DOI: 10.31793/1680-1466.2023.28-4.341

Oxidative stress as a mandatory participant in the pathogenesis of stress-induced reproductive disorders

A.G. Reznikov

State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine»

Abstract. One of the urgent medical problems of our time is a significant percentage of male and female infertility in various countries of the world. It is extremely aggravated under the influence of stressful factors, especially during natural disasters and wars. This review summarizes the latest research progress, concepts, and hypotheses regarding the role of free radical processes in the regulation of reproductive functions and in the pathogenesis of stress-induced reproductive disorders. One of the important metabolic processes in the body involved in stress reactions is lipid peroxidation (LPO) and oxidative modification of deoxyribonucleic acid (DNA), ribonucleic acid and proteins, which are carried out by reactive oxygen species (ROS). A state of long-term and severe stress generates a large number of ROS in mitochondria, microsomes, and other structures and cells, as a result of which a change in the pro-antioxidant balance occurs in the direction of a decrease in the redox potential in cells and their microenvironment. ROS cause LPO and modification of the structure of DNA, ribonucleic acid, and proteins in spermatozoa, eggs, and gonads, which leads to hypofertility or infertility. There are pathogenetically based proposals for the use of pharmacological and natural antioxidants for the treatment of male infertility or hypofertility. Conclusions. Oxidative-nitrosative stress is a standard metabolic reaction to the state of acute and long-term stress in the body. Free radical processes are considered a significant factor in the pathogenesis of generative and endocrine disorders of the reproductive system of men and women. Maintaining balance in the redox system is an important condition for the normal functioning of the reproductive system. It is necessary to strengthen efforts in the direction of counteracting oxidant and nitrosative stress in the reproductive organs in order to prevent and treat infertility caused by stress.
Keywords: reproductive system, oxidative stress, nitrosative stress antioxidants, sperm, egg, male, female.

VERTE

Introduction

The problem of hypo- and infertility is constantly under the attention of endocrinologists and reproductive specialists due to its prevalence. It is extremely aggravated under the influence of stressful factors, especially during natural disasters and wars, which are relevant for Ukraine. Stress limits a person's reproductive potential [1-6], which is appropriate from a biological point of view due to the deterioration of living conditions. In the modern world, the problem of stress is one of the most relevant in terms of health in general and reproductive health in particular.

A state of stress occurs when an agent acting on the body causes a strain of adaptive reactions, that is, to a certain extent, it has a protective nature. If the stressogenic factor is too intensive and overcomes the protective mechanisms of homeostasis, it initiates the development of pathological processes and can lead to chronic diseases. There are many etiological factors of stress (psycho-emotional stimulus, hypoxia, hypo- and hyperthermia, physical overload, chemical irritants, electric current, starvation, infectious diseases, radiation, etc.). The body reacts with stereotypical reactions of the sympatho-adrenal, endocrine, and immune systems. The reproductive systems of women and men are extremely vulnerable to the action of stressogenic factors, in particular, due to the hormonal and metabolic changes induced by them.

Pro-antioxidant balance and its changes during stress

One of the important metabolic processes in the body involved in stress reactions is LPO and oxidative modification of DNA, ribonucleic acid and proteins, which are carried out by ROS [7-9]. They have a very short lifetime, but extremely high reactivity [10-12]. More than 90% of the oxygen that cell utilizes processed by mitochondria. A prevailing part of it is converted to water, then another part is converted into superoxide anion, and then into hydroxide radical and hydrogen peroxide – the most toxic for cells. The generation of ROS occurs in the mitochondrial respiratory chain during the process of oxidative phosphorylation and in the electron transport chain by microsomes. In addition, ROS appear when oxyhemoglobin is converted to methemoglobin, or when xanthine is oxidized by xanthine oxidase.

There is an enzyme system that counteracts ROS: superoxide dismutase, glutathione peroxidase, and catalase, which remove peroxide from water. During the oxidation of glutathione (GSH) by glutathione peroxidase, hydrogen peroxide is decomposed into water. Peroxidases of other substrates (myeloperoxidase, cytochrome C-peroxidase, peroxyredoxins) act in a similar way. In addition to GSH, antioxidant protection is provided by other non-enzymatic compounds as follows: ascorbic acid, polyphenols, and alpha-tocopherol. In one second, the cell produces 50 hydroxyl radicals, which are neutralized by the antioxidant protection system.

Under normal conditions, ROS produced in a non-enzymatic way perform regulatory functions. In particular, they take part in the processes of apoptosis, and immune reactions, affect the conductivity of ion channels, and initiate the expression of some protective genes.

Changes in oxidant homeostasis are a mandatory link in the chain of metabolic responses to acute or chronic stress. Under the influence of stressogenic agents, the pro-antioxidant balance shifts towards the formation of a large amount of ROS. This leads to LPO, hyperactivation of proteinkinases through redox-sensitive transcription factors such as AP-1, p53, and NF-κB, damage to DNA and proteins, and an increase in intracellular concentrations of calcium, iron, and copper ions, which leads to cell death (**Fig.**).

