Review Article

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The Association between Free Radicals and the Ovarian Functions: A Review

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Abstract

Metabolites of oxygen are called reactive oxygen species (ROS). They are constantly synthesized by healthy cells and are a consequence of aerobic respiration and are necessary for proper cellular function. These species (ROS) cause oxidative stress as result generation exceeding the capabilities of the antioxidant system to neutralize it. It is a bifurcating factor in controlling the reproductive system of female, as it can influence various physiological activities or contribute to infertility in female. The current review notes that a number of ovarian function processes, including as reactive oxygen species have a major impact on follicular formation, ovulation, and corpus luteum function. Scavenging mechanisms also occur. However, the review concentrates on the detrimental impact that elevated ROS production has on the female reproductive system. This review concludes that free radicals play a variety of roles in ovarian function and that excess have negative effects on the female reproductive system.

Keywards: Reactive Oxygen Species, Oxidative Stress, Ovarian Function

الجذور الحرة وعلاقتها بوظائف المبيضين

الخلاصة

النواتج الايضية للاوكسجين تسمى أنواع الأكسجين التفاعلية (ROS). يتم تصنيعها باستمرار بواسطة الخلايا السليمة وهي نتيجة الاكسدة الهوائية وهي ضرورية للوظيفة الخلوية الضرورية. هذه الأنواع التفاعلية تسبب الإجهاد التأكسدي، بسبب زيادة انتاجها وعدم قدرة نظام الدفاع المضاد للأكسدة للتخلص منها. وهو عامل شائع في السيطرة على الجهاز التناسلي للأنثى، إذ يمكن أن يؤثر على الأنشطة الفسيولوجية المختلفة أو يساهم في العقم عند الأنثى. الهدف المراجعة الحالية إلى أن عددًا من عمليات وظائف المبيض، بما في ذلك أنواع الأكسجين التفاعلية، لها تأثير كبير على تكوين الجريبات، والإباضة، ووظيفة الجسم الأصفر. واليات الازالة لهذة الانواع لها أيضا. ومع ذلك، تركز المراجعة على التأثير الضار الذي يحدثه ارتفاع إنتاج أنواع الأكسجين التفاعلية على الجهاز التناسلي الأنثوي. نستنتج من هذة المراجعة إلى أن الجذور الحرة تلعب أدوارًا متنوعة في وظيفة المبيض وأن الزيادة يكون لها آثار سلبية على الجهاز التناسلي الأنثوي.

Introduction

Aerobic cells always face the problem of oxygen although its need oxygen to stay alive because the Reactive oxygen species (ROS) are formed from oxygen and include superoxide radical (O-), hydrogen peroxide (H2O2), and hydroxyl radical (OH–) (1). The excess reactive oxygen species and a breakdown in antioxidant defense mechanisms lead to oxidative stress. Certain reactive oxygen species have been demonstrated to induce lipid peroxidation, protein oxidation, and damage to DNA. Furthermore, a growing corpus of evidence indicates that reactive oxygen species might drive biologically active molecules' production or activation, controlling cell function in the process. Cells, however, have a defensive system against reactive oxygen species in an aerobic environment (2).(3) Some metalloenzymes can scavenge superoxide radicals. For example, superoxide dismutase converts superoxide radicals to hydrogen peroxide, whereby catalase or glutathione peroxidase or catalase can be further detoxified to H2O and oxygen (4). The ovary is the place where free radicals are created. Macrophages and neutrophils are two obvious sources of ROS known to exist in both follicles and corpus luteum and are among the many possible sources of reactive oxygen species in the ovary (5). Since free radicals are produced as by-products of regular metabolism, steroidogenic cells can also be a source of these pollutants (6). Important intracellular sources of ROS include mitochondrial electron transport, endoplasmic reticulum, and plasma membranes (7). The physiological functions and defects of reactive oxygen types in the ovary are reviewed in this article.

