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The role of different antioxidant agents in human infertility and assisted reproductive techniques

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Abstract
Reactive oxygen species (ROS) are a group of oxidants formed during oxygen metabolism. ROS appears to be involved in the pathogenesis of many human diseases. In reproductive medicine, ROS have both physiological and pathological role in male and female reproduction. Oxidative stress causes damage to spermatozoa, oocyte and embryos. It appears to play a role in both natural and in vitro fertilization and pregnancy. In In recent years there has been a tremendous increase in couples seeking assisted reproductive technology (ART) procedures in order to have children. However, the success rates of these procedures still remain very low. The negative impact of oxidative stress on fertility has become widely recognized. Several studies have demonstrated its negative effect on the number and quality of retrieved oocytes and embryos following in-vitro fertilization (IVF). One of the major contributing factors to the low success rate in ART has been the damage caused by free radicals to the gametes and the developing embryo. Oxidative stress can originate from the early steps of ART involving the oocyte, sperm and embryo, as well as in the endometrial environment later on following embryo transfer. The patients with oxidative stress may benefit from the strategies to reduce oxidative stress and treatment with antioxidants.
This review assessed the evidence for the effectiveness of different antioxidants in female and male subfertility.
Keywords: infertility, assisted reproductive techniques, antioxidants, vitamin E, coenzyme Q10, L-Carnitine , pentoxifylline, N-Acetyl cysteine, Zinc, melatonin, vitamin C

Introduction

Infertility, a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse ,affects 15% of all couples, with nearly a quarter of cases being without an identifiable causative factor (1). Recent advances in the field of reproductive medicine may allow for a select group of infertile couples to conceive and bear offspring by utilizing assisted reproductive techniques (ART)(2). Medical treatment for infertility include in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), which are the two most common interventions used in assisted reproductive technology (ART) (3) Among the crucial factors lacking in assisted reproduction procedures is the tight control of ROS levels maintained within physiological concentration by antioxidants in vivo (1) . The consequent development of oxidative stress is among the chief causes of defective gametes or poorly-developing embryos in ART(3). Several studies have reported impaired clinical outcomes of ICSI with ejaculated spermatozoa in men with elevated nuclear DNA damage (4). In 2003, a report by the Society for Assisted Reproductive Technology conceded that only 35% of ART transfer procedures result in a live birth delivery. In contrast, in vitro ART procedures are carried out without the protection of enzymatic antioxidants normally found in vivo, leading to unopposed, elevated levels of ROS, which have been shown to adversely affect gametes, gamete interaction, fertilization and pregnancy rates (2).

Intrauterine Insemination

Intrauterine insemination (IUI) is performed by threading a very thin, flexible catheter through the cervix and injecting washed spermatozoa into the uterus. This technique requires large numbers of forward-progressing motile spermatozoa (2).

In vitro Fertilization:

(IVF) is another assisted reproductive technique in which sperm-oocyte interactions take place within culture media , leading to fertilization (2).

Intracytoplasmic Sperm Injection

Intracytoplasmic sperm injection (ICSI) is a laboratory procedure in which a single sperm is injected directly into an oocyte's cytoplasm using a very fine needle. The process allows for oocyte fertilization regardless of the morphology and motility characteristics of the single spermatozoon injected (2).

What Is Oxidative Stress and How Does It Affect Fertility?

High generation of ROS by immature and abnormal spermatozoa, contaminating leukocytes, sperm processing accompanied by low scavenging and antioxidant levels in serum, seminal plasma, and/or sperm-processing

media will induce a state of oxidative stress. High levels of ROS endanger sperm motility, viability, and function by interacting with membrane lipids, proteins, and nuclear and mitochondrial DNA . The possible explanation of this damaging process is based on the fact that mammalian spermatozoa membranes are rich in polyunsaturated fatty acids that make them very fluid but at the same time very susceptible to free radical–induced peroxidative damage (5).

Peroxidative Damage to Spermatozoa
Peroxidative damage initiated by high ROS generation in the spermatozoa of infertile men is associated with not only a loss of membrane function, but also the appearance of damage to the DNA located in the sperm head in such patients, leading to a high incidence of DNA strand breaks (5).

Oxidative stress and sperm membrane lipid Peroxidation
Spermatozoa, unlike other cells, are unique in structure, function, and very susceptible to damage by ROS . Orientation of unsaturated fatty acids in the plasma membrane creates the fluidity necessary by the spermatozoa to perform normal physiological functions . Minor alterations in sperm membranes in selected cases of dyspermia can be reversed by glutathione (GSH) therapy (5).