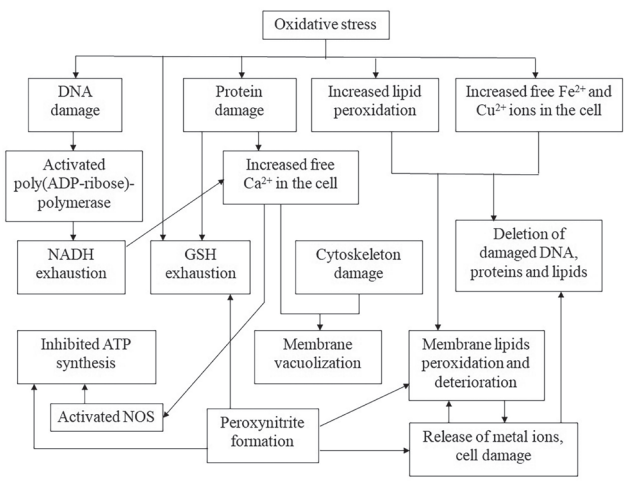

Figure. Mechanisms of the damaging effect of oxidative stress on cells.

Note: DNA – deoxyribonucleic acid, ADP – adenosine diphosphate, NADH- nicotinamide adenine dinucleotide reduced, GSH – glutathione, ATP – adenosine triphosphate, NOS – nitric oxide synthase.

The main target of LPO is double carbon bonds of polyunsaturated fatty acids in cell membranes, mitochondria, microsomes, peroxisomes, as well as lipoproteins. Due to this, water, ions of sodium, potassium, and calcium enter the cells, which leads to swelling of cells and organelles and their death. The final products of LPO are malonic dialdehyde and hydroxy-2-nonenal, which is formed from linolenic acid. The formation of 2,4-dinitrophenylhydrazones serves as the indicator of oxidative modification of proteins.

The role of oxidative stress in stress-induced disorders of the female reproductive system

There are numerous and irrefutable evidences that the reproductive system of women is three times more vulnerable to stress than that of men. This is explained both by the increased response of women to stressful stimuli, and by the more complex, compared to men, structural and functional organization of the reproductive system, as well as the cyclical nature of its activity. It is believed that about 30% of cases of female infertility are caused by chronic stress, mainly of psycho-emotional origin.

Due to stimulation of cortisol secretion and inhibition of gonadotropin-releasing hormone synthesis, secretion of luteinising hormone, follicle stimulating hormone and ovarian sex hormones is inhibited, which leads to menstrual dysfunction. Stress stimulates the release of prolactin from the pituitary gland, which, in turn, disrupts the biosynthesis of ovarian hormones, causes premature luteolysis and, through this mechanism, also reduces the production of progesterone in the ovaries, thus contributing to premature termination of pregnancy. The stress-induced increase in the level of progesterone in the first phase of the menstrual cycle is explained by the activation of the adrenal cortex, which is also the cause of menstrual dysfunction [13]. In the pathogenesis of stress-induced disorders of reproduction in women, there is thyroid dysfunction.

Manifestations of reproductive disorders induced in women by prolonged and severe stress are extremely diverse: insufficiency of the luteal phase of the ovarian cycle, hypothalamic oligo- or amenorrhea, premenstrual dysphoric disorders, impaired ovum quality [14], impaired embryo implantation, early pregnancy loss, premature birth, endometriosis, early menopause [15-17].

The role of lipid and protein peroxidation in the pathogenesis of stress-induced disorders of the female reproductive system is beyond doubt [9, 18-21]. It is also necessary to take into consideration that ROS are necessary participants in the formation of a pre-implantation embryo [22]. They are important for the formation of the pronucleus, the proliferation of cells, and the formation of the blastula due to the regulation of transcription factors, in particular, NF-κB. ROS interact with purine and pyrimidine bases of DNA, some metabolites of which are able to break DNA chains, which creates conditions for teratogenesis. Endogenous single-stranded DNA break repair mechanisms are important for egg preservation [23], but they are not able to resist ROS in case of their excessive formation. Free radicals attack eggs, change their microenvironment (follicular fluid, granulosa zone, etc.), the interaction with spermatozoa, development of the embryo at the early stages, and interfere with the process of embryo implantation. They play an equally important pathogenetic role in the «aging» of eggs, in particular, by preventing the separation of chromosomes at the first stage of meiosis [24].

One of the consequences of oxidative stress in some women is the formation of polycystic ovary syndrome [25-27]. In women with this syndrome, ROS cause structural and functional disturbances at all levels of cell organization. There is a correlation between markers of oxidative stress in blood serum and follicular fluid. The most significant consequence of the harmful effects of ROS is mitochondrial dysfunction [28, 29].

