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Parameters of Oxidative Stress in Women with Diffuse Mastopathy in the Menstrual Cycle Course

Lyudmila A. Grebenkina[1*], Marina A. Darenskaya[1], Elena V. Osipova[1], Evgeniya V. Galchenko[1], Anastasia S. Lyubochko[1], Sergey I. Kolesnikov[1] and Lyubov I. Kolesnikova[1]

[1]FSBSI "Scientific Center of Family Health Problems and Human Reproduction", 664003, Irkutsk, St. Timiryazeva 16, Russian Federation.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Despite the active study of the main pathogenetic mechanisms of benign breast diseases, there is still insufficient information on the lipid peroxidation – antioxidant defense processes activity in women with diffuse mastopathy in the course of menstrual cycle. Such knowledge is necessary for the early detection and prevention of hyperplastic processes and for the development of pathogenically based antioxidant therapy. Research hypothesis: the parameters of the lipid peroxidation – antioxidant defense system in women with diffuse mastopathy vary depending on the period of the menstrual cycle.
Objective: to assess the activity of lipid peroxidation and antioxidant system reactions in women with diffuse mastopathy during the menstrual cycle.
Materials and Methodology: The study included 29 women: 12 healthy ones (mean age 29.6 ± 2.32 years) and 17 women with diffuse mastopathy (mean age 28.8 ± 3.2 years). All women underwent standard collection of anamnesis and clinical examinations. For all women laboratory tests were performed to determine the concentration of lipid peroxidation products and antioxidant defense components. The tests were conducted every 3 days – on days 1–3, 4–6, 7–9, 10–12, 13–

**Corresponding author: E-mail: greblud@mail.ru;*

15, 16–18, 19–21, 22–24, and on days 25–28. Spectrophotometric and fluorometric methods were used.

Results: Patients with diffuse mastopathy showed an increase in double bonds on days 1–3 (by 1.3 times), days 7–9 (by 1.22 times), 19–21 (by 1.19 times), and on days 22–24 (by 1.53 times); in conjugated dienes – on days 1–3 (by 1.4 times), 4–6 (by 1.2 times), 7–9 (by 1.47 times), 16–18 (by 1.48 times; *P* = .02), and on days 19–21 (by 1.38 times); in ketodienes and conjugated trienes (during the whole cycle) – on days 1–3 (by 2.64 times), 4–6 (by 1.6 times), 7–9 (by 1.72 times), 10–12 (by 1.39 times), 13–15 (by 1.36 times), 16–18 (by 3.46 times), 19–21 (by 2 times), 22–24 (by 2.54 times), and on days 25–28 (by 3.1 times); in thiobarbituric acid reactants – on days 19–21 (by 1.36 times) and 22–24 (by 1.27 times) compared with the control group. Patients with diffuse mastopathy showed an increase in total antioxidant activity on days 10–12 (by 1.67 times) and 16–18 (by 1.5 times); a decrease in superoxide dismutase activity – on days 16–18 (by 1.09 times) and 25–28 (by 1.25 times), in oxidized glutathione levels – on days 16–18 (by 1.23 times), 22–24 (by 1.14 times), and days 25–28 (by 1.25 times); an increase in reduced glutathione – on days 1–3 (by 1.3 times); a decrease in retinol content – on days 1–3 (by 1.64 times), 4–6 (by 1.2 times; *P* = .044), 10–12 (by 1.36 times), 19–21 (by 1.24 times) and on days 25–28 (by 1.18 times), and in ascorbate content – on days 7–9 (by 1.11 times) and 10–12 (by 1.16 times).

Conclusion: During our study, we revealed an imbalance of lipid peroxidation – antioxidant defense system. For normalizing the balance in lipid peroxidation – antioxidant defense system, patients with diffuse mastopathy in the luteal phase of the menstrual cycle are recommended to use antioxidant drugs. To prove the general hypothesis further clinical trials are warranted.

Keywords: Diffuse breast pathology; women; lipid peroxidation; antioxidant defense; menstrual cycle.