Oxidative Stress and Protein Damage
ROS-induced peroxidation of critical thiol groups in proteins will alter structure and function of spermatozoa and ova with an increased susceptibility to attack by macrophages (5).

DNA damage
High levels of ROS mediate the DNA fragmentation that is commonly observed in the spermatozoa of infertile men . Spermatozoa are unique in that they cannot repair DNA and depend on the oocyte for repair after fertilization . Various types of DNA abnormalities occur in sperm that have been exposed to ROS artificially (6).

Apoptosis
ROS may also initiate a chain of reactions that ultimately lead to apoptosis. In human germ cells, apoptosis may help remove abnormal germ cells and prevent their overproduction. levels of ROS were positively associated with apoptosis in mature spermatozoa. Levels of caspases, which are proteases involved in apoptosis, correlated with levels of ROS (6).

ROS in assisted reproductive techniques
Although reactive oxygen species are physiologically required for various biochemical pathways necessary for reproduction, their in vivo levels are tightly controlled by enzymatic antioxidants that scavenge and neutralize free radicals to maintain an optimal, physiologic oxygen tension in the male and female reproductive system (2). OS-induced DNA damage may have important clinical implications in the context of ART. Studies have indicated that human spermatozoa significantly increased levels of ROS production in response to repeated cycles of centrifugation involved in conventional sperm preparation techniques used for ART . Spermatozoa selected for ART usually originate from an environment experiencing oxidative stress, and a high percentage of these sperm may have damaged DNA. When intrauterine insemination (IUI) or in vitro fertilization (IVF) is used; such damage may not be a cause of concern because the collateral peroxidative damage to the sperm plasma membrane ensures that fertilization cannot occur with a DNA-damaged sperm (7).

DNA Damage and Role of ART
Current focus on male factor infertility during oxidative stress suggests damage to integrity of DNA in the sperm nucleus resulting in base modification, DNA fragmentation, and chromatin cross-linking . Such DNA damage may accelerate the process of germ cell apoptosis. In the testis , that can lead to a decline in sperm counts and result in infertility (5).

Antioxidants and Their Role in ART and Infertility
Antioxidants, in general, are free radical scavengers that suppress the formation of ROS and/or oppose their actions. Superoxide dismutase (SOD), catalase, and glutathione peroxidase are well-known biological antioxidants that convert superoxide (O2 -) and peroxide (H2O2) radicals to form O2 and H2O .Glutathione peroxidase, removes peroxyl radicals from various peroxides including H2O2 to improve sperm motility. Because GSH has a likely role in sperm nucleus decondensation and may alter spindle microtubule formation in the ovum, it may help protect ova and embryo during ART, thus affecting the outcome of pregnancy. Another enzyme, a-glutamyl transpeptidase that is present in the midpiece and acrosomal regions of spermatozoa may further regulate GSH content of oocyte at the time of sperm penetration (8). It is possible that pentoxifylline, a

known sperm motility stimulator, can also act as a suppressor or scavenger of ROS to improve sperm motion in leukocytospermia . Also, the role of vitamins E and C, the chain breaking antioxidants that scavenge intermediate peroxyl and alkoxyl radicals in protecting spermatozoa against endogenous oxidative DNA and membrane damage, should be evaluated for their effects in improving the post thaw sperm parameters. Carotenoids (beta-carotene) and ubiquinols are also known to quench singlet oxygen and may play a role in reducing detrimental effects on sperm (5).

Role of antioxidant supplementation

As oxidative stress results in luteolysis, antioxidant supplementation has been shown to have beneficial effects in preventing luteal phase deficiency and resultant increased pregnancy rate .Improved pregnancy rates were also reported with combination therapy with the antioxidants pentoxifylline and vitamin-E supplementation for 6 months in patients with thin endometria who were undergoing IVF with oocyte donation .Many antioxidants (vitamins C and E, glutathione and beta-carotene, pentoxifylline,etc.), supplemented during sperm preparation and ART, improve sperm motility and acrosome reaction (9).

In Vitro Protection by Antioxidants

When added in vitro during IVF preparation or as sperm wash media, ascorbic acid (600 mmol/L), alphatocopherol (30 and 60 mmol/L), and urate (400 mmol/L) have each been reported to provide significant protection from subsequent sperm DNA damage . Many isoflavones (eg, genistein and equol) are plant products with antioxidant activity and may prevent sperm damage. Compared with ascorbic acid and alpha-tocopherol, genistein was shown to be more potent antioxidant when added to culture media (5).

