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STUDY OF LIPID PEROXIDATION INDICATORS IN WOMEN WITH EXTERNAL GENITAL ENDOMETRIOSIS

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Annotation: The article presents the results of a comprehensive clinical and biochemical study of women with external genital endometriosis (EGE) and infertility, aimed at elucidating the role of oxidative stress in the pathogenesis of endometriosis-associated infertility. The study included 117 women: 44 patients with EGE, 19 women with tubal-peritoneal infertility (comparison group), and 24 healthy women (control group). Analysis of gynecological and obstetric histories revealed a high incidence of primary infertility (67.4%), along with a significant prevalence of menstrual cycle disorders and chronic pelvic inflammatory diseases among women with EGE. Pain syndrome of varying severity was identified as the leading clinical manifestation of EGE, though it did not consistently correlate with the extent of tissue damage observed during laparoscopy. Biochemical analysis of lipid peroxidation (LPO) markers in blood plasma and peritoneal fluid showed a marked intensification of oxidative processes in women with EGE, especially in advanced stages (Stage III), compared to the comparison and control groups. Elevated levels of neutral lipids, lipid hydroperoxides, diene conjugates, and a higher oxidative index indicated a pronounced oxidative stress and a significant imbalance between pro-oxidant and antioxidant systems. The findings emphasize the critical role of oxidative stress in the development of EGE-associated infertility and highlight the potential of targeted antioxidant therapy as a strategy to improve reproductive outcomes in affected women.

Keywords: External genital endometriosis (EGE), infertility, oxidative stress, lipid peroxidation (LPO), pro-oxidant-antioxidant balance, peritoneal fluid, reproductive health, antioxidant therapy, chronic pelvic inflammation, pain syndrome.

Introduction.

Endometriosis is a chronic gynecological disease characterized by the presence of ectopic endometrial tissue outside the uterine cavity, often associated with pelvic pain, menstrual irregularities, and infertility. Among its various forms, external genital endometriosis (EGE) is one of the most common and challenging to treat, frequently affecting women of reproductive age. The multifactorial nature of endometriosis, including hormonal, immunological, genetic, and environmental factors, complicates its pathogenesis and management.

Endometriosis affects approximately 10% of women of reproductive age worldwide (WHO, 2021), with up to 50% of women diagnosed with infertility. Thus, according to WHO estimates, at least 190 million women and adolescent girls worldwide currently suffer from

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this disease during their reproductive age, although some women may suffer after menopause [1, 2, 4, 14].

All over the world, external genital endometriosis (EGE) is diagnosed with a significant delay [1, 4, 8, 12, 14]. Moreover, the first symptoms of the disease (chronic pelvic pain, dysmenorrhea) appear at an early age: up to 20 years - in 38% of patients, at 20-24 years - in 21% of patients [1, 14]. According to the World Endometriosis Society, on average, EGE is diagnosed 6.7 years after the appearance of the first symptoms of the disease [1, 14, 15]. The percentage of recurrence of EGE varies greatly in different studies and ranges from 6 to 67% [3, 5, 7]. On average, every second woman undergoes repeated surgery after surgical treatment [6, 13]. According to L.V. Adamyan et al., without subsequent hormonal therapy within 1 year, the disease recurs in 55% of women, and with each subsequent year, an episode of endometriosis recurs in 10% of patients [1, 2].

Material and methods of the study: 117 women with infertility who applied to the private clinic "ProfMedMax" in Karshi were examined for the period from 2022 to 2024. Of these, 38% (n = 44) were diagnosed with EGE, 16.2% (n = 19) - tubal-peritoneal infertility (TPI); 29 (25.2%) were diagnosed with endocrine infertility, and in 20.6% (n = 25) the genesis of infertility could not be identified. Of the 117 women with infertility, 44 women with EGE (main group) and 19 women with TPI (comparison group) were included in the study. The control group consisted of 24 women without infertility and with favorable obstetric and gynecological history. The criteria for inclusion of patients in the study were: female infertility associated with EGE, infertility of tubal-peritoneal origin. Exclusion criteria: malformations of the genitals, oncological diseases of the pelvic organs (including the ovaries), other genesis of infertility. All patients underwent a complete clinical and laboratory examination in accordance with the study of female infertility in outpatient settings. Specially developed examination cards were used, taking into account the somatic condition, gynecological and obstetric history, and the results of laboratory and clinical studies. The study of the redox balance of blood plasma and peritoneal fluid was performed using the immunoassay method on the HUMAN analyzer (Germany). Peritoneal fluid was aspirated from the Douglas pouch during laparoscopy immediately after the introduction of additional counter-openings before surgical manipulations. Samples were centrifuged to remove the cellular fraction, then stored at -20°C until the analytical stage, defrosting of samples was performed at room temperature.

