Dietary Complements and Phytotherapy

16

Bruno Giammusso

Infertility is a major health problem affecting 15 % of couples in the reproductive age group. The male partner is contributory in up to 50 % cases and the cause of male infertility remains unknown in 25 % of men [1]. These men with idiopathic infertility are usually treated with a number of empirical therapies. The basis of the treatment is the fact that these products appear rational because of their mode of action or because of uncontrolled human studies [2]. Many over-the-counter (OTC) therapies have been historically used for male fertility, including herbs, vitamins, and nutritional supplements [3]. Many studies demonstrate the positive effects of OTC supplementation on semen parameters and pregnancy outcomes. Conversely, many studies also demonstrate a lack of improvement and potential complications with supplementation. Current and historical OTC medication studies suffer from a variety of drawbacks, including small short-duration studies, failure to perform randomized double-blinded placebo-controlled studies, and lack of standardization of dose and efficacy [4]. Definitive conclusions as to their true effects on male subfertility and dosing regimen could not be identified.

16.1 Antioxidants

Oxidative stress has been a well-studied aetiology of abnormal semen parameters [5–7]. Because of this, many of the current OTC therapies rely on antioxidant properties. Seminal oxidative stress (OS) results from an imbalance between reactive oxygen species (ROS) production and ROS scavenging by seminal antioxidants. Seminal OS is believed to be one of the main factors in the pathogenesis of sperm

B. Giammusso
Unità di Andrologia, Policlinico Morgagni, Via Vivante, 3, Catania 95123, Italy
e-mail: bgiammusso@hotmail.it

G. Cavallini, G. Beretta (eds.), *Clinical Management of Male Infertility*,
DOI 10.1007/978-3-319-08503-6_16

dysfunction and sperm DNA damage in male infertility [8–11]. It is estimated that 25 % of infertile men possess high levels of seminal ROS, whereas fertile men do not have high levels of seminal ROS [12, 13]. Spermatozoa are particularly susceptible to oxidative injury due to the abundance of plasma membrane polyunsaturated fatty acids [14–16]. Seminal oxidative stress has been related to infection, industrial exposure, tobacco use, and elevated temperature [7]. The two main sources for antioxidants are physiologic and dietary. Physiologic antioxidants are present within seminal plasma and the spermatozoa themselves [5]. If the high seminal ROS levels are due to a decreased ROS scavenging capacity of semen, it would support the use of dietary antioxidant supplementation [17]. A higher intake of antioxidants can potentially improve semen quality as well as sperm DNA integrity [18]. In contrast, poor semen quality may be associated with a lower intake and resultant lower concentration of antioxidants within the body [19]. The practice of prescribing oral antioxidant is supported by the lack of serious side effects related to antioxidant therapy, although few studies have carefully evaluated the risk of overtreatment with antioxidants [20]. Despite a large body of literature, it is not possible to establish firm conclusions regarding the optimal antioxidant treatment for infertile men because the published studies report on different types and doses of antioxidants, the studies are small, the end points vary, and few of the studies are placebo controlled [8, 13]. The most commonly studied oral antioxidants (or antioxidant enzyme cofactors) include vitamin E, vitamin C, carnitines, lycopene, glutathione, selenium, omega-3 and omega-6 fatty acids, zinc, arginine, and coenzyme-Q10.

16.2 Vitamin E

Vitamin E is a fat-soluble vitamin within the tocopherol family. It is a major lipophilic chain-breaking antioxidant known to inhibit free-radical–induced damage to cell membranes, protect tissue polyunsaturated fatty acids against peroxidation, and improve the activity of other antioxidants [21, 22]. Its antioxidant activity is similar to that of glutathione peroxidase. Therond et al. found that vitamin E is present in widely varying concentrations in human spermatozoa and semen plasma with the percent of motile spermatozoa significantly related to sperm α-tocopherol content [23]. Infertile men may have lower vitamin E in serum and seminal plasma [24]. Vitamin E is also effective in decreasing seminal ROS in infertile males [25, 26]. Substantial literature supports improvements in sperm motility, seminal ROS, and DNA fragmentation rates with vitamin E supplementation. Six RCTs evaluated the effects of vitamin E alone or in combination with vitamin C or selenium. Two of these studies reported a significant improvement in sperm motility [27, 28] and one reported a significant improvement in sperm DNA integrity [29] in the treatment arm only. In a randomized study of 54 infertile men, 28 were supplemented daily with 400 mg of vitamin E and 225 mcg selenium for 3 months, while the remaining 26 received 4–5 gm vitamin B daily for the same duration [28]. In contrast, three RCTs reported no significant improvement in sperm parameters after vitamin E ± C treatment [25, 30, 31]. Rolf et al. performed a placebo-controlled, double-blind