The role of oxidative stress in stress-induced disorders of the male reproductive system

Chronic stress in men causes a decrease in the level of gonadotropic hormones and testosterone, depresses libido, decreases the number and quality of spermatozoa and seminal fluid, which is the cause of a decrease in fertility potential, and even more – impotence [1, 4, 6, 30, 31]. One cannot fail to notice that slightly more scientific publications are devoted to the problem of the effect of oxidative stress on the male reproductive system than on women. This is probably due to the greater availability of biological material, i.e. spermatozoa and seminal fluid, compared to eggs, follicular and tubular fluids.

One of the mechanisms of damage to the germinal cells of the testis and immature spermatozoa is the violation of the folding of regulatory proteins as a

VERTE

manifestation of oxidative stress in the endoplasmic reticulum [32, 33]. In contrast to acute stress, which stimulates mitochondrial biogenesis and activates transcription factors and associated kinases in rat Leydig cells [34], chronic stress disrupts the structure and functioning of mitochondria due to a significant increase in the formation of ROS in them. An increased level of markers of oxidative stress was found in the seminal fluid of 25-80% of infertile men [35, 36]. In addition, the content of antioxidants in it is reduced. The role of ROS in the pathogenesis of male infertility is considered proven [37]. As the examination of 16,945 men of different age categories showed, the degree of DNA defragmentation of spermatozoa increases with age, which correlates with a decrease in fertility and an increase in oxidative stress [38].

The main «killer» of spermatozoa is hydrogen peroxide, which carries out LPO. The ability of human and bull spermatozoa to produce ROS and the inhibitory effect of hydrogen peroxide on gamete respiration was first discovered in the 40s of the last century [39, 40]. The physiological level of ROS in the germinal cells of male gonads, spermatozoa, and their microenvironment is necessary for them to achieve structural and functional maturity. The extreme vulnerability of spermatozoa to the excess of ROS in these cells and seminal fluid, which is due to the activation of LPO, is explained by the high content of polyunsaturated fatty acids in their membranes. The high rate of cell division of the spermatogenic epithelium makes their DNA vulnerable to ROS. The situation is complicated by the fact that the content of an important antioxidant – GSH in spermatozoa is 30 times less than that in somatic cells, and there is no catalase there at all [41]. The scavenger system in spermatozoa is weaker than that in other cells [42]. The generation of ATP is disturbed; and as a result of these metabolic processes, morphological and functional defects of the gametes occur. The cytoplasm and membrane of spermatozoa contain NO synthase, and high concentrations of peroxynitrite contribute to the damage of these gametes. As a result of reduced mobility of spermatozoa, morphological abnormalities, and reduced concentration in seminal fluid, their fertilizing capacity is significantly reduced.

A relatively recent meta-analysis points to oxidative stress accompanying the COVID-19 disease as one of the leading pathogenetic mechanisms of male infertility, along with metabolic and psychological factors [43]. It is noteworthy that the quality of seminal fluid deteriorates immediately after the onset of the disease [44]. In men with COVID-19, a reduced level of testosterone in the blood serum, and its inverse relationship with the severity of the course of the disease are registered. Testicular morphology shows elongation of the seminiferous tubules, damage to Sertoli cells, and a decrease in the number of Leydig cells [45-47]. Oxidative stress activates apoptosis processes in the testes, which explains the decrease in the number of gametes and Leydig cells [46]. Oxidative stress changes the balance between the processes of apoptosis and autophagy in male germ cells [48]. They are determined by numerous signaling pathways (mTor, Atg12, p53, Beclin 1, Bcl 2). Oxidative stress causes epigenetic deregulation of genes that control apoptosis and autophagy, which leads to the death of spermatozoa at various stages of their generation. An examination of 376 infertile men showed elevated levels of cortisol and adrenaline, indicating a state of stress [49]. The level of testosterone was reduced compared to healthy men against the background of increased levels of gonadotropic hormones, which indicates the preservation of a negative reciprocal relationship between the gonads and the pituitary gland. It is noteworthy that the levels of superoxide dismutase and GSH were increased in patients, which can be considered an adaptive response to oxidative stress.

One of the factors that characterize sperm quality and the degree of its aging is the state of telomeres. Telomeres are threads of non-coding nucleotide sequences TTAGGG, which are located after the last coding combination of DNA nucleotides and are repeated thousands of times. During DNA replication, part of the telomere loses some nucleotides, but reverse transcriptase (telomerase) restores the lost nucleotides. Telomerase actively functions in germ and stem cells.

Usually, the length of telomeres decreases as the cell ages. Oxidative stress disrupts the integrity of telomeres in spermatogenic cells and spermatozoa, accelerating their aging [50]. However, there are many works that demonstrate a paradoxical phenomenon, lengthening of telomeres in sperm as they age [51] and under the influence of a moderate increase in ROS output [52]. They are trying to

explain this unusual phenomenon as an adaptive reaction of hormesis, but the question arises: why is it not observed in the egg cell, where aging is characterized by the shortening of telomeres? So, this phenomenon is still waiting for a convincing explanation.

