Title
The Role of Vitamin E in the Treatment of Male Infertility

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Introduction

Infertility affects 15% of couples and in 30% of these couples, the cause of infertility is associated with aberrations found in the male partner, termed male infertility (1, 2). Some causes of male infertility, such as varicocele, infection or hypogonadism, are found and treated with relative ease. In contrast, the cause of the most common type of male infertility, spermatozoal dysfunction, remains unclear (2). Recent research suggests that these idiopathic cases of male infertility may be related to oxidative damage to the sperm from pathologically increased levels of reactive oxygen species (ROS). Because spermatozoa are such specialized cells, they lack the common cytoplasmic antioxidants found in other cell types and are therefore particularly sensitive to oxidative damage. Supplementing infertile males with the antioxidant vitamin E has been suggested as a potential treatment for idiopathic male infertility. However, the efficacy of such treatment remains to be seen. This paper will review the studies that have examined the effects of treating male infertility with vitamin E supplementation.

Reactive oxygen species and male infertility

ROS are free radicals that are highly active oxidants and include superoxide anion, hydrogen peroxide, peroxyl and hydroxyl radicals (3). ROS can be produced by immature spermatozoa and leukocytes (3). In normal sperm physiology, low levels of ROS are beneficial and have been shown to stimulate sperm capacitation, enhance zona pellucida binding and promote acrosome reaction (4). In contrast, high levels of ROS are harmful and lead to lipid peroxidation of sperm plasma membrane and DNA fragmentation (4). Increased lipid peroxidation is associated with impaired sperm motility and diminished capacity for sperm-oocyte fusion (4). So what is the impact of this cellular damage on overall fertility? One study found that men with high levels of ROS were 7 times *less* likely to achieve a pregnancy than men with low levels (5).

Role of vitamin E in spermatozoa

The levels of ROS are normally limited by various antioxidant defense mechanisms, such as alpha-tocopherol (vitamin E) that are present within the seminal plasma and plasma membrane (4). Vitamin E is a lipid soluble, chain-breaking antioxidant. It is called a chain-breaking antioxidant because of its ability to terminate a free radical chain reaction, whereby one free radical reaction leads to the generation of another free radical and so forth. Specifically, vitamin E inhibits peroxidation of polyunsaturated fatty acids (PUFA), which is especially important in spermatozoa due to their high PUFA content (6). Of the many naturally occurring vitamin E compounds, d-alpha-tocopherol has the most biological activity and is the compound most available in food (7). The recommended dietary allowance for vitamin E is 15 mg/day with an adult upper limit of 1000 mg/day.

Studies also support a role for alpha-tocopherol in the pathogenesis of male infertility. When alpha-tocopherol was extracted from spermatozoa membranes, a positive correlation was found between alpha-tocopherol content and percentage motile, living and morphologically normal sperm (8). Furthermore, alpha-tocopherol levels were found to be decreased to 65.54% and 66.04% among oligo- and azoospermic men respectively as compared to normospermic men (9). In addition to protecting against

oxidative damage, vitamin E supplementation might improve these parameters in infertile males as well.

Support for vitamin E supplementation in the treatment of male infertility

A handful of studies have attempted to determine whether supplementing infertile males with vitamin E improves different aspects of fertility. Although many of the studies suffer from small sample sizes, there have been some positive results. A double-blind, randomized, cross-over controlled study by Kessopoulou *et al.* examined 30 men with high ROS production (10). Three hundred milligrams of vitamin E (the amount found in approximately 2.7 cups of sunflower oil) was supplemented twice daily for 3 months. During the supplementation, there was a significant improvement in the in vitro ability of spermatozoa to bind the zona pellucida of unfertilized oocytes as compared to binding during the 3 months of placebo (10).

A double-blind, randomized study by Suleiman *et al*. in 1996 looked at a group of 87 men with decreased sperm motility (asthenozoospermia) (11). Those who were randomized to receive vitamin E for 6 months (100 mg 3 times daily) had significantly decreased levels of lipid peroxidation product and improved sperm motility as compared to the placebo group (11). Percent motility in the treated group increased from a mean of 31.1% to 48.9% compared to an increase from 30.6% to 35.9% in the placebo group ($p<0.01$) (11). Furthermore, 21% of treated patients impregnated their partners while no pregnancies were reported in the placebo group (11).

Vitamin E supplementation may also play a role in reducing sperm DNA fragmentation. A prospective, double-blind, placebo-controlled study by Greco *et al.* identified a population of 64 men who had high levels of DNA fragmentation (12). The subjects were randomized to receive 2 months of either combined vitamins E and C (1 g daily of each) or a placebo (12). In contrast to the previous studies, no difference in the basic sperm parameters of sperm motility or morphology were seen (12). However, they did find a significant decrease in the percentage of spermatozoa with fragmented DNA in the treatment group (12).

Lastly, there is some evidence that suggests a relationship between daily antioxidant intake and better semen quality among healthy men (13). Semen analysis was performed on 97 healthy male volunteers and results were correlated with the results of a dietary assessment questionnaire (13). Higher levels of vitamin E intake were associated with higher levels of progressive sperm motility (13).

Support for vitamin E supplementation in assisted reproductive technology

Recent evidence suggests that oral vitamin E supplementation may also be beneficial in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI, where a single sperm is injected into an ovum). A 2005 meta-analysis concluded that IVF rates were negatively correlated with ROS levels and so decreasing ROS levels in couples undergoing IVF may be useful (14). A prospective study of IVF rates in 15 males supports this possibility as it found a decrease in lipid peroxidation and an increase in fertilization rate per cycle after 3 months of vitamin E supplementation (200 mg daily) (7).

