Introducing Wellman Conception

Professional Information
Not for Public Distribution

Updated August 2017

Contents

*This document is for internal use only to provide an introduction to the product, its formulation and supporting scientific evidence. Please note the content in this product dossier is **not EFSA compliant** and is not intended for use in any commercial context in the EU.*

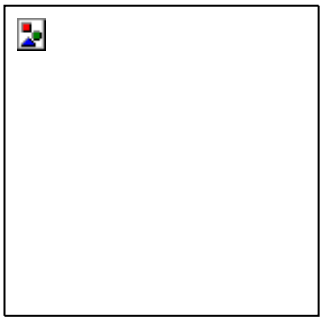
Introduction

Introduction to Wellman Conception

Wellman Conception recognises that men have an important influence on conception and have distinct reproductive health needs of their own. Many men now recognise the importance of getting themselves in shape and adopting a healthier lifestyle when trying for a baby. The advanced formula combines a potent blend of antioxidants**,** vitamins, and minerals with amino acids, L-Carnitine, L-Arginine and folic acid which have been specifically chosen for their role in male reproductive function and health.

Wellman Conception should be taken daily as an integral part of an overall healthy lifestyle, ideally three months before trying to conceive, while, at the same time, Pregnacare Conception has been specially designed for your partner with 400mcg folic acid.

Fertility facts

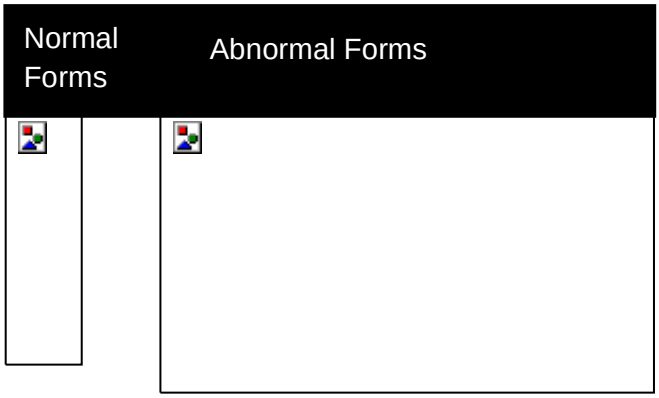


When couples decide to try for a family, it is not only women who need to look after their diet and lifestyle in order to maximise their health and support conception. A few simple changes may also significantly influence healthy strong viable sperm and the likelihood of conception.

Infertility is defined as the failure to become pregnant after one year of unprotected, well-timed sexual intercourse. In men, infertility is usually associated with a decrease in the number, quality, or motility (movement) of sperm.

There are many factors that can decrease or cease sperm production. Here are a few:

- Illness
- Excessive Caffeine
- Stress
- Excessive alcohol consumption
- Street and certain Prescription Drugs
- Some over the counter medications
- Injury to the testicles
- Excessive Heat to the testicles
- **Vitamin Deficiencies**



If pregnancy is not achieved after one year of regular, unprotected sex, both sexual partners should be tested for possible infertility problems. Low sperm count, decreased motility, or abnormal shape of the sperm are responsible for infertility in about 40% of these couples. Female causes account for 40% of infertility cases, and 20% are attributed to a combination of both.

At least one in five of the couples you know will be affected by some degree of infertility. A sobering thought but fortunately many of these couples can benefit from help. Statistics vary but it would seem that around **30% of men are sub-fertile** and at least **2% of men are totally infertile**. Infertility affects 10%–15% couples worldwide with male factor contributing to 20%–30% cases (Barik et al., 2019).

Furthermore, there is a great scientific debate going on just now about evidence suggesting that male fertility is decreasing markedly as a result of modern lifestyles. (source: http://www.malefertility.co.uk/statistics.html)

Background to the formulation

Wellman Conception targets different areas of reproductive health in males
Better fertility outcomes are observed in those who are on a healthy diet which includes supplements with high amounts of micronutrients and antioxidants (Hamadé et al., 2014).

Nutritional support for conception & spermatogenesis
It is now known that folic acid not only plays a critical role in female conception, for the early development of the foetus, but is also important for the man's role in conception too. In addition, L-Carnitine & L-Arginine, both present within the Wellman Conception formula, play a key role in sperm energy metabolism. L-carnitine provides valuable support for the male reproductive system. Clinical research over the last few decades has reported that L-carnitine is found in high concentrations in sperm, and may play a part in sperm energy metabolism and most importantly, may support sperm quality contributing to its ability to reach the egg.

L- Arginine may help support healthy sperm count as it may assist blood flow to the genital area by stimulating nitric oxide in the body.

