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STUDY OF REDOX BALANCE OF BLOOD PLASMA AND PERITONEAL FLUID IN WOMEN WITH EXTERNAL GENITAL ENDOMETRIOSIS

Saidzhalilova D.D., Kuzieva Yu.Kh.
Tashkent Medical Academy

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Abstract:

Endometriosis affects approximately 10% of women of reproductive age worldwide (WHO, 2021), up to 50% of women among them are diagnosed with infertility. Thus, according to WHO estimates, at least 190 million women and adolescent girls around the world currently suffer from this disease at their reproductive age, although some women may suffer after menopause [1, 2, 4, 14]. Endometriosis ranks 2nd in the structure of gynecological morbidity, This, in turn, naturally has a negative impact on the reproductive health of women [1, 3, 6, 9, 10].

Keywords: Endometriosis affects

INTRODUCTION. Endometriosis affects approximately 10% of women of reproductive age worldwide (WHO, 2021), up to 50% of women among them are diagnosed with infertility. Thus, according to WHO estimates, at least 190 million women and adolescent girls around the world currently suffer from this disease at their reproductive age, although some women may suffer after menopause [1, 2, 4, 14]. Endometriosis ranks 2nd in the structure of gynecological morbidity, This, in turn, naturally has a negative impact on the reproductive health of women [1, 3, 6, 9, 10].

Worldwide, external genital endometriosis (AGE) is diagnosed with a long delay [1, 4, 8, 12, 14]. At the same time, the first symptoms of the disease (chronic pelvic pain, dysmenorrhea) appear at an early age: up to 20 years of age - in 38% of patients, at 20-24 years - in 21% of patients [1, 14]. According to the World Endometriosis Society, on average, AGE is diagnosed 6.7 years after the onset 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 after surgical treatment undergoes surgery again [6, 13]. The probability of repeated episodes of endometriosis is very high: after 1-2 years, the disease develops again in 21% of patients, after 5 years - in almost 47%, and after 5 years - in more than 55% of patients [10, 11]. At the same time, 41% of patients operated on for endometriosis-associated infertility subsequently cannot become pregnant [10]. According to L.V. Adamyan et al., without subsequent hormonal therapy, the disease recurs in 55% of women within 1 year, and with each subsequent year, an episode of endometriosis recurs in 10% of patients [1, 2].

MATERIAL AND METHODS OF RESEARCH: From 2021 to 2023, 234 women with infertility who applied to the private clinic "ProfMed" in Karshi were examined, 38% (n=89) were diagnosed with AGE, 16.2% (n=38) were diagnosed with tubal-peritoneal infertility (TBB); 59 (25.2%) were diagnosed with endocrine infertility, and 20.6% (n=48) had infertility that could not be detected. Of the 234 women with infertility, 89 women with IED (the study group) and 38 women with TPB (comparison group). The control consisted of 24 women without infertility with a successful obstetric and gynecological history. The criteria for the inclusion of patients in the study were: female infertility associated with AGE, infertility of tubal-peritoneal origin. Exclusion criteria: malformations of the genital organs, oncological diseases of the pelvic organs (including ovaries), other genesis of infertility. All patients underwent a complete clinical and laboratory examination in accordance with the study of female infertility on an outpatient basis. Specially developed examination cards were used, taking into account the somatic state, gynecological and obstetric anamnesis, and the results of laboratory and clinical tests. The study of the redox balance of blood plasma and peritoneal fluid was carried out by ELISA using the HUMAN analyzer (Germany). Peritoneal fluid was aspirated from the Douglas space during laparoscopy immediately after the introduction of additional contrapertures prior to surgical manipulation. The samples were centrifuged to free themselves from the cell fraction, then stored at -20° C. until the analytical step, and the samples were thawed at room temperature.

RESEARCH RESULTS: The average age of patients with AGE (n=89) was 31.2 ± 2.9 years, patients with

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EG - 32.7±4.2. In the studied women with EG, primary infertility was diagnosed in 60 (67.4%) of the examined, secondary infertility - in 29 (32.6%) (Table 1). Whereas in the group of women with EG, the opposite trend was noted and primary infertility was detected only in 15 (39.5%) women, and secondary infertility in 23 (60.5%) women. The analysis of the obstetric history revealed that among the patients suffering from endometriosis-associated infertility, 60 (67.4%) patients had no history of pregnancy, 17 (19.1%) patients had a history of childbirth through the vaginal birth canal or by cesarean section, 12 (13%) patients had a history of abortions (8 patients had induced abortion and 4 patients had spontaneous abortion). Of the 23 (60.5%) patients with TBT who had a history of pregnancy, childbirth was noted in 17 (73.9%) patients, ectopic pregnancy was observed in 6 (26.1%) patients (all patients underwent unilateral tubectomy), induced abortion at the patient's request was performed in 13 (56.5%) cases, spontaneous termination of pregnancy was observed in 8 (34.8%) patients.