1. Oxidative Stress

When oxygen combines with specific molecules that have one or more unpaired electrons in their outer shell, very reactive atoms or molecules known as free radicals are produced (8). These radicals can serve as oxidizing or reducing agents in cells, forming, gaining one electron, or losing (9). According to (10), the radical and non-radical derivatives of nitrogen and oxygen are called reactive species of nitrogen (RNS) and reactive species of oxygen (ROS), respectively. Aerobic cells contain active forms of nitrogen and oxygen (RONS), which contribute to the formation of wrinkles and other aging-related diseases (11). The immune system, regulatory systems, the detection of harmful side effects, and the synthesis of energy from organic molecules all limit the creation of free radicals (RONS) (9). Endogenous and exogenous RONS sources are:

1.1. Endogenous sources of RONS

The following are some endogenous causes of free radicals: nicotinamide adenine dinucleotide phosphate oxidase (NADPH), Nitrous Oxide (NO),myeloperoxidase (MPO) and lipoxygenase (12).

1.1.1. NADPH Oxidase

The NADPH oxidase catalyzes the creation of the superoxide free radical, transferring one electron from NADPH to oxygen. During this process, O2• is moved from the extracellular space into the cell and H+ is exported (13).

$NADPH + 2O2 \leftrightarrow NADP+ + 2O2- + H+$

Superoxide dismutase (SOD) primarily produces hydrogen peroxide (H2O2) from oxygen (O2) (14). As result as hydrogen peroxide lacks unpaired electrons, it reacts strongly with phospholipids found in both proteins and cell membranes, forming highly reactive hydroxyionic ROS (OH•) through the Fenton or Haber-Weiss processes. When H2O2 is exposed to chloride and MPO in neutrophils, it can be transformed into hypochlorous acid (HA), which can destroy cellular proteins (15).

1.1.2. Nitrous Oxide (NO)

NO is produced by three primary subtypes of L-arginine nitric oxide synthase (NOS), including neuronal NOS, which is important in intracellular signaling, epithelial NOS, associated with vasodilation, and inducible NOS, activated by cytokines or other endotoxin-related signals. Finally, according to (16), O2 can react without

producing the intermediately peroxynitrite (ONOO-).

1.2. Exogenous Routes of RONS

According to (9), exogenous causes of radiation radiation sickness (RONS) include cigarettes, polluted air and water, heavy or transition metals, alcohol, drugs (such as bleomycin, tacrolimus, gentamicin, and cyclosporine), synthetic solvents, cooking, and exposure to wave length. These compounds are processed in the body into free radicals, which then bond to things like smoked meats, utilized fat, or oil.

All major cellular macromolecules, both endogenous and foreign, result from oxidative modification of RONS (12).

1.3. Markers of Oxidative stress

Protein carbonyl contents (PCC) are provided by the Fenton reaction of oxidizing agents with protein end-chain residues of lysine, proline, arginine, and threonine (17). The binding of lipid aldehyde oxidation products to lysine, cysteine, or histidine residues, known as Michael addition reactions, can also contribute to the production of carbonyl groups. RNS interactions with tyrosine-free residues or polypeptide sequences produce the synthesis of nitrotyrosine (NT) (18).

The Fenton reaction of oxidizing agents with protein end chain residues lysine, proline, arginine, and threonine provides protein carbonyl content (PCC) (17). The formation of carbonyl groups can also result from Michael addition reactions, which are oxidation products of aldehyde lipids binding to cysteine, histidine or lysine residues, Nitrotyrosine (NT) is produced through RNS processes involving non-tyrosine residues or polypeptide sequences (18).

Low-density lipoproteins are essential for transporting cholesterol (LDL) through body tissues. Trpkoyic et al.(2015) (19) describe LDL oxidation as a complex mechanism that involves oxidative damages in lipids, proteins and can cause to cholesterol accumulation.

The hydroxyl and peroxyl radicals' targets are polyunsaturated fatty acids (PUFAs), particularly linoleic and arachidonic acids. Other reactive aldehydes have been formed depending on the kind of polyunsaturated fats undergoing lipid oxidation, including isoprostanes (Isop), trans-4-hydroxy-2-nonenal (4-HNE), and malondialdehyde (MDA). (18). When glycoxidation occurs, the amino acid groups lysine and arginine combine with the carbonyl groups of carbohydrates to create advanced glycation end products (AGEs). The three major AGEs are glucosepane, pentosidine, and hydroimidazolone (20).

