Biol. Stud. 2023; 17(2): 15–26 • DOI: https://doi.org/10.30970/sbi.1702.719
www.http://publications.lnu.edu.ua/journals/index.php/biology

UDC: 616.697-008.8-06:616.72-002-092:612.015.11]-07

PROOXIDANT-ANTIOXIDANT BALANCE IN SEMINAL AND BLOOD PLASMA OF MEN WITH IDIOPATHIC INFERTILITY AND INFERTILE MEN IN COMBINATION WITH RHEUMATOID ARTHRITIS

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Fafula, R., Melnyk, O., Gromnatska, N., Vorobets, D., Fedorovych, Z., Besedina, A., & Vorobets, Z. (2023). Prooxidant-antioxidant balance in seminal and blood plasma of men with idiopathic infertility and infertile men in combination with rheumatoid arthritis. *Studia Biologica*, 17(2), 15–26. doi:10.30970/sbi.1702.719

Background. Male infertility is one of the most serious medical and social problems. Idiopathic infertility accounts for about 30 % of cases of infertile men. Rheumatoid arthritis is associated with a decreased fertility potential. The aim of the present work was to determine the lipid peroxidation level and the activity of antioxidant enzymes such as glutathione peroxidase and glutathione reductase in seminal plasma and blood plasma of infertile men with idiopathic infertility and concomitant autoimmune joint pathology (rheumatoid arthritis).

Materials and Methods. 45 infertile men aged 22–48 were examined. They were divided into 2 groups: first group – 23 somatically healthy patients with idiopathic infertility; second group – 22 infertile men with rheumatoid arthritis. The control group consisted of 27 males with normal semen profile according to the WHO criteria and confirmed parenthood. The concentration of thiobarbituric acid reactive substance and activity of antioxidant enzymes were measured in the blood and seminal plasma.

Results. When analyzing the seminal fluid, we found that the TBARS content was 4-fold greater in infertile men with autoimmune pathology compared to fertile men ($p < 0.001$), whereas, in patients with idiopathic infertility its level was within the normal range. The activation of lipid peroxidation in infertile men with idiopathic infertility and in combination with rheumatoid arthritis was accompanied by a statistically significant decrease in the activity of enzymes of glutathione antioxidant system. It should be noted

that more pronounced disorders of lipid peroxidation and antioxidant enzymes activity were found in seminal plasma compared to blood plasma.

Conclusions. (**1**) An increased lipid peroxidation was observed in seminal and blood plasma of infertile men in combination with rheumatoid arthritis compared to normospermic men, whereas no differences were observed between men with idiopathic infertility and fertile men; (**2**) An impaired antioxidant status was observed in seminal and blood plasma of both men with idiopathic infertility and infertile men in combination with rheumatoid arthritis compared to normospermic men; (**3**) infertile men in combination with rheumatoid arthritis showed a significantly higher lipid peroxidation levels compared to men with idiopathic infertility, whereas no differences were observed in GPx and GR activity between groups.

Keywords: male infertility, idiopathic infertility, rheumatoid arthritis, antioxidant enzymes, lipid peroxidation

INTRODUCTION

Male infertility is among the most serious medical and social problems worldwide. According to a study by the WHO and the European Association of Urologists, the incidence of infertility is increasing worldwide. The male factor causes up to 50 % of all cases of infertility in married couples. Infertility might be explained by a number of factors, such as anatomical defects, endocrinopathies, immunological problems, gene mutations, radiation, chemotherapy, ejaculation disorders and environmental impacts. In about 30% of infertile men the cause of infertility is unknown and these cases are referred to as idiopathic infertility (Agarwal *et al.*, 2019; Campbell *et al.*, 2021).

