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Selenium–vitamin E supplementation in infertile men: effects on semen parameters and pregnancy rate

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Objectives: Infertility is an important medical and social problem that has an impact on well-being. A significant development in the last 10 years in the study of human infertility has been the discovery that oxidative sperm DNA damage has a critical role in the etiology of poor semen quality and male infertility. Selenium (Se) is an essential element for normal testicular development, spermatogenesis, and spermatozoa motility and function. The predominant biochemical action of Se in both humans and animals is to serve as an antioxidant via the Se-dependent enzyme glutathione peroxidase and thus protect cellular membranes and organelles from peroxidative damage. We explored the efficacy of Se in combination with vitamin E for improving semen parameters and pregnancy rates in infertile men.

Materials and methods: The study included 690 infertile men with idiopathic asthenoteratospermia who received supplemental daily Se (200 µg) in combination with vitamin E (400 units) for at least 100 days. The mean age of cases was 28.5 years (range 20–45), and the median age was 30 years. These cases had presented with male factor infertility (primary or secondary) for at least 1 year. The longest and shortest duration of infertility was 10 years and 1 year, respectively. The median time of diagnosis of infertility was 1 year with a mean of 2.5 years.

Results: We observed 52.6% (362 cases) total improvement in sperm motility, morphology, or both, and 10.8% (75 cases) spontaneous pregnancy in comparison with no treatment (95% confidence interval: 3.08 to 5.52). No response to treatment occurred in 253 cases (36.6%) after 14 weeks of combination therapy. Mean difference between semen analyses of cases before and after treatment was 4.3% with a standard deviation of 4.29. On the basis of paired *t*-test results, combination therapy with oral Se and vitamin E was effective for treatment of asthenospermia or asthenoteratospermia or induction of spontaneous pregnancy ($P \leq 0.001$).

Conclusions: Supplemental Se and vitamin E may improve semen quality and have beneficial and protective effects, especially on sperm motility. We advocate their use for the treatment of idiopathic male infertility diagnosed with asthenoteratospermia or asthenospermia in semen analysis.

Keywords: asthenospermia, sperm, semen, teratospermia, infertility, male, selenium, vitamin E

Introduction

The World Health Organization (WHO) defines infertility as the inability of a couple to achieve conception or bring a pregnancy to term after 1 year or more of regular, unprotected sexual intercourse.[1] Conception is normally achieved within 12 months in 80%–85% of couples using no contraceptive measures. Although certain cases of male infertility are due to anatomical abnormalities, such as varicocele, ductal obstructions, or ejaculatory disorders, an estimated 40%–90% of cases are due to deficient sperm

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production of unidentifiable origin.[2] Infertility is a major clinical concern, affecting 15% of all reproductive age couples. Male factors, including decreased semen quality, are responsible for 25% of these cases.[3,4] Currently, the etiology of suboptimal semen quality is poorly understood, and many physiological, environmental, and genetic factors, including oxidative stress, have been implicated.[5] Selenium (Se) is important for reproductive functions such as testosterone metabolism and is a constituent of sperm capsule selenoprotein. The administration of Se to subfertile patients induced a statistically significant rise in sperm motility.[6] Se is an essential trace element occurring in organic and inorganic forms. The organic form is found predominantly in grains, fish, meat, poultry, eggs, and dairy products and enters the food chain via plant consumption. Typical dietary intake of Se in the US is 80–120 μg/daily, and the recommended daily allowance is 70 μg in men and 50 μg in women.[7] Selenoproteins participate in sperm structure integrity maintenance. Sperm capsular selenoprotein has an important structural role in spermatozoa in the form of glutathione peroxidase (GSH-Px).[8] Increased reactive oxygen species (ROS) decreases fertility because ROS attacks the membrane of the spermatozoa, decreasing their viability. Increasing Se encourages antioxidant GSH-Px activity, thus decreasing ROS and leading to increased male fertility.[9,10] Se could also protect against oxidative DNA damage in human sperm cells.