Oxidative damage to DNA is caused by a variety of mutagens, including 2-hydroxyadenine, 8-oxoadenine, 5-hydroxylsine, glycol, thymine, cytosine and glycol. According to Albercht et al. (2016) (21), oxidative stress mainly damages DNA through 8-oxo-dioguanine (8-oxo-guo) and 8-oxo-dihydro-2'-deoxyguanosine (8 -oxoD). However, 8-oxoguo can also result in transverse GT-T13 instances.

1.4. Antioxidant Agents

Enzymatic and non-enzymatic pathways are examples of endogenous antioxidants, glutathione peroxidase and catalase. Biological structures act as antioxidants, protecting the organism from free radicals' damaging effects, according to Adwas et al.(2019) (22), it involves both endogenous and exogenous chemicals.

Superoxide dismutase (SOD) is an antioxidant enzyme that converts superoxide anion (O2) into hydrogen peroxide and molecular oxygen. SOD is a key system for protecting cells and tissues from ROS-induced damage. Other enzymes promote the conversion of superoxide radicals to hydrogen peroxide, which then becomes oxygen and water (23). All mammalian tissues have three distinct types of SOD, each produced by a separate gene: Cu-Zn-SOD or SOD-1 is located in the cytoplasm; Mn-SOD, Mn-SOD, or SOD-2 is found in mitochondria; and EC-SOD or SOD 3 extracellular EC-SOD and Cu-Zn-SOD (24)

Through oxidizing reduced glutathione (GSH) to glutathione disulfide, which is then reduced to GSH by glutathione reductases, GSH-Px transforms peroxides and hydroxyl radicals into

non-toxic forms. Other antioxidant enzymes include glucose-6-phosphate dehydrogenase and glutathione S-transferase (25).

The blood contains bilirubin, vitamin E and β-carotene, and in the plasma 85% of the antioxidant potential comes from albumin and uric acid. Non-enzymatic antioxidants are substances that limit free radical reactions by interacting with RONS (26).

2. Oxidative stress impacts mammalian reproduction.

Stress is defined as environmental or management changes that disrupt internal equilibrium (27), and the incapacity of animals to cope with these changes, expressed as a failure to actualize genetic activity, which can negatively effect animal performance and reproduction (28). Etim et al. (2013) (29) explained the Stress is an instinctive response that occurs in animals when they encounter unfavorable environmental conditions. This can have a range of unpleasant consequences, from discomfort to mortality due to damage caused by oxidative changes. In addition Persson et al. (2014) (30). Mention that oxidative stress is caused by an imbalance between reactive oxygen species (ROS) and the body's ability to counteract their effects via antioxidant defense systems. The main biological molecules of ROS are classified as superoxide radical anion (O2-), hydroperoxyl (HO2-), ozone (O3), singlet oxygen (1O2), and radical compounds such as peroxyl (ROO-), alkoxyl (RO-), hydroxyl radical (OH-), hypochlorous acid (HOCl), and hydrogen peroxide (H2O2), called non-radical species (31).

The production of high quality offspring, reproduction of female mammals depends on the correct development of female gametes, and maturation involves a complex set of important processes such as implantation, embryonic growth and fertilization, which are associated with multiple signaling pathways (32). Fujii et al. (2015) (33) they observe that Changes in energy consumption and metabolism, as well as an excess of extremely powerful free radicals generated as a result of the regular process of oxygen consumption, are characteristics of the reproductive process. As well as Agarwal et al. (2008) (34) they found that oxidative stress has a dual effect on the control of the reproductive system in women: it either regulates many physiological processes or contributes to female infertility. A number of studies have shown the physiological role of ROS in mammalian reproduction, related to uterine function, corpus luteum, oocyte maturation and folliculogenesis (35). Similarly, ROS are required for male reproductive procedures, which include normal sperm-oocyte interaction, acrosomal reaction, hyperactivation, sperm capacitation, embryogenesis, embryonic implantation and fetoplacental development (34), in addition to spermatogenesis. oocyte connectivity (36). Overproduction of ROS can cause oxidative destruction of DNA, mitochondria, and cell membranes. This may ultimately accelerate cell death through necrosis or apoptosis, impairing embryonic development and oocyte competence, eventually leading to delayed embryonic development (37). (Figure 1). Likewise, elevated levels of ROS cause oxidative change to male germ cells, which interferes with fertilization and embryonic development, ultimately leading to miscarriage (38).