Antioxidant therapy

There are pathogenetically based proposals for the use of pharmacological and natural antioxidants for female and male infertility or hypofertility treatment. To restore redox balance, chemical and plant antioxidants were used [42, 53-59]. It is believed that antioxidant therapy in the form of an appropriate diet and antioxidant medications should be the first [54] or second [60] line of treatment for idiopathic male infertility. In order to counteract the damaging effects of ROS, quercetin, vitamins C, B and E, GSH, selenium, coenzyme Q10, melatonin, resveratrol, carotenoids, folate, cysteine, and L-carnitine are prescribed [18, 19, 21, 22, 59, 60]. D-chiro-inositol, mio-inositol, and other antioxidants are prescribed to women with polycystic ovary syndrome and other gynecological pathology [60], as well as in assisted reproductive technologies [61]. Nevertheless, the efficacy of antioxidant therapy of reproductive disorders is variable between individuals [54].

Nitrosative stress and reproductive disorders

Nitric oxide (NO), a short-lived lipophilic molecule, plays an important role in the metabolic regulation of numerous physiological functions. In the reproductive system, it participates in the regulation of the gonadotropic function of the pituitary gland, embryo implantation, gametogenesis, steroidogenesis, apoptosis of germinal cells, egg maturation, follicle growth, ovulation, etc.

Nitrosative stress can be considered a kind of oxidative stress. Under conditions of body stress, NO-synthase is activated, which generates NO from arginine. The result of the interaction of NO with the superoxide radical is the formation of peroxynitrite anion, which is a strong oxidant and is able to penetrate into cells through anion channels – an extremely toxic substance that oxidizes the proteins of the respiratory chain of mitochondria. As a result, the formation of macroergs, which are necessary to ensure the vital activity of the cell, decreases. The most significant process in terms of the harmful effect of nitrosative stress is tyrosine nitration, which leads to the activation of LPO, DNA breaks, mitochondrial damage, etc. [62].

The destructive effect of nitrosative stress in men is manifested in increased apoptosis of testicular germ cells and their damage, and in women, in particular, in immune inflammation of the endometrium, which causes rejection of the embryo during implantation [63]. A high concentration of NO stimulates LPO in the membrane of spermatozoa and reduces their motility and fertilizing ability. However, the data on the morphological changes of spermatozoa are extremely contradictory. A negative effect of nitrosative stress is leukocytospermia, which causes sperm agglutination.

In infertile women, the level of NO in blood serum is increased, and its high content in the follicular fluid of the ovaries is associated with the deterioration of the quality of the embryo and the results of artificial insemination [64].

Conclusions

Oxidative-nitrosative stress is a standard metabolic reaction to the state of acute and long-term stress in the body. Free radical processes are considered a significant factor in the pathogenesis of generative and endocrine disorders of the reproductive system of men and women. It is necessary to strengthen efforts to counteract oxidative and nitrosative stress in the reproductive organs to prevent and treat infertility caused by stress.

References

1. Negro-Vilar A. Stress and other environmental factors affecting fertility in men and women: Overview. Environ Health Perspect Suppl. 993;101(Suppl. 2):59-64. doi: 10.1289/ehp.93101s259.
2. Tilbrook AJ, Turner AI, Clarke IJ. Stress and reproduction: Central mechanisms and sex differences in non-rodent species. Stress.2002 Jun;5(2):83-100. doi: 10.1080/10253890290027912.
3. Tatarchuk TF. Stress and reproductive function of women. Int Endocr J. 2006;3(5):2-9. (Russian).
4. Nordkap L, Priskorn L, Bräuner EV, Hansen ÅM, Bang AK, Holmboe SA, et al. Impact of psychological stress measured in three different scales on testis function: A cross-sectional study of 1362 young men. Andrology. 2020 Nov;8(6):1674-86. doi: 10.1111/andr.12835.
5. Shatkovska AS, Grigorenko AP, Horbatyuk OG, Binkovska AM. Stress-induced disorders of the hypothalamic-pituitary and peripheral endocrine systems in a woman's body. Med Aspects Women's Health. 2021;(4):23-7. (Ukrainian).
6. Martelli M, Zingaretti L, Salvio G, Bracci M, Santarelli L. Influence of work on andropause and menopause: A systematic review. Int J Environ Res. Public Health. 2021;18:10074. doi: 10.3390/ijerph181910074.
7. Baraboy VA. Stress: nature, biological role, mechanisms, outcomes. Kyiv: Phytosociocenter; 2006. 424 p. (Russian).