Antioxidants and assisted reproductive technology

The presence of oxidant and antioxidant systems in various reproductive tissues has evoked great interest in the role of oxidative stress (OS) in human reproduction. OS is defined as an elevation of levels of various reactive oxygen species (ROS) that exceeds the body's antioxidant defenses(3).Scavenging of the ROS by various antioxidants has been proposed to lead to a better environment for the preimplanted embryos. Reduction in blastocyst degeneration, increased blastocyst development rates, increased hatching of blastocysts and reduction in embryo apoptosis, and other degenerative prooxidant influence has been reported. (9).

L-carnitine

L-Carnitine is a naturally-occurring molecule that scavenges ROS. A systemic review and meta-analysis of 9 RCTs concluded that oral supplementation with L-carnitine or L-acetyl-carnitine improves total sperm motility and pregnancy rates. In two separate studies, it was shown that the in vitro addition of L-carnitine to the culture media not only improved oocyte chromosomal structure and reduced embryo apoptosis , but also improved blastocyst development rate (1).

S.A. Abd El-baset et al. showed that L-carnitine treatment has ameliorative impact on the quality of spermatozoa in the infertile men, resulting in a decrease number in morphologically abnormal spermatozoa, indicating that this agent affects the quality of spermatozoa in infertile patients who need intra cytoplasmic sperm injection (ICSI) as a method for infertility treatment(10).Aliabadi E et al. found that Although the administration of L-carnitine and Pentoxifylline enhanced sperm motility, L-carnitine also impacted glycoconjugates on the sperm surface. Glycoconjugates are involved in the interaction between the sperm and the zona pellucida and subsequently fertilization, thereby probably influencing the male fertility state(11). L-carnitine has been found to improve the quality of spermatozoa in selected cases with male infertility. Here, we examined the efficacy of L-carnitine in improving sperm motility and vitality and reducing sperm DNA oxidation during cryopreservation. . We conclude that LC supplementation during vitrification is particularly efficient in improving the pre-implantation development from GV-oocytes which have lower developmental competence in culture(12).

Pentoxifylline

Since pentoxifylline treatment significantly increases the sperm capacity to undergo the acrosome reaction in response to both natural and artificial stimuli, there is a reasonable concern about possible untimely occurrence of extensive acrosome reactions (13). Data are presented covering various studies on the use of the phosphodiesterase inhibitor pentoxifylline in the sperm preparation for procedures in assisted reproduction. Significant improvements have been shown in the fertilization rate of oocytes along with a reduced risk of failed fertilization cycles utilizing oligo/asthenozoospermic semen samples. Fertilization is also improved for normozoospermic samples when the acrosome reaction is suboptimal. pentoxifylline has proven effects on sperm motility, increasing the proportion of hyperactivated spermatozoa. It can also enhance the acrosome reaction and this may be the more relevant function for clinical prediction. There is a further action as a suppressor or

scavenger of reactive oxygen species although higher concentrations than that in current clinical use may be required to optimize this effect(14).
Esteves SC et al. described the effects of the direct addition of pentoxifylline to the ejaculates of men with poor sperm quality before freezing on post-thaw sperm motility, viability, acrosome integrity, and agonist-induced acrosome reaction. The data showed that pre-freeze treatment of poor quality human sperm with pentoxifylline did not improve post-thaw motility or viability nor did it prevent acrosomal loss during the freeze-thaw process. However, pentoxifylline, as used, improved the ability of thawed spermatozoa to undergo the acrosome reaction in response to calcium ionophore. The data indicated that treatment of poor quality human sperm with pentoxifylline may enhance post-thaw sperm fertilizing ability(15).Guasti PN et al. investigated whether pentoxifylline present in the flushing extender influenced the function of equine epididymal spermatozoa after recovery and after thawing. The results showed that the pentoxifylline present in the flushing extender improved motility parameters of recently recovered epididymal sperm and had no deleterious effects on plasma membrane integrity and freezability of equine epididymal sperm(16).

