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Activity of Antioxidant System in Patients with Uterine Fibroids

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Abstract--- *Uterine fibroids are one of the most common benign tumors of the female reproductive system [1]. According to modern concepts, uterine fibroids are defined as a benign non-specific hyperplastic process in the myometrium, in the pathogenesis of which a number of factors take part [2]. Nowadays the hormonal theory in the etiology of the growth and occurrence of uterine fibroids is the most relevant [3]. A number of authors connect the growth of fibroids with an increased level of estrogen that develops in the tissues of the tumor itself [4]. Recently, the role of endogenous intoxication as the main pathogenic mechanism of the development of this disease has been studied in detail. Researches aimed at studying this problem prove that all the main pathophysiological manifestations of endogenous intoxication are determined by a destruction of structural and functional organization of the membranes, which ultimately leads to destabilization and disruption of cell growth and Division.*

Keywords--- *Activity of Antioxidant, Uterine Fibroids, Growth and Division.*

I. ANNOTATION

Uterine fibroids are one of the most common benign tumors of the female reproductive system [1]. According to modern concepts, uterine fibroids are defined as a benign non-specific hyperplastic process in the myometrium, in the pathogenesis of which a number of factors take part [2]. Nowadays the hormonal theory in the etiology of the growth and occurrence of uterine fibroids is the most relevant [3]. A number of authors connect the growth of fibroids with an increased level of estrogen that develops in the tissues of the tumor itself [4]. Recently, the role of endogenous intoxication as the main pathogenic mechanism of the development of this disease has been studied in detail. Researches aimed at studying this problem prove that all the main pathophysiological manifestations of endogenous intoxication are determined by a destruction of structural and functional organization of the membranes, which ultimately leads to destabilization and disruption of cell growth and division.

There are many reasons for the depletion of "antioxidant status." The most important of them:

1) Decreased intake of exogenous antioxidants. This factor manifests itself in temperate latitudes in the winter - spring period, when food is sharply depleted in antioxidants or in other periods of limited consumption of vegetables and fruits, for example, for dietary reasons.

2) Neuro-emotional load on the body.

3) The intake of prooxidants, which include many pesticides, drugs - oxidizing agents, photochemical products, etc.

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4) Hypokinesia with its reduced level of biological oxidation.

5) Excess intake of fats and carbohydrates into the body with insufficient consumption.

6) Physical factors (increase in radioactive background, ultraviolet radiation or electromagnetic fields)

7) Violation of the pro- and antioxidant balance, in various diseases, allows us to consider the activation of the body's reactions to extreme effects, and the accumulation of products of the free radical lipoperoxidation reaction in the body of protection that occurs in the critical phase of endotoxemia.

Along with the significant role of lipid peroxidation processes in the development and course of many diseases, the study of the intensity of the rate of oxidation reactions during tumor growth is of particular importance.

With the development of the tumor process in the body, the potential for initiating free radical reactions is realized and numerous experimental studies and clinical data confirm the intensification of LP.

Since one of the main links in endotoxemia is the activation of lipid peroxidation, according to some authors, it becomes necessary to pharmacologically correct this pathological condition by using antioxidants [5].

The clinical manifestations of uterine fibroids depend on the size of the tumor, the location of the myomatous nodes and their number.

Abnormal uterine bleeding (usually hypermenorrhea and polymenorrhea) is the most pathognomonic sign of uterine fibroids. The severity of bleeding is gradually increasing, this leads to severe iron deficiency anemia. Sometimes intermenstrual bleeding can be observed.

Uterine fibroids without complications are usually not accompanied by pain. Clinic of pelvic compression usually occurs if the myomatous uterus or node reaches sizes corresponding to 10-12 weeks of pregnancy or more. Violation of urination and defecation occur when myoma is compressed by the anatomically nearby organs - the bladder and rectum. In connection with passive outpatient monitoring of patients with uterine myoma, until the onset of indications for surgery, patients often have severe hemostasis disorders. Which, as is known from clinical observations, are not only not eliminated, but in some cases even exacerbated, which requires lengthy rehabilitation measures. That is why it is necessary earlier, from the moment of detection of the disease, the conduct of therapeutic and preventive measures. The latter should precede surgery and sometimes avoid it. Absolute contraindications for conservative treatment is a suspicion of sarcomatous degeneration of the tumor, the birth of a submucosal node, a combination of uterine fibroids with an ovarian tumor, uterine cancer, rapid tumor growth during pregnancy, impaired function of adjacent organs, with a uterus greater than 12 weeks, with an interstitial node with centripetal growth, with menorrhagia causing anemia.

