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Male Infertility: Pathogenetic Significance of Oxidative Stress and Antioxidant Defence (Review)

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Abstract. The basis of the pathogenesis of male infertility is the processes of peroxide oxidation of biological substrates, especially lipids and proteins. By destroying the sperm membrane, toxic peroxidation products reduce its motility and ability to fertilize the egg, which is determined by a decrease in the number of motile sperm in the ejaculate. These changes lead to complete or partial male infertility. The authors of the review found that is accompanied by a damaging effect on the structural and functional activity of the gonads and is manifested, in particular, by an imbalance in the hormonal background of the male body. Similar effects are characteristic of an increase in the content of reactive Nitrogen species and its metabolites, which cause nitrosative stress, which is also the cause of male hypofertility and is inseparable from the state of oxidative stress. In scientific work it is determined that the accumulation of harmful peroxidation products leads to damage and destruction of sperm DNA, reduced activity of acrosomal enzymes and mitochondrial potential of sperm, reduced overall antioxidant activity. This makes it impossible for an adequate response of the body. Multi component antioxidant defense system resists stress. It is represented by enzymatic and non-enzymatic links, which can neutralize harmful radicals and peroxidation products. It contributes to the full manifestation of reproductive function. The presence of powerful antioxidant properties of catalase, superoxide dismutase, and enzymes of the thiol-disulfide system, which form the enzymatic system of antioxidant protection, as well as selenium, zinc, copper, other trace elements, retinol, tocopherol, ascorbic acid, and vitamins as parts of the non-enzymatic system is shown. The efficiency of registration is substantiated thin biochemical shift detectors or complex methods, such as total antioxidant status of sperm or sperm plasma, mitochondrial membrane potential, etc along with simple markers of oxidative stress, such as diene conjugates, malonic dialdehyde, and metabolites of the Nitrogen Oxide cycle. Given the leading role of oxidative stress in the development of male hypofertility, the prospect of further research is the search for modern means for correction, especially among substances with pronounced redox activity

Keywords: reproductive ability, lipoperoxidation, antioxidant enzymes, Nitrogen oxide cycle

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INTRODUCTION

The reproductive system of males depends on various factors. It is subject to many negative influences of the external and internal environment and, as a rule, is not able to respond adequately [1; 2]. The main link in the pathogenesis of pathologies of the reproductive system in males, causing a decrease in sperm quality, is considered to be the state of oxidative stress (OS) of their bodies [3]. Oxidative stress is an excessive increase in the processes of lipid peroxidation, proteins, etc. (increased synthesis and/or accumulation of oxygen radicals) against the background of low activity of antioxidant protection (AOP).

The role of reactive oxygen species (ROS) in spermatogenesis, germ cell function, and fertilization has been studied for over 80 years. Thus, we know that low concentrations of ROS are important for physiological processes in sperm, such as acrosomal response and interaction of sperm with oocytes, in return the high levels of ROS underlie the imbalance of the prooxidant-antioxidant system, causing OS, which is one of the most destructive factors affecting sperm function and reducing male reproductive potential [4-9].

Similar data exist on the relationship between high concentrations of Nitrogen Oxide and metabolites of its cycle, which are formed by increasing the synthesis of reactive Nitrogen species (RNS), with the state of the male reproductive system [10]. ROS/RNS in the body can play both a physiological role and have a negative impact on reproductive ability, causing stress, such as OS and nitrosative stress, accompanied by a decrease in the number of motile sperm, damage to their membranes and acrosomal enzymes, mitochondrial dysfunction of germ cells. The biochemical relationship between oxidative and nitrosative stress is inseparable and, as a rule, these processes take place in the body of animals in parallel [10-15].

Widely used in urological practice, the term male infertility states a complete inability to fertilize the oocyte, while in the practice of reproductive endocrinology and andrology the term hypofertility is used, i.e., reduction of male fertility, given the possibility of effective correction/treatment [16-18]. Increases in the content of ROS/RNS are found in natively obtained and epididymal sperm and sperm plasma of almost half of men with hypofertility, while observing different dynamics of the components of ROS [19; 20]. Thus, the study of this problem does not lose its relevance, and taking into account the results is a necessary condition for the development of effective means of correcting male hypofertility.