VERTE

8. Baraboy VA, Reznikov AG. Physiology, biochemistry and psychology of stress. Kyiv: Interservice; 2013. 314 p. (Ukrainian).
9. Aitken RJ, Bromfield EG, Gibb Z. Oxidative stress and reproductive function: The impact of oxidative stress on reproduction: a focus on gametogenesis and fertilization. Reproduction. 2022 Oct 26;164(6):F79-94. doi: 10.1530/REP-22-0126.
10. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev. 2014;2014:360438. doi: 10.1155/2014/360438.
11. Polumbryk MO, Polumbryk OM, Balion Y.H, Reznikov AG. Human pro- and antioxidant system, oxidative stress, its consequences and ways to overcome. Proceed Natl Univ Food Technol. 1. Oxidative stress. 2014;20(4):19-29. (Ukrainian).
12. Reznikov AG, Polumbryk OM, Balion YH, Polumbryk MO. Pro- and antioxidant systems and pathological processes in humans. Bull Natl Acad Sci Ukraine. 2014;(10):17-29. doi: 10.15407/visn2014.10.017 (Ukrainian).
13. Burlaka O, Vahnier V. Menstrual disorders in the aspect of stress-related reproductive health disorders of women servicemen in the ATO/JFO zone. Psychosomatic Medicine and General Practice. 2021 May 30;6(2):e0602290. doi: 10.26766/pmgp.v612.290 (Ukrainian). Available from: https://e-medjournal.com/index.php/psp/article/view/290/496. [Cited 22th August 2023].
14. Prasad Sh, Tiwari M, Pandey AN, Shrivastav TG, Chaube ShK. Impact of stress on oocyte quality and reproductive outcome. J Biomed Sci. 2016;23:36. doi: 10.1186/s12929-016-0253-4.
15. Palomba S, Daolio J, Romeo S, Battaglia FA, Marci R, La Sala GB. Lifestyle and fertility: the influence of stress and quality of life on female fertility. Reprod Biol Endocrinol. 2018 Dec 2;16(1):113. doi: 10.1186/s12958-018-0434-y.
16. Appleyard CB, Flores I, Torres-Reverón A. The link between stress and endometriosis: from animal models to the clinical scenario. Reprod Sci. 2020 Sep;27(9):1675-86. doi: 10.1007/s43032-020-00205-7.
17. Fontana L, Garzia E, Marfia G, Galiano V, Miozzo M. Epigenetics of functional hypothalamic amenorrhea. Front Endocrinol (Lausanne). 2022 Aug;13:953431. doi: 10.3389/fendo.2022.953431.
18. Agarwal A, Gupta S, Sharma R. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol. 2005 Jul 14;3:28. doi: 10.1186/1477-7827-3-28.
19. Agarwal A, Gupta S, Sharma R. Oxidative stress and its implications in female infertility – a clinician's perspective. Reprod Biomed Online. 2005;11:641-50. doi: 10.1016/S1472-6483(10)61174-1.
20. Aitken RJ. Oxidative stress and reproductive function. Reproduction. 2022a Nov 18;164(6):E5-8. doi: 10.1530/REP-22-0368.
21. Adeoye O, Olawumi J, Opeyemi A, Christiania O. Review on the role of GSH on oxidative stress and infertility. JBRA Assist Reprod. 2018 Mar 1;22(1):61-6. doi: 10.5935/1518-0557.20180003.
22. Deluao JC, Winstanley Y, Robker RL, Pacella-Ince L, Gonzalez MB, McPherson NO. Oxidative stress and reproductive function: Reactive oxygen species in the mammalian pre-implantation embryo. Reproduction. 2022 Oct 26;164(6):F95-108. doi: 10.1530/REP-22-0121.
23. Giridharan S, Hutt KJ, Winship AL. Does single-strand DNA break repair capacity influence oocyte maintenance and quality? Reproduction. 2022 Nov 18;164(6):V15-8. doi: 10.1530/REP-22-0325.
24. Martin JH, Nixon B, Cafe SL, Aitken RJ, Bromfield EG, Lord T. Oxidative stress and reproductive function: Oxidative stress and *in vitro* ageing of the post-ovulatory oocyte: an update on recent advances in the field. Reproduction. 2022 Oct 26;164(6):F109-24. doi: 10.1530/REP-22-0206.
25. Mohammadi M. Oxidative stress and polycystic ovary syndrome: a brief review. Intern J Prevent Med. 2019; 10:86. doi: org/10.4103/ijpvm.IJPVM_576_17.
26. Rudnicka E, Duszewska AM, Kucharski M, Tyczyński P, Smolarczyk R. Oxidative stress and reproductive function: Oxidative stress in polycystic ovary syndrome. Reproduction. 2022 Nov 22;164(6):F145-54. doi: 10.1530/REP-22-0152.
27. Hager M, Dewailly D, Marculescu R, Ghobrial S, Parry JP, Ott J. Stress and polycystic ovarian morphology in functional hypothalamic amenorrhea: a retrospective cohort study. Reprod Biol Endocrinol. 2023;21:42. doi: 10.1186/s12958-023-01095-5.
