The Impact of Oxidative Stress on Male Infertility

Dr. Vanita Goel
Sr. Consultant, Obs & Gyn Geeta Hospital, Faridabad.

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Abstract:

Infertility is a global issue affecting many couples. Oxidative stress (OS) damages sperm through lipid peroxidation and protein oxidation, reducing seminal quality. The imbalance between antioxidants and reactive oxygen species (ROS) due to various factors like lifestyle, diet, genetics, and OS contributes to male infertility. High ROS levels damage sperm parameters, including DNA and protein structures. Addressing OS through lifestyle changes and antioxidant therapy can help manage male infertility. However, identifying the exact causes of OS-induced infertility remains challenging. This review explores the role of oxidative stress in male infertility and current management strategies.

Introduction:

Infertility, defined as the inability to conceive after 12 months of regular, unprotected intercourse, affects about 40-50% of men, with 2% showing suboptimal sperm parameters. Infertility causes emotional, sociocultural, and physical issues and is linked to sexually transmitted infections, undeveloped testes, and hormonal abnormalities. Globally, around 186 million individuals and 48 million couples are infertile, with the highest rates in South Asia, sub-Saharan Africa, North Africa/Middle East, Central/Eastern Europe, and Central Asia. Males are solely responsible for 20-30% of infertility cases and contribute to 50% of overall cases. Infertility is classified as primary (no pregnancy after 1 year) and secondary (inability to conceive after a previous pregnancy). About 50% of infertility cases are due to male factors, such as poor sperm quality, motility, and morphological defects. Oxidative stress is a significant mechanism in idiopathic male infertility, with sperm exhibiting excessive ROS production and reduced antioxidant capacity. Despite its association with idiopathic infertility, definitive treatments for OS-induced infertility are lacking. This review focuses on oxidative stress's role in male infertility and its management.

Seminal ROS and Male Infertility

Human sperm cells are particularly vulnerable to oxidative stress due to their high levels of polyunsaturated fatty acids (PUFA) in their plasma membrane and the absence of cytoplasmic antioxidant enzymes. An excess of reactive oxygen species (ROS) and their by-products can harm lipids, proteins, and DNA, resulting in cell death, changes in enzyme activity, and impaired sperm parameters crucial for fertilization.

Oxidative stress occurs when there is an imbalance between ROS production and the body's antioxidant defenses, disrupting cellular functions. ROS are oxygen-based molecules, including superoxide anion, hydrogen peroxide (H_2O_2), hydroxyl radical, singlet oxygen ($^1O_2$), peroxyl radical, alkoxyl radical, lipid hydroperoxide (LOOH), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and ozone (O_3).

Human semen consists of various cell types, such as immature and mature spermatozoa, different spermatogenesis stages cells, epithelial cells, and leukocytes. The primary sources of ROS are leukocytes (especially macrophages and neutrophils) activated during infection and inflammation, as well as immature, morphologically abnormal spermatozoa. Leukocytes can produce ROS at rates up to 1000 times higher than spermatozoa.

Mitochondrial oxidoreductase and sperm plasma membrane oxidase, both dependent on sperm-specific NADPH, are suggested as ROS production sources. Furthermore, unhealthy lifestyle factors like smoking, excessive

alcohol intake, poor diet, psychological stress, sedentary habits, and environmental exposures (e.g., radiation, metals, and toxins) can increase ROS levels in spermatozoa, contributing to male infertility.

Conversely, low levels of ROS generated by spermatozoa are essential for proper sperm function. ROS play a role in physiological processes such as tyrosine phosphorylation, capacitation, hyperactivation, acrosome reaction, and sperm-oocyte fusion. For instance, during capacitation, increased ROS levels, intracellular calcium, and tyrosine kinase activity lead to elevated cyclic AMP and subsequent hyperactivation.

Measurement Techniques for Oxidative Stress in Human Semen

Oxidative stress in human semen is measured using both direct and indirect assays. Indirect assays, such as myeloperoxidase, 8-hydroxy-2-deoxyguanosine, TBARS (thiobarbituric acid reactive substances), and TAC (total antioxidant capacity), determine the extent of damage caused by ROS. Direct assays provide a more accurate measurement of ROS levels.

To detect ROS, various methods are used, including chemiluminescence, dihydroethidium probes, nitroblue tetrazolium (NBT) tests, electron spin resonance, and cytochrome c reduction analysis. These methods directly quantify ROS in semen samples.