Antioxidant support
Vitamins C, E, and selenium are important antioxidants central to overall reproductive health and wellness. Vitamin C is a water-soluble antioxidant that is actively secreted into semen. Vitamin E is a fat-soluble antioxidant vitamin and helps to improve the overall health of sperm. Sperm can be damaged by free radicals and Vitamin E is an antioxidant which helps to reduce the number of free radicals. Selenium is also a powerful antioxidant and is thought selenium may help increase sperm motility.

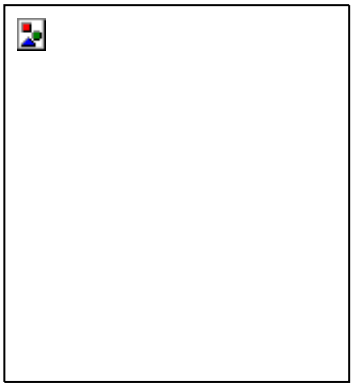
The important role of Zinc in male conception health
Zinc is arguably one of the most important minerals for the male reproductive system as semen contains 100 times more zinc than is found in the blood.

Deficiencies in Zinc are one of the main causes of problems associated with male fertility. The mineral is essential for healthy cell division and the production of quality and quantity sperm. Men just as women require adequate amounts of Vitamin B6 and Zinc to improve the chances of successful conception and pregnancy.

High levels of caffeine, smoking, stress, and drinking cause depletion of the Zinc level in the body. Even normal sexual activity reduces the Zinc level. With every ejaculation a man loses about 5 mg of the mineral. Factors such as tea and high fibre intake may also inhibit the absorption of the mineral.

Zinc can also be obtained through the diet through certain foods such as:

- Parsley
- Oysters
- Eggs
- Pumpkin
- Wheat germ
- Mushrooms
- Meat
- Chicken
- Oats
- Rye



- Whole grains
- Fish

Zinc helps to improve:

- Testosterone metabolism
- Sperm production
- Motility
- Stress handling
- Testicle growth
- Cell division
- Sperm count

The formula also includes other key nutrients that are ideal for all men when trying for a baby with their partner:

Peruvian MACA Extract – Sourced from the Peruvian herbaceous plant, this organic source Maca contains important nutrients including amino acids and fatty acids, which are essential for male reproductive health.

Co-Enzyme Q10 – Acts as an antioxidant and energy-releasing agent and is thought to stabilize the integrity of the sperm flagella.

Folic Acid – Studies suggest that supplementation of folic acid along with zinc supports sperm health.

Lycopene - Highly regarded for its exceptional antioxidant properties, nutritional studies have shown intake of Lycopene linked to prostate health.

Siberian Ginseng Extract – Widely used to help maintain overall male vitality.

Pine Bark Extract – A highly effective antioxidant which may play a role in protecting sperm. Free radicals (responsible for oxidative cell) are said to be responsible for 40 percent of sperm damage.

Nutritional Information

Nutritional Information	Av. per Tablet	% NRV†
Siberian Ginseng Extract eq. to	30 mg	—
Maca Extract eq. to	250 mg	—
Coenzyme Q10	2 mg	—
L-Carnitine	50 mg	—
Citrus Bioflavonoids	10 mg	—
L-Arginine	10 mg	—
Lycopene Extract	1.5 mg	—
Pine Bark Extract	30 mg	—
Octacosanol	3 mg	—
Inositol	40 mg	—
L-Glutathione	2.5 mg	—
Vitamin A (2500 IU)	750 µg RE	94
Vitamin D (as D3 600 IU)	15 µg	300
Vitamin E (Natural Source)	30 mg α-TE	250
Vitamin C	90 mg	113
Thiamin (Vitamin B1)	12 mg	1091
Riboflavin (Vitamin B2)	5 mg	357
Niacin (Vitamin B3)	18 mg NE	113
Vitamin B6	10 mg	714
Folic Acid	400 µg	200
Vitamin B12	75 µg	3000
Biotin	150 µg	300
Pantothenic Acid	10 mg	167
Magnesium	60 mg	16
Iron	6 mg	43
Zinc	15 mg	150
Copper	1000 µg	100
Manganese	0.5 mg	25
Selenium	150 µg	273
Chromium	50 µg	125

†NRV – Nutrient Reference Value
µg – microgram, mg – milligram, IU – International Units

DIRECTIONS

ONE TABLET PER DAY WITH YOUR MAIN MEAL.
Swallow with water or a cold drink. Not to be chewed. Do not exceed the recommended intake. To be taken on a full stomach.

This comprehensive formula replaces other Wellman® multivitamins. There is no need to take an additional multivitamin.

www.wellman.co.uk

Frequently asked questions

Why has Wellman Conception been developed?

