Strategies for Preventing Oxidative Stress-Induced Injury to Human Spermatozoa

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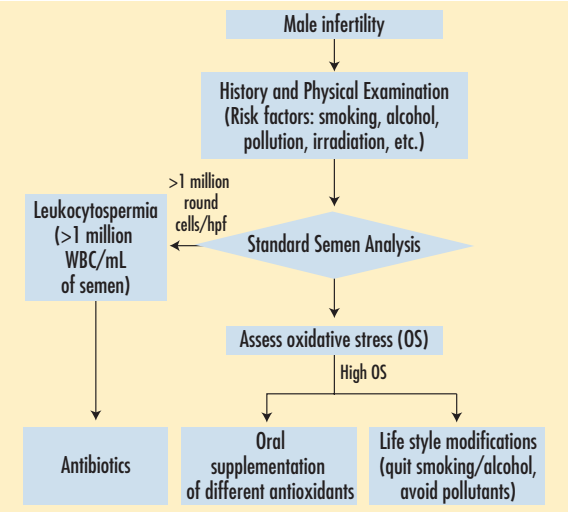
Oxidative stress (OS) due to excessive generation of reactive oxygen species (ROS) has been implicated as a major cause of sperm dysfunction. Spermatozoa are susceptible to OS-induced damage because their plasma membranes are rich in polyunsaturated fatty acids. Factors increasing the production of ROS include lifestyle habits, infections, intrinsic defects in spermatozoa, and many methods of sperm handling, processing, and storage, which have evolved with the advent of assisted reproductive techniques (ART).

It is difficult to block OS-induced injury to cells or tissues because ROS are continuously produced by the aerobic metabolism of cells. Spermatozoa contain very limited cytoplasmic enzymes, which are required for the repair of peroxidative damage. With the aim of preventing OS-induced injury, several clinical trials are under way at The Cleveland Clinic to determine how OS damage can be minimized.

There are two types of antioxidants: prevention and scavenger. Prevention antioxidants include metal chelators and metal binding proteins, which block the formation of new ROS, whereas scavenger antioxidants remove the ROS that have already formed. Both prevent the action of ROS on spermatozoa.



Prevention Antioxidants

Transition metal ions such as iron, lead and cadmium adversely affect the male reproductive system either by directly acting on the sperm plasma membrane or by catalyzing ROS formation (Fenton's reaction). Metal chelators control lipid peroxidation of the sperm plasma membrane and protect the integrity of the spermatozoon, and also prevent DNA damage. Metal chelators such as DL-penicillamine, 2,3-dimercaptopropan -1 sulphonate, and meso-2, 3-dimercapto-succinimic acid are being used to improve the quality of sperm in ART. Albumin, ceruloplasmin, and metallothionein are proteins that interact with iron and copper and decrease ROS formation.

Scavenger Antioxidants

OS may also be limited by using chain-breaking antioxidants such as vitamin E and vitamin C. Vitamin C neutralizes hydroxyl, superoxide, and hydrogen peroxide radicals and prevents sperm agglutination. In addition, it also helps recycle vitamin E, which neutralizes H2O2 and protects the plasma membrane from lipid peroxidation.

Other important antioxidant components include carotenoids such as beta-carotene and lycopene. Glutathione plays an important role in protecting lipids, proteins, and nucleic acids against oxidative damage, and selenium is a necessary component for the synthesis of glutathione peroxidase and works synergistically with vitamin E. Other antioxidants may also protect against OS.

Modifying lifestyle habits such as smoking cessation, reducing alcohol intake, and avoiding exposure to environmental pollution can reduce the occurrence of OS. The use of specific sperm separation techniques, such as migration-sedimentation, density gradient centrifugation, and glass-wool filtration significantly reduce the level of ROS by removing leukocytes, which are the major source of ROS. In vitro supplements used during sperm preparation and ART also help protect spermatozoa against ROS. Moreover, adding antioxidants to the culture media neutralizes ROS produced by the leukocytes and immature spermatozoa and improves sperm-oocyte fusion. Similarly, it has been found that adding N-acetyl-L-cysteine, glutathione and hypotaurine protects spermatozoa against oxidative damage induced by H2O2. Pentoxifylline – a methylxanthine derivative that inhibits phosphodiesterase – has been approved by the FDA. It has a beneficial effect on sperm motility and acrosome reaction and reduced the $O2^{\bullet -}$ release by the human spermatozoa. The use of vitamin E in vitro has been also documented to improve sperm motility and viability.

Summary

Studies are under way at The Cleveland Clinic to determine the safe dose of antioxidants for human consumption.

Development of new antioxidants that target specific types of ROS and various measures that can be used to protect spermatozoa against the OS-induced injury are the areas of future research.