Measuring intracellular ROS levels is essential due to their high susceptibility to ROS-induced oxidation by agents such as peroxynitrite and hydrogen peroxide. Fluorescent probes like H2DCF-DA, used alongside cytochrome c centers, help study intracellular ROS production in spermatozoa and leukocytes.

The TBARS assay is frequently employed to assess malondialdehyde and 4- hydroxyalkenals, markers of lipid peroxidation. For low malondialdehyde levels, high-pressure liquid chromatography is recommended, while mass spectrometry investigates lipid peroxidation products like isoprostanes.

Chemiluminescence uses a luminometer and a chemiluminescent probe like luminol to quantify ROS in semen. The light emitted during the reaction is converted to an electrical signal by the luminometer, indicating ROS levels in relative light units (RLU) per second per million sperm. The normal ROS range in washed sperm suspensions is 0.10–1.03 × 10^6 photons per minute per 20× 10^6 sperm. This method is highly reliable and sensitive but requires testing within four hours of sample collection for best results.

Management of MOSI

Despite progress in measuring oxidative stress in semen, there are no standardized treatment protocols for male infertility due to oxidative stress, mainly because the causes of male infertility are not fully understood. This section reviews treatment options, including empirical treatments for men with high ROS levels, specific treatments, and methods to reduce iatrogenic oxidative stress.

Empirical Medical Treatment for Men with Elevated ROS: Evidence for Antioxidants Empirical medical treatment (EMT) is widely applied to men with idiopathic infertility and is divided into hormonal therapy and antioxidant supplementation. Hormonal treatments focus on correcting subclinical endocrine disorders by targeting the hypothalamic-pituitary-gonadal axis and include aromatase inhibitors, gonadotropins, androgens, and selective estrogen receptor modulators. Although hormonal therapy is well-established for men with identifiable issues like hypogonadotropic hypogonadism, only 10% of infertility cases are due to endocrine imbalances. Therefore, EMT is recommended for idiopathic infertility, but there is limited evidence of successful birth outcomes from in-vitro studies. For men without genetic issues, bacterial infections, or endocrine imbalances, identifying the primary cause of male oxidative stress infertility (MOSI) is preferable to using EMT.

Antioxidant Therapy

The imbalance between ROS production and antioxidant levels is a key cause of idiopathic male infertility. Scavenging

enzymes in the cytoplasm and antioxidants in seminal fluid are vital for defending against ROS. However, due to the low concentration of these enzymes and high PUFA content in sperm plasma membranes, spermatozoa are vulnerable to lipid peroxidation by ROS. Antioxidant defenses can be either enzymatic or non-enzymatic.

Numerous studies have investigated the efficacy of antioxidants such as vitamins C and E, zinc, selenium, L-carnitine, folic acid, and coenzyme Q10 on reducing oxidative stress in seminal fluid and improving sperm parameters.
Some studies have reported improvements in semen parameters, including reduced DNA fragmentation, enhanced sperm motility, morphology, and concentration, as well as better sperm redox status and pregnancy outcomes. For example, taking oral antioxidants for three months significantly improved sperm health and count in men with idiopathic infertility, potentially increasing the chances of natural conception. Although the effectiveness of antioxidant therapy is still debated, it should be considered after diagnosing infertility caused by oxidative stress. Combining MOSI diagnosis with ORP monitoring may enhance the effectiveness of antioxidant therapy. Compared to hormonal EMT and assisted reproductive technology (ART), antioxidants are generally safe, affordable, and readily available.

Non-enzymatic antioxidants like vitamins C and E, GSH, coenzyme Q10, carnitine, and minerals such as zinc, copper, selenium, and chromium are crucial for maintaining sperm health. GSH, a tripeptide thiol, performs various biological functions, including maintaining the redox state and detoxifying compounds. Vitamin C is a vital antioxidant for protecting sperm.

Conclusion and Future Directions:

ROS at physiological levels are crucial for sperm functions such as capacitation and the acrosome reaction. However, an excess of ROS leads to oxidative stress, resulting in lipid peroxidation of sperm membranes and adversely affecting sperm motility, viability, and morphology, which in turn negatively impacts pregnancy outcomes and artificial reproductive techniques. While there have been advancements in diagnosing and treating infertility related to oxidative stress, there is still not enough evidence to endorse a specific oxidative stress test. More research is required to overcome these challenges and enhance the understanding and treatment of oxidative stress in male infertility.

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