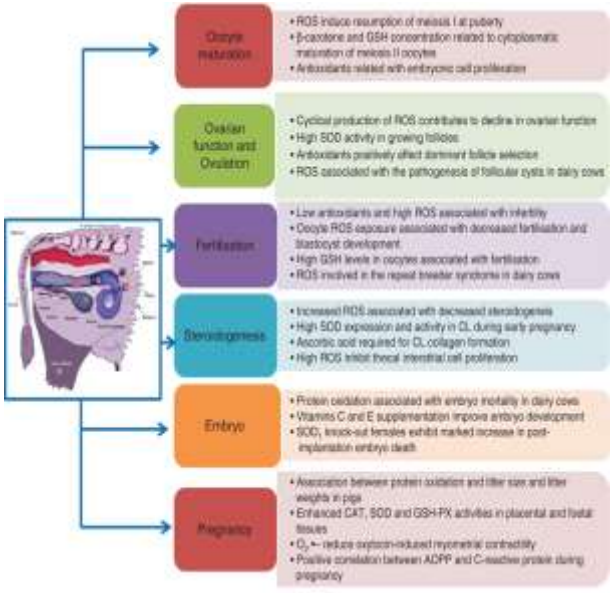

Figure 1.1: Effects of oxidative stress on female reproductive and fertility. Adapted from (39).

2.1. Oxidative stress in follicular development, oocyte growth, and ovulation

Follicle-stimulating hormone (FSH) causes an increase in estrogen synthesis during folliculogenesis, which in turn causes the dominant follicle to produce catalase (CAT) in an attempt to avoid ROS-induced apoptosis (40). In addition, due to increased P450 enzyme activity and ROS production, granulosa cells exhibit higher metabolic activity and steroid synthesis (31).The LH surge, associated with the activation of inflammation-related genes, caused the dominant follicle to release a mature egg. These inflammatory genes were discovered to be related with ROS generation, the ovulation process is affected by a decrease in inflammatory genes (41). The structure that appears after ovulation is called the corpus luteum. It produces reactive oxygen species (ROS) through luteal cells and macrophages (42), which influences progesterone production (43). Due to early embryonic death, deficiency of antioxidants, especially SOD1, is associated with decreased fertility. In addition, SOD1 deficiency increased ovarian intracellular ROS, which was associated with increased corpus luteum apoptosis and decreased progesterone synthesis (44). Immunostaining the Cumulus cells revealed greater SOD concentrations, which may suggest that Cumulus cells shield oocytes from oxidative stress by triggering antioxidants. In addition, granulosa cells, ovulatory follicles, and developing follicles generate antioxidants, both enzymatic and non-enzymatic, to guard against ROS-induced oxidative damage. Increased intracellular ROS buildup hindered the development of oocytes in meiotic arrest (45). Conversely, another study found that antioxidants prevented oocyte development (46). Consequently, for optimal oocyte maturation, the generation of reactive oxygen species (ROS) and the antioxidant system must remain in equilibrium.

Conclusion

The goal of this review is to highlight the critical roles that free radicals and their scavenging mechanisms play in a number of ovarian function processes, such as follicular atresia, ovulation, oocyte maturation, and follicular development. This review indicates that free radicals play a variety of roles in ovarian function and that an excess of them can have negative consequences on the female reproductive system.

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Confect Of Interest

There was none disclosed by the authors.

References

1. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, et al. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. Arch Toxicol. 2023;1–76.
2. Wang R, Liang L, Matsumoto M, Iwata K, Umemura A, He F. Reactive Oxygen Species and NRF2 Signaling, Friends or Foes in Cancer? Biomolecules. 2023;13(2):353.
3. Abed SK, Al-Azawi TSS. Selenium Enriched Yeast Modifies the Effects of Methandienone in Male Rabbits on the HPA Axis and Adrenal Gland Oxidative Stress. Anbar J Vet Sci. 2020;13(2).
4. Chen F, Chen L, Liang J, Chen Z, Zhang C, Zhang Z, et al. Potential Role of Superoxide Dismutase 3 (SOD3) in Resistance to Influenza A Virus Infection. Antioxidants. 2023;12(2):354.
5. Ahmad G, Almasry M, Dhillon AS, Abuayyash MM, Kothandaraman N, Cakar Z. Overview and sources of reactive oxygen species (ROS) in the reproductive system. In: Oxidative Stress in Human Reproduction. Springer; 2017. p. 1–16.
6. Darbandi M, Darbandi S, Agarwal A, Sengupta P, Durairajanayagam D, Henkel R, et al. Reactive oxygen species and male