1. INTRODUCTION

The non-specific biochemical processes occurring at the cellular level play the essential role in the pathogenesis of neuroendocrine diseases of the reproductive system [1,2]. One of the regulatory mechanisms of metabolism is the processes of lipid peroxidation (LPO) and antioxidant defense (AOD), the balance between which ensures cellular homeostasis at an optimal level for the body [3]. Adequacy of defense is ensured by the coherence of all links of the multi-stage anti-oxygen, anti-peroxide and anti-radical systems [4]. It includes low molecular weight compounds such as vitamins (α-tocopherol, ascorbate, retinol), proteins (transferrin, ceruloplasmin, etc.), which inactivate reactive oxygen species and secondary radicals formed with their participation [5]. Particular attention is paid to the low molecular weight non-protein thiol disulfide system based on glutathione. An equally important role is played by antioxidant enzymes (superoxide dismutase, glutathione peroxidase, glutathione reductase, etc.), which can inactivate reactive oxygen species, and toxic LPO products [6]. In pathological conditions in the body, the balance in the LPO-AOD system changes, which leads to the development of "oxidative stress" [4, 7].

In recent years, there has been an upward trend of benign breast diseases, which are detected in every fourth woman under the age of 30 [8]. About 75–80 % of women of reproductive age suffer from various diseases of the mammary glands, united by the general term mastopathy [9]. In accordance with the generally accepted classification principles, benign breast diseases are divided into focal and diffuse forms (diffuse mastopathy). In 26% of women of reproductive age, nodular forms of mastopathy were diagnosed, and in 54 % – a diffuse form, which is a benign process [10]. Despite the active study of the main pathogenetic mechanisms of benign breast diseases, there is still no information on the activity of LPO-AOD processes in women with diffuse mastopathy in the dynamics of the menstrual cycle. Such studies are necessary for the early detection and prevention of hyperplastic processes, as well as for the development of pathogenetically based antioxidant therapy for patients. In accordance with this, we formulated a research hypothesis: the parameters of the lipid peroxidation – antioxidant defense system in women with diffuse mastopathy change depending on the period of the menstrual cycle.

The aim of this work is to study the activity of the reactions of the LPO-AOD system in women with diffuse mastopathy during the different phases of menstrual cycle.

2. MATERIALS AND METHODS

Seventeen women with breast pathology aged 18 to 35 years were examined. Their mean age was 28.8 ± 3.2 years, the age of the first menstruation (menarche) – 12.7 ± 0.2 years, the average duration of the menstrual period – 4.8 ± 0.5 days, the duration of the menstrual cycle – 28.2 ± 1.6 days. Data from 12 somatically healthy women aged 18 to 34 years were used as a control. Their mean age was 29.6 ± 2.32 years, the age of the menarche – 13.0 ± 0.3 years, the average duration of the menstrual period – 5.2 ± 0.6 days, the duration of the menstrual cycle – 27.5 ± 1.2 days. Blood sampling was performed every 3 days (on the 1–3, 4–6, 7–9, 10–12, 13–15, 16–18, 19–21, 22–24, and 25–28th days of the cycle). The criteria for the inclusion of patients in the study were: age (from 18 to 35 years), the presence of diffuse mastopathy, the absence of nodular mastopathy (all patients were consulted by a mammologist), malignant neoplasms, decompensated mental, neurological, cardiovascular, endocrine diseases of moderate and severe severity, infectious diseases, acute diseases of the gastrointestinal tract and urinary system, as well as exacerbations of chronic diseases. In our work we used general clinical, instrumental, laboratory research methods. The presence and form of dyshormonal changes in the mammary glands, as well as their absence, were confirmed by the data of anamnesis, examination and palpation of the mammary glands, ultrasound scanning, X-ray mammography, and cytological examination. Mammography and ultrasound examination of the mammary glands were performed in phase I of the menstrual cycle. Ultrasound examination of the mammary glands was performed using Toshiba 140A and 340A devices (Japan).

Patient blood samples were centrifuged for 5 min at 1500 g at 4°C; and the erythrocytes were washed three times with 0.9% NaCl (w/v). Aliquots of ethylenediaminetetraacetic acid plasma and washed erythrocytes were used immediately or stored frozen at -40°C, but not more than one month. The intensity of LPO-AOD parameters was assessed using blood plasma concentrations of antioxidant parameters (total antioxidant activity (TAA), superoxide dismutase (SOD) activity, α-tocopherol, retinol, and ascorbate), double bonds (DB), primary and secondary products of lipid peroxidation (conjugated dienes (CD), ketodienes and conjugated trienes (KD-CT) and thiobarbituric acid reagents (TBAR)). Concentration of DB, CD and KD-CT was detected spectrophotometrically in heptane plasma extracts [11]. TBAR levels were detected by fluorometry [12]. To determine the SOD activity in the hemolysate activity, fluorometry was used [13,14]. The concentration of ascorbic acid was determined by the colorimetric method [15]. The content of reduced (GSH) and oxidized (GSSG) glutathione was measured by the fluorometric method [16]. The level of TAA of blood plasma was determined photometrically [17].