As a rule, uterine fibroids develops against the background of concomitant systemic disorders in the woman’s body, the severity of which depends on the duration of the disease, even despite the clinically un symptomatic course of the disease. With the rapid growth of the tumor and severe clinical symptoms in the form of chronic pathological blood loss, the manifestations of secondary functional and metabolic disorders develop significantly quickly. An indirect assessment of changes occurring under the influence of changes in the hormonal status of women before and after a hysterectomy can be done by identifying differences in the content of normal parameters of blood serum metabolites. Objective: to study the activity of various indicators of the antioxidant system and hormonal levels of women with uterine myoma before and after hysterectomy.

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II. METHODS

The basis of the study was Republican Clinical Hospital №4, Department of Surgical Gynecology, Saransk. During the period from November 2018 to December 2019, we examined 30 patients with uterine fibroids from 31 to 45 years old, average age was 39 (0,5) years. The largest number of women - 12 (41.2%) had a fibroid size corresponding to 10-12 weeks of pregnancy. Patients were conditionally divided into 3 groups depending on the increase in myomatous nodes before and after hysterectomy. Group A included 8 women with a submucous node and uterus size corresponding to 6–9 weeks of pregnancy. Group B included 12 women with uterus size corresponding to 10-12 weeks of pregnancy. Group C included 10 women with uterus size corresponding to 13-15 weeks of pregnancy. As a control, 20 women who did not suffer from uterine fibroids and other extragenital pathology accompanied by endogenous intoxication were examined. The age of the women in control group corresponded to the age of the patients in research group. Clinical examination of women was carried out according to the traditional plan, including a medical history taking and assessment of general somatic and gynecological statuses.

III. RESULTS

In 18 patients (59.6%), the age interval was 31–40 years, that shows the trends of this pathology toward decrease in middle age. The duration of the disease averaged 4.5 (0.3) years, for the first time this disease was diagnosed in 5 (3.7%) patients. A disease duration of more than 3 years was detected in 14 (44.3%) patients. In gynecological history of the women examined, we studied: the formation of menstrual function, the types of its disorders, the number of pregnancies, childbirths, induced abortions, spontaneous miscarriages and non-developing pregnancies, the presence of concomitant gynecological diseases and surgical interventions on the internal and external genital organs. An analysis of the formation and features of menstrual function revealed a later formation of 1-3 years in 12 patients (40%) and its disorder in the form of menorrhagia - in 24 (80%) women. In control group, a larger percentage of women had an early formation of menstrual function - 6 patients (20%), and their disorder as menorrhagia was not observed. Most often, in women with uterine myoma, endometrial polyps were observed - in 9 patients (30%), endometritis - in 4 patients (13.3%), cervical canal polyps - in 3 patients (10%), 6 (20%) patients had previously suffered inflammation of uterine appendages. A combination of this tumor with the pathology of the mammary glands (mainly fibrocystic mastopathy, diffuse mastopathy) was also noted - 11 (36.6%) patients (Table 1).

Table 1: Concomitant Gynecological Diseases in the Examined Women with Uterus Fibroids

Nosological forms	Groups of women examined			
	Main group		Comparison group	
	Abs.	%	Abs.	%
Endometritis	4	13,3	2	10
Salpingoophoritis	6	20	3	15
Endometrial polyps	9	30	4	20
Endometriosis	2	6,6	-	-
Pelvioperitonitis	1	3,3	-	-
Genital Cysts	1	3,3	-	-
Cysts and ovarian cystomas	1	3,4	2	11
Ectopia of the cervix	2	6,6	3	16
Cervical Canal Polyp	3	9,9	2	10
Colpit	1	3,3	1	5
Concomitant gynecological diseases not detected	-	-	3	15

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According to the results of previous histological studies of the endometrium, the most common in patients with this pathology was endometrial hyperplasia - in 12 (40%). Thus, the analysis of the examination indicates that the gynecological health indicators in patients with uterine fibroids are lower than in women in the comparison group . Of the somatic diseases in patients with uterine myoma, the most common pathologies were: anemia - 26 (86.6%), obesity - 17 (56.6%), arterial hypertension - 12 (40%). Given the data on extragenital pathology, it can be assumed that the examined women of the main group have somatic health lower than the examined women of the control group, which suggests that there is an unfavorable premorbid background that contributes to the development of this pathology.