Wellman Conception has been specifically designed to support the nutritional requirements of men who:

- Wish to support their reproductive health
- Are about to try for a family and wish to look after their diet and lifestyle in preparation

The special formula has been developed on the basis of worldwide studies showing that certain nutrients can play an important role in helping to build nutritional stores to help support good reproductive health. Wellman Conception provides a carefully balanced comprehensive formulation of micronutrients for the maintenance of reproductive health in men , including the specific nutrients Lycopene, L-Carnitine, L-Arginine, MACA, ginseng, Zinc & selenium.

Why is nutrition important in male fertility?

Sperm can be highly susceptible to free radical or oxidative damage from environmental toxicants and natural aging. Vitamins C and E, and selenium are all potent antioxidants that may help maintain sperm counts and quality by reducing free radical damage. Zinc and B vitamins (especially B6 and B12) are critical nutrients in male reproductive systems for several reasons, including hormone metabolism, sperm formation and motility. The amino acids, L-arginine and L-carnitine have also been shown to play an important role in the formation of healthy sperm.

When is Wellman Conception recommended?

Wellman Conception should be used as soon as you start trying for a baby with your partner. To help build the body's nutritional stores it can even be for 3-6 months before you physically start to try for a baby.

What do I need to know before starting to use Wellman Conception?

Wellman Conception is a food supplement. It has been carefully developed by a team of experts including highly qualified pharmacists and nutritional consultants, and is based upon scientific research evidence, as a nutritional safeguard for men's reproductive health. Wellman Conception replaces your usual daily multivitamin.

Can Wellman Conception be used alongside medicines?

As a general rule, Wellman Conception can be taken alongside medications because it contains only moderate levels of vitamins, minerals and natural botanicals. However, if you are under medical supervision, already taking prescribed supplements or medications or have an underlying condition, seek advice from your doctor or health professional first.

How many tablets does one pack of Wellman Conception contain?

Wellman Conception contains 30 tablets per pack and it is recommended to take one per day.

How and when should Wellman Conception be used?

One tablet per day is recommended with or immediately after your main meal, with a full glass of water or a cold drink. Taking the tablet with a large meal maximises the absorption of the nutrients, and can reduce nausea which is sometimes experienced if multivitamins are taken on an empty stomach. Wellman Conception should only be taken on a full stomach. Always ensure that Wellman Conception is taken with plenty of liquid to wash down the tablet. We do not recommend chewing the tablets because they have not been formulated as a chewable preparation. Chewable tablets usually include flavourings, sweeteners and/or added ingredients to help break the tablet up in the mouth. Wellman Conception tablets are suitable for vegetarians.

Are there any undesired effects whilst taking Wellman Conception?

Wellman Conception has no known side-effects when taken as directed. Do not exceed the recommended tablet intake. In case of overdose, seek medical advice immediately.

Is there anything my partner should take too?

Yes. Pregnacare® Conception has been specifically designed to support the nutritional requirements of women who are trying to conceive. The special formula has been developed on the basis of worldwide studies showing that certain nutrients can play an important role in helping to build nutritional stores ready for pregnancy and support good reproductive health. Pregnacare® Conception provides a carefully balanced comprehensive formulation of micronutrients for the maintenance of reproductive health in women, including the specific nutrients inositol, l-arginine, n-acetyl cysteine and selenium. The formula also includes vitamin B12, and **folic acid at 400mcg, the exact recommended level for all women who are trying for a baby** to help safeguard the early stages of foetal development.

What are the active ingredients?

Wellman Conception contains**:** Lycopene Extract 1.5 mg; Maca Extract 250 mg; Pine Bark Extract 30 mg; Octacosanol 3 mg; Inositol 40 mg; L-Glutathione 2.5 mg; L-Arginine 10 mg; Siberian Ginseng Extract 30 mg; Co-enzyme Q10 2 mg; L-Carnitine Tartrate 50 mg; Citrus Bioflavonoids 10 mg; Vitamin A (2500 IU) 750 µg RE; Vitamin D3 (as D3 600 IU) 15 µg; Vitamin E 30 mg α- TE; Vitamin C 90 mg; Thiamin (Vitamin B1) 12 mg; Riboflavin (Vitamin B2) 5 mg; Niacin (Vitamin B3) 18 mg NE; Vitamin B6 10 mg; Folacin (Folic Acid) 400 µg; Vitamin B12 75 µg; Biotin 150 µg; Pantothenic Acid 10 mg; Magnesium 60 mg; Iron 6 mg; Zinc 15 mg; Copper 1000 µg; Manganese 0.5 mg; Selenium 150 µg; Chromium 50 µg.