Results of the research: The average age of patients with EGE (n=44) was 31.2 ± 2.9 years, patients with TPI - 32.7 ± 4.2. In the studied women with EGE, primary infertility was diagnosed in 30 (67.4%) examined, secondary infertility - in 14 (32.6%) (Table 1). Whereas in the group of women with TPI, the opposite trend was noted and primary infertility was detected only in =7 (39.5%) women, and secondary infertility in 12 (60.5%) women. When analyzing the obstetric history, it was found that among patients suffering from endometriosis-associated infertility, 30 (67.4%) patients had no history of pregnancy, 8 (19.1%) of those observed had given birth through the natural birth canal or by cesarean section, 6 (13%) patients had a history of abortions (4- artificial abortion and 2 - spontaneous). Of the 12 (60.5%) patients with TPI who had a history of pregnancy, childbirth was noted in 8 (73.9%) patients, ectopic pregnancy was observed in 3(26.1%)

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patients (all patients underwent unilateral tubectomy), artificial abortion at the request of the patient was performed in 6 (56.5%) cases, spontaneous termination of pregnancy was observed in 4 (34.8%) of those examined.

When collecting the gynecological anamnesis, it was established that at least once in 12 (28.1%) patients of the EGE group, the doctor of the antenatal clinic diagnosed an exacerbation of chronic salpingo-oophoritis, the basis for diagnosing this pathological condition was complaints of chronic pelvic pain. The second place in frequency of occurrence was occupied by menstrual cycle disorders, more often of the anovulatory cycle type, which were observed in 9 (20.2%) women with EGE. Hyperplastic processes of the endometrium (polyp and hyperplasia), which were detected in 7 (14.6%) patients. Background diseases of the cervix were noted in the anamnesis of 3 (7.9%) patients with EGE. The remaining 8 (19.1%) patients with endometriosis-associated infertility had an uncomplicated gynecological anamnesis.

In 8 (42.1%) patients in the group with TPI, the gynecological anamnesis was complicated by previous PID, a common cause of which was urogenital infection.

Table 1

Obstetric and gynecological history of the women studied

Anamnesis	Group with infertility and EGE (n=44)		Group with TPI (n=19)		Control (n=24)	
	Abc	%	Abc	%	Abc	%
Childbirth	8	19,1**▲	9	44,7*	24	100
Spontaneous miscarriage	2	4,5▲▲	4	21,1**	1	4,2
Abortion	4	9,0▲▲	6	34,2**	2	8,3
Ectopic pregnancy	2	3,4*▲▲	3	15,8**	0	0
Primary infertility	30	67,4**▲	7	39,5**	0	0
Secondary infertility	14	32,6**▲	12	60,5**	0	0
Menstrual cycle disorders	9	20,2*▲	2	13,2	3	12,5
IDPO	12	28,1*	8	42,1**	4	16,7
Hyperplastic processes in the endometrium	6	14,6**	2	10,5**	0	0
Uterine fibroids	2	4,5*▲	1	2,6*	0	0
Adenomyosis	3	5,6*	0	0	0	0
Diseases of the cervix	4	7,9*▲▲	3	18,4**	1	4,2
Absence of gynecological	8	19,1**	2	13,2**	16	66,7

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diseases						

Notes: * - significant difference in indicators from the control group (*-p<0.05; **-p<0.001); ▲ - significant difference in indicators from the group of women with TPI(▲ -p<0.05; ▲▲ - p<0.001).

The clinical picture of EGE was characterized by a variety of symptoms of the disease. The most pronounced clinical sign of endometriosis in women was the presence of pain the day before the onset of menstruation and in the following days of the menstrual cycle. Pain was also localized in the lower abdomen, lower back, with a pronounced manifestation during the period of menstruation itself. Complaints of dyspareunia were presented in 5.6% of cases. Mostly, women had a moderate degree of pain syndrome (59.6%), mild pain was 19.1%, and severe pain was 21.3% of cases. It should be taken into account that the degree of pain syndrome was subjective. The psychological component of pain assessment is largely related to the psycho-emotional state of the woman herself, which may not be related to actual tissue damage by endometriosis. Often, the volume of tissue damage by endometriosis, determined later by laparoscopy, did not correspond to the course of the pathological process and the severity of clinical symptoms. In some cases, with large sizes of endometrioid cysts, pain syndrome could be present in minimal values, and with insignificant spread of endometrioid foci to the abdominal surface of the sacrouterine ligaments and the rectovaginal septum, it could be accompanied by severe pain syndrome.

