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Antioxidants and Infertility

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Abstract

Infertility has a profound social, emotional and psychological impact on individuals. The couples are often desperate for quick results and are willing to follow any treatment advised for quick results. This desperation invariably catches up with the medical professionals treating them. As a result, various Add-ons have been included in the prescription. This is the genesis of Add-ons in the practice of reproductive medicine. Of these, antioxidants have emerged as the most commonly used medications as a panacea for severe male infertility and for enhancing female fertility. In this paper, we try to dispel this claim with scientific rationale and bring in evidence for its potential adverse effects.

Introduction

Based on a meta-analysis of population surveys published since 1990, the infertility prevalence was estimated to range from 3.5-16.7% in developed regions and from 6.9-9.3% in developing nations.[1] Recent trends indicate a decline in fertility and an increase in the prevalence of primary infertility. South Asian women had the highest average rate of change (40.9 per 100,000). Regarding primary infertility in men, South Asia (with an average rate of change of 16.5 per 100,000) had the highest increasing rates.[2]

Data from the four rounds of the Indian National Family Health Survey has been used to analyse the change in infertility rates over time. It has shown a remarkable increase in 2015–16 compared to 2005–06. The infertility rate has increased largely in the Southern states.[3]

Diagnosis of infertility leads to a chain of emotional disturbances, resulting in loss of self-esteem, disturbances in career, sexual dysfunction and even marital disharmonies. While we see a rise in very reassuring technologies and specialized care to help these couples, there is also an alarming rise in unproven medications and techniques offering promises of high success rate sites.[4] Sheer desperation and competition have driven the 'fertility market' to exploit the unfortunate victims.

Antioxidants are leading this market in their extensive use in infertile men, and also in women to 'reduce oxidative stress and help their gametes achieve the goal of pregnancy. It is time to understand Nature's way of tackling oxidative stress and explore the relevance of commercial antioxidants proclaimed as a panacea for the problem of infertility.[5]

What is Oxidative stress and how does it affect Health and Disease?

Oxidative stress occurs when there is an imbalance between the production and clearance of Reactive Oxygen Species (ROS). Reactive Oxygen Species are by products of cellular metabolism in all tissues. Free radicals (superoxide radicals and super nitrous radicals) are produced by mitochondria. Low levels are required for several physiological processes like cell growth, differentiation, activation of several transcription factors, apoptosis and immunity. Increased endogenous production of ROS occurs due to inflammation, injury, infections, ischemia, cancers, stress and excessive exercises. All tissues have intrinsic scavenging ability and cells deploy anti-oxidant protective systems to shield themselves against ROS-inflicted effects.

Excessive production of ROS occurs due to environmental pollutants, chemotherapeutic drugs, heavy metals, cigarette smoking, alcohol and irradiation. When the intrinsic scavenging system is overpowered with excessive amounts of ROS, harmful effects are experienced by important cellular components like proteins, lipids

and nucleic acids, resulting in pathological states of acute, chronic and degenerative diseases and their progression. It is still unclear whether the endogenous excess of ROS is the Cause or the Consequence of metabolic processes and their presence, which is a simple association with pathological states without being the causative factor. Natural antioxidants present in the body include enzymatic and non-enzymatic forms. Antioxidant enzymes are catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. Other nonenzymatic antioxidants include ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), ferritin, and transferrin.[6]

Role of ROS in Infertility:

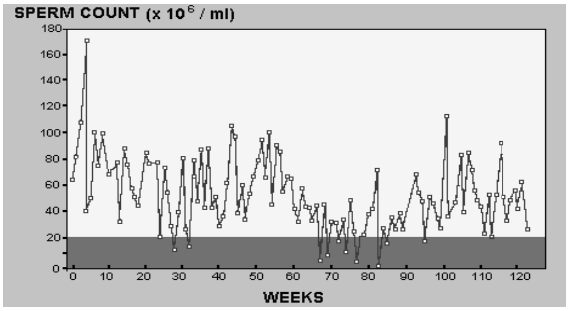
Male infertility:

Human spermatozoa are vulnerable to the ill effects of Oxidative stress due to the high Poly Unsaturated Fatty Acid content (PUFA) in their plasma membrane. The natural antioxidants present in seminal plasma protect them against ROS-induced damage right from the stage of spermatogenesis. ROS perform several key physiological functions in a male reproductive system like gene regulation, vascular tone regulation, fertilization, sperm capacitation, hyperactivation, sperm motility and acrosome reaction.[7]

The exact level at which ROS inflicts damage on the spermatozoa is also not certain. While it is clear that Nutrition is vital for good health and deficiency states lead to several diseases, the exact role Nutrition plays in infertility is yet to be understood. Folic acid, L-Carnitine, Zinc and Selenium have been claimed to play key roles in fertility.[8]Young et al associate a reduction of sperm aneuploidy due to intake of Folic acid, Zinc.[9]

Ranjani et al, in their paper on 'Nutraceuticals in Sperm abnormalities',[7] point out the lacunae in the WHO classification of Reference values in Semen parameters. There have been several revisions in the Reference values in their successive manuals. There is a natural variation from time to time in all semen parameters as has been given in their beautiful graph.[10]

Besides, we all know that Semen Analysis is a numbers game and all the parameters vary from time to time.[11] The semen parameters over time progress or regress to a mean value.