Rheumatoid arthritis is a chronic inflammatory systemic disease of unknown etiology, which primarily affects the synovium of the joint and involves the progressive destruction of peri-articular tissues and their subsequent transformation into connective tissue. Rheumatoid arthritis is the most common autoimmune arthritis, with a prevalence of up to 1 % worldwide and 0.4 % in Ukraine (van der Woude *et al.*, 2018). This disease is characterized by a very high risk of disability (80 % of cases) and reduced life expectancy (Widdifield *et al.*, 2014). Rheumatoid arthritis is associated with possible systemic manifestations, a high frequency of detection of comorbid pathologies, progression of many extra-articular manifestations (Skeoch & Bruce, 2015; Anyfanti *et al.*, 2020). A decreased fertility potential is not unusual among patients of both genders with rheumatic diseases (Tiseo *et al.*, 2016). Some drugs used in therapy of rheumatoid arthritis can affect male fertility potential. For example, sulfasalazine/methotrexate can cause reversible infertility, whereas irreversible infertility is occasionally observed after treatment with alkylating agents (cyclophosphamide-CYC and chlorambucil) in both genders (Dooley & Nair, 2008).

The violation of the process of spermatogenesis is the most likely cause of infertility. This process is difficult to study and treat. Currently, there is not enough data about the factors which lead to abnormalities of spermatogenesis and spermatozoa and, as a result, to infertility (Bisht *et al.*, 2017; Agarwal *et al.*, 2019; Vaughan *et al.* 2020). There are a number of studies demonstrating the involvement of oxygen and nitrogen free radicals in sperm damage. In particular, the idiopathic factor of male infertility is associated with oxidative stress, which is defined as an imbalance between the production of reactive oxygen

species (ROS) and the protective function of antioxidant systems responsible for their neutralization (Agarwal *et al.* 2018; Tan *et al.*, 2019). Oxidative stress might affect sperm quality (Walczak-Jedrzejowska *et al.*, 2013). Men diagnosed with idiopathic infertility have higher ROS concentrations and lower antioxidant properties (Agarwal *et al.*, 2019; Tan *et al.*, 2019). The plasma membrane of spermatozoa is enriched in polyunsaturated fatty acids, which makes them very sensitive to lipid peroxidation (Alahmar, 2019). Our previous studies have shown that lipid peroxidation plays a significant role in impairing sperm function and quality, particularly sperm count, motility, and morphology (Fafula & Vorobets, 2019; Vorobets *et al.*, 2021).

Unlike somatic cells, mature spermatozoa have virtually no cytoplasm which contains enzymatic and non-enzymatic antioxidant systems. However, this deficit is partially compensated by the antioxidant systems of seminal plasma (Agarwal *et al.*, 2018; Alahmar, 2019). Thus, a decrease in the activity of the antioxidant system and an increase in the ROS levels disrupts the physiological functions of spermatozoa, in particular, their motility and the fertilization process (Agarwal *et al.*, 2019; Panner Selvam *et al.*, 2021). An important role among the antioxidant systems of the cell is attributed to the glutathione system (Adeoye *et al.*, 2018). However, the processes of free-radical lipid oxidation and antioxidant protection have been poorly understood in infertile men with idiopathic infertility and in combination with rheumatoid arthritis.

The aim of the present work was to determine the lipid peroxidation level and the activity of antioxidant enzymes such as glutathione peroxidase and glutathione reductase in seminal plasma and blood plasma of infertile men with idiopathic infertility and concomitant autoimmune joint pathology (rheumatoid arthritis).