28. Zhang J, Bao Y, Zhou X, Zheng L. Polycystic ovary syndrome and mitochondrial dysfunction. Reprod Biol Endocrinol. 2019;17:67. doi:org/10.1186/s12958-019-0509-4.
29. Shukla P, Mukherjee S. Mitochondrial dysfunction: an emerging link in the pathophysiology of polycystic ovary syndrome. Mitochondrion. 2020;52:24-39. doi: 10.1016/j.mito.2020.02.006.
30. Drevet JR, Hallak J, Nasr-Esfahani MH, Aitken RJ. Reactive oxygen species and their consequences on the structure and function of mammalian spermatozoa. Antioxid Redox Signal. 2022 Sep;37(7-9):481-500. doi: 10.1089/ars.2021.0235.
31. Madhu NR, Sarkar B, Slama P, Jha NK, Ghorai SK, Jana SK, et al. Effect of environmental stressors, xenobiotics, and oxidative stress on male reproductive and sexual health. Adv Exp Med Biol. 2022;1391:33-58. doi: 10.1007/978-3-031-12966-7_3.
32. Santiago J, Silva JV, Fardilha M. First insights on the presence of the unfolded protein response in human spermatozoa. Int J Mol Sci. 2019 Nov 5;20(21):5518. doi: 10.3390/ijms20215518.
33. Santiago J, Santos MAS, Fardilha M, Silva JV. Stress response pathways in the male germ cells and gametes. Mol Hum Reprod. 2020 Jan 1;26(1):1-13. doi: 10.1093/molehr/gaz063.
34. Gak IA, Radovic SM, Dukic AR, Janjic MM, Stojkov-Mimic NJ, Kostic TS, et al. Stress triggers mitochondrial biogenesis to preserve steroidogenesis in Leydig cells. Biochim Biophys Acta. 2015 Oct;1853(10 Pt A):2217-27. doi: 10.1016/j.bbamcr.2015.05.030.
35. Makker K, Agarwal A, Sharma R. Oxidative stress & male infertility. Indian J Med Res. 2009;129:357-67.
36. Agarwal A, Allamaneni SS. Free radicals and male reproduction. J Indian Med Assoc. 2011 Mar;109(3):184-7.
37. Takalani NB, Monaneng EM, Mohlala K, Monsees TK, Henkel R, Opuwari CS. Role of oxidative stress in male infertility: A review. Reprod Fertil. 2023 Jun 1:RAF-23-0024. doi: 10.1530/RAF-23-0024.
38. Vaughan DA, Tirado E, Garcia D, Datta V, Sakkas D. DNA fragmentation of sperm: a radical examination of the contribution of oxidative stress and age in 16 945 semen samples. Hum Reprod. 2020 Oct 1;35(10):2188-96. doi: 10.1093/humrep/deaa159.
39. MacLeod J. The role of oxygen in the metabolism and motility of human spermatozoa. Amer J Physiol. 1943 Feb 1;138:512-8. doi: 10.1152/ajplegacy.1943.138.3.512.
40. Tosic J, Walton A. Formation of hydrogen peroxide by spermatozoa and its inhibitory effect of respiration. Nature. 1946 Oct 5;158:485. doi. 10.1038/158485a0.
41. O'Flaherty C, Scarlata E. Oxidative stress and reproductive function: The protection of mammalian spermatozoa against oxidative stress. Reproduction. 2022 Oct 26;164(6):F67-78. doi: 10.1530/REP-22-0200.
42. Solorzano Vazquez JF, Maldonado Rosas I, Villar Muñoz LG, Leyva Macias LB, Ramirez Dominguez LB, Kesari KK, et al. Oxidative stress-induced male infertility: Role of antioxidants in cellular defense mechanisms. Adv Exp Med Biol. 2022;1391:275-309. doi: 10.1007/978-3-031-12966-7_16.
43. Mintziori G, Duntas LH, Veneti S, Goulis DG. Metabolic, oxidative and psychological stress as mediators of the effect of COVID-19 on male infertility: A literature review. Int J Environ Res Public Health. 2022 Apr 26;19(9):5277. doi: 10.3390/ijerph19095277.
44. Aitken, R.J. COVID-19 and male infertility: An update. Andrology. 2022 Jan;10(1):8-10. doi: 10.1111/andr.13098.
45. Yang M, Chen S, Huang B, Jhong JM, Su H, Chen YJ, et al. Pathological findings in the testes of COVID-19 patients: Clinical implications. Eur Urol Focus. 2020 Sep 15;6(5):1124-9. doi: 10.1016/j.euf.2020.05.009.
46. Moghimi N, Eslami Farsani B, Ghadipasha M, Mahmoudiasl GR, Piryaei A, Aliaghaei A, et al. COVID-19 disrupts spermatogenesis through the oxidative stress pathway following induction of apoptosis. Apoptosis. 2021 Aug;26(7-8):415-30. doi: 10.1007/s10495-021-01680-2.
47. Yao Y, Yuan X, Wu L, Guo N, Yin L, Li Y. COVID-19 and male reproduction: Current research and unknown factors. Andrology. 2021 Jul;9(4):1027-37. doi: 10.1111/andr.12970.