reproductive hormones. Reproductive Biology and Endocrinology. 2018;16(1):1–14.
7. Nolfi-Donegan D, Braganza A, Shiva S. Mitochondrial Electron Transport: Oxidative Phosphorylation, Mitochondrial Oxidant Production, and Methods of Measurement. Redox Biol. 2020;101674.
8. Martemucci G, Costagliola C, Mariano M, D'andrea L, Napolitano P, D'Alessandro AG. Free radical properties, source and targets, antioxidant consumption and health. Oxygen. 2022;2(2):48–78.
9. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. Indian journal of clinical biochemistry. 2015;30(1):11–26.
10. Powers SK, Ji LL, Kavazis AN, Jackson MJ. Reactive oxygen species: impact on skeletal muscle. Compr Physiol. 2011;1(2):941–69.
11. Ozcan A, Ogun M. Biochemistry of reactive oxygen and nitrogen species. Basic principles and clinical significance of oxidative stress. 2015;3(5):37–58.
12. Salisbury D, Bronas U. Reactive oxygen and nitrogen species: impact on endothelial dysfunction. Nurs Res. 2015;64(1):53–66.
13. García JG, Ansorena E, Izal I, Zalba G, de Miguel C, Milagro FI. Structure, regulation, and physiological functions of NADPH oxidase 5 (NOX5). J Physiol Biochem. 2023;1–13.
14. Ma MW, Wang J, Zhang Q, Wang R, Dhandapani KM, Vadlamudi RK, et al. NADPH oxidase in brain injury and neurodegenerative disorders. Mol Neurodegener. 2017;12(1):7.
15. Genestra M. Oxyl radicals, redox-sensitive signalling cascades and antioxidants. Cell Signal. 2007;19(9):1807–19.
16. Prosser JI, Hink L, Gubry-Rangin C, Nicol GW. Nitrous oxide production by ammonia oxidizers: physiological diversity, niche differentiation and potential mitigation strategies. Glob Chang Biol. 2020;26(1):103–18.
17. Paraboni MLR, Kalinoski J, Braciak BG, Wilk AE, Santos LS dos, Schmitt EG, et al. Protein carbonyl products, malondialdehyde, glutathione and vitamins C/E of breast cancer patients subjected to chemotherapy. Brazilian Journal of Oncology. 2022;18:1–8.
18. Frijhoff J, Winyard PG, Zarkovic N, Davies SS, Stocker R, Cheng D, et al. Clinical relevance of biomarkers of oxidative stress. Antioxid Redox Signal. 2015;23(14):1144–70.
19. Trpkovic A, Resanovic I, Stanimirovic J, Radak D, Mousa SA, Cenic-Milosevic D, et al. Oxidized low-density lipoprotein as a biomarker of cardiovascular diseases. Crit Rev Clin Lab Sci. 2015;52(2):70–85.
20. Reynaert NL, Gopal P, Rutten EPA, Wouters EFM, Schalkwijk CG. Advanced glycation end products and their receptor in age-related, non-communicable chronic inflammatory diseases; Overview of clinical evidence and potential contributions to disease. Int J Biochem Cell Biol. 2016;81:403–18.
21. Albrecht DS, Granziera C, Hooker JM, Loggia ML. In vivo imaging of human neuroinflammation. ACS Chem Neurosci. 2016;7(4):470–83.
22. Adwas A, Elsayed A, Azab A, Quwaydir FA. Oxidative stress and antioxidant mechanisms in human body. J Appl Biotechnol Bioeng. 2019;6(1):43.
23. Davari S, Talaei SA, Alaei H. Probiotics treatment improves diabetes-induced impairment of synaptic activity and cognitive function: behavioral and electrophysiological proofs for microbiome–gut–brain axis. Neuroscience. 2013;240:287–96.
24. Wang X, Tao L, Hai CX. Redox-regulating role of insulin: the essence of insulin effect. Mol Cell Endocrinol. 2012;349(2):111–27.
25. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organization Journal. 2012;5(1):9–19.
26. Wu JQ, Kosten TR, Zhang XY. Free radicals, antioxidant defense systems, and schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2013;46:200–6.

