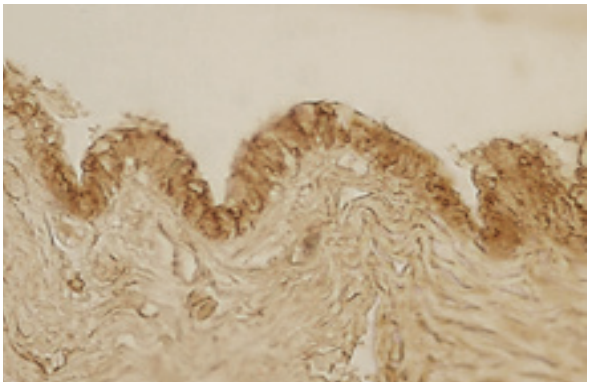

FIGURE 2. INCREASED INTENSITY OF IMMUNOHISTOCHEMICAL COLORING OF iNOS IN THE MUCINOUS CYSTADENOMA WALL. IMMUNOHISTOCHEMISTRY WITH PAT TO NOS TYPE 2, × 200

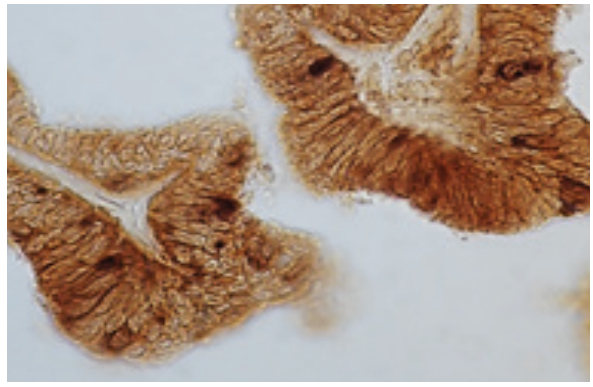

FIGURE 3. iNOS OVEREXPRESSION IN THE HIGH-GRADE CYSTADENOCARCINOMA WALL. IMMUNOHISTOCHEMISTRY WITH PAT TO NOS TYPE 2, × 300

CONCLUSIONS

1. NO and iNOS effect of on hyperproliferation processes in the ovaries is twofold.

2. NO and iNOS reducing expression and their minor activity may impact on the cystic tumor formation and benign tumor formation in the ovaries.

3. NO overexpression and iNOS increased activity associated with the malignancy processes in cystic formations of epithelial origin.

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Ovarian tumors are in second place (6–8%) from of all the female genital tumors. Benign forms are found in 75–80% of true ovarian tumors. Despite the fairly detailed knowledge of ovarian tumors, causes of origin and benign tumors of ovarian cysts remain open. Several studies have shown the important role of NO in ovarian physiology. It was shown that NO is synthesized locally ovaries and may play a role in the development of follicles, ovulation and luteal formation. Data on changes in the content NO derived and NOS activity in benign ovarian tumor are absent.

The aim of the study was to investigate the characteristics of nitrosative status of benign epithelial cystic ovarian tumors of nonendometrioid origin. 220 patients of reproductive age were examined: 40 patients with ovarian follicular cysts, 60 – with serous cystadenomas, 60 – with mucinous cystadenomas, 30 – with cystadenocarcinomas of nonendometrioidnogo origin, 30 patients consist control group. NO_x level of in the serum and in intracystic content, iNOS imunoreactivity in the walls of the remote masses were investigated.

Study of NO_x levels in biological fluids revealed the likely reduction of serum neutral NO metabolites in the cystadenocarcinomas, serous and mucinous cystadenomas in comparison with follicular cysts and control. Differences of intracystic NO_x concentrations in mucinous, serous cystadenomas and follicular cysts was small.

Immunohistochemical study of iNOS expression showed its small level in follicular cysts and benign cystadenomas, but high level in cystadenocarcinomas.

Thus, NO and iNOS effect of on hyperproliferation processes in the ovaries is twofold. NO and iNOS reducing expression and their minor activity may impact on the cystic tumor formation and benign tumor formation in the ovaries. NO overexpression and iNOS increased activity associated with the malignancy processes in cystic formations of epithelial origin.

Keywords: nitrosative status, cystic ovarian tumors of nonendometrioid origin, NO_x, iNOS, immunohistochemistry.

НІТРОЗАТИВНИЙ СТАТУС ПРИ ДОБРОЯКІСНИХ ЕПІТЕЛІАЛЬНИХ КІСТОЗНИХ ПУХЛИНАХ ЯЄЧНИКІВ НЕЕНДОМЕТРІОЇДНОГО ПОХОДЖЕННЯ

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Серед усіх пухлин жіночих статевих органів пухлини яєчників займають друге місце (6–8%) за частотою. Доброякісні форми зустрічаються в 75–80% всіх справжніх пухлин яєчників. Незважаючи на досить докладну вивченість новоутворень яєчників, причини походження їхніх доброякісних пухлин і кіст залишаються нез'ясованими.