Some Recommended Daily Allowance (RDA) levels are above 100%. Is this safe?
Certain vitamins are very safe at levels tens or even hundreds of times the RDA, whereas for others the safety level is much closer to the RDA. For this reason every vitamin and mineral needs to be considered on an individual basis in terms of its upper safe level. The Recommended Daily Allowance (RDA) is the amount of a vitamin or mineral which has been calculated to help prevent basic deficiency states in the general population. However, certain vitamins and minerals at optimal levels, above the RDA, have consistently been shown to have positive benefits in specific areas of health. This is why some Vitabiotics formulas have certain nutrient levels greater than 100% RDA.

All Vitabiotics products have been developed using the latest research and contain effective levels of vitamins and minerals, while **avoiding any excessive amounts, in accordance with official upper safe limits for vitamins and minerals.**

Scientific References

General

Abstract
We investigated effects of multivitamin/mineral supplementation on element levels in serum and follicular fluid of women undergoing IVF. We used three groups in this study. The first group was used as an age-matched and nonpregnant control (n = 13). Group 2 (n = 30) constituted the IVF group and women in the third group who were undergoing IVF also received a multivitamin/mineral tablet daily for 45 days. Follicular fluid and serum selenium and zinc levels and follicular fluid copper levels were lower in IVF patients than in controls although follicular fluid aluminum and iron levels were higher in IVF patients than in controls. However, follicular fluid and serum aluminum, copper, zinc and selenium levels, and serum magnesium levels were higher in the multivitamin/mineral group than in the IVF group although follicular fluid iron levels were lower in the multivitamin/mineral group than in the IVF group. In conclusion, we observed that copper, zinc, and selenium in serum and follicular fluid decreased in women undergoing IVF. Multivitamin/mineral supplementation in serum and follicular fluid of women undergoing IVF normalized the trace element. *(Biol Trace Elem Res. 2011 Jan;139(1):1-9. Epub 2010 Feb 24. Effects of multivitamin/mineral supplementation on trace element levels in serum and follicular fluid of women undergoing in vitro fertilization (IVF). Özkaya MO, Nazıroğlu M, Barak C, Berkkanoglu M. Department of Obstetrics and Gynecology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey.)*

Analysis of the properties in semen ejaculation concluded that there is 16.5mg of zinc per 100 ML. (*D Owen, D F Katz , A Review of the Physical and Chemical Properties of Human Semen and the Formulation of a Semen Simulant. 02 January 2013. 2005 American Society of Andrology*). The average ejaculation is 3.4ml in volume. Therefore, based on the findings on the ratio of zinc in ejaculation, the average ejaculation contains around 0.5mg of zinc.

Abstract
We investigated effects of multivitamin and mineral supplementation on lipid peroxidation, reduced glutathione, glutathione peroxidase, vitamin A, vitamin C and vitamin E values in serum and follicular fluid of 56 women undergoing IVF and 13 age matched control. We concluded that multivitamin and mineral supplementation in serum and follicular fluid of women undergoing IVF may strengthen the antioxidant defense system by decreasing oxidative stress. *(Fertil Steril. 2010 Nov;94(6):2465-6. Multivitamin and mineral supplementation modulates oxidative stress and antioxidant vitamin levels in serum and follicular fluid of women undergoing in vitro fertilization. Ozkaya MO, Nazıroğlu M. Department of Obstetrics and Gynecology, Faculty of Medicine, Suleyman Demirel University, Isparta, Turkey)*

Studies confirm that male sperm counts are declining, and environmental factors, such as pesticides, exogenous estrogens, and heavy metals may negatively impact spermatogenesis. A number of nutritional therapies have been shown to improve sperm counts and sperm motility, including carnitine, arginine, zinc, selenium, and vitamin B-12. Numerous antioxidants have also proven beneficial in treating male infertility, such as vitamin C, vitamin E, glutathione, and coenzyme Q10. Acupuncture, as well as specific botanical medicines, have been documented in several studies as having a positive effect on sperm parameters. A multi-faceted therapeutic approach to improving male fertility involves identifying harmful environmental and occupational risk factors, while correcting underlying nutritional imbalances to encourage optimal sperm production and function. (Male infertility: nutritional and environmental considerations. Green Valley Health, Hagerstown, MD 21742, USA. 2000 Feb;5(1):28-38.)