Graph 1: *Variability of spermatozoa concentration of a male over a period of time.*[10]

It is very evident from the above seminogram of a fertile male over a period of 120 weeks that there are inherent variations in the semen picture. While those could be the background for the so-called improvement of semen profiles claims have been made for the use of innumerable drugs and supplements for infertile males. This is especially true in men with low sperm concentration, motility and morphology, and also in men with idiopathic infertility.[10]

Men with Obstructive Azoospermia have the options of either surgical corrections if feasible or surgical sperm retrieval and assisted reproductive techniques. Medical treatment has no place here. In Non-Obstructive Azoospermia (NOA), Gonadotropin therapy is highly effective in patients diagnosed with Hypogonadotropic hypogonadism.[12]

The other patients with the testicular cause of NOA can benefit from surgical spermatozoa retrieval from the testis and assisted reproductive techniques to a fairly significant extent.[13]The pregnancy outcome ranges between 26% and 44.6% in men undergoing surgical spermatozoa retrieval.[14] Dr Divya et al observed and quoted in the thesis submitted towards the

fulfilment of Fellowship in Andrology and Reproductive Medicine, that the pregnancy outcome of surgical spermatozoa retrieval in cases of obstructive and non-obstructive azoospermia does not vary significantly.

Without proper diagnosis and directions, many of these infertile men are more likely to be administereda variety of medical treatments including antioxidants. These drugs are not only futile,and expensive but can also waste their precious time besides the possibility of adverse reactions. A good example of this is a reduction of motile spermatozoa in patients given Selenium as a supplement alone or in combination with other antioxidants.[15] Similarly, Vit C and E supplements have increased the DNA fragmentation and plasma membrane damage of spermatozoa, as cited by Lewis et al.[15]

While there are a plethora of studies supporting the empirical use of antioxidants in male infertility, there are also many others which raise a concern about the negative influence of these drugs on individuals.[16]

Ralf Henkel, Inderpreet Singh and A. Agarwal in their interesting paper in Andrologia raise concerns about 'reductive stress resulting in antioxidant paradox'. They opine that the easily commercially available antioxidants (Vit C, E and N-acetyl cysteine) have high concentrations and are likely to cause reductive stress as dangerous as oxidative stress and may result in diseases such as cancers and cardiomyopathies.[17]The authors conclude that a clear risk/benefit analysis is mandatory with further elaborate studies in male infertility on the use of antioxidants.

Antioxidants in female infertility:

As opposed to much work on the impact of increased ROS on male fertility, there are not enough studies to associate ROS in infertile women. Trevisan et al suggested that there could be a moderate positive correlation between BMI to increased ROS levels in women, impairing their fertility.[18]

Besides delayed time to pregnancy, there are also doubts about how ROS can influence early pregnancy outcomes. The physiological events of folliculogenesis, atresia and luteal regression contribute to oxidative stress and ROS. Maintaining a balance between the ROS and antioxidant levels is essential for the cumulus and oocyte to function and this is taken care of by the free radical scavenging effects of melatonin around ovulation.[19] Hence it is unlikely that gamete fusion and further progress of the embryo are affected by ROS naturally generated and handled with adequate antioxidant defences in the natural milieu.

Roos Marthe Smits et al, in their Views and Review paper, summarized that though commercially available antioxidants are plenty, easily accessible and inexpensive, there is very little high-quality evidence currently available to show their benefit to infertile couples.[20]

A recent Cochrane database systematic review analyzed 63 randomized control trials up to 2019, comparing antioxidants with placebo or no treatment in 7760 women. Their conclusion was again there is very little evidence for routine supplements with antioxidants for subfertile women.[21]

Adverse reactions of Oral antioxidant supplements:

Nature has its checks and balances for every physiological action and counteraction. While this is a model to follow, it is not easy to mimic every step in the innate regulatory mechanisms. This is very true and rightly applicable to the use and misuse of antioxidants for subfertile men and women. The antioxidants available through the dietary sources are in low concentrations and anything above is limited by the absorptive capacity of the gastrointestinal system. Whereas high concentrations in many of the commercial preparations have a potential side effect on our bodies causing adverse reactions.

Moreover, the actual type of antioxidant supplements, exact dose and duration of therapy

are still unknown. There is no demonstrated mechanism of action for any of them.