When collecting a gynecological anamnesis, it was found that at least once in 25 (28.1%) patients of the NGE group, a 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 terms of frequency was occupied by menstrual disorders, more often by the type of anovulatory cycle, which were observed in 18 (20.2%) women with AEH. Hyperplastic processes of the endometrium (polyp and hyperplasia), which were detected in 13 (14.6%) patients. Underlying cervical diseases were noted in the anamnesis of 7 (7.9%) patients with AEH. In the remaining 17 (19.1%) patients with endometriosis-associated infertility, the gynecological history was not burdened.

In 16 (42.1%) patients of the group with TBD, the gynecological history was aggravated by PID, the common cause of which was urogenital infection.

Table 1
Obstetric and gynecological history of the women studied

Anamnesis	Infertility and IEG Group (n=89)		Group with TBB (n=38)		Control (n=24)	
	Abs	%	Abs	%	Abs	%
Birth	17	19,1**▲	17	44,7*	24	100
Spontaneous miscarriage	4	4,5▲▲	8	21,1**	1	4,2
Abortion	8	9,0▲▲	13	34,2**	2	8,3
Ectopic pregnancy	3	3,4*▲▲	6	15,8**	0	0
Primary infertility	60	67,4**▲	15	39,5**	0	0
Secondary infertility	29	32,6**▲	23	60,5**	0	0
MC disorders	18	20,2*▲	5	13,2	3	12,5
PID	25	28,1*	16	42,1**	4	16,7
Hyperplastic processes in the endometrium	13	14,6**	4	10,5**	0	0
Uterine fibroids	4	4,5*▲	1	2,6*	0	0
Adenomyosis	5	5,6*	0	0	0	0
Cervical diseases	7	7,9*▲▲	7	18,4**	1	4,2
Absence of gynecological diseases	17	19,1**	5	13,2**	16	66,7

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

Menstrual irregularities (MC), more often in the form of polymenorrhea during ovulatory cycles, were observed in 5 (13.2%) patients with TBD. In 4 (10.5%) patients of this group, hysteroscopies with separate diagnostic curettage were performed for hyperplastic processes and endometrial polyp. Cervical pathology was noted in anamnesis in 7 (18.4%) patients with TBD. The absence of indications of previous gynecological diseases in anamnesis was revealed in 5 (13.2%) patients of this group.

The clinical picture of IEG 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

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following days of the menstrual cycle. Pain was also localized in the lower abdomen, lower back with a pronounced manifestation during menstruation itself. Complaints about dyspareunia were made in 5.6% of cases. Mainly in women, the average degree of severity of pain syndrome was determined (59.6%), the mild degree was 19.1%, respectively, in 21.3% of cases - severe. It should be borne in mind that the degree of severity of the pain syndrome was subjective. The psychological component of the assessment of pain is largely related to the psycho-emotional state of the woman herself, which could not be associated with 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 endometrioid cysts, pain syndrome could be present in minimal values, and with a slight spread of endometrioid foci to the abdominal surface of the sacrouterine ligaments and the rectovaginal septum, it could be accompanied by a pronounced pain syndrome.

Ultrasound of the pelvic organs made it possible to clarify the localization, size of endometrioid cysts, but did not reveal superficial implants determined later 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 which in 71.9% (n=64) of cases a double contour was revealed, 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. In half of the cases, the cysts were of uniform consistency in the form of a finely dispersed non-displaced suspension, in some cases there were thickened formations, mainly oval-shaped, and were blood clots. The ultrasound picture of retrocervical endometriosis was characterized by the formation of a dense consistency located in the posterior cervical retrovaginal tissue, with localization both under the cervix and above and on the side of the cervix.

At the 2nd stage of the study, a laparoscopic examination was performed. Among the women of the main group (external genital endometriosis), the presence of endometrioid cysts was noted in 89 women (100%), who were mainly in the I and II stages of spread (Fig. 1). In this group, in 40.5% of cases (n=36), stage I was diagnosed, which was characterized by the presence of small punctate formations on the surface of the ovaries, as well as formations including the peritoneum of the rectal-uterine space, but no cystic formations were noted.