study of high-dose oral vitamins C and E for 56 days in 31 infertile men with asthenozoospermia and a normal or only moderatedly decreased sperm concentration. Of the patients 15 received 1,000 mg vitamin C and 800 mg vitamin E, while 16 received placebo capsules. No changes occurred in semen parameters and no pregnancies were initiated.

16.3 Vitamin C

Vitamin C is a water-soluble vitamin that is an important cofactor for hydroxylation and amidation reactions. Vitamin C also functions as an important antioxidant and assists in recycling oxidized vitamin E [7]. It is highly concentrated within seminal plasma [32]. Vitamin C has been associated with various improvements in semen quality, although most studies have involved concurrent use of other vitamins and antioxidants. One RCT evaluated the effects of vitamin C alone and reported a significant improvement in sperm parameters in the treatment arm only [33]. Daily vitamin C supplementation with doses greater than 200 mg (up to 1,000 mg) was found to improve ($P < .05$) sperm count, motility, and viability in heavy smokers. A direct correlation was found between serum and seminal vitamin C concentrations and improvements in sperm quality, with those receiving 1,000 mg daily having the most improvements. These included improvements ($P < .05$) in count and viability of 34 %, motility of 5 %, and morphology of 33 % compared with baseline. Vitamin C plays an important role in protecting sperm and sperm DNA against oxidative damage by neutralizing ROS in a concentration-dependent manner [29]. Adequate vitamin C intake has also been shown to increase seminal vitamin C concentrations and reduce sperm DNA fragmentation [19, 34]. Greco demonstrated a reduction in DNA damage by 13 ($P < .001$) after treatment, as measured by terminal deoxyribonucleotidyl transferase–mediated dUTP nick-end labelling (TUNEL) assay [29]. Vitamin C is available in many fruits and vegetables [35]. The RDA is 90 mg to maintain body stores [36]. Side effects, occurring above the daily upper limit of 2,000 mg, include dyspepsia, headache, and increased risk of nephrolithiasis [35].

16.4 Carnitines

Carnitines are quaternary amines synthesized from the amino acids lysine and methionine. They are responsible for transporting long-chain fatty acids into the mitochondria for intracellular metabolism through β-oxidation. Carnitines assist sperm metabolism as an energy source for spermatozoa and affect motility and sperm maturation [37]. They have been proposed to have a role in sperm maturation during transit through the epididymis. They are also antioxidants protecting against ROS [38]. The two main forms of importance are *L*-carnitine (LC) and *L*-acetylcarnitine (LAC). Both are concentrated in the epididymis, spermatozoa, and seminal plasma [39]. Multiple randomized controlled studies supplementing

with carnitine therapy for idiopathic infertility demonstrate improvements in concentration, motility, and morphology. Four RCTs evaluated the effects of *L*-carnitine alone or in combination with *L*-acetylcarnitine and three of the four reported a significant improvement in sperm parameters in the treatment arm only [40–43]. Lenzi et al. demonstrated significant improvements of total motile sperm count in the carnitine treatment arm, with an increase of 19 million ($P = .042$). The treatment group had a 13 % pregnancy rate compared with no pregnancies in the placebo group ($P > .05$) [44]. Balercia also demonstrated significant improvements with a 20–41 % increase in motility and a 13 % increase in morphology with LC or LAC supplementation or both for 24 weeks compared with placebo ($P < .05$) [40]. Nine pregnancies occurred in the treatment arms and three in the placebo arm ($P > .05$). Cavallini studied the effects of a combination of carnitine and cinnoxicam (nonsteroidal anti-inflammatory drug [NSAID]) therapy on sperm function [41]. Patients with no varicocele or small- or moderate-grade varicoceles treated with carnitine, alone or in combination with NSAID therapy, had significant improvements, with sperm concentration increases of 6–25 million/mL, motility increases of 2–22 %, and morphology increases of 8–23 % compared with placebo groups (*P* value not reported). Conversely, carnitine therapy has also been found to have nonsignificant effects on semen parameters by some investigators. Sigman et al. [43] performed a small randomized, double-blinded, placebo-controlled study on 21 patients. Patients were treated with carnitine therapy (2 g of LC and 1 g of LAC) or placebo daily for 24 weeks. At the end of the treatment period, there appeared to be a nonsignificant trend toward improvement in motility, with a 5.3 % increase in the treatment group compared with a 9.3 % increase in the placebo group ($P > .05$).