Dimitriadis et al raise this question in their article and urge an immediate need for more studies to assess the risk/benefit analysis of antioxidants in male infertility.[22]

Readily available OTC (Over Counter medications) are often combined with multiple agents, are unregulated and without any scientific backup.[23]

Potential side effects in the body after over-the-counter consumption of antioxidants are listed in Table 1.

Table 1:*List of Antioxidants and potential side effects*

Antioxidants	Recommen-ded dose	OTC consumption and potential side effects
L - Arginine	7 - 15 g/ day[24]	Aggravate cancer[7], asthma and herpes infection[24] Close monitoring is required when administered in patients with hepatic and renal pathologies[24] Gastric disturbances[25]
Vitamin A	50,000 – 100,000 IU/day[26]	Nausea, vomiting, anorexia, desquamation of skin, hair loss[26] Osteoporosis, headache, calcinosis, and bone resorption[27] intrahepatic cholestasis – rare[28]
Vitamin C	2-6 g/day[26]	Diarrhoea, renal calculi, interferes with warfarin, dental erosions[26] Hemolytic anemia, hemochromatosis, renal calculi[29]
Vitamin E	15 mg/day[30]	Risk of bleeding, cataract, fatigue, gastric disturbances, thrombophlebitis, breast tenderness, emotional disorder[30] The blurring of vision, bruising, and cardiovascular effects[23]
Folic acid	5 mg/day[31]	Itching, rashes, fever, wheezing[26] Gastric disturbances. Rashes, sleep disturbances, irritability, confusion, seizure, allergy[23]
Lycopene	-	Gastric disturbances, altered skin pigmentation[23]
L-Carnitine	-	Seizure, gastric discomfort[23] Diarrhea, Fish odor syndrome,[32]
Zinc	10 mg/day[33]	Abdominal cramps, nausea, vomiting, lethargy, leukopenia, anemia, dizziness[34] Increases the risk of prostate cancer[35]
Selenium	55 µg[23]	Nausea, vomiting, discoloration of nails, fatigue, hair loss, irritability, garlic breath[36]
Coenzyme Q-10	200 mg/day[37]	Rash, diarrhea[37]

Yves JR Ménézoa et al have encountered an unexpected adverse effect of antioxidants in male infertility, 'an increase in sperm decondensation with the same order of magnitude (+22.8%, $P < 0.0009$). The opening of interchain disulphide bridges in protamines may explain this aspect, as antioxidant vitamins, especially vitamin C, can open the cystin net, thus interfering with paternal gene activity during preimplantation development. This raises a deep concern regarding

the use of antioxidant vitamins as a routine supplement for male infertility.[38]

Various harmful effects of antioxidant supplements in male infertility have been brought to light by Massimiliano Creta et al in a very recent paper (2022) in the journal 'Antioxidants'. Their study is a systematic review of randomized clinical trials on the toxicity of antioxidants till 2021.

Side effects ranged from 0.8%-60%.Gastrointestinal upsets are the most common. Headache, vertigo, dizziness, pruritus and also decrease in platelets, RBC, and white cell counts were also encountered.[39]

The following authors also list out the various adverse reactions, including 'all-cause mortality' due to high doses of Vit E. These are attributed to their 'reductive stress effect'. This is as bad as oxidative stress and may lead to many pathologies.[40, 41, 42, 43, 44]

The beneficial effects of antioxidants are best experienced through natural food sources (fresh vegetables, fruits, nuts, seeds, raisins, cereal grains, legumes, and Oil seeds to name some) in optimal proportions along with other synergistic compounds which are not present in commercial preparations. The whole is greater than the sum of its parts

For Female subfertile patients, a well-balanced diet with fresh vegetables, fruits, and nuts along with Folic acid supplementation seems sufficient for the requirement for natural antioxidants. Beyond this, the majority of studies have not proved any beneficial effect of commercial antioxidants for improving subfertility, decreasing miscarriages, preventing pre-eclampsia, intrauterine growth restriction of the foetus or preventing preterm labour.[45]

Conclusion:

Nutrition plays an important role in not only general health but also in the health of gametes and future generations. A balanced diet with fresh vegetables, fruits, nuts, and healthy grains helps the natural protective mechanisms in force for all body functions. The deficiency states call for supplements when natural resources are not available or in scarce supply or not utilized in the body. Empirical use of supplements in lieu of good nutrition is attended with adverse reactions and defeats the very purpose of their use. To date, most clinical trials and systematic reviews have not categorically proven that the routine use of various commercial antioxidants in high concentrations actually improves male and female infertility and certainly does not avert pregnancy complications.[46]

It is to be borne in mind that caution has to be exercised before prescribing antioxidants as the magic pill to enhance human reproduction. Prevention is always better than cure. It is wise to prevent conditions causing excess production of ROS and not mitigate them after the damage has been done.

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