27. Lu S, Wei F, Li G. The evolution of the concept of stress and the framework of the stress system. Cell Stress. 2021;5(6):76.
28. Khansari DN, Murgo AJ, Faith RE. Effects of stress on the immune system. Immunol Today. 1990;11:170–5.
29. Etim NN, Williams ME, Evans EI, Offiong EEA. Physiological and behavioural responses of farm animals to stress: Implications to animal productivity. Am J Adv Agric Res. 2013;1:53–61.
30. Persson T, Popescu BO, Cedazo-Minguez A. Oxidative stress in Alzheimer's disease: why did antioxidant therapy fail? Oxid Med Cell Longev. 2014;2014.
31. Rizzo A, Roscino MT, Binetti F, Sciorsci RL. Roles of reactive oxygen species in female reproduction. Reproduction in Domestic Animals. 2012;47(2):344–52.
32. Ye X, Hama K, Contos JJA, Anliker B, Inoue A, Skinner MK, et al. LPA 3-mediated lysophosphatidic acid signalling in embryo implantation and spacing. Nature. 2005;435(7038):104–8.
33. Fujii J, Iuchi Y, Okada F. Fundamental roles of reactive oxygen species and protective mechanisms in the female reproductive system. Reproductive biology and endocrinology. 2005;3(1):43.
34. Agarwal A, Gupta S, Sekhon L, Shah R. Redox considerations in female reproductive function and assisted reproduction: from molecular mechanisms to health implications. Antioxid Redox Signal. 2008;10(8):1375–404.
35. Rizzo A, Minoia G, Trisolini C, Mutinati M, Spedicato M, Jirillo F, et al. Reactive oxygen species (ROS): involvement in bovine follicular cysts etiopathogenesis. Immunopharmacol Immunotoxicol. 2009;31(4):631–5.
36. Chen S jian, Allam JP, Duan Y gang, Haidl G. Influence of reactive oxygen species on human sperm functions and fertilizing capacity including therapeutical approaches. Arch Gynecol Obstet. 2013;288(1):191–9.
37. Dennery PA. Effects of oxidative stress on embryonic development. Birth Defects Res C Embryo Today. 2007;81(3):155–62.
38. Baker MA, Aitken RJ. Reactive oxygen species in spermatozoa: methods for monitoring and significance for the origins of genetic disease and infertility. Reproductive Biology and Endocrinology. 2005;3(1):1–9.
39. Talukder S, Kerrisk KL, Gabai G, Celi P. Role of oxidant–antioxidant balance in reproduction of domestic animals. Anim Prod Sci. 2017;57(8):1588–97.
40. Behrman HR, Kodaman PH, Preston SL, Gao S. Oxidative stress and the ovary. J Soc Gynecol Investig. 2001;8(1_suppl):S40–2.
41. Shkolnik K, Tadmor A, Ben-Dor S, Nevo N, Galiani D, Dekel N. Reactive oxygen species are indispensable in ovulation. Proceedings of the National Academy of Sciences. 2011;108(4):1462–7.
42. Sugino N, Shimamura K, Tamura H, Ono M, Nakamura Y, Ogino K, et al. Progesterone inhibits superoxide radical production by mononuclear phagocytes in pseudopregnant rats. Endocrinology. 1996;137(2):749–54.
43. Sawada M, Carlson JC. Intracellular regulation of progesterone secretion by the superoxide radical in the rat corpus luteum. Endocrinology. 1996;137(5):1580–4.
44. Noda Y, Ota K, Shirasawa T, Shimizu T. Copper/zinc superoxide dismutase insufficiency impairs progesterone secretion and fertility in female mice. Biol Reprod. 2012;86(1):11–6.
45. Tatemoto H, Sakurai N, Muto N. Protection of porcine oocytes against apoptotic cell death caused by oxidative stress during in vitro maturation: role of cumulus cells. Biol Reprod. 2000;63(3):805–10.
46. Takami M, Preston SL, Toyloy VA, Behrman HR. Antioxidants reversibly inhibit the spontaneous resumption of meiosis. American Journal of Physiology-Endocrinology And Metabolism. 1999;276(4):E684–8.