MATERIALS AND METHODS

Research was carried out at the urology department of the Lviv Regional Clinical Hospital (Lviv, Ukraine). 45 infertile men aged 22–48 were examined. They were divided into 2 groups: group 1 – 23 somatically healthy patients with idiopathic infertility; group 2 – 22 infertile men with a systemic autoimmune disease – rheumatoid arthritis. The idiopathic infertility of an unstudied etiopathogenesis was diagnosed by the lack of fertilization during a year of the couple's life and the impossibility of finding out the cause of the disease. This form of infertility included men with oligozoospermia, oligoasthenozoospermia, asthenozoospermia, and leucospermia. The second group included individuals with the diagnosis of rheumatoid arthritis without concomitant inflammatory diseases of the connective tissue, other inflammatory diseases and oncological pathology at the time of the study. All patients with rheumatoid arthritis were diagnosed with asthenozoospermia or leukocytospermia. Exclusion indications were infertility over 10 years, azoospermia, hematospermia, necrozoospermia, testicular varicocele, hormonal abnormalities, genetic diseases, diabetes, infections, or other diseases. Subjects who reported drug consumption, alcohol abuse, smoking habits, and a history of any chronic disease were excluded from the study. Likewise, any diseases that may cause secondary infertility were included in the exclusion criteria.

The control group consisted of 27 males with normal semen profile according to the WHO criteria and confirmed parenthood (married for 3–10 years and have healthy 1–3 children). Age-matched, normozoospermic controls were randomly picked.

Prior to the study, all men gave informed consent to participate in the research. Terms of sample selection meet the requirements of the principles of the Helsinki

Declaration on protection of human rights, Convention of Europe Council on human rights and biomedicine and the provisions of laws of Ukraine. Approval for the study was taken from the ethics committee of Danylo Halytsky Lviv National Medical University (protocol No 2 from 25 February 2019).

The semen samples were collected using the standard method according to the World Health Organization. Semen specimens were collected via masturbation after 3 days of abstinence. All semen specimens from patients and controls were collected by masturbation into sterile containers. Semen analyses were performed within 30 min of sample arrival in the laboratory.

Blood was collected by venipuncture (20 mL) from the elbow vein in the morning, under conditions of physiological rest, on an empty stomach, in test tubes stabilized with heparin (final dilution 1:100). Seminal fluid and blood plasma were stored at -20 °C until the beginning of the studies, mostly for two weeks.

The concentration of thiobarbituric acid reactive substance and activity of antioxidant enzymes were measured in the blood and seminal plasma. The marker of lipid peroxidation – thiobarbituric acid reactive substance (TBARS) was evaluated by measuring substances reacting with thiobarbituric acid (Timirbulatov & Seleznev, 1981). Concentrations were given in μmol/L. Glutathione peroxidase (GPx) activity was determined by the oxidation of glutathione (Moin, 1986). The GPx activity was expressed as nmol GSH/min·mg protein. Glutathione reductase (GR) activity was measured by the oxidation of NADPH (Vlasova *et al.*, 1990). GR activity was expressed as nmol NADPH/ min·mg protein. Protein concentration was determined by the generally accepted Lowry method.

Statistical analysis. Experimental data were processed by methods of variation statistics using software MS Office and BioStat LE. Data are expressed as the mean ± standard error of the mean. Inter-group differences were determined using one-way analysis of variance parametric (parametric ANOVA) and nonparametric (Kruskal–Wallis ANOVA) analysis for independent samples. Shapiro–Wilk's test was used to verify normality. P values of <0.05 or lower were interpreted as statistically significant.

RESULTS AND DISCUSSION

It is known that under physiological conditions, the processes of lipid peroxidation take place in all biological systems of the body, including sperm cells. However, the intensification of lipid peroxide oxidation processes causes the formation of toxic products. This results in a membrane- and cytotoxic effects that lead to damage to the structure of biomembranes and the destruction of cells. One of the most sensitive markers of lipid peroxidation and oxidative stress is thiobarbituric acid reactive substance (TBARS).

It was shown that TBARS content in the blood plasma of infertile men with idiopathic infertility was 2.15-fold ($p < 0.001$) greater than in fertile men. The TBARS content in blood plasma of infertile men with rheumatoid arthritis was 2.25-fold ($p < 0.001$) greater than the control values in fertile men (**Fig. 1**). When analyzing the seminal fluid, we found that the TBARS content was 4-fold greater in infertile men with autoimmune pathology compared to fertile men ($p < 0.001$), whereas, in patients with idiopathic infertility its level was within the normal range. This probably indicates that mechanisms other than the activation of oxidative stress are involved in the pathogenesis of infertility.