In ICSI the degree of DNA fragmentation in spermatozoa can be crucial to producing viable and healthy embryos. Elevated levels of DNA fragmentation have been

associated with poor pregnancy and implantation rates (15). Thirty-eight men with elevated percentages of DNA fragmentation were treated with vitamins E and C (1 g daily of each) for 2 months after 1 failed ICSI attempt (15). While no differences in fertilization rates or embryo morphology were found between the 2 ICSI attempts (pre- versus post-treatment), there was an improvement in clinical pregnancy and implantation rates (15).

Evidence against vitamin E supplementation in the treatment of male infertility

There has been one double-blind, randomized, placebo-controlled study in which no benefit in sperm parameters was observed with supplementation. In this study, 31 asthenozoospermic men were randomized to receive vitamin E (800 mg daily) and vitamin C (1000 mg daily) or placebo for 56 days (16). No changes in sperm motility, count or morphology were observed in the treatment group (16).

Other studies call into question the validity of the mechanism behind vitamin E improving sperm parameters. Moilanen *et al.* treated 15 unselected male volunteers with alpha-tocopherol for 3 weeks at dosages of 600, 800 or 1200 mg per day (17). The measured concentrations of alpha-tocopherol in the seminal plasma were increased, but remained lower than the levels considered to have a protective effect based on in vitro studies (17). No improvement in sperm motility was observed (17). This suggests that oral supplementation of vitamin E negligibly raises the levels that are actually seen by spermatozoa and are therefore of no benefit.

An in vitro study examined the effects of supplementing preparation media with ascorbate and/or alpha-tocopherol (18). This study found that while production of ROS was decreased with ascorbate and alpha-tocopherol in combination or singly, progressive sperm motility was actually inhibited with either treatment alone or in combination (18). This implies that increasing seminal plasma levels of alpha-tocopherol may actually impair male fertility by decreasing motility.

Discussion

Many studies have demonstrated the damaging effects of elevated ROS on sperm function. Increasing oral vitamin E intake in the hopes of preventing the oxidative damage was a proposed solution. In the past decade, a number of studies were undertaken to determine whether such a solution is truly helpful. Unfortunately, the few studies, the small sample sizes and conflicting data have made it difficult for researchers and physicians to agree on a recommendation. However, the existing studies do seem to be encouraging.

The studies by Kessopoulou *et al.* and Suleiman *et al.* are commended for their double-blind, placebo-controlled study design, as well as for their appropriately selected patient population (increased ROS and asthenozoospermia respectively), given the proposed mechanism of vitamin E protection. Their positive results indicate that further research is warranted. However, the study by Kessopoulou *et al.* did not assess the actual increase in fertility, that is, pregnancy or fertilization rate in treated versus untreated. Theoretically, increased zona binding should positively affect conception rates. The impressive number of pregnancies observed by Suleiman *et al.* in the treated group (21% treated vs. 0% placebo) suggests that perhaps improvements in sperm function do translate to improved fertility.

The study by Moilanen *et al.* suggested that vitamin E is less likely to have a protective role, given that its seminal plasma concentrations were below the beneficial levels (17). As described above, a study found that alpha-tocopherol concentration in the spermatozoal membrane, rather than in the seminal plasma, is positively correlated with improved sperm parameters (8). Therefore, the effects of vitamin E may be mediated through increases in spermatozoal membrane concentration rather than through seminal plasma concentration.

The other studies combined vitamin E with other supplements, obscuring the role of vitamin E alone. In general, the combination of vitamin E and C was less effective than vitamin E alone at improving sperm parameters such as motility. It has been suggested that the ascorbic acid and alpha-tocopherol combination may form ascorbic radicals with a detrimental peroxidative effect (19). Alternatively, the combination of vitamins could substantially reduce ROS levels and impair its normal physiologic function. This could account for the impaired motility seen with in vitro treatments of alpha-tocopherol alone, where spermatozoa are most likely exposed to higher concentrations than concentrations found in the seminal plasma following oral administration. It is also unclear just how applicable the results of brief in vitro exposure to vitamin E are to studies that look at months of in vivo vitamin E supplementation.

Lastly, the studies that did not support vitamin E supplementation had noticeably shorter treatment durations. The two clinical studies that found no effect with supplementation had treatment intervals of 56 days and 3 weeks, as compared to the studies with positive findings, which lasted anywhere from 2 to 6 months. Considering that the entire process of sperm generation takes approximately 3 months, a longer duration of supplementation may be necessary for effects to be observed.

Conclusion

Vitamin E supplementation has the potential to help numerous couples that suffer from male infertility. The studies that supplemented with vitamin E alone produced promising results, which have not been reproduced as recent studies have chosen to focus on vitamin E supplementation in combination with other antioxidants. More may not be better and improved results might be found by supplementing with vitamin E alone. Future research should focus on isolating the population of infertile men who are most likely to benefit from vitamin E supplementation. Potential populations could include men with increased ROS levels, increased DNA fragmentation or asthenozoospermia. Among the identified group, a large, multi-center, double-blind, randomized, placebo-controlled study would be most informative. The dosage and duration of vitamin E supplementation also needs to be explored and optimized. At this point, high levels of vitamin E supplementation cannot be recommended as a treatment for male infertility. However, since studies have found that only 8% of US men consume sufficient amounts of vitamin E (19), it is reasonable to encourage infertile males to maintain adequate dietary intakes of vitamin E through diet or supplements.

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