48. Sharma P, Kaushal N, Saleth LR, Ghavami S, Dhingra S, Kaur P. Oxidative stress-induced apoptosis and autophagy: Balancing the contrary forces in spermatogenesis. Biochim Biophys Acta Mol Basis Dis. 2023 Aug;1869(6):166742. doi: 10.1016/j.bbadis.2023.166742.
49. Rehman R, Amjad S, Tariq H, Zahid N, Akhter M, Ashraf M. Oxidative stress and male infertility: a cross sectional study. J Pak Med Assoc. 2020 Mar;70(3):461-6. doi: 10.5455/JPMA.12992.
50. Moazamian A, Gharagozloo P, Aitken RJ, Drevet JR. Oxidative stress and reproductive function: Sperm telomeres, oxidative stress, and infertility. Reproduction. 2022 Oct 26;164(6):F125-33. doi: 10.1530/REP-22-0189.
51. Aston KI, Hunt SC, Susser E, Kilura M, Factor-Litvak P, Carrell D, et al. Divergence of sperm and leucocyte age-dpendent telomere dynamics: implications for male-driven evolution of telomere length in humans. Mol. Hum Reprod 2012;18:517-22. doi. org/10.1093/molehr/gas028.
52. Mishra S, Kumar R, Malhotra N, Singh N, Dada R. Mild oxidative stress is beneficial for sperm telomere length maintenance. World J Methodol. 2016 Jun 26;6(2):163-70. doi: 10.5662/wjm.v6.i2.163.
53. Barati E, Nikzad H, Karimian M. Oxidative stress and male infertility: current knowledge of pathophysiology and role of antioxidant therapy in disease management. Cell Mol Life Sci. 2020 Jan;77(1):93-113. doi: 10.1007/s00018-019-03253-8.
54. Pereira SC, Moreira MV, Silva BM, Oliveira PF, Alves MG. Roles of oxidative stress in the male reproductive system: Potential of antioxidant supplementation for infertility treatment. Adv Exp Med Biol. 2022;1391:259-74. doi: 10.1007/978-3-031-12966-7_15.
55. Raj CJ, Aishwarya CVS, Mounika KVSSN, Mishra B, Sumithra B, Vishal B, et al. Deciphering the nexus between oxidative stress and spermatogenesis: A compendious overview. Adv Exp Med Biol. 2022;1391:1-16. doi: 10.1007/978-3-031-12966-7_1.
56. Kefer JC, Agarwal A, Sabanegh E. Role of antioxidants in the treatment of male infertility. Int J Urol. 2009 May;16(5):449-57. doi: 10.1111/j.1442-2042.2009.02280.x.
57. Agarwal A, Makker K, Sharma R. Clinical relevance of oxidative stress in male factor infertility: an update. Am J Reprod Immunol. 2008 Jan;59(1):2-11. doi: 10.1111/j.1600-0897.2007.00559.x.
58. Aitken RJ, Gibb Z. Sperm oxidative stress in the context of male infertility: current evidence, links with genetic and epigenetic factors and future clinical needs. Minerva Endocrinol (Torino). 2022 Mar;47(1):38-57. doi: 10.23736/S2724-6507.21.03630-7.
59. Yefimenko OO, Yusko TI, Iarotska NV. Oxodative stress and reproductive health. Reprod Endocrinol. 2018;(3):66-72. (Russian).
60. Agarwal A, Sekhon LH. The role of antioxidant therapy in the treatment of male infertility. Hum Fertil (Camb). 2010 Dec;13(4):217-25. doi: 10.3109/14647273.2010.532279.
61. Bevilacqua A, Carlomagno G, Gerli S, Montanino Oliva M, Devroey P, Lanzone A, et al. Results from the International Consensus Conference on myo-inositol and D-chiro-inositol in Obstetrics and Gynecology-assisted reproduction technology. Gynecol Endocrinol. 2015 Jun;31(6):441-6. doi: 10.3109/09513590.2015.1006616.
62. Wang F, Yuan Q, Chen F, Pang J, Pan C, Xu F, et al. Fundamental mechanisms of the cell death caused by nitrosative stress. Front Cell Dev Biol. 2021 Sep 20;9:742483. doi: 10.3389/fcell.2021.742483.
63. Dutta S, Sengupta P. The role of nitric oxide on male and female reproduction. Malays J Med Sci. 2022 Apr;29(2):18-30. doi: 10.21315/mjms2022.29.2.3.
64. Lee TH, Wu MY, Chen MJ, Chao KH, Ho HN, Yang YS. Nitric oxide is associated with poor embryo quality and pregnancy outcome in *in vitro* fertilization cycles. Fertil Steril. 2004;82(1):126-31. doi.org/10.1016/j. fertnstert.2004.02.097.

