

## The Effects of Oxidative Stress and Some of the Popular Antioxidants on Reproductive System: A Mini Review

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### Abstract

According to worldwide statistics, at least one out of six couples has fertility problems. Oxidative stress is an important cause of infertility. Excess reactive oxygen radicals could lead to male and female infertility and also some pregnancy complications. Antioxidants are widely used for detoxify the excess reactive oxygen species as called "scavengers". In this mini-review our aim is to inform about the effects of oxidative stress and some of the popular antioxidants in the reproductive system and also experimental use of this antioxidants under different cases especially in studies which is conducted in the last few years.

**Keywords:** Oxidative stress; Antioxidants; Reproductive system; Infertility; Experimental designs

### Introduction

The reproductive failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse is called as infertility [1] and it is an important public health problem [2]. According to worldwide statistics, at least one out of six couples has fertility problems [3]. 40%-50% of the etiology of infertility studied is due to female [4] and 30% of the etiology of infertility studied is due to male factor of infertile couples [5]. 15% to 25% of the couples affect from infertility without an identifiable causative factor [1,6]. Modern life affects the fertility problems by increasing through endocrine disrupting chemicals, pesticides, xenoestrogens, polychlorinated bisphenyls, bisphenol A, phthalates and etc. Oxidative stress is increased by an important part from these compounds [3]. As reported by The World Health Organization guidelines [7], the male factor is the cause of infertility about half of these cases and oxidative stress is an important cause of infertility, especially male infertility [6].

### Free radicals, reactive oxygen species (ros), antioxidants and oxidative stress

Free radicals are unstable and highly reactive molecules or atoms [8] with an unpaired number of valence electrons [1]. Free radicals only become stable by obtaining electrons from lipids, proteins, carbohydrates, nucleic acids or any nearby molecules [8]. ROS consist of free and non-free radical reactive molecules [9]. A certain amount of reactive oxygen species are necessary for physiological body functions and normal cell functions but it is harmful in larger amounts may overpower the body's natural antioxidant defense system that cause various diseases [1,9]. Antioxidants are widely used for detoxify the excess reactive oxygen species as called "scavengers" and also an imbalance between pro-oxidants and antioxidants is cause to oxidative stress [9].

### The sources of the reactive oxygen radicals in reproductive system

ROS that in low and controlled levels, play an important role in capacitation, hyperactivation, acrosome reaction and sperm-oocyte fusion in male reproductive system [1,10]. But excess reactive oxygen radicals are detrimental to the spermatozoa functionality and could lead to male infertility [6]. The endogenous sources of ROS in male reproductive system are; leukocytes, immature spermatozoa and varicocele [1,6]. Radiation, toxins, smoking and alcohol consumption are the exogenous sources of ROS in male reproductive system. ROS cause lipid peroxidation, DNA damage and apoptosis pathologically in male reproduction [6]. In physiological levels, ROS play an important role in female reproduction including ovarian steroidogenesis, oocyte maturation, folliculogenesis, ovulation and luteolysis [11,12]. Also; oocyte, cumulus mass cells and follicular fluid are the endogenous sources of ROS in female reproductive system [1].

### Relationship between infertility and oxidative stress

ROS decrease the sperm number and motility and inhibition of sperm-oocyte fusion and also some experimental studies in men indicate that dietary antioxidants appears to be crucial role in preventing oxidative damage to sperm DNA [2]. The imbalance between pro-oxidants and antioxidants can lead to a number of female reproductive diseases such as endometriosis, polycystic ovary syndrome and unexplained infertility [9]. Also some pregnancy complications like spontaneous abortion, recurrent pregnancy loss and preeclampsia can also develop in response to oxidative stress [9].

### Some of the popular antioxidants and its experimental use in the reproductive system under different cases

**Vitamin C and Vitamin E:** Vitamin E has an antioxidant activity that is protecting the cell membrane from oxidation [13]; also vitamin C may prevent DNA damage by neutralizing free radicals and oxidants [14]. Subchronic oral administration of 5 mg/kg organophosphate insecticides Methyl parathion, cause the induction of lipid peroxidation in the endometrium due to ROS. Treatment with a

combination of 50 mg/kg Vitamin E and 20 mg/kg Vitamin C by intramuscular way after Methyl parathion administration reduced endometrial damage and apoptosis in Wistar albino female rats [15]. In another study, vitamin C administration in 250 mg bid levels for 3 months after varicocelectomy in case of the men with infertility and clinical varicocele with abnormal semen analyses, after 3 months, vitamin C can play a role as adjuvant treatment in infertile men specifically on quality and not quantity of sperm [16].