Vitamin E

In a small prospective study, Geva's group showed that oral vitamin E (200 mg for 3 months) increased oocyte fertilization rate per IVF cycle in fertile, normozoospermic men who initially had low fertilization rates during a previous IVF attempt. The in vitro effects of vitamin E on normal and abnormal spermatozoa during cryopreservation are improved post-thaw motility and DNA integrity , while addition during incubation improved motility and viability of abnormal spermatozoa(1). Moslemi and Tavanbakhsh studied the effects of vitamin E and selenium therapy for 14 weeks in 690 asthenoteratozoospermic infertile men from couples with male factor infertility. Semen analysis was found to be improved in 362 or 52.6% patients: 299 patients showed improved motility, 21 patients showed improved morphology and 42 patients showed improvement in both sperm motility and morphology. However, 253 cases (36.6%) showed no change in their semen analysis, while the remaining 75 patients (10.8%) achieved spontaneous pregnancy (17). Following antioxidant therapy with vitamin E, these men also experienced lower lipid peroxidation levels in their spermatozoa [150]. In women with unexplained infertility, oral vitamin E intake improved the endometrial response, possibly due to its antioxidant and anticoagulant effects as well as by modulating the anti-estrogenic effect of clomiphene citrate(1).

zinc

Trace element supplementation has shown to improve sperm quality. For example, in vitro zinc supplementation to sperm media, either alone or in combination with other antioxidants , reduced sperm DNA fragmentation [166,167], and loss of motility [167]. Addition of zinc to cryomedia also protects against post-thaw loss of spermatozoa function and sperm DNA damage (1). Seminal studies have demonstrated the importance of Zn in several stages of sperm development following the discovery that Zn uptake is required to maintain optimal functioning of the testis, prostate and epididymis . Indeed, in animal models, an overall reduction of intracellular Zn concentration impairs germinal cell proliferation, a phenomenon likely due to activation of caspase-3 and caspase-8 systems and triggering of germ cell apoptosis. In mammals, Zn also plays a role in spermiogenesis, when the DNA is packed in a highly condensed state inside the head of the sperm by protamine-1 and protamine-2. Besides the influence on germ cell differentiation, Zn ions appear to have a profound influence on other sperm functions. Indeed, it has been documented that Zn exerts a specific inhibitory effect on citrate oxidation by acting on mammalian mitochondrial aconitase, a citrate 3 cis-aconitate-converting enzyme involved in the Krebs cycle (18). The results of the sperm parameters show a high significant ($P< 0.001$) decrease in sperm concentration and a highly significant ($p\leq0.001$) decrease in sperm motility mean in treated groups as compared to control. Moreover, administration of (zinc) with Cd in showed a highly significant ($p\leq0.001$) increase in percentage of progressively motile sperms as compared to the group received Cd only. The Levels of serum hormones shows a significant decrease ($P<0.05$) in the level of testosterone hormone after cadmium administration with non significant deference in testosterone level after cadmium plus zinc administration when compared with control, while highly significant ($p\leq0.01$) increase in the follicle stimulating hormone (FSH) after cadmium administration with significant increase in FSH level after cadmium plus zinc administration when compared with control. Also the results showed significant decrease in LH level after cadmium administration with non significant deference in LH level after cadmium plus zinc administration when compared with control. In conclusion, these findings suggest that cadmium, like all other heavy metals, could induce oxidative stress and the concomitant administration of antioxidants like (zinc) can ameliorate the toxic effect of Cadmium on spermatogenesis(19).In a clinical study, infertile men with elevated level of anti-sperm antibodies and poor basic parameters of seminal fluid characters can be treated with zinc sulfate protocol with great chance for decreasing the level of serum and seminal plasma anti-sperm antibodies, and alleviating the serious side effects associated with corticosteroids(20). Once the fertilizing spermatozoon enters the ooplasm, its nucleus undergoes a series of ultrastructural changes that eventually lead to pronuclear formation . Zn appears to have a key role

also in this process since freshly ejaculated human sperm can be experimentally decondensed in vitro by exposure to extracellular chelating agents such as EDTA. In fact, metal depletion interrupts the SH-Zn-SH bridges interspersed between protamine macromolecules, inducing subsequent chromatin unpacking . Thus, optimal integration of Zn into sperm chromatin contributes to rapidly reversible chromatin compaction leading to both chromatin condensation during spermiogenesis and rapid decondensation after fertilization (18).