Ultrasound of the pelvic organs allowed us to specify the location and size of endometrioid cysts, but did not allow us to identify superficial implants, which were later identified during laparoscopy. On ultrasound, endometrioid ovarian cysts were round ovoid formations, and in most cases cysts up to 5.0 cm in size were detected, in 71.9% (n=32) of which a double contour was detected, in which the thickness of the inner layer corresponded to an average of 0.12-0.13 cm, but the thickness of the capsule was 0.2-0.4 cm. Often, when pressing with the sensor, the cyst was displaced. In half of the cases, the cysts were of uniform consistency in the form of a finely dispersed, non-displaceable suspension; in some cases, there were thickened formations, mainly oval in shape, and were blood clots. The ultrasound picture of retrocervical endometriosis was characterized by the formation of a dense consistency located in the retrocervical retrovaginal tissue, with localization both under the cervix and above and on the side of the cervix.

To study the relationship between EGE and redox balance in the development of infertility, we conducted studies of lipid peroxidation indices and their detoxification system in the women under study. As was stated above, the problem of EGE development from a pathophysiological point of view has a multicomponent mechanism, which involves many systems. This dictates the need to search for a mechanism of pathogenetic changes in EGE leading to infertility. To some extent, such a system can be used to determine the intensity of lipid peroxidation processes and the antioxidant defense system. To determine the relationship between the severity of EGE and the processes of lipid peroxidation and antioxidant protection, we divided 44 women with EGE into 2 subgroups: 1 subgroup - 37 women with EGE of I-II degree; 2 subgroup - 7 women with EGE of III degree.

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The study of the indicators of LPO processes in blood plasma between the main subgroups and the comparison group of women with TPI showed a significant increase in the content of dien ketones (DK) (P<0.01), and other indicators, such as neutral lipids (NL), lipid hydroperoxide (LHP) did not have significant changes (P>0.05).

The data presented in Table 2 show that in the groups of women with grades I-II EGE, significant intensification of the LPO processes in the peritoneal fluid is observed relative to the comparison group, which is manifested in an increase in NL (P<0.01), GPL (P<0.001), DK (P<0.001), and OI (P<0.01). In the group of women with grade III EGE, relative to the values of the comparison group, the value of GPL increases by 5.1 times (P<0.001), and DK - by 6.4 times (P<0.001), with a smaller increase in NL by 2.1 times (P<0.01), leading to an increase in the oxidative index (OI) by 2.5 times (P<0.001). The values of the group of women with TPI were as close as possible to the reference values of the laboratory.

Table 2.

Values of LPO products in peritoneal fluid in the studied groups of women (M±m)

Indicators lipid peroxidation	1 subgroup with EGE I-II (n=37)	1 subgroup with EGE III (n=7)	Comparison group with TPI (n=19)
NL, ed.op.pl./ml0	1,724±0,161	2,93± 0,21*▲	1,374±0,143
LH, ed.op.pl./ml	0,721±0,097	2,713±0,371**▲▲	0,537±0,083
DK, ed.op.pl./ml	0,193±0,029*	0,421±0,089**▲▲	0,066±0,011
OI	0,431±0,081	0,906±0,105*▲	0,369±0,069

Note: * - significant difference from the indicators of the group with TPI (* - p<0.01; ** - <0.001); ▲ - significant difference from the indicators of the group of women with grade 1-2 EGE (▲ - p<0.01; ▲▲ - p<0.001).

Thus, studies of women with EGE and infertility have shown that, despite the presence of fairly clear clinical symptoms of endometriosis, women differ from each other in the stage and depth of the lesion, which undoubtedly requires additional diagnostic measures, and

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subsequently treatment tactics.It should also be noted that with a full-blown clinical picture of the disease, the quality of life of patients is significantly reduced, reproductive function becomes impaired, which does not allow a woman to fully realize her reproductive potential. The presented data show that women with EGE develop oxidative stress as a result of changes in the functioning between the processes of lipid peroxidation and the AOP system, with the prevalence of radical formation processes over their inhibition processes. The reasons for this are the active inflammatory process in endometrioid foci, peritoneum, and pelvic organs.

The capabilities of the AOP system in EGE are insufficient to limit oxidative processes during its prolonged expression. All this creates additional conditions for maintaining oxidative stress, due to the disruption of lipid regulation by the AOP system and the positive feedback of the functioning of the pathological cycle between oxidative phosphorylation and the degree of LPO activity.

Consequently, in women with EGE, various etiological factors cause increased secretion of lipid-based inflammatory mediators, and with insufficiency of the AOP system, an inflammatory process develops in endometrioid foci, the peritoneum, and pelvic organs. Apparently, short intervals between menstrual cycles create favorable conditions for the action of peroxide radicals, in which the immune system of the female body is unable to cope with the utilization of menstrual material, which affects and grows on the uterine appendages, peritoneum and other tissues.

Conclusions:

1. The frequency of external genital endometriosis in the structure of infertility was 38%.
2. An important link in the pathogenesis of external genital endometriosis is the activation of lipid peroxidation and local antioxidant function, which depends on the severity of the pathology.
3. All women with EGE, in combination with hormonal and surgical therapy, need to include antioxidant therapy to reduce the recurrence of the pathology.

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