Antioxidant Therapy in Male Infertility : Fact or Fiction?

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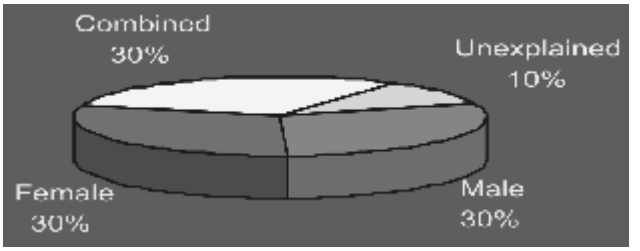
Infertility is regarded as **'male factor'** when an alteration in sperm concentration and/or motility and/or morphology is present in at least one sample of two sperm analyses, which comply with the World Health Organization **(WHO) 2011 guidelines**, collected between one to four weeks apart.

In 30% of infertility couples – male factor appears to be singularly responsible and in an additional 20% both male and female factor can be identified.

Therefore male factor is at least partly responsible for difficulties in conception in roughly 50% of these couples.



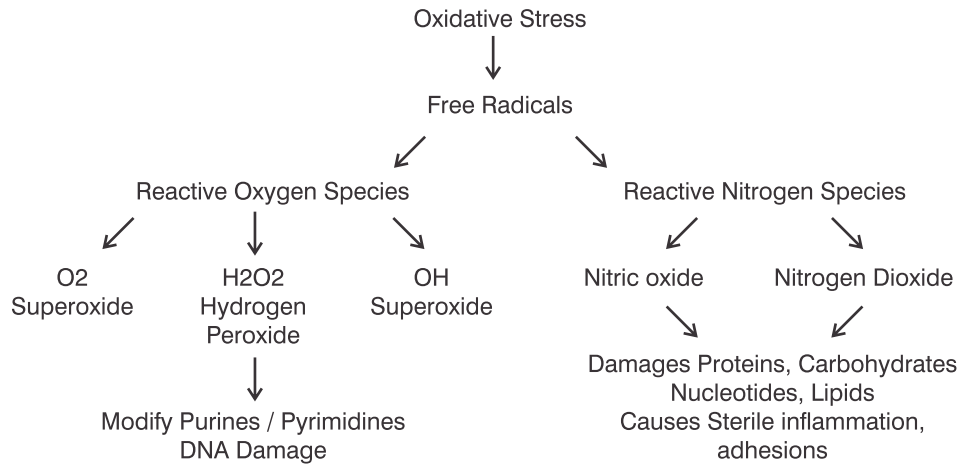
In all these years of treatment for male infertility, there was a **high incidence of implantation failure and early pregnancy loss in spite of doing ART**. Was there a link between quality of sperms and outcome of pregnancy? If the DNA of sperm i.e the genetic material of the sperm is damaged, obviously it will result in a poor pregnancy outcome.

- Extraordinary advances have been achieved in the field of male infertility in the last decades. There are new concepts in sperm physiology and several modern tools for the assessment of spermatogenesis kinetics in vivo. New tests using molecular biology and DNA damage assays allow the clinician to correctly diagnose men so far classified as having idiopathic male infertility.
- Between **30% to 80%** of idiopathic male subfertility cases are considered to be due to the damaging effects of **oxidative stress** on sperm.
- Oxidative damage means the presence of excess of reactive oxygen species. **Reactive oxygen species** (ROS) are molecules that have at least one unpaired electron, rendering them highly unstable and highly reactive in the presence of lipids, amino acids and nucleic acids.