16.5 Lycopene

Lycopene is a powerful non-provitamin A carotenoid antioxidant that quenches singlet oxygen and scavenges peroxyl radicals. Its multiple roles include protection of lipid peroxidation, gap junction communication, cell growth regulation, gene expression modulation, and immune responses [45]. Palan and Naz measured seminal lycopene by high-pressure liquid chromatography in 37 men and noted significantly lower lycopene in the seminal plasma of immuno-infertile men than in fertile men [46]. Increased dietary intake or supplementation has been demonstrated to have positive effects on semen parameters [19]. Gupta and Kumar treated 30 infertile men with 4 mg lycopene for 3 months and found a significant improvement in sperm counts and motility with no significant changes in morphology. A 20 % pregnancy rate was seen during the course of the study [47].

16.6 Glutathione

Glutathione is the most abundant nonprotein thiol in mammalian cells. Glutathione reductases are selenoproteins. Glutathione is an endogenous antioxidant produced in the liver and is one of the most abundant antioxidants found in the body. It is a

molecule synthesized from cysteine, glutamic acid, and glycine that plays an important role in maintaining exogenous antioxidants (i.e., vitamins C and E) in their active (reduced) roles [48]. The selenoprotein phospholipid hydroperoxide glutathione peroxidase occurs in the active form in spermatids. It reduces phospholipid hydroperoxide and scavenges hydrogen peroxide in human spermatozoa. Decreased phospholipid hydroperoxide glutathione peroxidase expression has been found in the spermatozoa of infertile men. Raijmakers et al. evaluated 25 men and found that fertile men had significantly higher glutathione in seminal fluid than subfertile men [49]. Significant associations of glutathione with sperm motility and sperm morphology were also observed. Ochsendorf et al. found that glutathione in the spermatozoa of patients with oligozoospermia was significantly lower than in controls [50]. Lenzi et al. [51, 52] have demonstrated improved sperm motility in infertile men with glutathione supplementation in multiple studies. They also treated men with varicoceles with intramuscular glutathione, noting a 10 % increase over baseline in total sperm motility with therapy ($P < .01$) [53]. Glutathione supplementation has been associated with improved sperm concentration and decreased sperm DNA fragmentation in a nonrandomized study using a combination of glutathione, vitamin C, and vitamin E [54]. Dietary sources of glutathione include fresh meat products, fruits, and vegetables [55].

16.7 Selenium

In human beings, the nutritional functions of selenium are achieved by 25 selenoproteins that have selenocysteine at their active centre [56]. In men, selenoprotein GPx4 is found in the mitochondria that make up the midpiece sheath of the sperm tail. In the early phase of spermatogenesis, GPx4, as a peroxidase, protects spermatozoa by its antioxidant function, whereas in the later phase, it forms cross-links with midpiece proteins to become a structural component of the mitochondrial sheath surrounding the flagellum, which is essential for sperm motility [57]. The selenium intake required for optimal activity and concentration of GPx4 and selenoprotein P is around 75 mcg per day. Supplementation might not be necessary if adequate daily intake is obtained through a diverse diet [58]. Selenium has been associated with positive effects on male infertility, which appear synergistic when used with other OTC supplements. Optimal dosing appears to be between 100 and 210 μg on the basis of the studies. In a randomized trial, selenium supplementation (100 mcg per day) of subfertile men with low selenium intake significantly increased sperm motility and enabled 11 % of the men to achieve paternity, compared with none in the placebo group [56]. However, high selenium intake (about 300 mcg per day) was shown to decrease sperm motility [59]. Selenium in combination with other antioxidants has been noted to improve sperm count, motility, and morphology [60]. Selenium deficiency has been found to decrease sperm motility, affect spermatozoa midpiece stability, and result in abnormal sperm morphology [61]. Multiple studies have demonstrated selenium's synergistic effects with other OTC supplements on sperm motility. In one prospective randomized study, infertile men with OAT receiving a 3-month course of selenium (210 μg) and vitamin E (400 mg)

had a significant increase in sperm motility of 8 % ($P < .05$) and a decrease in lipid peroxidation levels, measured by an 8 % decrease in the malondialdehyde (MDA) level ($P < .05$) [28]. Three RCTs evaluated the effects of selenium alone or in combination with *N*-acetyl cysteine and two of the three studies reported a significant improvement in sperm parameters in the treatment arm only [60, 62, 63]. Contrary to the previous studies, one noncontrolled study treating 33 men with idiopathic infertility with 200 μg of selenium daily for 12 weeks noted no improvements in concentration, morphology, and motility despite increases in serum and seminal selenium levels [64].

