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Infertility, Oxidative Stress and Antioxidant Supplementations. Is There A Correlation? A Review Article

*Ahmed A Morsy[1] and Nagwa A. Sabri[2]**

[1]Department of Clinical Pharmacy, Misr University for Science and Technology, Giza, Egypt

[2]Department of Clinical Pharmacy, Ain Shams University, Cairo, Egypt

Abstract

It is well-known that infertility has a great burden on individuals and societies worldwide, for that reason this review article will discuss the role of different antioxidants in managing infertility in both sexes has been of a great interest and scope of research in the last decade. Our objective is to held, on scientific basis, a detailed evidenced comparison between the effect of several antioxidants investigated in several clinical studies on the ovulation process, semen analysis and pregnancy outcome. It has been reported in a multi-center study including nearly 12 studies about the role of antioxidant in infertility in both men and women that antioxidants as selenium, Co-enzyme Q10, L-carnitine, vitamin E and vitamin D, Myoinositol might have a beneficial effect on improving infertility and pregnancy outcome. Finally, it was concluded that antioxidants might have a great effect in decreasing rate of infertility in both sexes and improving birth outcome.

Keywords: Infertility-Male; Female- Oxidative; Stress-Antioxidants; Vitamin E; Vitamin D

Introduction

Infertility and subfertility have been defined by the World Health Organization (WHO) as the failure to get pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Approximately 15% to 20% of couples of reproductive ages are infertile, which can be attributed equally to both male and female factors [2]. Infertility has a great influence on about 48 to 186 million persons [3].

Subfertility is considered to be an annoying problem to couples and society which need efficient treatment of this problem and may need high costs with risk of complications [4]. Subfertility can affect man, women, or both; when no cause is detected, it is termed unexplained subfertility [5].

Oxidants

Reactive Oxygen Species (ROS) are chemical species with a single unpaired electron. The well-known ROS include Hydrogen Peroxide (H_2O_2), Superoxide Anion (O_2), and Hydroxyl Radical (OH). Some cells possess specific mechanisms to produce ROS that are required for cellular functions in low concentrations [6]. There are many origins of oxidative stress including ROS inside human body. The main source is derived from aerobic environment through *in vivo* mechanisms such as electron leakage during biologic oxidations and by physical activation of oxygen by external agents such as irradiation, e.g. UV sunlight. The ability to react with any molecule can characterize ROS making them able to modify its oxidative impact. This modification can result in structural and functional changes that impair many cellular processes. According to their tissue concentration, they can either apply beneficial physiologic effects (e.g. Play role in fertilization process) or pathological damage to cellular components, including lipids, proteins and nucleic acids [7].

Antioxidants

The body has established competent defensive tools against unnecessary accretion of ROS. As ROS can be neutralized by releasing antioxidants as a defending parameter including; superoxide dismutase, catalase and glutathione peroxidase/reductase and others as non-enzymatic antioxidants e.g. vitamin A vitamin C, vitamin E, pyruvate, glutathione, taurine and hypotaurine [8]. In a healthy body, pro-oxidants and antioxidants maintain a ratio and a shift in this ratio towards pro-oxidants gives rise to oxidative stress. Oxidative stress can be either mild or severe according to the degree of

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Correspondence:
Nagwa A. Sabri, Department of Clinical Pharmacy, Ain Shams University, Cairo, Egypt, Tel: +201223411984; Fax: +202 24051107;
E-mail: nagwa.sabri@pharma.asu.edu.eg

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shift. When ROS levels become pathologically elevated, antioxidants begin to work and help to decrease the oxidative damage. Male and female genital tracts of are rich in different types of natural produced antioxidants [9].

Cellular mechanisms that are required for fertilization are inhibited. It is possible to predict the extent of peroxidative damage can be done by measuring levels of malondialdehyde [10].

DNA damage

Susceptibility of DNA to oxidative damage is indicated by the presence of oxidatively modified substances like 8-hydroxy-2-deoxyguanosine. Deoxyribonucleic acid bases and phosphodiester backbones are sites that are susceptible to peroxidative damage. High levels of ROS mediate the DNA fragmentation that is commonly observed in the spermatozoa of infertile men [11]. Sperm DNA has the characteristic compact organization and their antioxidant was monitored in seminal fluid which protects it from oxidative insult. Spermatozoa are unique in that they cannot repair DNA and depend on the oocyte for repair after fertilization [12].