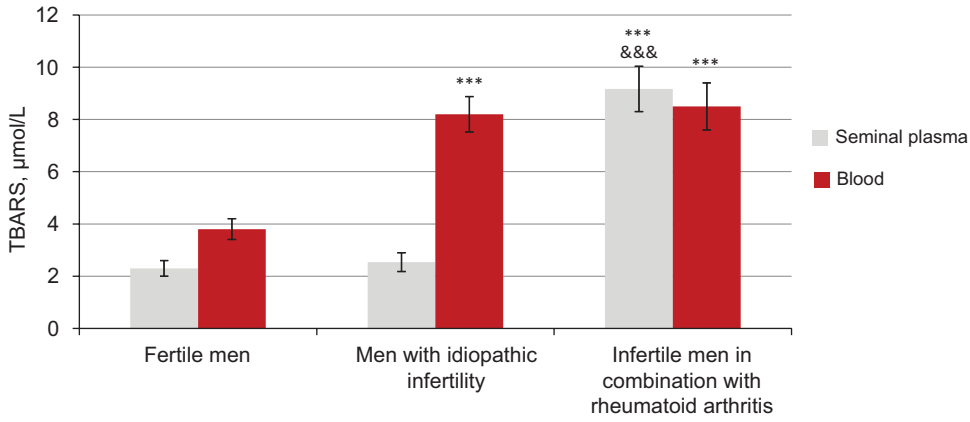

Fig. 1. TBARS level in seminal plasma and blood plasma of men with idiopathic infertility and infertile men in combination with rheumatoid arthritis, M±m, n = 22–27
Designations. Compared to the control group (fertile men): ***p <0.001; compared to men with idiopathic infertility: &&& – P <0.001

The activation of lipid peroxidation in infertile men with idiopathic infertility and in combination with rheumatoid arthritis was accompanied by a statistically significant decrease in the activity of enzymes of glutathione antioxidant system. As is widely recognised, GPx is a key antioxidant enzyme that regulates ROS levels and protects sperm cells against oxidative stress. In fact, we showed that GPx activity in seminal plasma was decreased 1.5-fold (p<0.001) in men with idiopathic infertility and 2.2-fold (p <0.001) in infertile men in combination with rheumatoid arthritis compared with healthy men with normozoospermia (**Fig. 2**). Similar changes in GPx activity were found in blood plasma, however a decrease in enzyme activity is less expressed.

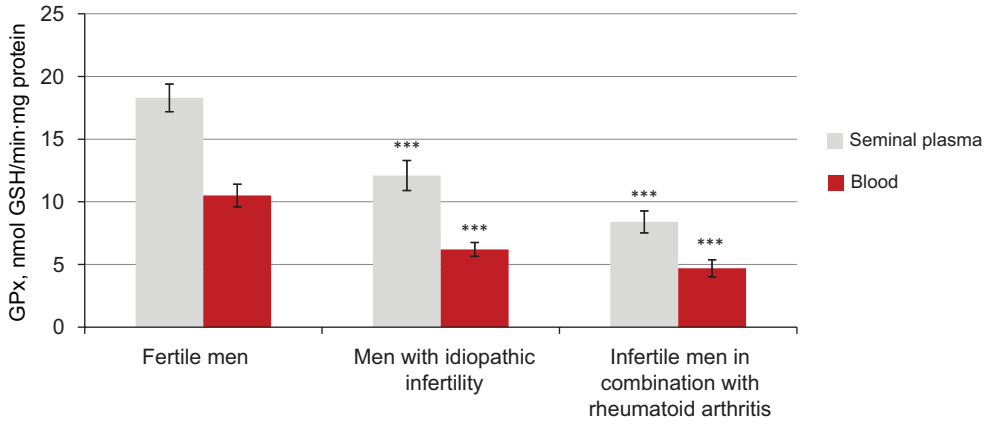

Fig. 2. Glutathione peroxidase activity in seminal plasma and blood plasma of men with idiopathic infertility and infertile men in combination with rheumatoid arthritis, M±m, n = 22–27
Designations. Compared to the control group (fertile men): ***p<0.001