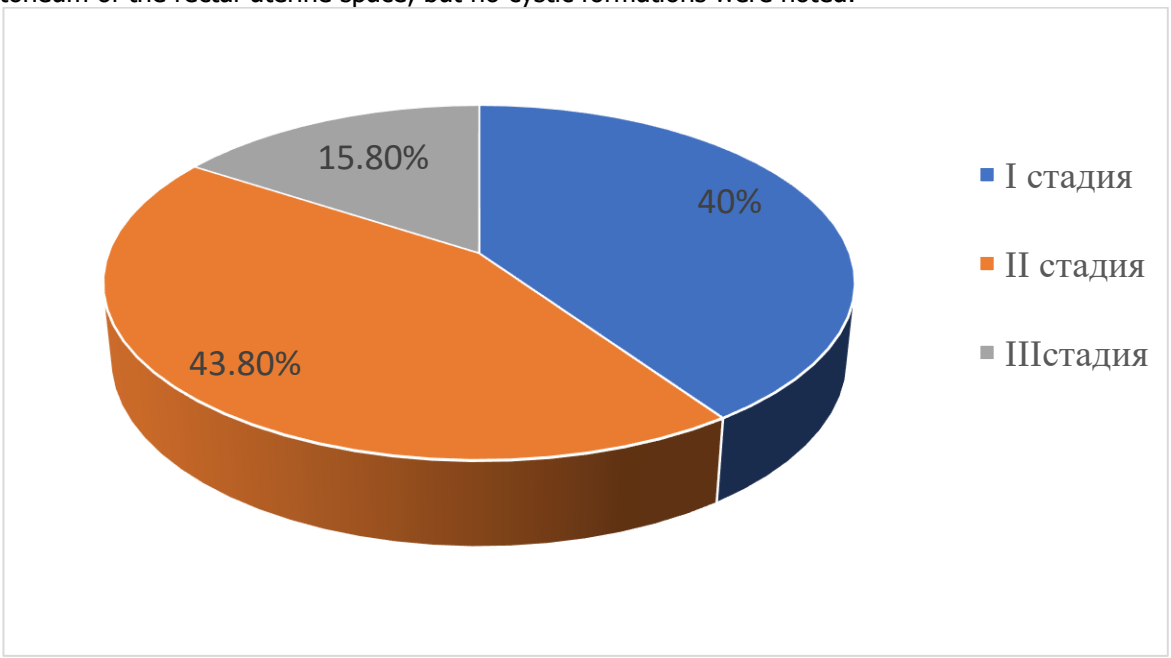

Fig.1. Distribution of women with endometrioid ovarian cysts by stages.

In 43.8% of cases (n=39), the second stage of ovarian endometriosis was diagnosed, while the size of the formed ovarian cysts in most cases was 3-4 cm (3.4±1.2 cm), with the presence of fine-point formations on the peritoneal tissue of the pelvis. There were also single adhesions around the ovaries and fallopian tubes, without involvement of intestinal tissue. In 15.7% of cases (n=14), stage III of the spread of ovarian endometriosis was diagnosed, while the size of the cysts averaged 5.11±0.2 cm. The presence of stage IV ovarian cysts was not observed in our studies, i.e. women with this stage of development were absent during diagnostic measures.

The accuracy of laparoscopic diagnosis of endometrioid cysts was 100%. The insufficiency of laparoscopic manipulations was the difficulty of establishing the boundaries of growths in the infiltrative processes of endometriosis foci. In difficult-to-diagnose cases, the diagnosis of endometriosis was confirmed on the basis of histological examination of the biopsy obtained or removed endometrioid foci.

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To study the relationship between AGE and redox balance in the development of infertility, we studied the indicators of lipid peroxidation and the system of their detoxification in the women under study. As mentioned above, the problem of the development of IEG from a pathophysiological point of view has a multicomponent mechanism in which many systems are involved. This dictates the need to search for the mechanism of pathogenetic changes in AGE leading to infertility. To some extent, such a system can be the determination of the intensity of lipoperoxidation processes and the system of antioxidant protection. To determine the relationship between the severity of IEU and the processes of POL and AOS, we divided 89 women with IEG into 2 subgroups: 1 subgroup – 75 women with IED of I-II degrees; Subgroup 2 – 14 women with IEG III degree.

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

From the data presented in Table 2, it can be seen that in the groups of women with IEG of I-II degrees, there is a significant intensification in the indicators of LPO processes in the peritoneal fluid compared to the comparison group, which is manifested in an increase in NL ($P<0.01$), GPL ($P<0.001$), DK ($P<0.001$), OI ($P<0.01$). In the group of women with grade III EGE relative to the values of the comparison group, the values of the HPL increase by 5.1 times ($P<0.001$), and the DC – by 6.4 times ($P<0.001$), with a smaller increase in NL by 2.1 times ($P<0.01$), leads to an increase in the value of the oxidative index (OI) by 2.5 times ($P<0.001$). The values of the group of women with TBP were as close as possible to the reference values of the laboratory.