Male infertility, oxidative stress and clinical applications

For the clinician it is important to know the clinical conditions in which oxidative stress may play a role in the etiology of infertility. Many clinical conditions were proved to be associated with increased oxidative stress [13]. Also, infections and inflammations involving the male reproductive tract are obvious conditions associated with oxidative stress in view of excessive generation of ROS by leukocytes [14]. It was found that very high percentages of persons with spinal cord damage were reported to have elevated levels of oxidative stress [15]. Mechanism of infertility in patients with varicocele is poorly understood and ROS is postulated as a possible mediator [16]. Therefore, the higher percentages of ROS and depressed levels of Total Antioxidant Concentration (TAC) were associated with varicocele [17] and patients who undergone vasectomy reversal also had high levels of ROS [18]. In addition, it was reported that history of smoking was correlated with increased values of oxidative stress [19].

Role of oxidants in female infertility

ROS have a great impact in female reproductive tract including many processes such as: Fertilization, oocyte development, luteal deterioration, and endometrial detaching [20]. Thus, ROS levels in follicular fluid may be used as markers for predicting the achievement of Assisted Reproductive Techniques (ART) [21].

Whenever there is imbalance in the levels of ROS and antioxidants in favor of ROS, a potential damage can occur to oocytes and embryos through several pathological mechanisms described previously. Thus, oxidative stress can affect the female fertility potential in number of ways, including, ovulation, fertilization, endometrium receptivity [4].

The sources of ROS in Graffian follicle may be macrophages, neutrophils and granulosa cells, while, there are high levels of antioxidants in follicular fluid, which protect oocytes from ROS-induced damage. Moreover, falling levels of selenium were observed in follicular fluid of women with unexplained infertility in comparison with cases include male factor infertility [22].

On the other way; baseline TAC levels were higher in follicles whose oocytes fertilized successfully [23].

It is worthy to mention that, an elevated level of ROS in peritoneal fluid may be the cause of infertility in some women who do not have any other obvious cause as ROS can damage the ovum after its release from the ovary, the zygote/embryo and most importantly, spermatozoa [24].

Aim of Study

To evaluate the effect of antioxidant supplementation in decreasing rate of infertility in both sexes and improving birth outcome.

Patients and Methods

Considered studies must fulfill certain criteria:

Type of studies:

Inclusion criteria

- Randomized Control (RCTs).
- Cross-over trials are included.

Exclusion criteria

Any quasi-randomized trials.

Types of participants:

Inclusion criteria

- Trials that included sub-fertile women and men who had been referred to a fertility clinic and might or might not be undergoing Assisted Reproductive Techniques (ART) such as *In Vitro* Fertilization (IVF), or Intrauterine Insemination (IUI) or Intracytoplasmic Sperm Injection (ICSI).

Exclusion criteria

- Participants who give history of vitamin D deficiency (Figure 1).

Discussion

Infertility is known to be inability to establish a viable pregnancy after at least 12 months of regular and unprotected sexual intercourse in the fertile phase of the menstrual cycles. It represents a major public health issue as about 17% of couples in the world suffer from this problem [25]. It is well agreed that the Assisted Reproductive Technique (ART) field achieved a great success allowing a satisfied number of infertile couples to successfully conceive. Despite of these attempts, only 35% of couples attending ART succeeded to obtain a live birth delivery [26]. It has been shown that success of ART was depend on Reactive Oxygen Species (ROS) which are highly reactive molecules that, at physiologic levels, are naturally involved in various physiological cell processes [27].

Despite of the different positive and beneficial role of antioxidants, in several cases of infertility, it may be non-effective according to the underlying pathology of infertility [28]. Drugs with antioxidant properties have been evaluated to show weather beneficial outcomes were achieved or not. On the other hand, WHO recommends application of traditional drugs in medical health service system and this give a great interest in finding natural antioxidants from plant materials to replace synthetic medicines [29].

This review included about 12 studies (2,037 subjects) which was conducted on cases of male or female infertility to evaluate the effect of different antioxidant supplementation in different types of infertility.