16.8 Omega-3 and Omega-6 Fatty Acids

The significant effects of dietary fatty acids (FAs) on male fertility have been well documented both in animal and human studies [65, 66]. Polyunsaturated fatty acids (PUFAs) are essential FAs, because they cannot be synthesized by the human body. Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-linolenic acid are the main omega-3 PUFAs. Linoleic acid, γ-linolenic acid, and arachidonic acid (AA) are the main omega-6 PUFAs. The first mechanism by which omega-3 and omega-6 PUFAs affect spermatogenesis is by the incorporation into the spermatozoa cell membrane [67]. Omega-3 and omega-6 PUFAs are structural components of cell membranes [68]. The lipid bilayer of cellular membranes is maintained by the presence of these PUFAs [69]. The successful fertilization of spermatozoa depends on the lipids of the spermatozoa membrane [70]. Increased omega-6/omega-3 ratio in spermatozoa has also been implicated in impaired semen quality in oligozoospermic and/or asthenozoospermic men [71]. Safarinejad et al. [72] investigated PUFA composition of the blood plasma and spermatozoa in men with idiopathic OAT. They found that fertile men had higher blood and spermatozoa levels of omega-3 PUFAs compared with the infertile counterparts. Attaman et al. [73] evaluated the relation between dietary fats and semen quality in 99 men. They concluded that higher intake of omega-3 PUFAs was positively correlated with sperm morphology.

16.9 Zinc

Zinc has roles in testicular steroidogenesis, testicular development, spermatozoa oxygen consumption, nuclear chromatin condensation, the acrosome reaction, acrosin activity, sperm chromatin stabilization, and conversion of testosterone to 5α-dihydrotestosterone [74]. The male genitourinary tract has a high concentration of zinc, especially in the prostate. Chronic mild zinc deficiency is associated with oligospermia, decreased serum testosterone levels, and compromised immune system function [75]. Five RCTs evaluated the effects of zinc alone or in combination with folic acid and all five reported a significant improvement in sperm parameters in the treatment arm only [60, 76–81]. Young studied the association of folate, zinc,

and antioxidant intake with sperm aneuploidy in 89 healthy nonsmoking men through a dietary and supplement questionnaire and sperm FISH studies [18]. In a controlled study 45 infertile men with asthenozoospermia were treated with three different regimens of zinc—200 mg orally twice daily with or without vitamin C, vitamin E for 3 months, and both regimens—compared with controls [78]. Zinc therapy with or without additional vitamins was associated with increases in sperm motility of at least 24 % ($P < .001$).

16.10 Arginine

Arginine is a biologic precursor of nitric oxide. In the male reproductive system, arginine is a biochemical precursor for synthesizing spermidine and spermine and is thought to be essential for sperm motility [82]. Multiple studies have evaluated arginine's effect on semen. Some studies have reported that supplementation up to 4 g/day improves sperm concentration and motility [83, 84], whereas others have failed to demonstrate improvement in semen parameters or pregnancy rates [85, 86].

16.11 Coenzyme Q-10

Coenzyme Q-10 (CoQ10) plays a key role in transporting electrons in the mitochondrial respiratory chain [87]. It stabilizes and protects the cell membrane from oxidative stress [88]. CoQ10 levels are measurable within seminal fluid and can be directly correlated with sperm count and motility [89]. In a placebo-controlled, double-blinded, randomized controlled study, Balercia et al. [90] treated men with idiopathic subfertility with decreased motility (<50 %) with CoQ10. There was a 6 % absolute motility improvement in the treatment group after 6 months of treatment compared with the placebo group ($P < .0001$) although no difference in pregnancy rates. In a placebo-controlled study, Safarinejad [91] demonstrated absolute increases in total sperm count of 9.8 %, motility of 4.5 %, and morphology of 1.8 % over baseline with CoQ10 therapy when compared with placebo ($P = .01$).