Coenzyme Q10 (CoQ10)

In recent years, Coenzyme Q10 (CoQ10) has gained considerable attention as a dietary supplement capable of influencing cellular bioenergetics and counteracting some of the damage caused by free radicals. CoQ10 is a vitamin like, fat-soluble substance existing in all cells. It is intimately involved in several important roles in the body including the transferring of electrons within the mitochondrial oxidative respiratory chain and hence, ATP production; acting as an essential antioxidant and supporting the regeneration of other antioxidants; influencing the stability, fluidity and permeability of membranes; and, stimulating cell growth and inhibiting cell death (21). The oocyte requires a vast supply of energy after fertilization to support critical events such as spindle formation, chromatid separation, and cell division. Until blastocyst implantation, the developing zygote is dependent on the existing pool of mitochondria. That pool size within each cell decreases with each cell division. Previous reports suggested that mitochondrial activity within oocytes may be supplemented by donor cytoplasmic transfer at the time of intracytoplasmic sperm injection (ICSI). Those reports showed success; however, safety concerns arose due to the potential of two distinct populations of mitochondrial genomes in the offspring (22). Results of a systematic review and meta-analysis on coenzyme Q10 therapy in male infertility show that oral supplementation with coenzyme Q10 increased seminal coenzyme Q10 levels, spermatozoa concentration and motility. However, there was no increase in pregnancy rates while data for live births was lacking . In 4 double-blind, placebo-controlled RCTs using coenzyme Q10 or ubiquinol therapy in men with idiopathic infertility, study outcomes also reported of lower lipid peroxidation and oxidative stress levels in seminal plasma , increase in seminal enzymatic antioxidant activity and ubiquinol (a potent antioxidant) levels. Prospective studies on coenzyme Q10 intake in men with idiopathic infertility reported of improved acrosome reaction and pregnancy rates. In infertile men with prior failed IVF/ICSI, coenzyme Q10 supplementation increased fertilization rates in the subsequent cycle. The group also found that adding coenzyme Q10 into media with asthenozoopermic spermatozoa increased spermatozoa motility (1).Talevi et al. assess the influence of zinc, D-aspartate and coenzyme Q10, included in the dietary supplement Genadis (Merck Serono), on human sperm motility, DNA fragmentation and lipid peroxidation. Zinc, D-aspartate and coenzyme Q10 exert a direct protective effect on human spermatozoa preventing the decrease of motility and the increase of DNA fragmentation and lipid peroxidation during in vitro culture (23).There is some evidence that CoQ10 treatment can improve the movement and density of sperm in men with certain type of infertility(24). Lafuente et al. evaluate the effect of coenzyme Q10 treatments in male infertility, specifically in these parameters: live birth and pregnancy rates, CoQ10 seminal concentration, sperm concentration, and sperm motility. They concluded that There is no evidence in the literature that CoQ10 increases either live birth or pregnancy rates, but there is a global improvement in sperm parameters. Adequately powered, robust trials of individual and combination antioxidant therapies are required to guide clinical practice (25). May-Panloup et al. investigated the relationship between defective mitochondrial biogenesis and the lack of oocyte maturity observed during IVF procedures with patients suffering from ovarian dystrophy and ovarian insufficiency. They concluded that low mtDNA content is associated with the impaired oocyte quality observed in ovarian insufficiency.

N-Acetyl cysteine (NAC)

N-Acetyl cysteine (NAC) is a commonly used safe mucolytic drug, In addition, NAC increases the cellular levels of antioxidant and reduces glutathione at higher doses (27).A randomized trial investigated 404 and 400 women with unexplained infertility as study and control groups, respectively. The study group was treated with clomiphene citrate (50-mg tablets) twice daily and with N-acetylcysteine (1200 mg, daily) for five days, starting on second day of the cycle, and the control group was treated with clomiphene citrate and sugar powder as placebo. No significant differences were observed between two groups in the number and size of follicles, mean estrogen levels, serum progesterone, and endometrial thickness ($P > 0.05$). In addition, the authors reported that pregnancy rates were comparable in both group (27% vs. 22.2%) (28).In a large double blind placebo-controlled RCT involving infertile men with idiopathic oligoasthenoteratozoospermia combined oral intake of selenium and N-acetyl-cysteine correlated positively with spermatozoa quality. The additive effects were significantly better when compared to either selenium or N-acetyl-cysteine intake (1).In addition to that, N-acetyl-cysteine showed significant improvement in pregnancy and ovulation rate as compared to placebo (27).

Melatonin

Melatonin is a hormone produced especially at night in pineal gland. Its secretion is stimulated by dark and inhibited by light, which takes place in the pinealocytes, the cellular unit of the pineal gland. Melatonin is a ubiquitous natural neurotransmitter involved in numerous aspects of biological and physiological regulation of body functions. The role of endogenous melatonin in circulation rhythm disturbances and sleep disorders is well established. Melatonin may be a key factor in the regulation of seasonal variation in gonadal activity. Exposure to bright light, suppressing the concentration of melatonin in circulation, is hypothesized to be useful in treatment of both male and female infertility in couples with abnormal melatonin metabolism (29).