Glutathione reductase is an enzyme that maintains physiological levels of reduced glutathione in cells. The GR activity was decreased 1.5-fold (p <0.001) in seminal

plasma in both studied groups of infertile men, however these changes in blood were not statistically significant (**Fig. 3**). It should be noted that more pronounced disorders of lipid peroxidation and antioxidant enzymes activity were found in seminal plasma compared to blood plasma.

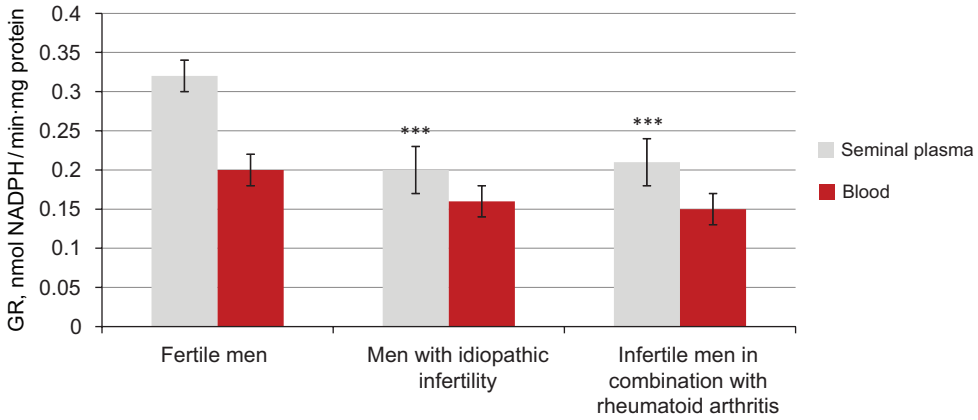

Fig. 3. Glutathione reductase activity in seminal plasma and blood plasma of men with idiopathic infertility and infertile men in combination with rheumatoid arthritis, M±m, n = 22–27
Designations. Compared to the control group (fertile men): ***p <0.001

The interdependence between fertility and health is exacerbated by many concomitant factors. Obesity, smoking, drug treatment negatively affect both ejaculate parameters and the general health condition. The lack of data on all components of the pathogenesis of many diseases makes it difficult to study the relationship between somatic and reproductive health (Sharma *et al.*, 2013; Ilacqua *et al.*, 2018; Mumford *et al.*, 2020). Male infertility in patients with rheumatoid arthritis is a remarkably common phenomenon.

The present study was carried out on 45 patients (23 men with idiopathic infertility and 22 infertile men in combination with rheumatoid arthritis) and 27 men were controls (patients with spontaneous conception), the results were compared between control and cases regarding the value of TBARS, GPx, and GR.

The increased lipid peroxidation at the general level detected in both examined groups can affect the reproductive function locally. Therefore, it was important to study the TBARS level both in blood plasma and seminal fluid. It should be noted that the average values of TBARS content in blood plasma were the highest in patients with autoimmune pathology among all infertile men, which is probably related to the main pathological process. These results are in agreement with some other studies which also demonstrated an increased malondialdehyde content in infertile men. It has been found that the idiopathic form of infertility may be associated with changes in the intracellular production of ROS (Mayorga-Torres *et al.*, 2017). An increase in the content of lipid peroxide oxidation products was also found in the seminal plasma of infertile men with disorders of spermatogenesis and varicocele.