16.12 Phytotherapy

Herbal therapy is increasingly popular worldwide as a way to treat infertility. In the United States, 17 % constantly visited herbal therapies in the past 18 months out of the 29 % of infertile couples who use complementary and alternative medicine [92]. Ginseng is one of the most popular herbs used in the phytotherapy of male infertility. Both oligoasthenospermic patients and age-matched healthy counterpart showed an increase in spermatozoa density and motility after the use of *Panax ginseng* [93]. Asthenospermic patients treated with ginseng also showed a significant increase in progressive sperm motility [94]. In the last few years Maca, a perennial plant of the *Lepidium meyenii* species, has been extensively studied for

its pharmacological properties on human spermatogenesis. An open-label study conducted by administering daily 1,500–3,000 mg of Maca for 4 months resulted in increased seminal volume, sperm count, and sperm motility [95]. A strong natural lipophilic antioxidant, astaxanthin, has been studied in a prospective, double-blind, randomized trial, designed to evaluate the effect of 16 mg/day astaxanthin compared to placebo in 30 infertile men. At the end of the study, ROS and inhibin B decreased significantly and sperm linear velocity increased in the treated group. The total and per cycle pregnancy rates among the placebo cases (10.5 and 3.6 %) were lower compared with 54.5 and 23.1 %, respectively, in the astaxanthin group ($P=0.028$; $P=0.036$) [96].

References

1. Siddiq FM, Sigman M (2002) A new look at the medical management of infertility. Urol Clin North Am 29:949–963
2. Kumar R, Gautam G, Gupta NP (2006) Drug therapy for idiopathic male infertility: rationale versus evidence. J Urol 176:1307–1312
3. Ko EY, Sabanegh ES (2012) The role of over-the-counter supplements for the treatment of male infertility – fact or fiction? J Androl 33:292–308
4. Agarwal A, Sekhon LH (2010) The role of antioxidant therapy in the treatment of male infertility. Hum Fertil 13:217–225
5. Tremellen K (2008) Oxidative stress and male infertility—a clinical perspective. Hum Reprod Update 14:243–258
6. Agarwal A, Sharma RK, Desai NR et al (2009) Role of oxidative stress in pathogenesis of varicocele and infertility. Urology 73:461–469
7. Kefer JC, Agarwal A, Sabanegh E (2009) Role of antioxidants in the treatment of male infertility. Int J Urol 16:449–457
8. Zini A, San Gabriel M, Baazeem A (2009) Antioxidants and sperm DNA damage: a clinical perspective. J Assist Reprod Genet 26:427–432
9. Aitken RJ, de Iuliis GN, Finnie JM et al (2010) Analysis of the relationships between oxidative stress, DNA damage and sperm vitality in a patient population: development of diagnostic criteria. Hum Reprod 25:2415–2426
10. Fraga CG, Motchnik PA, Shigenaga MK et al (1991) Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. Proc Natl Acad Sci U S A 88:11003–11006
11. Iwasaki A, Gagnon C (1992) Formation of reactive oxygen species in spermatozoa of infertile patients. Fertil Steril 57:409–416
12. Zini A, Sigman M (2009) Are tests of sperm DNA damage clinically useful? Pros and cons. J Androl 30:219–229
13. Agarwal A, Nallella KP, Allamaneni SS et al (2004) Role of antioxidants in treatment of male infertility: an overview of the literature. Reprod Biomed Online 8:616–627
14. Aitken RJ, Clarkson JS (1987) Cellular basis of defective sperm function and its association with the genesis of reactive oxygen species by human spermatozoa. J Reprod Fertil 81:459–469
15. de Lamirande E, Gagnon C (1992) Reactive oxygen species and human spermatozoa. I. Effects on the motility of intact spermatozoa and on sperm axonemes. J Androl 13:368–378
16. Zini A, Garrels K, Phang D (2000) Antioxidant activity in the semen of fertile and infertile men. Urology 55:922–926
17. Lewis SE, Boyle PM, McKinney KA et al (1995) Total antioxidant capacity of seminal plasma is different in fertile and infertile men. Fertil Steril 64:868–870
18. Young SS, Eskenazi B, Marchetti FM et al (2008) The association of folate, zinc, and antioxidant intake with sperm aneuploidy in healthy non-smoking men. Hum Reprod 23:1014–1022