The study aimed at the analysis of professional literature sources regarding modern ideas about the importance of oxidative stress in the pathogenesis of male hypo-/infertility, as well as substantiation of the role of the antioxidant defense system in maintaining reproductive potential.

PATHOGENETIC SIGNIFICANCE OF OXIDATIVE STRESS IN MALE HYPOFERTILITY

The concept of oxidative stress and the role of reactive oxygen species

The results of many years of research by scientists from all over the world prove the need to assess the balance of the prooxidant-antioxidant system in various pathological states. OS is a condition characterized by an excess of ROS and/or by deficiency of antioxidants. OS is the leading cause of decreased reproductive capacity (hypofertility) and infertility in males. The destructive force of OS is damage to lipids, membrane proteins and organelles and cell DNA, as a result of which the cyclic cascade of redox reactions weakens the functions of sperm and the reproductive system in general (Fig. 1) [21].

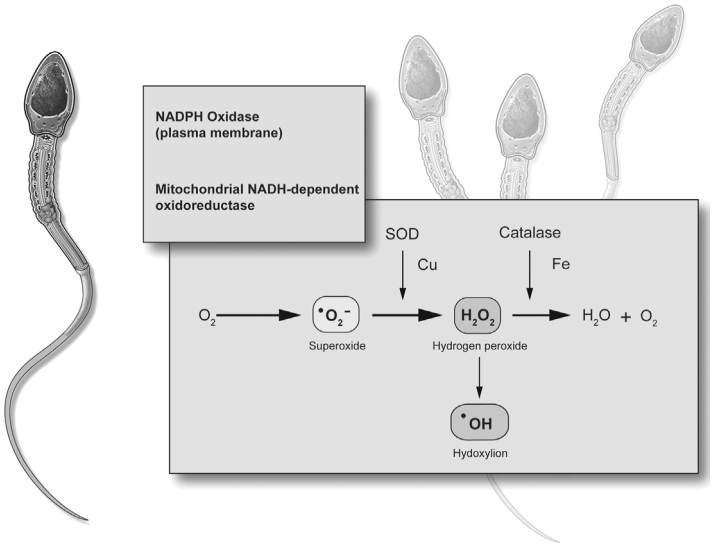

Figure 1. *Reactive oxygen species in sperm*

Source: *[21]*

Certainly oxidative damage to the genital system is found in various reproductive diseases with toxic poisoning, long-term use of drugs. For example, sulfur mustard, as a cytotoxic and chemical agent, damages tissues, including the reproductive system and causes male infertility on the background of OS [22]. OS is also considered to be the cause of male sperm hyperviscosity syndrome, and, at the same time, sperm hyperviscosity syndrome induces increased ROS synthesis, i.e. causes OS [23].

Also, current data suggest the involvement of OS as a central element contributing to hypofertility in males with varicocele, to which the testes respond by heat stress, ischemia, or the production of vasodilators such as Nitrogen Oxide [24; 25]. OS is also observed in prostatitis at the local and systemic level with a decrease in sperm quality mainly due to elevated concentrations of ROS [26; 27]. ROS are formed in sperm plasma from endogenous sources such as leukocytes or immature sperm and are physiologically necessary for sperm motility and oocyte fertilization. The effect of ROS on male fertility is regulated by an oxidative paradox, which is determined by a delicate balance between oxidative stress and antioxidant activity. With proper regulation, ROS ensure the effective functioning of the male reproductive system. On the contrary, with the increasing generation, a disproportionate number is formed, which causes a decrease in sperm reproductive function and is the cause of male hypofertility [28].

In general, with a small accumulation of ROS, the body can respond adequately and prevents the negative consequences of their impact. However, with the inferiority of diets, metabolic disorders, under the influence of various environmental pathogens, reveal an imbalance in the interaction of free radical oxides with scavenger substances. Such changes are the cause of most cases of idiomatic forms of infertility (Fig. 2) [21].