Abbreviation

DNA – deoxyribonucleic acid
GSH – glutathione
LPO – lipid peroxidation
NO – nitric oxide
ROS – reactive oxygen species

Оксидативний стрес – обов'язковий учасник патогенезу стрес-індукованих розладів репродукції

О.Г. Резніков

ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України»

Резюме. Однією з актуальних медичних проблем сучасності є значний відсоток безпліддя чоловіків і жінок у різних країнах світу. Вона надзвичайно загострюється під впливом стресогенних чинників, особливо під час природних катаклізмів і війн. Ця оглядова стаття підсумовує новітні результати наукових досліджень, концепції і гіпотези стосовно ролі вільнорадикальних процесів у регуляції репродуктивних функцій та в патогенезі стрес-індукованих розладів репродукції. Одним із важливих метаболічних процесів в організмі, які беруть участь у стресових реакціях, є перекисне окислення ліпідів і окислювальна модифікація ДНК, РНК і білків, які здійснюються за допомогою активних форм кисню. Стан тривалого і сильного стресу генерує в мітохондріях, мікросомах та інших структурах і клітинах велику кількість активних форм кисню, внаслідок чого відбувається зміна про-антиоксидантного балансу в бік зменшення редокс-потенціалу в клітинах та їх мікрооточенні. Активні форми кисню викликають у сперматозоїдах, яйцеклітинах і статевих залозах перекисне окислення ліпідів та модифікацію структури ДНК, РНК і білків, що призводить до гіпофертильності або безпліддя. Існують патогенетично обгрунтовані пропозиції щодо застосування фармакологічних і природних антиоксидантів для лікування чоловічого безпліддя або гіпофертильності. **Висновки.** Оксидативно-нітрозативний стрес є стандартною метаболічною реакцією на стан гострого і тривалого стресу організму. Вільнорадикальні процеси вважають суттєвим чинником у патогенезі генеративних і ендокринних розладів репродуктивної системи чоловіків і жінок. Важливою умовою нормального функціонування репродуктивної системи є підтримання рівноваги в редокс-системі. Необхідно посилити зусилля в напрямку протидії оксидативному та нітрозативному стресу в репродуктивних органах із метою запобігання та лікування безпліддя, зумовленого стресом.

Ключові слова: репродуктивна система, оксидативний стрес, нітрозативний стрес, антиоксиданти, сперматозоїд, яйцеклітина, чоловік, жінка.

Для цитування: Резніков ОГ. Оксидативний стрес – обов'язковий учасник патогенезу стрес-індукованих розладів репродукції. Ендокринологія. 2023;28(4):341-348. DOI: 10.31793/1680-1466.2023.28-4.341.

Адреса для листування: Резніков Олександр Григорович, reznikov39@gmail.com, ДУ «Інститут ендокринології та обміну речовин ім. В.П. Комісаренка НАМН України», вул. Вишгородська, 69, Київ 04114, Україна.

VERTE

Відомості про автора: Резніков Олександр Григорович, д-р мед. наук, проф., чл.-кор. НАН України, акад. НАМН України, завідувач відділу ендокринології репродукції та адаптації, ORCID: 0000-0002-0018-399X.
Особистий внесок: Резніков О.Г. – повна підготовка статті.
Фінансування: стаття підготовлена за власні кошти автора.
Декларація з етики: автор задекларував відсутність конфлікту інтересів і фінансових зобов'язань.
Стаття: надійшла до редакції 15.10.2023 р.; перероблена 30.10.2023 р.; прийнята до друку 28.11.2023 р.; надрукована 30.12.2023 р.

For citation: Reznikov AG. Oxidative stress as a mandatory participant in the pathogenesis of stress-induced reproductive disorders. Endokrynologia. 2022;28(4):341-348. DOI: 10.31793/1680-1466.2023.28-4.341

Correspondence address: Reznikov Alexander Grigorievich, reznikov39@gmail.com, State Institution «V.P. Komisarenko Institute of Endocrinology and Metabolism of the NAMS of Ukraine», Vyshgorodska Str., 69, Kyiv 04114, Ukraine.
Information about the author: Reznikov Alexander Grigorievich, – Dr. Sci. (Medicine), Prof., Cor. Member of the NAS of Ukraine, Acad. of the NAMS of Ukraine, Head of the Department of Endocrinology of Reproduction and Adaptation; ORCID: 0000-0002-0018-399X.
Personal contribution: Reznikov A.G. – full preparation of the article.
Funding: the article was prepared at the author's own expense.
Declaration of Ethics: The authors have declared no conflicts of interest or financial obligations.
Article: received October 10, 2023; revised October 30, 2023; accepted November 28, 2023; published December 30, 2023.