The use of antioxidants in treatment of infertile men has been suggested, although the evidence base for this practice is unclear. A systematic review of randomized studies was conducted to evaluate the effects of oral antioxidants (vitamins C and E, zinc, selenium, folate, carnitine and carotenoids) on sperm quality and pregnancy rate in infertile men. MEDLINE, EMBASE, Cochrane Library and

CINAHL were searched for relevant trials published from respective database inception dates to May 2009. Study selection, quality appraisal and data extraction were performed independently and in duplicate. Seventeen randomized trials, including a total of 1665 men, were identified, which differed in the populations studied and type, dosage and duration of antioxidants used. Only two-thirds of the studies (11/17) reported using allocation concealment and three studies (18%) used intention-to-treat analysis. Despite the methodological and clinical heterogeneity, 14 of the 17 (82%) trials showed an improvement in either sperm quality or pregnancy rate after antioxidant therapy. Ten trials examined pregnancy rate and six showed a significant improvement after antioxidant therapy. The use of oral antioxidants in infertile men could improve sperm quality and pregnancy rates. Adequately powered robust trials of individual and combinations of antioxidants are needed to guide clinical practice
Reproductive BioMedicine Online Volume 20, Issue 6 , Pages 711-723, June 2010.

Abstract

Background
Between 30% to 80% of male subfertility cases are considered to be due to the damaging effects of oxidative stress on sperm. Oral supplementation with antioxidants may improve sperm quality by reducing oxidative stress.

Objectives
This Cochrane review aimed to evaluate the effect of oral supplementation with antioxidants for male partners of couples undergoing assisted reproduction techniques (ART).

Search strategy
We searched the Cochrane Menstrual Disorders and Subfertility Group Register, CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, CINAHL, PsycINFO and AMED databases (from their inception until Febuary 2010), trial registers, sources of unpublished literature, reference lists and we asked experts in the field.

Selection criteria
We included randomised controlled trials comparing any type or dose of antioxidant supplement (single or combined) taken by the male partner of a couple seeking fertility assistance with placebo, no treatment or another antioxidant. The outcomes were live birth, pregnancy, miscarriage, stillbirth, sperm DNA damage, sperm motility, sperm concentration and adverse effects.

Data collection and analysis
Two review authors independently assessed studies for inclusion and trial quality, and extracted data.

Main results
We included 34 trials with 2876 couples in total.

Live birth: three trials reported live birth. Men taking oral antioxidants had an associated statistically significant increase in live birth rate (pooled odds ratio (OR) 4.85, 95% CI 1.92 to 12.24; P = 0.0008, I^2 = 0%) when compared with the men taking the control. This result was based on 20 live births from a total of 214 couples in only three studies.

Pregnancy rate: there were 96 pregnancies in 15 trials including 964 couples. Antioxidant use was associated with a statistically significant increased pregnancy rate compared to control (pooled OR 4.18, 95% CI 2.65 to 6.59; P < 0.00001, I^2 = 0%).

Side effects: no studies reported evidence of harmful side effects of the antioxidant therapy used.

Authors' conclusions
The evidence suggests that antioxidant supplementation in subfertile males may improve the

outcomes of live birth and pregnancy rate for subfertile couples undergoing ART cycles. Further head to head comparisons are necessary to identify the superiority of one antioxidant over another. *(Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD007411. DOI: 10.1002/14651858.CD007411.pub2.)*

Lycopene Extract

Reference 1
Excessive generation of reactive oxygen species (ROS) containing free oxygen radicals has been identified as one of the causes of male infertility. Lycopene is a component of human redox defence mechanism against free radicals. It is found in high concentrations in the testes and seminal plasma and decreased levels have been demonstrated in men suffering from infertility. We evaluated the effect of oral lycopene therapy in men with idiopathic infertility. Beginning March 2000, thirty men with idiopathic non obstructiveoligo/ astheno/ teratozoospermia were enrolled for the trial. All patients were administered 2000mcg of Lycopene, twice a day for three months. Semen analysis was performed at three months and sperm concentration, motility and morphology were evaluated. All patients completed the trial without any complications. Twenty patients (66%) showed an improvement in sperm concentration, sixteen (53%) had improved motility and fourteen (46%) showed improvement in sperm morphology. In cases showing an improvement, the median change in concentration was 22 million/ml, motility 25%and morphology 10%. The improvement in concentration and motility were statistically significant. Baseline sperm concentration less than 5 million/ml was associated with no significant improvement. Higher baseline concentrations were associated with significant improvement and resulted in six pregnancies in 26 patients (23%). Oral Lycopene therapy seems to have a role in the management of idiopathic male infertility. Maximum improvement seems to occur in the sperm concentration (66% cases).Patients without severe oligospermia (sperm density >5 million/ml) may be given a trial of therapy with lycopene. (Department of Urology, All India Institute of Medical Sciences, Ansari Nagar, 110029 New Delhi, India)