Statistical analysis was performed using the Statistica 6.1 software (Stat-Soft Inc., USA). To present quantitative data, the following characteristics were used: mean (M) and standard deviation (σ). To determine the normality of quantitative traits distribution, we used the visual-graphic method and the Kolmogorov – Smirnov goodness-of-fit test with corrections by Lilliefors and Shapiro – Wilk. Further, depending on the type of distribution, a parametric Student's t-test (for a normal distribution of data) or a nonparametric Mann – Whitney test (for a distribution other than normal) were used. Spearman's correlation analysis was used to analyze the intragroup relationship of quantitative traits. The critical level of significance was taken equal to 5% (.05).

3. RESULTS AND DISCUSSION

The content of DB in the blood serum of patients was statistically significantly higher than in the control group on days 1–3 (by 1.3 times; P = .002), 7–9 (by 1.22 times; P = .041), 19–21 (by 1.19 times; P = .044), and days 22–24 (by 1.53 times; P = .001) (Fig. 1a). It should be noted that in the middle of the menstrual cycle, the parameters under study in patients with diffuse mastopathy did not differ from the reference values.

The results of the studies showed that in patients with diffuse mastopathy in the middle of the cycle corresponding to the ovulatory period of healthy women, the concentration of CD in the blood serum was comparable to the control parameters. However, in other periods of the menstrual cycle, the content of CD increased: on days 1–3 (by 1.4 times; P = .001), 4–6 (by 1.2 times; P = .043), 7–9 (by 1.47 times; P = .044), 16–18 (by 1.48 times; P = .02), and days 19–21 (by 1.38 times; P = .015). The content of KD-CT increased relative to control throughout the entire menstrual cycle: on days 1–3 (by 2.64 times; P = .001), 4–6 (by 1.6 times;

P = .007), 7–9 (by 1.72 times; *P* = .001), 10–12 (by 1.39 times; *P* = .034), 13–15 (by 1.36 times; *P* = .045), 16–18 (by 3.46 times; *P* = .01), 19–21 (by 2 times; *P* = .001), 22–24 (by 2.54 times; *P* = .001), and days 25–28 (by 3.1 times; *P* = .002). On days 16–18, the concentrations of CD and KD-CT in the blood increased sharply by 1.5 and 3.4 times, respectively (Fig. 1b, 1c). serum of women with diffuse mastopathy

The content of TBAR in women with diffuse mastopathy compared with the control parameters increased: on days 19–21 – by 1.36 times (*P* = .049), on days 22–24 – by 1.27 times (*P* = .048) (Fig. 1d).

Activation of LPO processes in patients with breast pathology led to an increase in the blood TAA, increasing 1.67 times on days 10–12 (*P* = .004) and 1.5 times on days 16–18 (*P* = .018), which may indicate adaptive and compensatory capabilities of the body (Fig. 2a).

SOD activity was statistically significantly reduced on days 16–18 (by 1.09 times; *P* = .002) and days 25–28 (by 1.25 times; *P* = .031) (Fig. 2b). Reduced glutathione level increased on days 1–3 (by 1.3 times; *P* = .009), while oxidized glutathione level decreased on days 16–18 (by 1.23 times; *P* = .007), 22–24 (by 1.14 times; *P* = .047), and days 25–28 (by 1.25 times; *P* = .023) (Fig. 2c, 2d). The concentration of retinol in the blood serum of patients decreased on days 1–3 (by 1.64 times; *P* = .001), 4–6 (by 1.2 times; *P* = .044), 10–12 (by 1.36 times; *P* = .001), 19–21 (by 1.24 times; *P* = .025) and days 25–28 (by 1.18 times; *P* = .045) compared to the control parameters (Fig. 2e).