19. Mendiola J, Torres-Cantero AM, Vioque J et al (2010) A low intake of antioxidant nutrients is associated with poor semen quality in patients attending fertility clinics. Fertil Steril 93:1128–1133
20. Henkel RR (2011) Leukocytes and oxidative stress: dilemma for sperm function and male fertility. Asian J Androl 13:43–52
21. Palamanda JR, Kehrer JR (1993) Involvement of vitamin E and protein thiols in the inhibition of microsomal lipid peroxidation by glutathione. Lipids 23:427–443
22. Brigelius-Flohé R, Traber MG (1999) Vitamin E: function and metabolism. FASEB J 13:1145–1155
23. Therond P, Auger J, Legrand A et al (1996) Alpha-tocopherol in human spermatozoa and seminal plasma: relationships with motility, antioxidant enzymes and leucocytes. Mol Hum Reprod 2:739–741
24. Omu AE, Fatinikun T, Mannazhath N et al (1999) Significance of simultaneous determination of serum and seminal plasma α–tocopherol and retinol in infertile men by high-performance liquid chromatography. Andrologia 31:347–351
25. Kessopoulou E, Powers HJ, Sharma KK et al (1995) A double-blind randomized placebo crossover controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril 64:825–831
26. Ross C, Morriss A, Khairy M et al (2010) A systematic review of the effect of oral antioxidants on male infertility. Reprod Biomed Online 20:711–723
27. Suleiman SA, Ali ME, Zaki ZM et al (1996) Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl 17:530–537
28. Keskes-Ammar L, Feki-Chakroun N, Rebai T et al (2003) Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. Arch Androl 49:83–94
29. Greco E, Iacobelli M, Rienzi L et al (2005) Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment. J Androl 26:349–353
30. Moilanen J, Hovatta O, Lindroth L (1993) Vitamin E levels in seminal plasma can be elevated by oral administration of vitamin E in infertile men. Int J Androl 16:165–166
31. Rolf C, Cooper TG, Yeung CH et al (1999) Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. Hum Reprod 14:1028–1033
32. Dawson EB, Harris WA, Rankin WE et al (1987) Effect of ascorbic acid on male fertility. Ann N Y Acad Sci 498:312–323
33. Dawson EB, Harris WA, Teter MC et al (1992) Effect of ascorbic acid supplementation on the sperm quality of smokers. Fertil Steril 58:1034–1039
34. Colagar AH, Marzony ET (2009) Ascorbic acid in human seminal plasma: determination and its relationship to sperm quality. J Clin Biochem Nutr 45:144–149
35. Alpers DH, Stenson WF, Taylor BE, Bier DM (eds) (2008) Manual of nutritional therapeutics, 5th edn. Lippincott Williams & Wilkins, Philadelphia
36. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (2000) Dietary reference intakes for vitamin C, vitamin E, selenium, and beta-carotene and other carotenoids. National Academies Press, Washington, DC
37. Palmero S, Bottazzi C, Costa M et al (2000) Metabolic effects of l-carnitine on prepubertal rat Sertoli cells. Horm Metab Res 32:87–90
38. Vicari E, La Vignera S, Calogero A (2002) Antioxidant treatment with carnitines is effective in infertile patients with prostatovesiculoepididymitis and elevated seminal leukocyte concentrations after treatment with nonsteroidal anti-inflammatory compounds. Fertil Steril 6:1203–1208
39. Bohmer T, Hoel P, Purvis K et al (1978) Carnitine levels in human accessory sex organs. Arch Androl 1:53–59
40. Balercia G, Regoli F, Armeni T et al (2005) Placebo-controlled double-blind randomized trial on the use of *L*-carnitine, *L*-acetylcarnitine, or combined *L*-carnitine and *L*-acetylcarnitine in men with idiopathic asthenozoospermia. Fertil Steril 84:662–671