Vitamin E is one of the most important antioxidative molecules, residing mainly in the cell membranes. It is thought to interrupt reactions with lipid peroxidation and is a free radical scavenger generated during the univalent reduction of molecular oxygen and also normal activity of oxidative enzymes.[11] These radicals will lead to peroxidation of phospholipids in the mitochondria of the sperm and thus to their ultimate immotility.[12] It is possible that vitamin E enhances the production of the scavenger antioxidant enzymes.[13]

We studied the effect of daily oral supplementation of Se and vitamin E on the quality of semen parameters and pregnancy rate of couples with male factor infertility.

Materials and methods

Subjects

From March 2007 to February 2010, 855 men with a mean age of 28.5 years (range 20–45 years) presenting with male factor infertility (primary or secondary) for at least 1 year were screened for enrollment in this prospective single-arm study in one center. Any infertile male with asthenoteratospermia according to WHO guidelines was enrolled in our study. Any patient with teratospermia of 1% or 2% in combination with 10%–30% asthenospermia was enrolled in the study. There was no known medical condition that could account for infertility. Only patients seeking medical attention for the disease were included in the study. The lowest age was 20 years, the highest age 45 years, and the median 30 years. The longest duration of infertility was 10 years; the shortest duration was 1 year. The median time of diagnosis of infertility was 1 year with a mean of 2.5 years. A total of 752 cases (88%) had primary infertility, and 103 cases (12%) suffered from secondary infertility (Table 1). Patients were included in the study after fulfilling certain criteria, including a sperm count of $>20 \times 10^6$/mL, more than 1 year of failed attempt at conception, and no female factors. Exclusion criteria were abnormal testes on physical examination, such as bilateral or unilateral testicular atrophy; reproductive hormone levels (follicle stimulating hormone and luteinizing hormone) outside normal limits (increased or decreased in the case of primary testicular failure or secondary hypogonadotropic hypogonadism, respectively); genital diseases, such as undescended testes, varicocele; and history of genital surgery, oligo, or azoospermia. In the evaluation of cases, a history was taken, and on each patient we performed a physical examination. All patients who met study inclusion and exclusion criteria provided informed consent before study entry, which was done in accordance with the Declaration of Helsinki.[14] The Human Ethics Committee approved the study protocol. Of the 985 screened patients, 855 cases met study inclusion and exclusion criteria and consented to proceed with the study protocol. The study consisted of a 14-week treatment phase. All patients were required to have ceased all medical therapy 6 weeks before study initiation. Eligible patients were assigned to fixed-dose treatment with 200 μg oral Se tablet (L-selenomethionine) daily in combination with 400 IU synthetic vitamin E (α-tocopherol). Safety and tolerability of drugs were evaluated based on spontaneously reported adverse effects and physical examination

Table 1 Demographic data

Total number of cases	855
Lost to follow-up cases	165
Final number of eligible cases	690
Cases with primary infertility	752
Cases with secondary infertility	103
Mean age and range (years)	28.5 and 20–45

during each patient visit. Patients were asked to report all treatment-emergent adverse events. Treatment-emergent adverse events were defined as any adverse event that first occurred or worsened after the treatment trial or during it. Patients voluntarily reported adverse events throughout the study.

Semen collections

Semen was obtained from patients consulting the Highly Specialized Jihad Daneshgahi Infertility Center, Qom Branch (ACECR), which is affiliated to the Jihad Daneshgahi Center in Tehran, Iran. This center is the only infertility center in the province. After liquefaction of the sample, the semen volume, sperm concentration, and morphology of sperm were determined using standard procedures.[15] In each case, we did a semen analysis before treatment and another semen analysis at the end of 100 days of treatment. Before semen sample collections, patients were instructed to abstain from ejaculation for at least 48 h. Instructions regarding proper semen collection techniques were provided to patients at screening and throughout treatment. All procedures and interpretations were in accordance with 1992 WHO criteria, and morphology was established according to the Kruger parameters. Samples were assessed at least twice for volume, pH, sperm concentration, progressive and total motility, and the percentage of normal forms. Two technicians were used. Standardized semen analysis techniques were taught to each technician at our infertility clinic. Normal WHO values included a sperm concentration of 20×10^6 spermatozoa/mL or greater and 50% or greater motility with forward progression. Using Kruger strict criteria, males with >14% normal forms were considered normal. Semen classification was as follows: normospermia was indicated by a sperm concentration of $\geq 20 \times 10^6$/mL, motility ≥50%, and ≥14% normal morphology; asthenospermia was indicated by a sperm concentration of $\geq 20 \times 10^6$/mL, <50% motility, and normal morphology; and asthenoteratospermia was indicated by a sperm concentration of $\geq 20 \times 10^6$/mL, <50% motility, and <14% normal morphology.