Seminal plasma contains antioxidants and an enzymatic antioxidant system that protect sperm from oxidative damage. When oxidants suppress the antioxidant defense system, oxidative stress occurs. It induces apoptosis, lipid peroxidation of sperm

membrane lipids and DNA fragmentation, which impairs sperm function. GPx is a key antioxidant enzyme that regulates the production of ROS and protects cells against lipid peroxidation and oxidative stress. In the present study, we have shown that GPx activity was significantly decreased in infertile men of both groups. Similar results were obtained by W. D. Zhang *et al.* (Zhang *et al.*, 2014). They reported a significantly lower T-SOD and GSH-Px antioxidant activity compared with the normal semen samples. However, it was shown that native specific activity of GPx-1 and phospholipid hydroperoxide GPx (PHGPx) does not differ between normo- and hypomotile human sperm samples (Tramer *et al.*, 2004; Ursini & Maiorino, 2005).

It is generally acknowledged that pathophysiology of rheumatoid arthritis is associated with oxidative stress. ROS-induced oxidative damage was related to the pathophysiology of rheumatoid arthritis in several studies (Kaur *et al.*, 2021; Jing *et al.*, 2023). It was found that patients with rheumatoid arthritis had higher oxidative damage to proteins and lipids compared with controls. Antioxidant enzyme activities were higher in rheumatoid arthritis patients than in controls, but they were insufficient to prevent oxidative damage (García-González *et al.*, 2015). It is also known that the development of rheumatoid arthritis is associated with various cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 which play a crucial role in pathogenesis of rheumatoid arthritis (Kondo *et al.*, 2021). Changes in seminal plasma proinflammatory cytokines affect semen quality (Kozopas *et al.*, 2021). Cytokines and ROS demonstrate a complex interplay, in particular some cytokines can modulate pro- and antioxidant systems and ROS production (Jiang *et al.*, 2016; Chyra-Jach *et al.*, 2018).

The results of the present research should be evaluated in the context of its limitations. Patients of the studied groups contained a highly heterogeneous population, with large variations in spermogram parameters and infertility histories. Present study investigated prooxidant-antioxidant balance only with 45 cases. It is therefore essential to validate our findings with greater sample sizes. The possible role of lifestyle factors and additional disease have to be taken into account when studying prooxidant-antioxidant balance.

CONCLUSIONS

The key results in this study are: (**1**) An increased lipid peroxidation was observed in seminal and blood plasma of infertile men in combination with rheumatoid arthritis compared to normospermic men, whereas no differences were observed between men with idiopathic infertility and fertile men; (**2**) An impaired antioxidant status was observed in seminal and blood plasma of both men with idiopathic infertility and infertile men in combination with rheumatoid arthritis compared to normospermic men; (**3**) infertile men in combination with rheumatoid arthritis showed a significantly higher lipid peroxidation levels compared to men with idiopathic infertility, whereas no differences were observed in GPx and GR activity between groups.

ACKNOWLEDGMENTS AND FUNDING SOURCES

The publication presents the results of the research project „Ionic, molecular and membrane mechanisms of reduction of the fertilization potential of male spermatozoa and its correction” financed by the state budget (the Ministry of Health of Ukraine), 2023–2025.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: The authors declare that the study was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Animal rights: This article does not include animal studies.

Human rights: All studies were conducted in accordance with the Declaration of Helsinki guidelines. Approval for the study was taken from the ethics committee of Danylo Halytsky Lviv National Medical University (protocol No 2 from 25 February 2019).

AUTHOR CONTRIBUTIONS

Conceptualization, [F.R.; G.N.; V.Z.]; methodology, [M.O.; V.D.; V.Z.]; validation, [F.Z.; M.O.]; formal analysis, [M.O.; G.N.; F.Z.; B.A.].; investigation, [M.O.; V.D.; B.A.]; resources, [F.R.]; data curation, [F.R.; G.N.; F.Z.; B.A.]; writing – review and editing, [F.R.; M.O.; V.D.]; visualization, [M.O.; F.Z.] supervision, [F.R.; V.D.; V.Z.]; project administration, [F.R.]; funding acquisition, [F.R.; V.Z.].