41. Cavallini G, Ferraretti AP, Gianaroli L et al (2004) Cinnoxicam and L-carnitine/acetyl–carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. J Androl 25:761–770; discussion 71–72
42. Lenzi A, Lombardo F, Sgro P et al (2003) Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. Fertil Steril 79:292–300
43. Sigman M, Glass S, Campagnone J et al (2006) Carnitine for the treatment of idiopathic asthenospermia: a randomized, double-blind, placebo-controlled trial. Fertil Steril 85:1409–1414
44. Lenzi A, Sgro P, Salacone P et al (2004) A placebo-controlled double-blind randomized trial in the use of combined l-carnitine and l-acetylcarnitine treatment in men with asthenozoospermia. Fertil Steril 81:1578–1584
45. Rao AV, Mira MR, Rao LG (2006) Lycopene. Adv Food Nutr Res 51:99–164
46. Palan P, Naz R (1996) Changes in various antioxidant levels in human seminal plasma related to immunoinfertility. Arch Androl 36:139–148
47. Gupta NP, Kumar R (2002) Lycopene therapy in idiopathic male infertility—a preliminary report. Int Urol Nephrol 34:369–372
48. Irvine DS (1996) Glutathione as a treatment for male infertility. Rev Reprod 1:6–12
49. Raijmakers MT, Roelofs HM, Steegers EA et al (2003) Glutathione and glutathione S-transferases A1-1 and P-P1 in seminal plasma may play a role in protecting against oxidative damage to spermatozoa. Fertil Steril 79:169–175
50. Ochsendorf FR, Buhl R, Bastlein A et al (1998) Glutathione in spermatozoa and seminal plasma of infertile men. Hum Reprod 13:353–357
51. Lenzi A, Lombardo F, Gandini L et al (1992) Glutathione therapy for male infertility. Arch Androl 29:65–68
52. Lenzi A, Picardo M, Gandini L et al (1994) Glutathione treatment of dyspermia: effect on the lipoperoxidation process. Hum Reprod 9:2044–2050
53. Lenzi A, Culasso F, Gandini L et al (1993) Placebo-controlled, double blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod 8:1657–1662
54. Kodama H, Yamaguchi R, Fukuda J et al (1997) Increased oxidative deoxyribonucleic acid damage in the spermatozoa of infertile male patients. Fertil Steril 68:519–524
55. Jones DP, Coates RJ, Flagg EW et al (1992) Glutathione in foods listed in the National Cancer Institute's Health Habits and History Food Frequency Questionnaire. Nutr Cancer 17:57–75
56. Rayman MP (2000) The importance of selenium to human health. Lancet 356:233–241
57. Ursini F, Heim S, Kiess M et al (1999) Dual function of the selenoprotein PHGPx during sperm maturation. Science 285:1393–1396
58. Xia Y, Hill KE, Li P et al (2010) Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional requirement: a placebo-controlled, double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects. Am J Clin Nutr 92:525–531
59. Hawkes WC, Turek PJ (2001) Effects of dietary selenium on sperm motility in healthy men. J Androl 22:764–772
60. Safarinejad MR, Safarinejad S (2009) Efficacy of selenium and/or N-acetylcysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. J Urol 181:741–751
61. Watanabe T, Endo A (1991) Effects of selenium deficiency on sperm morphology and spermatocyte chromosomes in mice. Mutat Res 262:93–99
62. Scott R, MacPherson A, Yates RW et al (1998) The effect of oral selenium supplementation on human sperm motility. Br J Urol 82:76–80
63. Hawkes WC, Alkan Z, Wong K (2009) Selenium supplementation does not affect testicular selenium status or semen quality in North American men. J Androl 30:525–533
64. Iwanier K, Zachara BA (1995) Selenium supplementation enhances the element concentration in blood and seminal fluid but does not change the spermatozoal quality characteristics in subfertile men. J Androl 16:441–447
65. Bongalhardo DC, Leeson S, Buhr MM (2009) Dietary lipids differentially affect membranes from different areas of rooster sperm. Poult Sci 88:1060–1069