L-Carnitine (LC)

Jamilian et al. [30] revealed that after 12 weeks intervention with

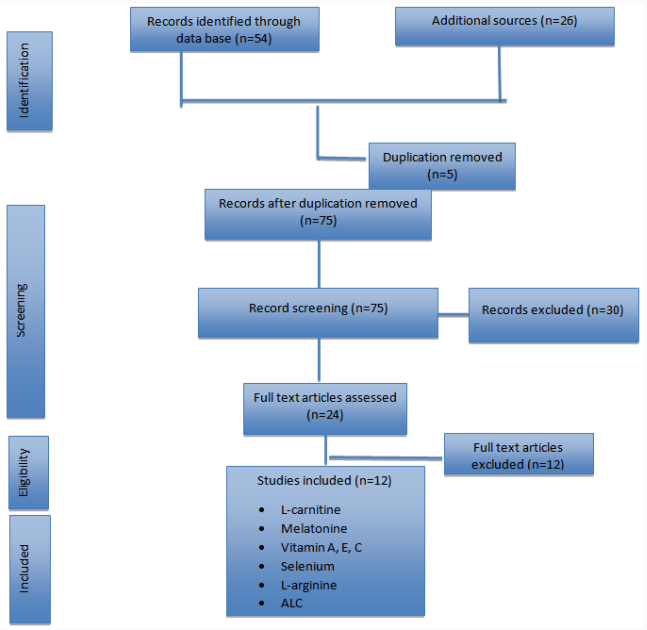

Figure 1: A flow chart of study identification and inclusion in the review.

L-carnitine, there was a significant improvement in Beck Depression Inventory total score (p<0.001) and depressive disorders scale scores (p=.001). In addition, changes in plasma total antioxidant capacity (TAC) (p=0.01), Malondialdehyde (MDA) (p=0.01) and MDA/TAC ratio (p=0.003) in the supplemented group [30].

Another study by Wu et al. [31] revealed that adding L-carnitine in *In Vitro* Maturation/*In Vitro* Culture (IVM/IVC) medium enhanced maturation and developmental competence of porcine oocytes *in vitro*. On statistical analysis of obtained results, it was found that no significant difference was present in oocyte maturation rates when given at doses of \0, 0.25, 0.5, or one g/L of LC added during IVM. When compared with control oocytes, those treated with 0.5 g/mL of LC during *in vitro* maturation increases the production of blastocyst after parthenogenesis potentiation owing less apoptosis characteristics. Adding 0.5 g/L of LC in cases of IVM had significantly higher glutathione concentrations and decreased intracellular ROS in case glucose is given or not, also, 0.5 g/L of LC in the IVM atmosphere will make nuclear ripening of oocytes significantly increased. Also, supplementing the *in vitro* maturation atmosphere with either glucose or LC lead to (P<0.05) high percentages of oocytes that reached the Metaphase II (MII) step, in comparison with control group. A non-significant difference of maturated rates of IVM medium with glucose or L-carnitine. However, 0.5 g/L of LC in *in vitro* maturation atmosphere significantly decreased oxidants levels and apoptosis in activated blastocysts, But GSH levels were not significantly changed [31].

Double blinded, RCTs including 170 females suffering from PCOS were observed to be resistant to clomiphene citrate CC. The women were randomly classified into two groups: Group one (n=85), where patients received 250 mg CC from third day of the cycle for 5 days with LC 3000 mg per day; and Group two (n=85) given 250 mg CC with placebo. LC with CC significantly enhance ovulation and cumulative pregnancy rates in women with CC resistant PCOS (55 (64.4%) *vs.* 15 (17.4%) and 44 (51.5) % *vs.* 5 (5.8) %). Number of mature follicles was significantly higher in LC group (2.2 ± 0.77 *vs.* 0.16 ± 0.79; p<0.0001). Less days for ripening of follicles which were needed for having more endometrium thickness and higher E2 concentration at the time of HCG injection (10.1 ± 0.1 mm *vs.* 6.8 ± 0.4 mm). Serum progesterone was significantly higher in group one (13.55 ± 0.99 *vs.* 10.6 ± 0.98 ng; p<0.0001). Clinical pregnancy rates also differ significantly (42 (49.4%) *vs.* (1) 1.1% respectively p value <0.0001) [32].