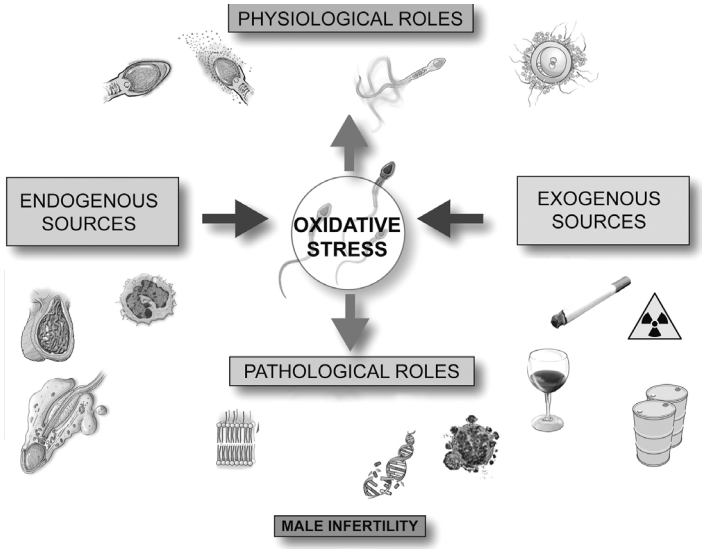

Figure 2. *Scheme of the physiological/pathological roles of reactive oxygen species and sources leading to increased production*

Source: *[21]*

The reasons for the development of OS are various: these are inflammatory processes in the genital system, including varicocele, nutritional deficiencies, obesity, metabolic syndrome, sexually transmitted infections (*Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema palldum*, etc.), prostatitis, including bacterial genesis, mutations in microorganisms that lead to OS, viral infections (e.g., human immunodeficiency virus, hepatitis, etc.) [4; 29]. The development of OS is noted under the action of gamma radiation, which was found in experiments on rats of both sexes combined with a state of hemodynamic stress [30]. Factors contributing to the development of hypofertility in men include smoking and alcohol abuse, which contributes to lower sperm quality and sex hormone levels [31].

Particularly dangerous is the effect of organophosphorus compounds, such as dimethoate, which affects the reaction of OS in rat sperm *in vitro*, on the antioxidant protection of sperm [32]. Sperm DNA fragmentation due to impaired spermatogenesis, probably caused by OS, is observed in men with obesity, the influence of which in parents can adversely affect the reproductive and metabolic health of offspring [33].

Intensity of lipoperoxidation processes and reproductive potential

Numerous studies have shown that the decrease in reproductive potential is accompanied by an increase in the intensity of lipoperoxidation processes, for example, researchers at the Department of Obstetrics and Gynecology JIPMER, India, found statistically significant differences in the content of MDA in men with abnormal sperm parameters, and they had a reduced index of oxidative stress, compared with the group of men with normal

sperm counts [34]. This is due to the presence of large amounts of polyunsaturated fatty acids in mammalian sperm membranes, which makes them particularly sensitive to lipid peroxidation (LPO) [35]. This has been repeatedly proven experimentally – scientists at the University "Rovira i Virgili", Spain have created an experimental model of hypofertility of male rats, induced by sulfasalazine, with the introduction of which there is an increase in the content of substances reacting with thiobarbituric acid (TBARS), a decrease in the content of SOD and GSH in the testes and their appendages [36].

Determination of ROS concentration and LPO intensity in sperm and sperm plasma are used as a means of determining male fertility. In men with a decrease in sperm quality, there is an increase in the content of primary products of LPO – DC: while in sperm and sperm plasma the concentration of MDA also increases significantly [37; 38].