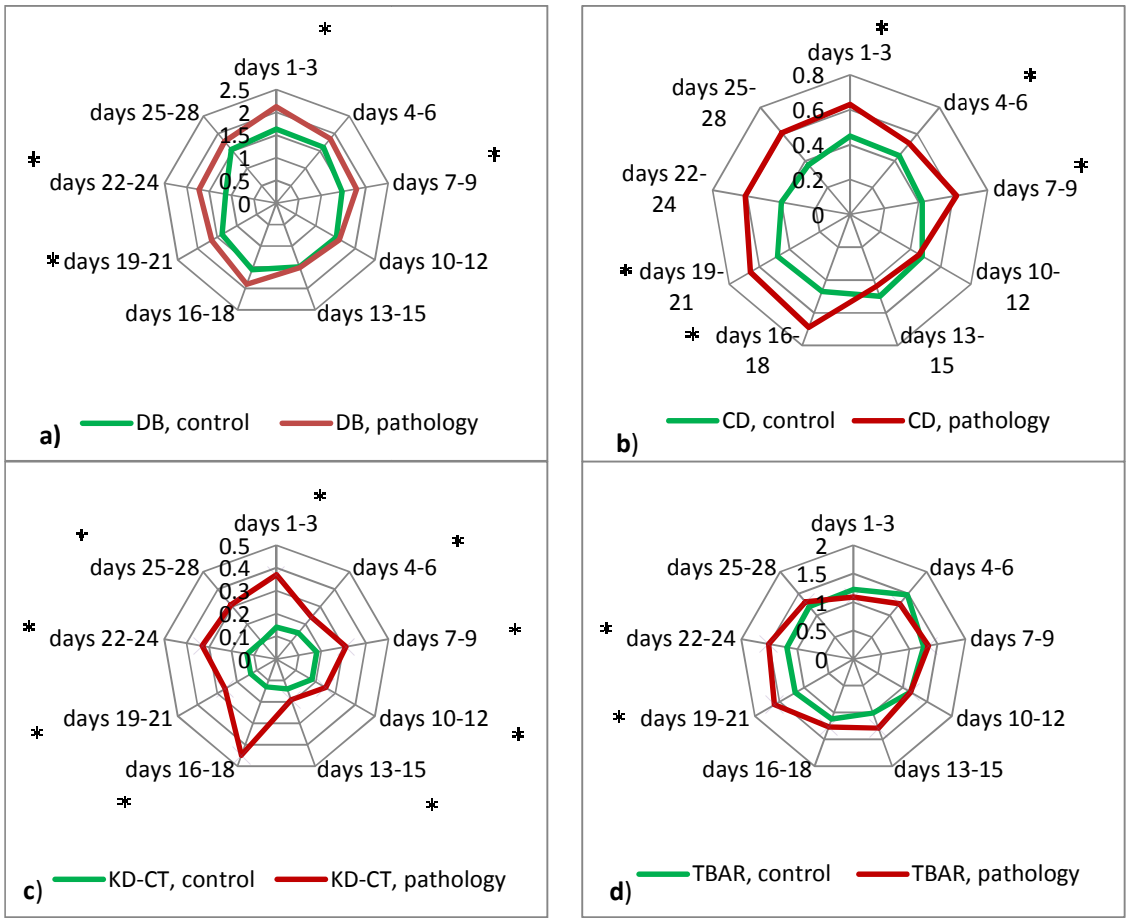

Fig. 1. Content of LPO products in the blood serum of women in the control group and patients with diffuse mastopathy: a) double bonds (DB), standard units; b) conjugated dienes (CD), μmol/l; c) ketodienes and conjugated trienes (KD-CT), standard units; d) thiobarbituric acid reactants (TBAR), μmol/l; statistically significant differences compared to control group