A bimanual examination, supplemented by the results of ultrasound, dopplerometry, diagnostic curettage of the endometrium and the study of a macrodrug after hysterectomy for fibroids, revealed that the nodular form of fibroids was observed in 30 (100%) patients. The size of the nodes ranged from 5 to 10 cm in diameter. The distribution of patients by the localization of nodes in the uterus was carried out by the location of the node of the largest diameter.

The nodes were more often localized in the body of the uterus - 18 (60.3%) women, of which intramurally - 9 (30%) patients, submucous - 8 (26.6%), subserous - 1 (3.3%) patients. Interstitial nodes were located more often in the bottom of the uterus - in 4 patients (13.3%) and in its posterior wall - in 3 patients (9.9%). The growth of submucous nodes was also diagnosed more from the bottom of the uterus - 4 (13.3%) and from its lateral walls - 3 (9.9%). Subperitoneal nodes were more often localized in the bottom of the uterus - 1 (3.3%). Thus, the analysis of the location of all nodes (intramural, subserous, submucous) in the uterine body revealed their greatest localization in its bottom - 9 (30%) and lateral wall 4 (13.3%).

To analyze the state of the level of endogenous intoxication in women of research group, laboratory studies were carried out upon admission to the hospital (before treatment), on the 3rd, 5th day and at the end of treatment.

The following biochemical parameters were determined in the blood serum of patients: 1. Indicators of the lipid and lipoprotein spectra of blood serum (total lipids, triglycerides, total cholesterol, HDL, LDL). 2. Middle molecules 3. The content of the final product of the oxidation of malondialdehyde (MDA) in plasma and red blood cells. 4. Catalase activity. 5. The level of estradiol and progesterone.

The study of the content of total lipids in the blood serum of patients was carried out using test kits manufactured by "Olveks-Diagnosticum" (St. Petersburg). The content of MDA in blood plasma was studied using reagents of "Agat" company (Moscow), serum catalase activity was determined by spectrophotometric method, the content of estradiol and progesterone in serum was studied by enzyme-linked immunosorbent assay before and after hysterectomy in the examined patients and women of the control group. Statistical processing of the results of experimental and clinical studies was performed using the MEDSTAT program (author V.L. Akimov). The arithmetic mean (M) and the standard deviation of the arithmetic mean (m) were calculated.

As the small sample sizes do not guarantee the normal distribution of the studied indicators, the use of parametric statistical criteria, in particular, the Student criteria, seems incorrect and can only be used as accessory methods. To assess the statistical significance of the differences of the compared average values, the Mann-Whitney

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test was used, an assessment of the structure of concomitant gynecological pathology (Table 1), was carried out by checking the ratio of sample percentage by the Pearson criteria using the XI2TEST function of Microsoft Excel. The results of the Anna-Whitney test turned out to be quite consistent with the Student criteria, which we use as an additional one.

Differences were recognized as statistically significant at a value level of at least $p < 0.05$.

3.1. Determination of Malondialdehyde (MDA) in Plasma and Red Blood Cells of Patients

Lipid peroxidation is the most important physiological mechanism which controls the cellular functions that lie in the formation of a common adaptation syndrome. However, the free-radical mechanism of lipid peroxidation gives this process a twofold character: along with the regulatory mechanism, there is a possibility of transition of reversible changes in cell membranes to irreversible, and adaptive changes to pathological [6]. Therefore, we set the task to study some indicators of lipid peroxidation in patients with uterine fibroids, in order to identify the role of damage of cell membranes in the pathogenesis of this disease.