The mechanism of hypofertility of males under the influence of high concentrations of ROS

Sperm morphology is an important and complex characteristic of their fertilizing ability. It is shown that OS affects the morphology of sperm, causing the development of its abnormal forms, damage to membranes. Thus, the frequency of teratozoospermia may be directly related to excess ROS production; this shows that the assessment of sperm morphology is no less important criterion for assessing sperm quality, in addition to the activity and concentration of sperm [39]. OS in hypofertility causes in males a significant decrease in sperm motility, an increase in the percentage of morphological abnormalities, mainly the tail of sperm, with a significant decrease in the total antioxidant capacity of serum, the content of uric acid and albumins.

Thus, a decrease in the antioxidant capacity of blood serum, content of uric acid and albumin leads to the destruction of the sperm membrane, which, in turn, reduces the progressive motility of cells [40]. The negative effect of OS is realized by the action of high concentrations of ROS, which lead to oxidative damage to sperm membranes and DNA of male gametes as a result of gene mutations and by direct destruction of the DNA backbone, mitochondrial dysfunction and apoptotic cell death [41]. OS causes damage to both mitochondrial and nuclear DNA, while affecting the sperm epigenome, which leads to infertility, recurrent miscarriages, the negative course of pregnancy and increased morbidity of offspring [42].

It is believed that OS also affects normal embryonic development. Studying the phenomenon of OS sperm, researchers have identified the role of antioxidant protection in the male germline [43]. At the same time, sperm can't repair damage caused by OS due to limited AO potential. With the development of infertility on the background of OS, note a probable increase in the content of copper in serum and sperm plasma and the level of iron in sperm plasma, which indicates their direct participation in spermatogenesis and suggests that these ions act as mediators of oxidative damage [44].

Our research has proven the leading role of OS in reducing the reproductive capacity of boars. Thus, we have noted the intensification of LPO with a decrease in the quality of boar sperm. It is confirmed by the reliable growth of primary – DC and secondary – MDA products of lipoperoxidation [2]. Data on the effect of ROS on the histohematological barriers of the male body were obtained. Thus, in the testes of mammals, the blood-testicular barrier, in contrast to the blood-encephalic and blood-ophthalmic barriers, consists of coexisting dense tissues and adhesions, however, these compounds must be opened (or disengaged) to adapt to migration of preleptoten and leptotene spermatocytes through the blood-testicular barrier during spermatogenesis while maintaining its integrity [45]. The temporary opening of the blood-testicular barrier, which promotes the movement of germ cells, is mediated through the effect of ROS, testosterone and cytokines on the kinetics of endocytosis and recirculation of integral membrane proteins [46]. It should be noted that such changes are also likely to be involved in the pathogenesis of male infertility.

Features of OS development in semen during cryopreservation and thawing

The widespread use of a variety of media for the selection, use, and storage of sperm of men with pronounced antioxidant capacity allows not only to preserve the reproductive potential of cells but also to investigate in a standardized medium with high AO dynamically or indirectly ROS production of sperm or other contaminating cells [47]. The ability to protect sperm from oxidative damage is particularly critical for the artificial insemination industry due to the increased synthesis of ROS by sperm during processing. Many studies have focused on reducing the fertility of boar sperm after cryopreservation and thawing due to an increased tendency to oxidative damage compared to other species, which is hindered by the use of antioxidants – GSH, SOD, vitamin E, etc. [48]. Increased ROS generation as a side effect of bull sperm cryopreservation leads to OS, protein degradation, DNA fragmentation, and cell death. To prevent this, the lycopene effect, which reduces ROS synthesis in semen and promotes the preservation of acrosomal response and mitochondrial potential of sperm, has been studied [49].

NITROGEN OXIDE CYCLE AND ITS INFLUENCE ON SPERMATOGENESIS AND SPERM QUALITY

Nitrogen oxide (NO) has a critical role in the functioning of the male reproductive system, represented by NO itself, its metabolites, and a specific enzyme – NO synthase (NOS) and its isoforms. NO at low concentrations plays a leading role in the signaling pathways regulation,