Reference 2
Objective: to investigate whether lycopene levels in blood and seminal plasma increase after dietary supplementation with a natural source of the compound, and whether any potential increase of lycopene levels in semen translates into increased free-radical trapping capacity in the seminal plasma.
Methods: reactive oxygen species are detrimental to the health and function of spermatozoa. Semen contains enzymatic and non-enzymatic defence mechanisms to combat such species, and lycopene, a dietary antioxidant, forms part of the non-enzymatic arm. Immuno-infertile men have significantly lower levels of lycopene in their semen, and oral lycopene therapy can improve various seminal variables in idiopathic infertility. Whether this improvement is a direct consequence of increased lycopene levels in semen, resulting in an increased radical scavenging ability, remains unknown. Blood and seminal lycopene levels were measured in healthy volunteers, using high-performance liquid chromatography, before and after a period of dietary supplementation. The antioxidant capacity of seminal plasma was also assayed to determine if supplementation results in a measurable increase in seminal radical scavenging ability.
Results: there were statistically significant increases in blood and seminal plasma lycopene levels after dietary supplementation. The increase in seminal and blood lycopene levels showed a strong positive correlation ($r = 0.84$, $P < 0.05$). There was no measurable increase in the total radical scavenging capacity of semen.
Conclusion: this study confirms the presence of lycopene in human semen, the levels of which can be significantly increased after dietary supplementation with a natural source of lycopene. (Goyal, A., Chopra, M., Lwaleed, B.A., Birch, B. and Cooper, A.J. (2007) The effects of dietary lycopene supplementation on human seminal plasma. *BJU International*, 99, (6), 1456-1460.)

Reference 3
Lycopene, a principle phytochemical pigment responsible for the bright red color in tomatoes, is being extensively studied for its potent anti-oxidant and anti-cancerous properties. Now, two studies

presented at the 64th Annual Meeting of the American Society for Reproductive Medicine, San Francisco (November 8-12, 2008) suggested that the plant antioxidant protects sperms and eggs from damage caused by oxidative stress, indicating a potential positive impact on the reproductive cells.
In order to examine the anti-oxidative effect of lycopene on sperms, Libman J and colleagues from McGill University, Quebec, Canada, conducted an experimental study, wherein fresh sperm samples isolated from fertile sperm donors were pretreated in solutions with and without lycopene. The samples were then subjected to hydrogen peroxide to induce DNA damage. It was noted that sperms samples treated with lycopene solution sustained less genetic damage when compared to the control samples, suggesting the positive impact of lycopene against oxidative stress-induced damage.
Another study presented at the meeting reported the antiadhesion effects of lycopene. Adhesions, fibrous bands formed during the process of healing after surgery, is one of the common causes of tubular dysfunction, which leads to infertility. Since increased oxidative stress is also known to play an important role in adhesion formation, Dbouk T, et al. from the Wayne State University, Detroit, Michigan, investigated the effect of lycopene on adhesion development. On treatment of adhesive tissue samples with lycopene, it was shown that the antioxidant significantly reduces the expression of proteins associated with adhesions.
Earlier, Mohanty, et al. (*Indian Journal of Urology*, 2001) had conducted a study to investigate whether lycopene was effective in managing idiopathic oligoasthenospermia, a condition associated with low sperm count and motility, and accounting for about 24% of all male infertility. Fifty patients with idiopathic oligoasthenospermia were administered with 8mg of lycopene (Lycored) daily, until significant improvement in sperm counts or pregnancy was achieved. Following regular follow-up for a period of one year, study results documented a 36% pregnancy rate, with significant improvement in sperm count (70%), functional sperm concentration (60%), sperm morphology (38%), sperm motility (54%) and sperm motility index (46%). From the findings, researchers suggested that lycopene has a distinct role in the management of idiopathic oligoasthenospermia.
The presence of excess reactive oxygen species (ROS), resulting from oxidative stress status (OSS) in ejaculates, is considered to be one of the major causative factors of sperm damage, sluggish motility, and low sperm count, leading to idiopathic male infertility. Earlier studies have indicated that 40%-80% of men with infertility have high levels of seminal free oxygen radicals.
Several researches have documented significant anti-inflammatory and anti-coagulant activities of lycopene. Furthermore, lycopene is also associated with reduced risk of macular degenerative disease, serum lipid oxidation and cancers of skin, bladder, lung, ovary and cervix. In addition to other beneficial properties of the plant anti-oxidant, the current evidence suggesting the protective effect of lycopene on germ cells, could serve as a promising intervention to oxidative stress-associated infertility problems. (Lycopene Good for Sperm and Eggs. HIGHLIGHTS FROM THE 64th ANNUAL MEETING OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE. Press Release. *American Society for Reproductive Medicine*. Last accessed Nov 13, 2008. Mohanty NK, Kumar S, Jha AK, Arora RP. Management of idiopathic oligoasthenospermia with lycopene. *Indian Journal of Urology*. 2001;18(1):57-61.)