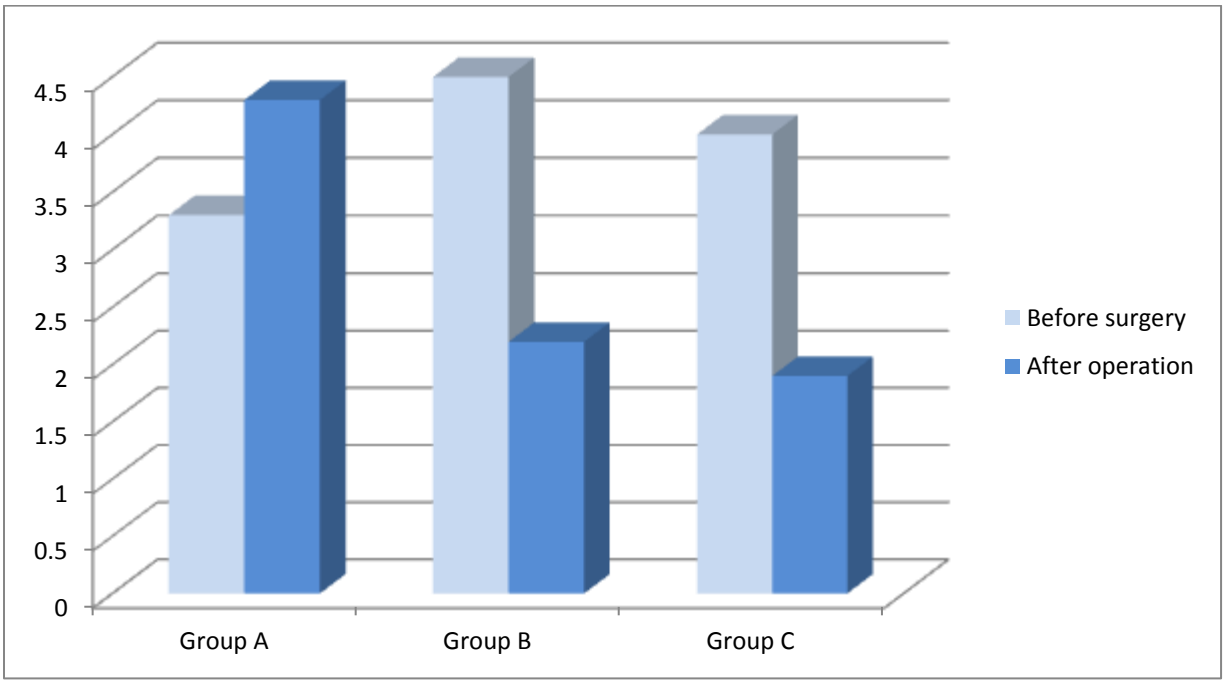

Figure 1: MDA Content (μmol / L) in Patients with Uterine Myoma After Hysterectomy

As can be seen from Figure 1, in patients of groups B and C, the concentration of MDA is higher than in the group A, and in this group its level is slightly lower than the reference values: 2.2 - 4.8 μmol / L. Catalase activity in these groups varies in accordance with the level of MDA. Hysterectomy leads to a small increase in the rate of lipid peroxidation in women with smaller fibroids, while in patients with large tumor sizes, the rate of lipid peroxidation is significantly reduced. It is important to note that after a surgical approach of removal the uterine body in group A, a slight increase in catalase activity is detected, while in the other two groups, the enzyme activity lowers sharply, and this decrease shows a positive correlation with the level of MDA. Most likely, this happens due to the traumatic effect of the surgical intervention itself and also antioxidant system of the macroorganism did not manage to adapt

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to pathological changes. A change in the rate of uncontrolled LPO reactions during hysterectomy can be a reason for suppressing the synthesis of reactive oxygen species due to the removal of a trigger factor, for example, a change in either the level of hormones or a interruption of their reception in the uterine myometrium. This is confirmed by changes in catalase activity, reflecting the functioning of the antioxidant system of the body. (Figure 2).