Studies have shown that high levels of melatonin are found in human preovulatory follicular fluid at concentrations which are much higher than those in serum. It has been reported that the follicular fluid melatonin levels depend on the follicular growth. The larger the follicle the higher the melatonin concentration. When oocytes are incubated in medium with melatonin supplementation during in vitro maturation, they have lower levels of ROS than control (without melatonin treatment) oocytes. The ability of melatonin to promote embryo development in different species has correspondingly been reported. When mouse embryos were cultured in medium containing melatonin, increased blastocyst development rates were observed. This suggests that melatonin may be involved in embryo development (30).

Only one meta-analysis has been performed specifically assessing the use of melatonin in IVF. This recent systematic review and meta-analysis of five randomise controlled trials found a pooled risk ratio of 1.21 (95% CI 0.98 - 1.50) in favour of melatonin for the outcome of clinical pregnancy rate. However, the authors suggested that the adequacy of the data evaluating the usefulness of melatonin is poor, and that it should not yet be recommended for routine use. While they did not find any worsening of the outcomes of IVF, the authors commented on the lack of live birth rate as an outcome measure as well as the imprecision encountered in all studies considered . On the other hand, melatonin is also known to be remarkably safe, with the Cochrane systematic review and meta-analysis finding no association between antioxidant supplementation and adverse effects for women involved in treatment . This meta-analysis which considered studies of melatonin as well as other antioxidants, found a similar non-statistically significant improvement in clinical pregnancy rate when using any antioxidant with a total sample size of over 2000 patients . Melatonin shows promise as an adjunctive therapy in the treatment of infertility. Its unique anti-oxidative characteristics and safety profile make it an ideal potential adjuvant therapy to be further investigated in well designed double blind randomised placebo-controlled trials(31).

Vitamin C

C Vitamin C (L-ascorbic acid, ascorbate) is a water-soluble, naturally-occurring, chain-breaking antioxidant. It is unstable, easily oxidized and perishable in high temperatures . Ascorbic acid taken as dietary intake or oral therapy, improves spermatozoa quality . In a large, placebo-controlled, double blind RCT, vitamin C supplementation for a period of 14 days starting on the day of follicle aspiration in women undergoing IVF-ET showed no improvement in clinical pregnancy or implantation rates . However, smaller prospective studies showed that oral vitamin C supplementation in women, either undergoing IVF-ET treatment or with luteal phase defects, lead to increased pregnancy rates. Addition of vitamin C in cryomedia improved motility and reduced DNA damage in post-thaw spermatozoa. Similarly, vitamin C supplemented culture media reduced lipid peroxidation andDNA damage, while improving spermatozoa motility and viability (1).Antioxidant supplementation with ascorbic acid has long been hypothesized to have a favorable influence on ART procedures for female factor infertility. A significant correlation is known to exist between the level of ascorbic acid in a woman's blood serum and follicular fluid, with the follicles having a higher concentration of ascorbic acid . Crha et al. conducted an investigation in which a group of women supplemented with vitamin C during the period of hormonal treatment in IVF had a statistically insignificant increase in the ability to achieve pregnancy compared with the control group that did not receive oral antioxidant supplementation . Griesinger et al. evaluated the role of ascorbic acid on women undergoing IVF procedures . In contrast to the findings of Crha et al., the results of this study failed to reveal clinical evidence of any beneficial effect of ascorbic acid on IVF (32).

CONCLUSION

The issue of using antioxidant therapy to treat male and female infertility and to alleviate the burden of infertility by improving IVF and ICSI procedures and their outcomes continues to be the subject of much debate. The data from the existing literature provide many advantages regarding specific antioxidant supplementation in infertility patients and clearly showed increasing successful pregnancy rate , many evidence suggests that antioxidants has the potential to combat oxidative stress, a known contributor to ART failure. There is no doubt that there is an underlying link between OS and difficulty in achieving fertilization and eventual pregnancy with IVF and ICSI.

These data suggest that the antioxidants exert beneficial effects on embryo development, possibly by a reduction in the incidence of apoptosis. Antioxidant supplementation has also been reported to have beneficial effects on sperm morphology and preimplantation embryo development and leads to reduction of developmental defects.

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