Reference 4
A number of population studies have found a strong correlation between high blood levels of insulin-like growth factor-I (IGF-1) and increased risk of colon, prostate and breast cancer. New research suggests lycopene supplementation may provide some protection by significantly lowering IGF-1. (Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, Giovannucci E. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev. 2005 Apr;14(4):850-5.)

Reference 5
An optimal intake of lycopene is essential for men. This important nutrient acts as an antioxidant and helps to protect against certain forms of cancer, namely prostate cancer. (Nkosi CZ et al. Effect of pumpkin seed (Cucurbita pepo) protein isolate on the activity levels of certain plasma enzymes in CCl4-induced liver injury in low-protein fed rats. Phytother Res. 2005 Apr;19(4):341-5.)

Maca Extract

Reference 1
Much of the evidence for maca comes from animal studies. In one study in rats, use of maca

enhanced male sexual function. (Cicero AF, Piacente S, Plaza A, et al. Hexanic Maca extract improves rat sexual performance more effectively than methanolic and chloroformic Maca extracts. *Andrologia*. 2002;34:177-179.)

Reference 2
In one small 12-week, double-blind, placebo-controlled study, use of maca at 1,500 mg or 3,000 mg increased male libido. (Gonzales GF, Cordova A, Vega K, et al. Effect of *Lepidium meyenii* (Maca) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia*. 2002;34:367.)

Reference 3
Another study found that 4 months of maca use increased sperm count and sperm function. (Gonzales GF, Cordova A, Gonzales C, et al. *Lepidium meyenii* (Maca) improved semen parameters in adult men. *Asian J Androl*. 2002;3:301-303.)

Reference 4
A dose–response study was performed to determine the effect of 7 days oral administration of an aqueous lyophilized extract of Maca at 0.01–5 g/kg (corresponding to 0.022–11 g dry hypocotyls of Maca/kg) on body and different organ weights, stages of the seminiferous tubules, epididymal sperm count and motility, and serum testosterone and estradiol levels in rats. In doses up to 5 g extract/kg, no toxicity was observed. Almost all organ weights were similar in controls and in the Maca extract-treated groups. Seminal vesicles weight was significantly reduced at 0.01 and 0.10 g extract/kg. Maca increased in length of stages VII–VIII of the seminiferous tubules in a dose–response fashion, with highest response at 1.0 g/kg, while caput/corpus epididymal sperm count increased at the 1.0 g dose. (Dose–response effects of *Lepidium meyenii* (Maca) aqueous extract on testicular function and weight of different organs in adult rats; Volume 98, Issues 1-2, 8 April 2005, Pages 143-147)

Reference 5
Numerous animal studies show that maca extracts can increase sex drive and improve fertility. (Cicero AF, Piacente S, Plaza A, et al. Hexanic maca extract improves rat sexual performance more effectively than methanolic and chloroformic maca extracts. *Andrologia* 2002;34:177–9. Gonzales GF, Ruiz A, Gonzales C, et al. Effect of Lepidium meyenii (maca) roots on spermatogenesis of male rats. *Asian J Androl* 2001;3:231–3. Ruiz-Luna AC, Salazar S, Aspajo NJ, et al. Lepidium meyenii (maca) increases litter size in normal adult female mice. *Reprod Biol Endocrinol* 2005;3:16.)

Reference 6
Preliminary studies have shown that maca can increase libido in healthy men. (Gonzales GF, Cordova A, Vega K, et al. Effect of Lepidium meyenii (maca) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia* 2002;34:367–72.)

Reference 7
Healthy men who take maca have also been shown to have increased semen volume, increased sperm counts, and enhanced sperm motility. (Gonzales GF, Cordova A, Gonzales C, et al. Lepidium meyenii (maca) improved semen parameters in adult men. *Asian J Androl* 2001;3:301–3.)

Pine Bark Extract

Reference 1
Pine bark is a rich source of proanthocyanidins (OPCs), known to be potent antioxidants with many benefits associated with circulatory health – such as helping venous insufficiency and vascular constriction. OPCs are 50 times more potent as antioxidants than vitamin E or C and are protective against both fat and water soluble free radicals. Improvements in blood flow and peripheral circulation can assist male reproductive function. (M. Murray. Encyclopedia of Nutritional Supplements. 1996 M. Murray and J. Pizzorno. Male infertility. P.1377-1386. Textbook of Natural Medicine. Second edition. 1999 Sinclair S. Male infertility: nutritional and environmental considerations. Altern Med Rev. 2000 Feb;5(1):28-38.)

Octacosanol

Reference 1
Octacosanol, a waxy substance found in wheat germ oil, has been investigated as an ergogenic agent. Preliminary studies have suggested that octacosanol improves endurance, reaction time, and other measures of exercise capacity (Cureton TK. The physiological effects of wheat germ oil on humans. In: *Exercise*. Illinois: Charles C Thomas, 1972, 296–300.)