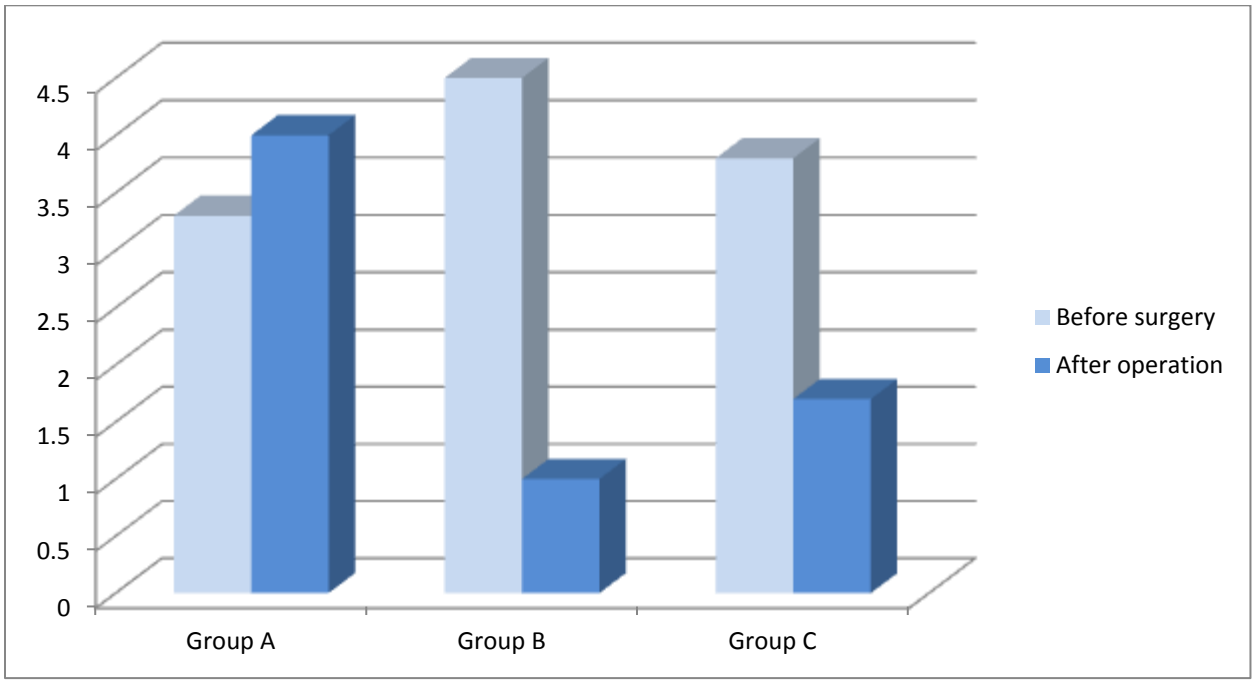

Figure 2: Catalase Activity (µcat / L) in Patients with Uterine Myoma After Hysterectomy

When comparing the indicators with parameters of control group, it was found that the content of MDA in plasma and erythrocytes exceeded in patients with uterine myoma and amounted to 6.87 ± 0.05 µm / L and 54.82 ± 1.22 µm / L, which is higher control group indicators by 34.6% ($p < 0.001$) and 52.3% ($p < 0.001$). Blood catalase activity reached the level of 2052.17 ± 27, 82 mmol / min / l, which is only 3.3% more than the similar indicator in the control group ($p < 0.05$).

3.2. Determination of Middle Molecules Content in Blood Serum

One of the universal markers of endotoxin is middle molecules content. In the blood of healthy people, they present in small amounts in plasma and deposited on red blood cells, accumulating in the body with inhibition of the natural mechanisms of detoxification and metabolic disorders in various diseases, including uterine fibroids [7]. They are able to connect and block the receptors of any cell, adversely affecting its metabolism and function. (Table 2).

Table 2: Content of Middle Molecules

Indicators	Examined groups of women	
	Main group (n = 30)	Comparison group (n = 20)
MSM, 254 nm	273,14 ± 2,37	246,02±1,68
MSM, 280 nm	432,38±2,91	258,43±1,87

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A higher level of the indicator at a wavelength of 280 nm in patients with this pathology indicates a clear violation of the detoxification properties of the liver. Analysis of the presented data revealed the predominance of peroxidation reactions in patients with uterine fibroids, which leads to damage of the biological membranes of cells. Thus, the antioxidant system can't cope with the neutralization of the damaging effects of free radicals. The obtained LPO indices, together with the data of middle molecules, prove the existence of pronounced endogenous intoxication in patients with uterine fibroids [8].