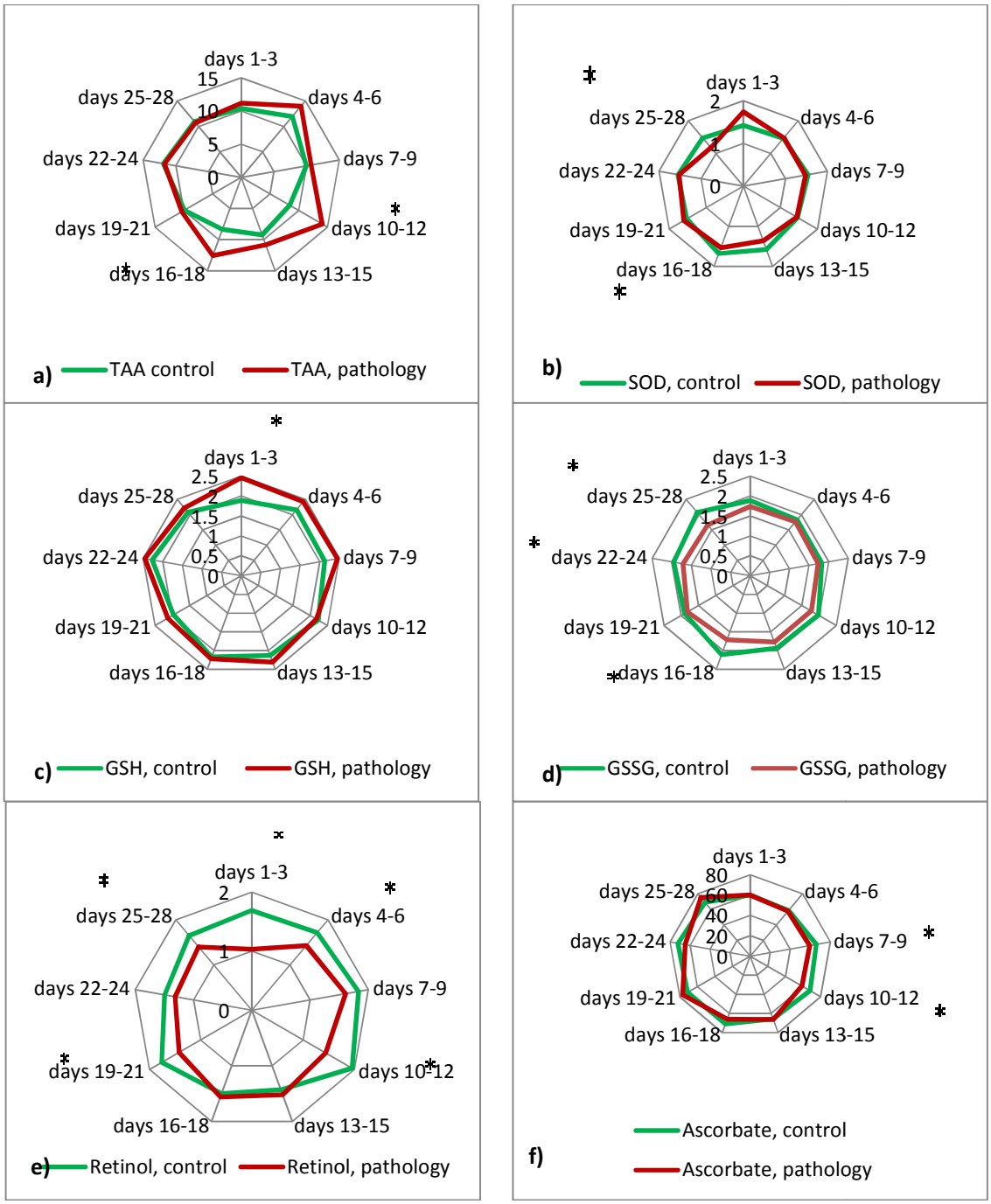

Fig. 2. Content of components of the AOD system in the blood of women in the control group and patients with diffuse mastopathy: a) total antioxidant activity (TAA), standard units; b) superoxide dismutase (SOD), standard units; c) reduced glutathione (GSH), mmol/l; d) oxidized glutathione (GSSG), mmol/l; e) retinol, μmol/l; f) ascorbate, μmol/l; statistically significant differences compared to control group

The serum ascorbate content of patients with diffuse mastopathy decreased on days 7–9 (by 1.11 times; *P* = .008) and 10–12 (by 1.16 times; *P* = .008) (Fig. 2f). The content of

α-tocopherol in the dynamics of the menstrual cycle in patients with diffuse mastopathy did not change.

It is known that physiological changes in a woman's reproductive system are controlled by the endocrine system, which ensures the regularity of the menstrual cycle, clearly dividing it into certain phases – follicular, ovulatory and luteal. It is obvious that such cyclicity can cause synchronous changes in various biochemical parameters of carbohydrate, lipid, protein metabolism, and the content of micro- and macronutrients [18,19]. In our study, it was found that the presence of a benign disease (diffuse mastopathy), has a certain effect on the indicators of the LPO-AOD system. Thus, the content of double bonds in patients with breast pathology at the main stages of the cycle significantly exceeded the control values.

There is evidence of an increase in the number of double bonds in the blood plasma in breast cancer patients compared with healthy women [20]. Therefore, an increase in the level of double bonds in the blood serum of patients with diffuse mastopathy can be regarded as an indicator of a pathological process.