Genazzani et al. [33] studied the effect of LCA in 24 patients with Hypothalamic Amenorrhea (HA) who were divided into 2 groups according to LH plasma levels; group A, hypo LH (LH ≤ 3 Mlu/; no=16), and group B, normo-LH (LH>3 mlU; n=8), were treated with ALC (1 g/day orally) for 16 weeks and revealed significant increase in LH plasma levels (from 1.4 ± 0.3 to 3.1 ± 0.5 ml U/ml, p<0.01) and in LH pulse amplitude (p<0.001) and no changes were observed in noro-LH group. LH response to naloxone was restored under ALC therapy [33].

The beneficial effects of melatonin supplementation on culture media [34], gametes [35], embryos [36], and luteal functions [33] have suggested that indoleamine can be useful in management of human infertility. A pilot study by Espino et al. [37] was carried out in 40 women with history of infertility, were divided into 4 groups; group 1 (control) included healthy fertile females (n=10), and 30 patients with UI (group two; 10 females by using a random computer-generated program, group 2, UI women who did not take melatonin, group 3, UI women who took daily dose of 3 mg melatonin, group 4, UI women who took a daily dose of 6 mg melatonin. They revealed that melatonin supplementation significantly (p<0.05) decreased intrafollicular 8-OHdG levels in those UI patients who were given 3 mg (group 3) or 6 mg melatonin/day (group 4), bedsides intrafollicular concentrations of 8-OHdG were significantly and negatively correlated with intrafollicular concentrations of melatonin (p<0.05) [37].

Myoinositol

It was revealed that Myoinositol (MI) causes an improvement in semen quality in patients with asthenozoospermia with significant increase in sperm motility with P-value <0.05. [38].

Moreover, the advantages of MI are also in making balance between metabolic and hormonal of the patients thus, regulating the action of several hormones such as FSH, insulin, and TSH [39].

Furthermore, MI improves properly the quality of the semen, through improving the spermatozoa motility, ameliorating the mitochondrial potential membrane and improving the morphology of the mitochondrial membrane and their volume. This is easily observable in a better morphology of spermatozoa sheath. Allow quality semen seems to be strictly related to the presence of amorphous material in the semen and, on this regard, MI is able to remove it, reducing semen viscosity and consequently improving the chances to obtain a spontaneous pregnancy [38].

Selenium and Vitamin E

Selenium antioxidant activity, mediated by several selenoproteins, is involved in crucial physiological pathways, in particular, the Phospholipid Hydroperoxide Glutathione peroxidase (PHGx) is crucial for male fertility preserving from the strong oxidative stress due to the numerous and rapid divisions that characterize the germ cells.

On the other hand, selenium is a necessary component of the structural integrity of the sperms. In fact, natural levels of selenium

are related to normal motility and number of sperm [40].

The combination of selenium (225 mg/day) and vitamin E (400 mg/day) results in a reduction of oxidative stress reflected by spectrophotometric assessment of malondialdehyde after 3 months of treatment. Vitamin E is localized in body walls, forming a protective layer against free radicals and reducing the levels of malondialdehyde, it improves sperms motility. Also, the addition of selenium increases the efficacy of vitamin E [41].

Vitamins C and E act as chain-breaking antioxidants and thus prevent the propagation of peroxidation process.

Conclusion

Oxidative species can have an influence on infertility in men and women, and different types of antioxidants as selenium, L-carnitine, vitamin E, vitamin D, myo-inositol, vitamin C and coenzyme Q can have a vital role in improving semen, sperm characters, and ovulation in women. When L-carnitine was added in CC resistant PCOS patients it greatly enhanced Ovulation and pregnancy rates in addition to lipid profile improvement with no adverse effects reported by the patients. Moreover, detection of the important and unique role ALC in counterbalancing the abnormalities induced by the stress in hypo-LH patients which affect by hypothalamic amenorrhea. The beneficial addition of ALC was detected in stress induced problems in patients with low LH modulated by amenorrhea due to defect in signals of hypothalamus. In addition to, LC was found to improve bovine oocytes and also the quality of parthenogenesis embryos which may accelerate nuclear maturation, and prevent oxidative damage and apoptosis.

Finally, antioxidants have a beneficial and useful effect on improving sperm motility and semen characteristics especially in cases with asthenozoospermia.

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