Table 2.
Values of LPO products in peritoneal fluid in the study groups of women (M±m**)**

POL indicators	1 subgroup with NGE I-II (n=75)	Subgroup 2 with NGE III (n=14)	Comparison group with TPB (n=38)
NL, units op.pl./ml	1,724±0,161	2,93± 0,21*▲	1,374±0,143
GPL, units op.pl./ml	0,721±0,097	2,713±0,371**▲▲	0,537±0,083
DC units op.pl./ml	0,193±0,029*	0,421±0,089**▲▲	0,066±0,011
Olympic Games	0,431±0,081	0,906±0,105*▲	0,369±0,069

Note: * - a significant difference from the indicators of the group with TPB (* - $p<0.01$; ** - <0.001); ▲ - a significant difference in indicators from the group of women with EGE of 1-2 degrees (▲ -$p<0.01$; ▲▲ - $p<0.001$).

Activation of lipoperoxidation processes is directly related to changes in the functioning of the antioxidant system (AOS), which is interrelated with the degree of severity of cellular mechanisms of inflammatory reactions. While in the comparison group, the total antioxidant activity (AOA) in the peritoneal fluid, catalase activity, and the concentration of mean molecular weight peptides (SMP) did not have statistical differences ($P>0.05$), in the main study group of women with IEU, total AOA and catalase activity had significantly low values ($P<0.01$; $P<0.05$), and the NSR concentration increases to a lesser extent, but also significantly ($P<0.05$).

Table 3.
Indicators of the AOC system in the study groups of women
groups of women (M±m**)**

POL indicators	1 subgroup with NGE I-II (n=75)	Subgroup 2 with NGE III (n=14)	Comparison group with TPB (n=38)
AOA, %	22,4±1,05	16,6±0,84**▲	25,1±0,97
Catalase, mcat/l	20,7±1,3	15,9±0,93*▲	22,35±1,03
SMP, u/l	0,23±0,022	0,286±0,024*▲	0,221±0,028

Note: * - a significant difference from the indicators of the group with TPB (* - $p<0.05$; ** - <0.01); ▲ - a significant difference in the indicators from the group of women with IE of 1-2 degrees ($p<0.05$).

Determination of the intensity of LPO processes in women with AGE showed that, despite the tendency to increase the intensity of lipoperoxidation depending on the severity of the disease, these values do not reach significant changes in grade I-II ($p>0.05$), and are significantly increased in grade III EHE ($p<0.01$). In terms of AOC in women with endometrioid cysts, depending on the stage of the disease, there is a decrease in total AOA and catalase activity in stage II and III, compared to the data in stage I ($p<0.05$). The

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NSR values do not reach significant changes depending on the stage ($p>0.05$).

Thus, studies of women with AGE 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 in the future, treatment tactics. It should also be noted that with a developed clinical picture of the disease, the quality of life of patients significantly decreases, the reproductive function becomes impaired, which does not allow a woman to fully realize her reproductive potential. The presented data show that women with AGE develop oxidative stress as a result of a change in the functioning between the processes of lipid peroxidation and the AOP system, with the predominance of radical formation processes over the processes of their inhibition. The reasons for this are an active inflammatory process in the endometrioid foci, peritoneum, pelvic organs. The capabilities of the AOP system in NGGE are insufficient to limit oxidative processes with its long-term severity. All this creates additional conditions for maintaining oxidative stress, due to impaired lipid regulation by the AOP system and a positive feedback of the functioning of the pathological cycle between oxidative phosphorylation and the degree of LPO activity.

Consequently, in women with AGE, various etiological factors cause an increased secretion of inflammatory mediators of a lipid nature, and with the insufficiency of the AOP system, an inflammatory process develops in the endometrioid foci, peritoneum and pelvic organs. Apparently, with short intervals between menstrual cycles, favorable conditions are created for the effect of peroxide radicals, under which the immune system of the woman's body cannot cope with the utilization of menstrual material, which affects and grows on the appendages of the uterus, peritoneum and other tissues.

FINDINGS:

1. The incidence 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 depended on the severity of the pathology. The indicators of the antioxidant profile of the peritoneal fluid are 1.5 times higher in external genital endometriosis of I-II severity than in stage III.
3. All women with AGE in combination with hormonal and surgical therapy should include antioxidant therapy to reduce the recurrence of the pathology.

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