Activation of the LPO cascade process leads to the accumulation of toxic products, which is expressed in a statistically significant increase in the concentrations of CD, KD-CT, and TBAR during the menstrual cycle in women with diffuse mastopathy. The activation of LPO processes is indicated by the accumulation of intermediate (CD, KD-CT) and final (TBAR) products during the menstrual cycle. Their lowest concentrations were recorded in the middle of the cycle, which presumably corresponded to the ovulatory period of healthy women. These molecular products play an important role in the processes of structural modification and changes in the physical and chemical properties of biological membranes. Excessive amounts of hydroperoxides, unsaturated aldehydes, and TBAR formed during LPO are mutagens and have pronounced cytotoxicity [21,22]. It is believed that the increased lipid peroxidation of cell membranes, which occurs under pathological conditions, itself becomes a pathogenetic mechanism for the further development of the pathological process [23]. Under physiological conditions, the body has a constant balance between the level of free radicals (oxidants) and the activity of the antioxidant defense system. It implies the presence of systemic, multilevel regulatory relationships, reflecting a certain structure of interorgan and intersystem interactions at the level of the whole organism [24]. There is a dynamic relationship between LPO processes and the AOD reactions that limit them. If the body is able to maintain antioxidant homeostasis, some abnormalities are reversible. If the restoration of antioxidant homeostasis is delayed, then the clinical manifestations of the pathological condition increase.

Our study showed an increase in TAA in the middle of the cycle, which indicated the activation of certain adaptive-compensatory mechanisms. The SOD activity changed in the same way as the thiol-containing components – glutathions. An increase in the GSSG content is the earliest indicator of an increase in oxidative processes; therefore, the results obtained may indicate prooxidant activity in patients with diffuse mastopathy. It is believed that SOD forms a kind of antioxidant system with GSH, which prevents the reaction of hydrogen peroxide formation. The data obtained in women with diffuse mastopathy indicate the processes of GSH bioregeneration, the content of which in the serum of patients, compared with the control group, increases at the beginning of the menstrual cycle, remaining at the level of control values throughout the entire period of the menstrual cycle.

The activity of enzymes (SOD) and glutathione resulted in a gradual decrease in the content of double bonds in patients from the beginning (days 1–3) to the middle of the cycle. After that, there was a statistically significant accumulation of CD and KD-CT in the blood serum of patients with diffuse mastopathy, which indicated AOD deficiency.

The concentration of retinol in the serum of patients decreased compared to the control parameters at the beginning and at the end of the cycle. It is noteworthy that in the middle of the cycle, the level of retinol is comparable to its content in women in the control group. Retinol, ascorbate and α-tocopherol are closely interrelated, which is reflected in their combined antioxidant action. The nature of their interaction has not been sufficiently studied. However, it is known that in the presence of α-tocopherol, retinol eliminates oxygen free radicals, thereby preventing the development of the excess LPO processes in biomembranes [25]. Ascorbate and retinol enhance the antioxidant effect of α-tocopherol, being oxidized, they are consumed in the processes for its recovery. These

antioxidants also activate the incorporation of selenium into glutathione peroxidase, which together with tocopherol almost completely suppresses excessive activation of LPO in biological membranes. This is due to the fact that α-tocopherol effectively inhibits radicals, and the enzyme breaks down hydroperoxides, thereby preventing their participation in the oxidation cycle. The action of α-tocopherol allows us to consider it not only as an antioxidant, but also as a synergistic compound that supports AOD processes in the body at a certain stationary level [26]. Therefore, it is no coincidence that the content of α-tocopherol in the blood serum of patients with diffuse mastopathy did not change, remaining at the basal level. This probably caused an increase in the total antioxidant status of the blood in women with diffuse mastopathy in the most critical period – the middle of the menstrual cycle in order to maintain the most favorable conditions for ovulation.

4. CONCLUSION

In patients with diffuse mastopathy, an imbalance in the parameters of the LPO-AOD system was revealed throughout the entire menstrual cycle. In order to carry out a complex of therapeutic and prophylactic measures aimed at normalizing the balance in the LPO-AOD system, antioxidant drugs are recommended for patients with diffuse mastopathy in the luteal phase of the menstrual cycle. To prove the general hypothesis it is necessary to implement further clinical trials.

CONSENT AND ETHICAL APPROVAL

The study complied with the ethical principles of World Medical Association Declaration of Helsinki (1964, ed. 2013). The Ethics Committee of the Scientific Centre of Family Health Problems and Human Reproduction (Irkutsk, the Russian Federation) approved the research, and all women signed informed consent to participate in the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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