Декілька досліджень виявили важливу роль оксиду азоту (NO) в овариальній фізіології. Показано, що яєчники локально синтезують NO, і він може відігравати роль в процесах розвитку фолікулів, овуляції та лютеїнового формування. Дані про зміну рівня похідних оксиду азоту та активності синтази оксиду азоту (NOS) при доброякісному пухлинному процесі в яєчниках практично відсутні.

Метою проведеного дослідження було вивчення особливостей нітрозативного статусу при доброякісних епітеліальних кістозних пухлинах яєчників неендометріоїдного походження.

Обстежено 220 пацієнток репродуктивного віку: 40 пацієнток із фолікулярними кістами яєчників, 60 – із серозними цистаденомами, 60 – із муцинозними цистаденомами, 30 – із цистаденокарциномами неендометріоїдного походження, а також 30 пацієнток контрольної групи. Досліджений вміст NO_x в сироватці крові, інтракістозному вмісті, імунореактивність індуцибельної форми NOS (iNOS) у стінках видалених утворень.

Вивчення рівнів NO_x в біологічних рідинах пацієнток виявило вірогідне зниження вмісту сироваткових нейтральних метаболітів NO при цистаденокарциномах, серозних та муцинозних цистаденомах порівняно з фолікулярними кістами та контролем. Відмінності інтракістозних концентрацій NO_x в муцинозних, серозних цистаденомах та у фолікулярних кістах були хоча й вірогідними, але невеликими.

Імуногістохімічне дослідження експресії iNOS показало переважно слабкий її рівень у фолікулярних кістах і доброякісних цистаденомах, але високий – у цистаденокарциномах.

Отже, вплив NO та iNOS на процеси гіперпроліферації в яєчниках має двоякий характер. Зниження експресії NO та незначна активність iNOS можуть сприяти утворенню кістозних пухлиноподібних та доброякісних пухлинних утворень в яєчниках. Гіперекспресія NO і підвищена активність iNOS пов'язані з процесами малігнізації кістозних утворень епітеліального походження.

Ключові слова: нітрозативний статус, кістозні утворення яєчників неендометріоїдного генезу, NO_x, iNOS, імуногістохімія.

НИТРОЗАТИВНЫЙ СТАТУС ПРИ ДОБРОКАЧЕСТВЕННЫХ ЭПИТЕЛИАЛЬНЫХ КИСТОЗНЫХ ОПУХОЛЯХ ЯИЧНИКОВ НЕЭНДОМЕТРИОИДНОГО ПРОИСХОЖДЕНИЯ

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Среди всех опухолей женских половых органов опухоли яичников занимают второе место (6–8%) по частоте. Доброкачественные формы встречаются в 75–80% всех настоящих опухолей яичников. Несмотря на достаточно подробную изученность новообразований яичников, причины происхождения их доброкачественных опухолей и кист остаются невыясненными.

Несколько исследований обнаружили важную роль оксида азота (NO) в овариальной физиологии. Показано, что яичники локально синтезируют NO, и он может играть роль в процессах развития фолликулов, овуляции и лютеинового формирования. Данные об изменении уровня производных оксида азота и активности синтазы оксида азота (NOS) при доброкачественном опухолевом процессе в яичниках практически отсутствуют.

Целью проведенного исследования стало изучение особенностей нитрозативного статуса при доброкачественных эпителиальных кистозных опухолях яичников неэндометриоидного происхождения. Обследовано 220 пациенток репродуктивного возраста: 40 пациенток с фолликулярными кистами яичников, 60 – с серозными цистаденомами, 60 – с муцинозными цистаденомами, 30 – с цистаденокарциномами неэндометриоидного происхождения, а также 30 пациенток контрольной группы. Исследовано содержание NO_x в сыворотке крови, интракистозном содержимом, иммунореактивность iNOS в стенках удаленных образований.

Изучение уровней NO_x в биологических жидкостях пациенток выявило достоверное снижение содержания сывороточных нейтральных метаболитов NO при цистаденокарциномах, серозной и муцинозной цистаденомах по сравнению с фолликулярной кистой и контролем. Различия интракистозных концентраций NO_x в муцинозной, серозной цистаденомах и в фолликулярной кисте были хотя и достоверными, но небольшими.

Иммуногистохимическое исследование экспрессии iNOS показало преимущественно слабый ее уровень в фолликулярной кисте и доброкачественных цистаденомах, но высокий – в цистаденокарциноме.

Таким образом, влияние NO и iNOS на процессы гиперпролиферации в яичниках имеет двоякий характер. Снижение экспрессии NO и незначительная активность iNOS могут способствовать образованию кистозных опухолевидных и доброкачественных опухолевых образований в яичниках. Гиперэкспрессия NO и повышенная активность iNOS связаны с процессами малигнизации кистозных образований эпителиального происхождения.

Ключевые слова: нитрозативный статус, кистозные образования яичников неэндометриоидного генеза, NO_x, iNOS, иммуногистохимия.