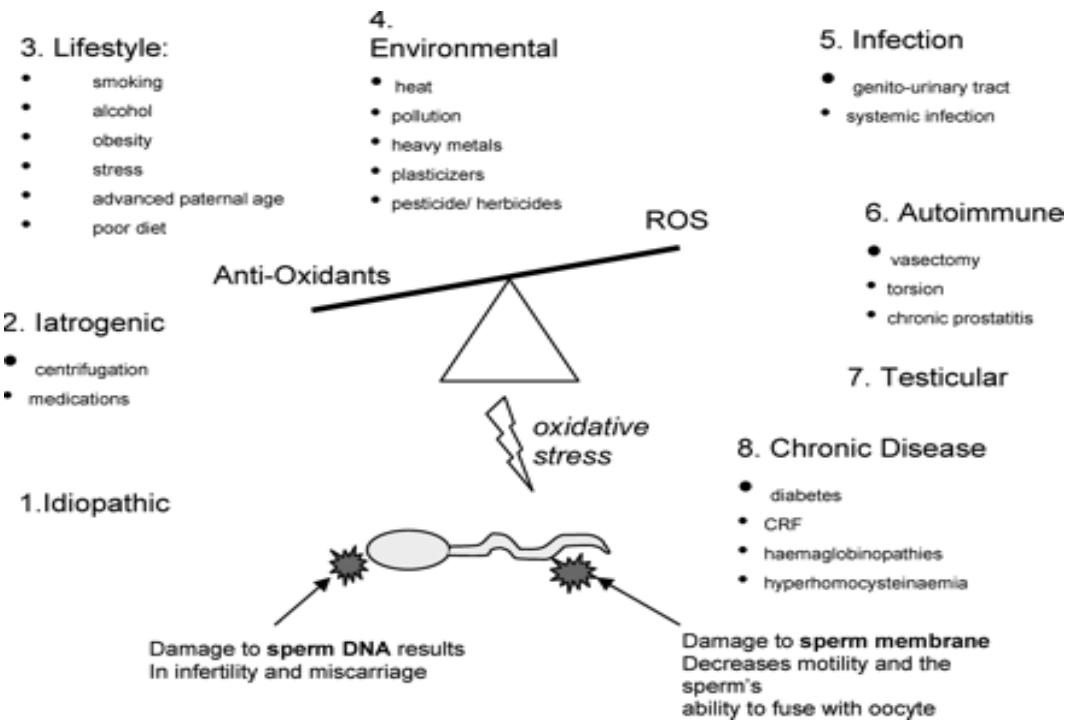
Physiologically they are present in ovaries, fallopian tubes and embryos.

At **physiologic levels**, ROS are essential for normal reproductive function, acting as metabolic intermediates in the metabolism of prostanoid, in the regulation of vascular tone, in gene regulation, in sperm and oocyte maturation and in facilitation of sperm capacitation and acrosome reaction, corpus luteal function etc.

- However, **at higher concentrations**, they exert negative effects. It is not known at which point the peroxidative damage to spermatozoa occurs, whether within semen (during the time required for liquefaction), in the epididymis (where spermatozoa are stored before ejaculation), or in the testis.

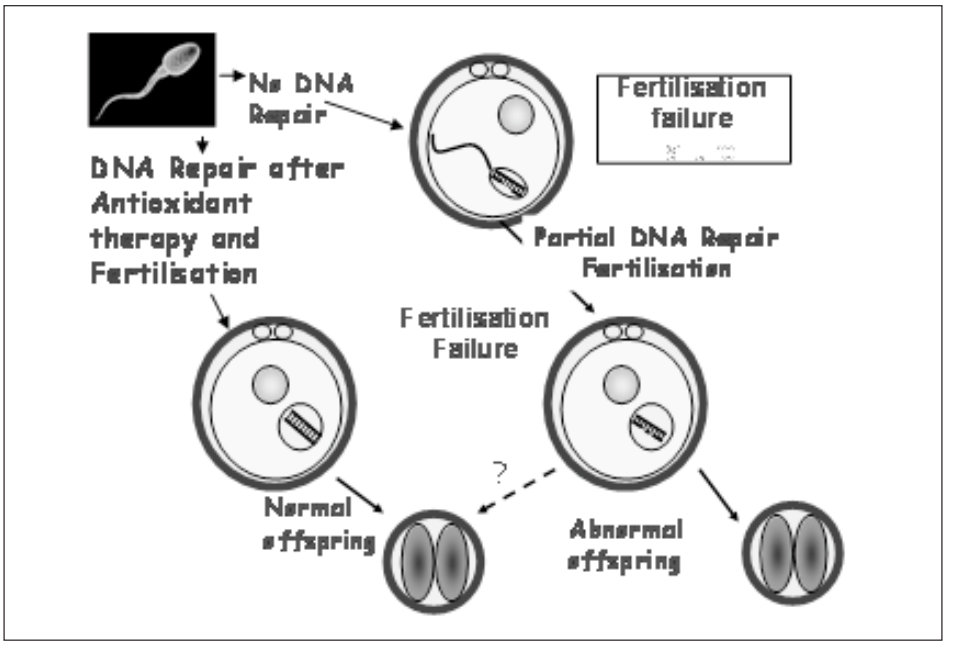


Hence there is a need for continuous inactivation by antioxidants, but maintaining small amount for normal cell function.



Oxidative stress causes

- Damage to the Plasma Membrane. (lipid peroxidation)
- DNA Fragmentation
- Decreased Fertilization rate and Early Embryo death
- Decreased sperm Motility
- Affects normal embryonic development



Why are sperms sensitive to oxidative stress?