**Selenium:** According to our past study in 2013 with female rats, 75 mg/kg cyclophosphamide was found to cause remarkable degenerative effects in normal ovarian tissue and this damage can be reduced by using 200 mg/kg ascorbic acid, 150 mg/kg  $\alpha$ -tocopherol and 40 ppm/day selenium and these antioxidants minimize the level of free oxygen radicals that might occur during chemotherapy [17]. Also the deficiency of selenium cause gestational complications, miscarriages and low birth weight of a newborn and may lead to male infertility by causing a deterioration in the quality of semen and sperm motility [18]. Selenium protects against oxidative damage to spermatozoa through the sperm maturation process. Some examines showed that abnormal spermatozoa occurs and it affects semen quality and fertility in gene knock-out studies of selenoproteins [19].

**Alpha-Lipoic Acid and N-Acetylcysteine:** These antioxidants have protective effects against reactive oxygen species-mediated oxidation by reducing tissue Glutathione (GSH) oxidation and enhance the mitochondrial membrane potential. Alpha-Lipoic Acid and N-Acetylcysteine are used together for protection in case of testicular damage which is induced by oxidative stress [20]. And also it has protective properties against experimental or xenobiotic mediated germ cell death [20-22]. Germ-cell and steroidogenesis depletions through the generation of reactive oxygen species which is caused by swimming-induced can be protected by co-administration of 3 mg/100 g body weight/day alpha-lipoic acid and 50 mg/100 g body weight/day N-Acetylcysteine in the rat testis [20].

**L-Carnitine:** In azoospermic men, the L-Carnitine concentrations were found very low compared with normospermic examples [23]. L-Carnitine supplementation increases the semen quality in oligoasthenoospermic men who have a low L-Carnitine concentrations [24]. In one case it was concluded that in normozoospermic samples, 0.5 mg ml<sup>-1</sup> L-Carnitine after incubation and centrifugation with  $5 \times 10^6$  sperm ml<sup>-1</sup> increased the sperm motility but not affect sperm viability and DNA oxidation [25].

**Coenzyme Q10 and Fish Oil:** Coenzyme Q10 is used as a dietary supplement and as an energy-promoting antioxidant commonly [26] and fish oil has protective effects against cardiovascular and respiratory diseases, diabetes and reproductive system [27,28]. 10 mg/kg administration of Coenzyme Q10 and 400 mg/kg administration of fish oil combination has protective effect against to aluminum chloride-induced testicular dysfunction in the rats [29].

**Green Tea:** Green tea has a potential health-promoting properties due to its catechins and it has an ability to scavenge reactive oxygen species including strong antioxidant activity [30,31]. 300 mg/kg green tea and 0,4 mg/kg vitamin E combination had a protective effect in the testicular tissue in diabetic rats which were induced by streptozotocin [32].

**White Tea:** White tea administration decreases insulin resistance and increases insulin sensitivity according to recent studies that it has the highest antioxidant potential [33,34]. And according to an experiment that is published in 2015, white tea consumption prevented

the testicular damage in prediabetic rats and also restores the sperm quality [35].

**Melatonin:** The neurohormone melatonin regulates physiological functions conforming to light and dark daily cycle [36]. Melatonin and its metabolites have an antioxidant activities and as free radical scavengers [37]. Melatonin that is exogenously administered during pregnancy may be helpful in protecting the mother and the fetus from oxidative stress [38] and melatonin administration normalized the enzymatic disorders in prostate due to its antioxidant properties under experimental diabetes in rats but even at low dosages [37].

## Conclusion and Future Perspective

In this mini-review we want to inform the effects of oxidative stress and some of the popular antioxidants which are especially worked in our department by us, in the reproductive system and also experimental use of this antioxidants under different cases especially in studies which is conducted in the last few years.

We suggest that, the studies which are including the analysis of antioxidant extracts and also will be concluded by *in vitro* and *in vivo* experiments after this analyse will be more useful on this subject.

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