3.3. Determination of Lipid Profile

In women prior to surgery an increased level of total cholesterol was observed (normal level is <5.0 mmol / L) with normal HDL, and in patients of group B and C the total cholesterol content was higher, which may be the reason of decreased excretory ability of the liver resulting from metabolic hepatitis that develops with uterine fibroids, and also reflect an increase in the synthesis of steroid hormones, the precursor of which is cholesterol. In addition, an increase can occur as the outcome of both interconnected processes, since cholesterol formed in hepatocytes is transported to the ovaries and adrenal cortex and acts as a substrate for the synthesis of sex hormones [9]. The last circumstance is confirmed with the observed decrease in the reverse transport of cholesterol in the form of HDL cholesterol, as well as changes in the level of female sex hormones - estradiol and progesterone. Before the treatment, the level of total lipids in patients of group A was 3.89 ± 0.59 g / l with normal triglycerides (0.97 ± 0.43 mmol / l), while in patients of the other two groups the concentration of total lipids and triglycerides was within normal limits. A hysterectomy leads to a decrease in the concentration of total lipids (in patients of group A their level dropped even lower than the initial limits (3.63 ± 0.75 g / l), while in patients of groups B and C a decrease in the concentration of total lipids was not out of initial limits. At the same time, an increase in the content of triglycerides is noted and its increase correlates with the size of the tumor. It is also important to note that before hysterectomy the triglyceride content has a negative correlation with the size of the tumor (the larger the size of the fibroids, the lower their level), while the operation leads to the opposite situation (the increase in the level of triglycerides in the blood serum of patients is greater, the greater size of the removed tumor). The changes we observe can also indicate either a change in the hormonal background of patients, or functional liver failure. The dynamics of triglycerides before and after surgical treatment is more evidence of the assumption of functional disorders that occur in hepatocytes [10], since the results obtained by subsequent measurement of estradiol and progesterone do not show consistency with changes in triglycerides in patients of group A, the tumor size of which corresponds to 6-9 weeks of pregnancy: before hysterectomy, higher values of the concentration of triglycerides are noted than in patients of the other two groups, while the content of female sex hormones in their serum is lower.

Thus, the study of indicators of the lipid spectrum has important clinical and prognostic value showing the change in the hormonal background of patients before and after hysterectomy, as well as the functional activity of the liver the timely restructuring of which significantly determines the compensatory and adaptive capabilities of the body.

3.4. Determination of the Concentration of Estradiol and Progesterone

In the study, the concentration of estradiol and progesterone in patients with uterine fibroids showed a positive

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correlation with the size of the tumor: the larger the size of the tumor, the higher the level of these hormones, although their content does not differ from the level of hormones in healthy women of reproductive age, depending on the phase of the menstrual cycle. Our results are consistent with the data of Vikhlyaeva E.M, 2016 [11], which noted that in about 2/3 of patients the level of hormones of the menstrual cycle does not differ from the corresponding normative indicators. Thus, in patients with uterine myoma, the concentration of estradiol in the blood in terms corresponding to the phase of the corpus luteum does not differ from that in healthy women of reproductive age, regardless of the nature of the menstrual cycle, while the content of progesterone corresponds to the nature of the menstrual cycle.

A hysterectomy leads to a decrease in the concentration of estradiol and progesterone in the blood of women, while the estradiol content does not exceed normal values and tends to decrease more markedly in individuals with small sizes of the removed tumor. At the same time, the level of progesterone in all patients, regardless of the phase of the menstrual cycle during hysterectomy, significantly decreases to values characteristic of the follicular phase of the cycle. It should also be noted that regardless of the size of the fibroids, the concentration of progesterone after amputation of the uterus is significantly reduced to the same numbers.

IV. CONCLUSIONS

Patients have a clear relationship between the rate of lipid peroxidation and the activity of the antioxidant system of the body. Changes in the parameters of lipid peroxidation rate and antioxidant defense during hysterectomy show better results for the correction of this system in operated patients with small fibroids than in women whose tumor size exceeds 13 weeks.

In women, prior to surgery of excision of the uterine body, there was an increased level of total cholesterol with a normal HDL value. Hysterectomy leads to a significant decrease in the level of total cholesterol simultaneously with a decrease in HDL and an increase in the proportion of LDL. This, most likely, is the reason for the change in the hormonal background of patients with hysterectomy, and such changes can also be the result of a change in the functional state of the liver. The content of triglycerides has a negative correlation with the size of the tumor in patients. Hysterectomy leads to the opposite situation.

The concentration of estradiol and progesterone in patients shows a positive correlation with the size of the tumor: the larger the mass of the tumor, the higher the level of these hormones. A hysterectomy leads to a decrease in the concentration of estradiol and progesterone in the blood of women, while the estradiol content does not exceed normal values and tends to decrease more markedly in individuals with small sizes of the removed tumor. The level of progesterone in all patients, regardless of the phase of the menstrual cycle during hysterectomy, is significantly reduced to values characteristic of the follicular phase of the cycle.

V. CONCLUSION

Based on the foregoing study, it is necessary to include in the examination program for patients with uterine fibroids the determination of biochemical parameters of lipid metabolism, lipid peroxidation rate, antioxidant system activity, level of endogenous intoxication and concentration of sex hormones.

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