Spermatozoa are vulnerable to ROS because their plasma membrane and cytoplasm contain large amounts of polyunsaturated fatty acids.

Significance of immature and abnormal sperms in semen

- Immature and abnormal sperms and pus cells produce a lot of ROS
- Poor sperm quality is linked to increased ROS generation as a consequence of the presence of excess residual cytoplasm.

How can oxidative stress be reduced?

- Treatment with Antibiotics- Infection can increase ROS production
- Supplementation of Media used for IUI, IVF/ICSI – Not proven to be useful
- Shorter Centrifuge time – Centrifugation increases ROS production
- Oral Supplementation - Found to be the most useful

Oral antioxidants available and used commonly

Vitamin C
Protects against DNA damage and supplementation helps increase the sperm count and reduces the agglutination
Smoking reduces Vitamin C

Vitamin E
Prevents ROS induced damage to sperm membrane and improves sperm counts and potency of sperms

Coenzyme Q (Co-Q 10)
Concentrated in the mitochondria in the middle piece and involved in energy production

Glutathione
Deficiency results in instability of middle piece resulting in abnormal motility

Ginseng
Improves sperm parameters and increases erectile capacity

Selenium
Helps to improve motilityand is synergetic with Vitamin E

Zinc
Involved in Testosterone production, sperm formation and motility

Arginine
Essential Amino acid found in sperm head

Lycopene
important in maintaining quality of gametes and support reproduction.

Omega 3 Fatty Acids
Fatty acids are used as source of energy by Sperms

Carnitor
Carnitines are used by spermatozoa for mitochondrial β-oxidation of long chain fatty acids, this being the principal shuttle and transfer system of the acyl to the mitochondrial CoA. Carnitines enhance the cellular energetics in mitochondria by facilitating the entry and utilization of free fatty acids within the mitochondria and also restore the phospholipid composition of mitochondrial membranes by decreasing fatty acid oxidation. Supplementation with carnitor improves the motility of sperm

Studies conducted

I **Cochrane Database Syst Rev. 2011 Jan 19 - Antioxidants for male subfertility.**

This Cochrane review aimed to evaluate the effect of oral supplementation with antioxidants for male partners of couples undergoing assisted reproduction techniques (ART).

Two review authors independently assessed 34 randomized controlled trials involving 2876 couples where male partner was given either placebo, no treatment or antioxidants The authors concluded that antioxidant supplementation in subfertile males may **improve the outcomes of live birth and pregnancy rate for subfertile couples undergoing ART cycles.**

II **Asian J Androl. 2011 Jun 20. -The role of antioxidant therapy in the treatment of male infertility: an overview.**

The authors in this study concluded that there is no linear correlation between sperm quality and pregnancy rates, **an improvement in semen parameters should not be the sole outcome**

considered in studies of antioxidant therapies. A definitive conclusion regarding the benefit of these therapies is difficult to obtain, as most of the studies lacked control groups, considered different antioxidants in different combinations and doses, or did not evaluate pregnancy rates in previously infertile couples. Even if beneficial effects were reported in a few cases of male infertility, more multicentre, double-blind studies performed with the same criteria are necessary for an increased understanding of the effects of various antioxidants on fertility

III **Hum Reprod. 2011 Jul; - The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy.**

Administration of antioxidants to infertile men has been assessed in numerous clinical studies was studied with at least 20 reports highlighting its effect on measures of oxidative stress in human spermatozoa. **A qualitative but detailed review of the results revealed that 19 of the 20 studies conclusively showed a significant reduction relating to some measure of oxidative stress in these cells.** Strong evidence also supports improved motility, particularly in asthenospermic patients

IV **Hum Reprod 2005 Sept - ICSI in cases of sperm DNA damage: beneficial effect of oral antioxidant treatment.**

No difference in fertilization and cleavage rate or in Embryo morphology.

Marked improvement of Clinical pregnancy (48.2% Vs 6.9%)

Implantation rate (19.65 Vs 2.2%)

Conclusion - **Oral antioxidant treatment appears to improve ICSI outcomes in those patients with sperm DNA damage, in whom this treatment reduces the percentage of damaged spermatozoa.**

General guidelines for medical management

- Treatment for 3-6 months
- At least for 74 days – 1 spermatogenesis cycle
- If no improvement or conception, then refer for ART
- Should be given before ART to improve the outcome of the cycle
- Majority of medical treatment needs further placebo controlled cross-over randomized double blind multicentric trials