66. Tavilani H, Doosti M, Abdi K et al (2006) Decreased polyunsaturated and increased saturated fatty acid concentration in spermatozoa from asthenozoospermic males as compared with normozoospermic males. Andrologia 38:173–178
67. Safarinejad MR, Safarinejad S (2012) The roles of omega-3 and omega-6 fatty acids in idiopathic male infertility. Asian J Androl 14:514–515
68. Mazza M, Pomponi M, Janiri L et al (2007) Omega-3 fatty acids and antioxidants in neurological and psychiatric diseases: an overview. Prog Neuropsychopharmacol Biol Psychiatry 31:12–26
69. Farooqui AA, Horrocks LA, Farooqui T (2000) Glycerophospholipids in brain: their metabolism, incorporation into membranes, functions, and involvement in neurological disorders. Chem Phys Lipids 106:1–29
70. Lenzi A, Gandini L, Maresca V et al (2000) Fatty acid composition of spermatozoa and immature germ cells. Mol Hum Reprod 6:226–231
71. Aksoy Y, Aksoy H, Altinkaynak K et al (2006) Sperm fatty acid composition in subfertile men. Prostaglandins Leukot Essent Fatty Acids 75:75–79
72. Safarinejad MR, Hosseini SY, Dadkhah F et al (2010) Relationship of omega-3 and omega-6 fatty acids with semen characteristics, and anti-oxidant status of seminal plasma: a comparison between fertile and infertile men. Clin Nutr 29:100–105
73. Attaman JA, Toth TL, Furtado J et al (2012) Dietary fat and semen quality among men attending a fertility clinic. Hum Reprod 27:1466–1474
74. Ebisch IM, Thomas CM, Peters WH et al (2007) The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. Hum Reprod 13:163–174
75. Prasad AS (2008) Zinc in human health: effect of zinc on immune cells. Mol Med 14:353–357
76. Ebisch IM, Pierik FH, de Jong FH et al (2006) Does folic acid and zinc sulphate intervention affect endocrine parameters and sperm characteristics in men. Int J Androl 29:339–345
77. Mahajan SK, Abbasi AA, Prasad AS et al (1982) Effect of oral zinc therapy on gonadal function in hemodialysis patients. A double-blind study. Ann Intern Med 97:357–361
78. Omu AE, Al-Azemi MK, Kehinde EO et al (2008) Indications of the mechanisms involved in improved sperm parameters by zinc therapy. Med Princ Pract 17:108–116
79. Omu AE, Dashti H, Al-Othman S (1998) Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. Eur J Obstet Gynecol Reprod Biol 79:179–184
80. Piomboni P, Gambera L, Serafini F et al (2008) Sperm quality improvement after natural antioxidant treatment of asthenoteratospermic men with leukocytospermia. Asian J Androl 10:201–206
81. Wong WY, Merkus HM, Thomas CM et al (2002) Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. Fertil Steril 77:491–498
82. Sinclair S (2000) Male infertility: nutritional and environmental considerations. Altern Med Rev 5:28–38
83. Schachter A, Goldman JA, Zukerman Z (1973) Treatment of oligospermia with the amino acid arginine. J Urol 110:311–313
84. de Aloysio D, Mantuano R, Mauloni M et al (1982) The clinical use of arginine aspartate in male infertility. Acta Eur Fertil 13:133–167
85. Miroueh A (1970) Effect of arginine on oligospermia. Fertil Steril 21:217–219
86. Pryor JP, Blandy JP, Evans P et al (1978) Controlled clinical trial of arginine for infertile men with oligozoospermia. Br J Urol 50:47–50
87. Hidaka T, Fujii K, Funahashi I et al (2008) Safety assessment of coenzyme Q10 (CoQ10). Biofactors 32:199–208
88. Bentinger M, Tekle M, Dallner G (2010) Coenzyme Q—biosynthesis and functions. Biochem Biophys Res Commun 396:74–79
89. Mancini A, de Marinis L, Oradei A et al (1994) Coenzyme Q10 concentrations in normal and pathological human seminal fluid. J Androl 15:591–594

90. Balercia G, Buldreghini E, Vignini A et al (2009) Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertil Steril 91:1785–1792
91. Safarinejad MR (2009) Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. J Urol 182:237–248
92. Smith JF, Eisenberg ML, Millstein SG et al (2010) The use of complementary and alternative fertility treatment in couples seeking fertility care: data from a prospective cohort in the United States. Fertil Steril 93:2169–2174
93. Salvati G, Genovesi G, Marcellini L et al (1996) Effects of Panax Ginseng C.A. Meyer saponins on male fertility. Panminerva Med 38:249–254
94. Morgante G, Scolaro V, Tosti C et al (2010) Treatment with carnitine, acetyl carnitine, L-arginine and ginseng improves sperm motility and sexual health in men with asthenospermia. Minerva Urol Nefrol 62:213–218
95. Gonzales GF, Cordova A, Gonzales C et al (2001) Lepidium meyenii (Maca) improved semen parameters in adult men. Asian J Androl 3:301–303
96. Comhaire FH, El Garem Y, Mahmoud A et al (2005) Combined conventional/antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial. Asian J Androl 7:257–262