All authors have read and agreed to the published version of the manuscript.

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ПРООКСИДАНТНО-АНТИОКСИДАНТНИЙ БАЛАНС СІМ'ЯНОЇ ПЛАЗМИ ТА ПЛАЗМИ КРОВІ ЧОЛОВІКІВ З ІДІОПАТИЧНИМ НЕПЛІДДЯМ І НЕПЛІДНИХ ЧОЛОВІКІВ ЗІ СУПУТНІМ РЕВМАТОЇДНИМ АРТРИТОМ

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Вступ. Чоловіче неплідддя є однією з гострих медико-соціальних проблем. Ідіопатичне неплідддя (неплідддя неясного генезу) є причиною близько 30 % випадків неплідддя у чоловіків. Ревматоїдний артрит пов'язаний зі зниженням фертилізаційного потенціалу. Метою роботи було визначення рівня пероксидації ліпідів і активності антиоксидантних ензимів, таких як глутатіонпероксидаза та глутатіонредуктаза, у сім'яній плазмі та плазмі крові неплідних чоловіків з ідіопатичним непліддям та супутньою аутоімунною патологією суглобів (ревматоїдний артрит).

Матеріали та методи. Обстежено 45 неплідних чоловіків віком 22–48 років. Їх поділено на 2 групи: перша група – 23 соматично здорових пацієнти з ідіопатичним непліддям; друга група – 22 неплідних чоловіків з ревматоїдним артритом. Контрольну групу склали 27 чоловіків із нормальними показниками сперматограм згідно з критеріями ВООЗ та підтвердженим батьківством. У плазмі крові та сім'яній плазмі вимірювали концентрацію ТБК-активних продуктів і активність антиоксидантних ензимів.

Результати. З'ясовано, що у сім'яній плазмі неплідних чоловіків з аутоімунною патологією суглобів вміст ТБК-активних продуктів був у 4 рази ($p < 0{,}001$) вищий, порівняно з фертильними чоловіками, тоді як у пацієнтів з ідіопатичним непліддям його рівень був у межах норми. Активація процесів перекисного окиснення ліпідів супроводжувалася статистично вірогідним зниженням активності ензимів глутатіонової ланки антиоксидантного захисту у неплідних чоловіків з ідіопатичним непліддям та зі супутнім ревматоїдним артритом. Варто зазначити, що більш виражені зміни процесів перекисного окиснення ліпідів і активності антиоксидантних ензимів відмічаються в сім'яній плазмі порівняно з плазмою крові.

Висновки. (**1**) Виявлено зростання інтенсивності процесів перекисного окиснення ліпідів у сім'яній плазмі та плазмі крові неплідних чоловіків зі супутнім рев-

матоїдним артритом порівняно з нормоспермічними чоловіками, тоді як між чоловіками з ідіопатичним непліддям і фертильними чоловіками не спостерігали відмінностей; (**2**) порушення антиоксидантного статусу спостерігали в сім'яній та плазмі крові чоловіків з ідіопатичним непліддям і неплідних чоловіків зі супутнім ревматоїдним артритом порівняно з нормоспермічними чоловіками; (**3**) у неплідних чоловіків зі супутнім ревматоїдним артритом відмічено вірогідно вищий рівень пероксидації ліпідів порівняно з чоловіками з ідіопатичним непліддям, водночас не зафіксовано різниці в активності глутатіон-пероксидази та глутатіон-редуктази між обома групами.

Ключові слова: чоловіче неплідддя, ідіопатичне неплідддя, ревматоїдний артрит, антиоксидантні ензими, перекисне окиснення ліпідів

Received / Одержано 04 April, 2023 | Revision / Доопрацьовано 31 May, 2023 | Accepted / Прийнято 01 June, 2023 | Published / Опубліковано 28 June 2023