Statistical analysis

Statistical analysis was performed using SPSS software, Version 16 (SPSS Inc., Chicago, IL, USA). Values determined before and after treatment were compared by the paired *t*-test. For all comparisons, $P \leq 0.05$ was considered significant.

Results

The primary endpoint was the proportion of patients who had a 5% or greater increase in improvement of motility or morphology or both from baseline following the 14-week treatment period or impregnating their partner. A total of 165 patients withdrew from study prematurely after treatment initiation. The reasons for discontinuation were withdrawal of consent in 45, missing data in 37, and loss to follow-up in 83. All participants had abnormal sperm morphology using the Kruger strict criteria as well as asthenospermia. In 253 cases (36.6%), no difference in semen analysis occurred. Normal pregnancy occurred in 75 cases (10.8%). In 382 cases (55%), improvement in parameters of semen analysis occurred. Improvement in motility of at least 5% occurred in 144 cases (20.5%), motility improvement of more than 10% occurred in 155 cases (22.5%), improvement in sperm morphology of at least 5% occurred in 21 cases (3%), and improvement in both morphology and motility occurred in 42 patients (6%) (Table 2). Mean difference between semen analyses of cases before treatment and after treatment was 4.3% with a standard deviation of 4.29.

Discussion

Se is an essential trace element for humans and animals.[16] Se is essential for sperm function and male fertility. Se deficiency has been linked to reproductive problems in rats, mice, chickens, pigs, sheep, and cattle,[17] and supplementation with Se has been reported to improve reproductive performance in sheep and mice.[18] However, high Se intake has been associated with impaired semen quality.[19] This improvement is supplementation dependent, as all of the parameters returned to baseline values during the post-treatment period.[20] Se is incorporated into enzymes that regulate normal body processes. One Se-dependent enzyme is GSH-Px. GSH-Px protects cellular membranes and lipid-containing organelles from peroxidative damage by inhibition and destruction of endogenous peroxides, acting in conjunction with vitamin E to maintain integrity of these membranes. GSH-Px catalyzes the breakdown of hydrogen peroxide (H_2O_2) and certain organic hydroperoxides produced by glutathione during the process of redox cycling. The toxicity of redox cycling compounds is generally increased by Se deficiency, which results in nearly a twofold increase in glutathione-S-transferase activity and glutathione synthesis in the liver. In order to protect human populations from excessive consumption of Se, 500 µg of Se was generally accepted as

Table 2 Results of treatment on the basis of semen analysis improvement or drug-induced spontaneous pregnancy

Quality of improvement	Motility improvement of at least 5%	Motility improvement of at least 10%	Improvement in both motility and morphology	Morphology (only) improvement	Spontaneous pregnancy	No difference in semen analysis
Number of cases	144 cases (20.5%)	155 cases (22.5%)	42 cases (6%)	21 cases (3%)	75 cases (10.8%)	253 cases (36.6%)
Semen analysis before treatment	Normal motility mean 10%–30%	Normal motility mean 10%–30%	Normal morphology mean, normal motility mean 1%, 10%–30%	Normal morphology mean 1%	Normal morphology mean, normal motility mean 1%, 10%–30%	Normal morphology mean, normal motility mean 1%, 10%–30%
Semen analysis after treatment	Normal motility mean 15%–35%	Normal motility mean 20%–40%	Normal morphology mean, normal motility mean 6%, 15%–35%	Normal morphology mean 6%	No semen analysis was done after spouse pregnancy	