regulates smooth muscle tone, controls the permeability of the blood-testicular barrier, erectile function, etc. [10; 50]. ROS/RNS-mediated redox signaling is extremely important for sperm reproductive function [51]. At low concentrations, the metabolites of the Nitrogen Oxide cycle act as scavengers of oxygen radicals. NO is produced by NOS and plays an important role in reproduction from the brain to the genitals. Germ cells and leydig cells in the testes show stage-dependent nuclear and cytoplasmic endothelial and inducible NOS immunoreactivity. All three isoforms of NOS were localized on the nuclear membrane and cytoplasm of epithelial cells in all ducts, in the tail and cytoplasmic droplets of sperm [52]. The male gonad-specific subclass nNOS, known as TnNOS, has recently been identified as a fairly powerful source of NO. TnNOS is located exclusively in Leydig cells – this confirms the involvement of the Nitrogen Oxide cycle in the hormonal function of the testes. With increasing NO content it is involved in the formation of AFN – peroxynitrite (ONOO-), NO_2, $N2O_3$, nitroxyl ion, nitrosyl-containing compounds that cause nitrosative stress [10]. Recently, new scientific data have been obtained on the properties of NO in conditions close to mammalian biology. Thus, it is proved that NO is not oxidized and not reduced by one-electron processes, reacts with other free radicals at a rate close to limited diffusion, and autoxidation rate is a second order in NO concentration, hence slow under bioregulatory conditions [53]. A study of the role of inducible NOS in testicular dysfunction in varicocele revealed a predominant expression of iNOS in the cytoplasm of Leydig cells and only a small percentage of its expression in Sertoli cells. Because iNOS activity was likely to be higher in Leydig cells in rats with varicocele, iNOS activity may play a leading role in testicular dysfunction associated with varicocele in adolescence [54].

Influence of nitrogen oxide cycle metabolites on spermatogenesis and sperm quality

Experimental studies have shown that the decrease in sperm function in male rats caused by nicotine improves a decrease in NOS activity, while investigating the effectiveness of L-arginine to inhibit NOS, found a reduction in spermatotoxic effects through a mechanism that depends on circulating testosterone levels [55]. On the other hand, data on NO_x content in the sperm plasm of healthy and infertile men were obtained and no reliable data were obtained on the correlation between NO content and sperm quality [56]. Contradictory results of researchers can be explained by the difference in the methodology of work. Our research revealed a reliable increase in the number of stable metabolites of the NO cycle due to a decrease in the reproductive capacity of boars in OS, accompanied by deterioration in sperm quality, especially motility and number of motile sperm in the ejaculate [2].

ANTIOXIDANT PROTECTION AND ITS ROLE IN THE REPRODUCTIVE POTENTIAL OF MALES

Features of the components of the antioxidant defense system functioning and their role in the activity of the male reproductive system

Sperm are highly sensitive cells to high levels of ROS due to the limited antioxidant system present in these terminal cells. However, to achieve the unique goal of sperm, i. e. to transfer the parental genome to a mature oocyst during fertilization, it is necessary to ensure strict regulation of ROS levels. Thus, active antioxidant systems are critical for sperm function [57]. AO are compounds that inhibit the synthesis or neutralize the action of prooxidants, in particular ROS [40; 58]. In the normal physiological state, sperm plasma contains a mechanism of AO enzymes that are able to neutralize toxic ROS, as well as have a protective effect on sperm from any possible damage. AO such as vitamins E and C, carotenoids and carnitine, when ingested, are able to increase the AO potential of cells, and, in general, have a positive effect on spermatogenesis [59-62]. Sperm are protected from OS by the enzymes of the AO system, which regulates the concentration of ROS. Sperm plasma is saturated with various AO to protect sperm from OS – enzymatic AO (SOD, catalase, GSH redox cycle enzymes) and non-enzymatic (ascorbate, tocopherol, GSH, etc.) [63].

We proved a decrease in the activity of AO enzymes when reducing the reproductive capacity of boars in the OS. In particular, both SOD and CAT activity – enzymes of the first link AO and GSH-Px and GSH-Rd in the serum of boars with low sperm quality [64]. Despite the antioxidant activity of sperm plasma, testicular appendage, and sperm, OS damages DNA integrity and disrupts sperm function [65; 66]. That is why an important issue is the functioning of antioxidant protection in the male reproductive system. Extracellular SOD has been found in the testes in relatively large quantities compared with other male organs. When studying some rat tissues and cells using a reverse transcriptase and polymerase chain reaction, we have shown that germ cells express approximately one-third of the expression of Sertoli cells. We can be suggesting that both cell types have the mechanisms necessary to protect against radicals. These studies demonstrate the importance of the SOD molecule for the male reproductive system, which is regulated by germ [67]. Researchers have obtained conflicting data on the effectiveness of endogenous antioxidants in inhibiting the effects of ROS as a means of treating male hypofertility or as a means of adding to the culture medium in the distribution of sperm has low efficacy [68].

The level of antioxidants in sperm plasma plays an important role in the etiology of sperm dysfunction and is closely related to male hypofertility, and a decrease in their concentration or intake of substances necessary for their synthesis may be one of the causes of infertility [69; 70]. The thiol-disulfide system, the so-called

glutathione redox cycle, occupies a considerable place in the antioxidant protection system of the male body. Glutathione – the primary AO of the body helps to preserve other types of AO. Its presence is noted in male and female gametes but in different quantities [71]. The level of antioxidants in semen is very vulnerable and variable. For example, cryopreservation reduces sperm quality and activity of sperm AO, which under the action of lycopene and α-lipoic acid increase in the experiment on cashmere goat [72].

Clinical studies have shown a decrease in antioxidant protection in the sperm plasma of infertile men, which correlates with sperm quality. Thus, the observed reduced activity of G-6-PDH causes increased ROS synthesis, which is confirmed by the reliably higher content of MDA. There is a decrease in the amount of GSH and SOD, which leads to the fragility of sperm membranes under the action of ROS and affects the ion exchange required for normal motility. Thus, the experiment showed a direct relationship between the antioxidant system with asthenospermia and the clinical parameters of sperm [73].

Other groups of researchers obtained similar results [74]. A group of scientists showed the effectiveness of selenium and vitamin E supplements to improve the quality of dog sperm and increase the antioxidant status of sperm, as evidenced by increased GP activity and overall antioxidant capacity of cells, which leads to normalization of sperm quality in animals with hypofertility [75]. Also, researchers obtained data on the negative impact of maternal obesity in rats on the antioxidant defense system of the testes in male offspring. The use of high-fat diets during fetal development causes phenotypic changes such as imbalance of lipid synthesis and increased OS, causing changes in male fertility, which, in turn, may explain the decrease in their reproductive capacity [76].

Markers of male reproductive potential: ROS and their metabolites, total antioxidant capacity, mitochondrial potential

Increased ROS production and DNA fragmentation are observed in infertile patients compared to the fertile group. Thus, changes in ROS synthesis may be associated with idiopathic infertility, i. e. assessment of the content of OS markers is a reliable prognostic criterion for male reproductive potential [77]. Spermatozoa are very vulnerable to ROS due to their inherent shortcomings of intracellular antioxidant enzymatic protection. Thus the body's overall antioxidant capacity becomes more vital for sperm protection [40]. There is an urgent need for reliable diagnostic tests that would allow you to quickly and comprehensively determine the state of the OS. The methods available to researchers to establish the OS allow determining only some components or their related substances [21]. Mitochondrial membrane potential indicates sperm functionality, which is determined using specific fluorescent markers [78]. Sperm DNA damage by OS is investigated in different ways. During spermiogenesis, which is the last stage of sperm maturation, there is a stage of remodeling of the sperm plasma membrane, which enhances the regulation of membrane receptors promoting the binding of the pellucid membrane, such as hyaluronic acid receptors. It was noted that spermatozoa selected using hyaluronic acid as a selector, show such characteristics as minimal DNA fragmentation, normal morphology and reduced frequency of chromosomal aneuploidies, which indicates the effectiveness of using the analysis of hyaluronic acid binding as a method of selecting mature, functionally active spermatozoa [79]. Practical reproductive medicine uses the indicator of DNA fragmentation as a reliable indicator of fertility, which is more specific than conventional indicators of sperm quality [80]. Testing for ROS content and antioxidant capacity could potentially provide additional prognostic information to standard laboratory tests for male infertility [81]. The overall antioxidant capacity of male sperm is also studied under conditions of different environments with a high content of AO [47]. As a biochemical predictor of male fertility, the effectiveness of the total antioxidant status use has been proven by determining this indicator in sperm plasma using the Randox kit in groups of healthy and infertile (with different types of reduced sperm quality) men in Pakistan. It proves reliably higher antioxidant protection levels in fertile men and the presence of a positive correlation with the concentration, motility of sperm, and content of cells with normal morphology [82; 83].