the maximum acceptable daily intake. Therefore, it can be predicted that chronic selenosis occurs with a daily intake of ~1000–1500 μg of elemental Se.[21] Glutathione is vital to sperm antioxidant defenses and has demonstrated a positive effect on sperm motility.[9] Se and glutathione are essential to the formation of phospholipid–hyperoxide GSH-Px, an enzyme present in spermatids that becomes a structural protein comprising over 50% of the mitochondrial capsule in the mid-piece of mature spermatozoa. Deficiencies of either substance can lead to instability of the mid-piece, resulting in defective motility.[3]

Vitamin E is a well-documented fat-soluble antioxidant and has been shown to inhibit free radical-induced damage to sensitive cell membranes.[22] In one study, lipid peroxidation in the seminal plasma and spermatozoa was estimated by malondialdehyde (MDA) concentrations. Oral supplementation with vitamin E significantly decreased MDA concentration and improved sperm motility.[13] The recommended dietary allowance of vitamin E is 15 mg/day, and the tolerable upper intake level of any α-tocopherol form is 1000 mg/day. Although in most healthy adults short-term supplementation with up to 1600 IU of vitamin E appears to be well tolerated and have minimal side effects, long-term safety is questionable.[23] Vitamins E and C also play critical roles as nonenzymatic antioxidants. Vitamin E plays a vital role in protecting cell membranes from oxidative damage trapping and scavenging free radicals within cellular membranes. Vitamin C is a water-soluble antioxidant that reduces radicals from a variety of sources and also serves to recycle oxidized vitamin E.

Suleiman et al[13] investigated the effects of vitamin E on sperm motility. A total of 11 out of 52 treated patients (21%) impregnated their spouses, and improved motility of sperm was seen in 31 subjects.

Oxidative stress is induced by ROS or free radicals. Although ROS have been shown to be required for sperm capacitation, hyperactivation, and sperm–oocyte fusion,[21] excessive levels of ROS can negatively impact sperm quality. Increased levels of ROS have been correlated with decreased sperm motility,[24] increased sperm DNA damage,[25] sperm cellular membrane lipid peroxidation,[26] and decreased efficacy of oocyte–sperm fusion.[27] The pathological effects of oxidative stress arise under conditions in which levels of unscavenged ROS increase or the antioxidant buffering capacity of the system decreases, thus perturbing the delicate oxidant–antioxidant balance. These free radicals induce sperm cell injury through several pathways and can significantly impact both sperm quality and function.[27,28]

In a systematic review of the effect of oral antioxidants (vitamins C and E, zinc, Se, carnitine) on male infertility by Ross et al[29] 17 randomized trials, including a total of 1665 men, were identified. Of the 17 trials, 14(82%) showed an improvement in either sperm quality or pregnancy rate after antioxidant therapy.

In one study, 69 infertile Scottish men were given placebo, Se, or Se in combination with vitamins A, C, and E for 3 months. At the end of the trial, both Se-treated groups had significant improvements in sperm motility; however, sperm density was unaffected. During the course of the study, 11% of the participants in the treatment groups impregnated their partner.[30] This rate was similar in our study.

Hawkes et al[19] investigated the effects of dietary Se on sperm motility in 11 cases of healthy men. Interestingly, they found that high Se diet (297 µg/day) could impair sperm motility. However, our prescribed dose was 200 µg/day, and our findings in a large series were the opposite.

Conclusion

After 14 weeks of treatment in 690 cases, mean motility increased significantly from baseline ($P \leq 0.005$) compared with that before the treatment period. A slight but statistically significant increase in the normal morphological sperm ratio from baseline was observed at the end of the 14-week period.

Based on our findings, medical therapy of asthenoteratospermia with oral antioxidants, such as a combination of Se and vitamin E, can improve quality of semen parameters or help in achieving normal pregnancy. The major limitation of our study is the lack of a placebo-controlled, double-blind design. However, more studies with a case control design are warranted.

Disclosure

The authors report no conflicts of interest in this work.

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