CONCLUSIONS

Oxidative stress is a leading pathogenetic mechanism of hypofertility (reduced reproductive capacity) of males, which due to the accumulation of toxic peroxidation products has a detrimental effect on the reproductive system by reducing the mitochondrial potential of sperm, and, consequently, their motility, damage to acrosomal fertilization. The vast majority of authors agree that this occurs under prolonged exposure to negative factors, as a result of which the antioxidant defense system loses the ability to adequately respond to the intensification of peroxidation processes and requires pharmacological correction. In this case, the definition of markers of OS and the dynamics of AOP should be used along with commonly used methods of testing male fertility, such as assessment of sperm quality and hormonal background. A promising area of research, in our opinion, is the search and scientific justification of safe and effective means for correcting male hypofertility under oxidative stress.

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Неплідність самців: патогенетичне значення оксидативного стресу та антиоксидантного захисту (огляд)

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Анотація. Основою патогенезу неплідності самців є процеси пероксидного окиснення біологічних субстратів, особливо, ліпідів і протеїнів. Руйнуючи оболонку спермія токсичні продукти пероксидації знижують його рухливість і здатність до запліднення яйцеклітини, що визначається зменшенням кількості рухливих сперміїв у еякуляті. Ці зміни призводять до виникнення повного або часткового чоловічого безпліддя. Авторами статті було встановлено, що це супроводжується ушкоджуючою дією на структурну і функціональну активність статевих залоз і проявляється, зокрема, дисбалансом у гормональному фоні організму самця. Аналогічними ефектами характеризується підвищення вмісту активних форм Нітрогену й метаболітів його циклу, що викликають нітрозивний стрес, який також є причиною гіпофертильності самців і перебігає нерозривно зі станом оксидативного стресу. У науковій роботі визначено, що накопичення шкідливих продуктів пероксидації призводить до ушкодження та руйнування ДНК сперміїв, зменшення активності акросомальних ензимів і мітохондріального потенціалу сперміїв, зниження загальної антиоксидантної активності, що унеможливлює адекватну відповідь організму. Стресовим станам протистоїть багатокомпонентна антиоксидантна захисна система, що представлена ензиматичною і неензиматичною ланками, здатна, до певної міри, знешкоджувати шкідливі радикали і продукти пероксидації, сприяючи повноцінному прояву репродуктивної функції. Показано наявність потужних антиоксидантних властивостей каталази, супероксиддисмутази і ензимів тіол-дисульфідної системи, що формують ензиматичну систему антиоксидантного захисту, та, Селену, Цинку, Купруму, інших мікроелементів, ретинолу, токоферолу, аскорбінової кислоти та вітаміноподібних речовин, як ланок неензиматичної системи. Обгрунтовано ефективність засобів реєстрації тонких біохімічних зсувів або комплексних методів – визначення загального антиоксидантного статусу сперміїв або спермальної плазми, потенціалу мітохондріальної мембрани, тощо поряд із простими маркерами оксидативного стресу, такими як дієнові кон'югати, малоновий діальдегід і метаболіти циклу Нітрогену оксиду. З огляду на провідну роль оксидативного стресу у розвитку гіпофертильності самців перспективою подальших досліджень є пошук сучасних засобів корекції, особливо серед речовин з вираженою редокс-активністю

Ключові слова: відтворна здатність, ліпопероксидація, антиоксидантні ензими, цикл Нітрогену оксиду