Reference 2
Long-term trials in humans using amounts up to 20 mg per day have not shown any negative effects (Pons P, Rodriguez M, Robaina C, et al. Effects of successive dose increases of policosanol on the lipid profile of patients with type II hypercholesterolaemia and tolerability to treatment. *Int J Clin Pharm Res* 1994;14:27–33.)

Reference 3
A study was carried out using 33 male student athletes .Of these, 20 students were used as controls and 13 consumed two "paks" daily (each "pak" contained 29 supplements, including 2,000µg of octacosanol). After eight weeks, all the supplemented subjects showed a decrease in body fat compared to only one in the control group. The supplemented subjects also showed a significant increase in muscle girth measurements, indicating the formation of lean body mass. (Cockerill DL, Bucci LR. Increases in muscle girth and decreases in body fat associated with a nutritional supplement program. Chiro Sports Med 1987;1:73-6.)

Reference 4
An experimental procedure carried out on mice showed that octacosanol enhanced swimming endurance, possibly by converting lipids into energy (Shimura S, Hasegawa T, Takano S, Suzuki T. Studies on the effect of octacosanol on motor endurance in mice. Nutr Rep Int 1987;36:1029-38.)

Inositol

Reference 1
Some preliminary results of studies on high dose inositol supplements show promising results for people suffering from problems such as bulimia, panic disorder, obsessive-compulsive disorder, and unipolar and bipolar depression (Nick, Gina L. (2004). "Inositol as a treatment for psychiatric disorders: a scientific evaluation of its clinical effectiveness". *Townsend Letter for Doctors and Patients* (October). http://findarticles.com/p/articles/mi_m0ISW/is_255/ai_n6211958. Retrieved on 2008-05-24.)

Reference 2
Studies from *in vitro* experiments, animal studies, and limited clinical experiences, claim that inositol may be used effectively against some types of cancer. (jn.nutrition.org)

L-Glutathione

Reference 1
Aside from being a powerful antioxidant booster and system detoxifier, glutathione helps produce, protect and repair deoxyribonucleic acid - DNA. In this protective role, glutathione boosts the immune system, thereby helping to power immune response and preventing the growth of cancerous cells. (Bounous G, Molson J. Competition for glutathione precursors between the immune system and the skeletal muscle: pathogenesis of chronic fatigue syndrome. Med Hypothesis 53;(4): 347-349. Sen CK. Nutritional biochemistry of cellular glutathione. Nutr Biochem 1997;8:660-72.)

Reference 2
Boosting glutathione levels have been shown to boost sperm count in infertile men. (Lenzi A, Culasso

F, Gandini L, et al. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod 1993;8:1657-62.)

Reference 3
Declines in glutathione levels are associated with ageing, and studies have shown that adults who took glutathione had better health than those who did not. (Julius M, Lang C, Gleiberman L, et al. Glutathione and morbidity in a community-based sample of elderly. J Clin Epidemiol 1994;47:1021-6.)

L-Arginine

Reference 1
Arginine, an amino acid found in many foods, is needed to produce sperm. Research, most of which is preliminary shows that several months of L-arginine supplementation increases sperm count, quality and fertility. (De Aloysio D, Mantuano R, Mauloni M, Nicoletti G. The clinical use of arginine aspartate in male infertility. *Acta Eur Fertil* 1982;13:133–67. Tanimura J. Studies on arginine in human semen. Part II. The effects of medication with L-arginine-HCl on male infertility. *Bull Osaka Med School* 1967;13:84–9. Scibona M, Meschini P, Capparelli S, et al. L-arginine and male infertility. *Minerva Urol Nefrol* 1994;46:251–3. Schacter A, Goldman JA, Zukerman Z. Treatment of oligospermia with the amino acid arginine. *J Urol* 1973;110:311–3. Schacter A, Friedman S, Goldman JA, Eckerling B. Treatment of oligospermia with the amino acid arginine. *Int J Gynaecol Obstet* 1973;11:206–9.)

Reference 2
Arginine participates in protein synthesis in cells and tissues. It is essential for the synthesis of urea, creatine, creatinine, and pyrimidine bases. It also strongly influences hormonal release and has an important role in vasculature dynamics, participating in the synthesis of nitric oxide (NO). (Division of Endocrinology, Department of Internal Medicine, University of Turin, Turin, Italy, 10.1081/E-EDS-120022067)

Siberian Ginseng Extract

Reference 1
Siberian ginseng is popular for invigorating and fortifying the body. It appears to boost energy levels in people suffering from acute or constant exhaustion. (Panossian A, Wagner H. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. Phytother Res. 2005 Oct;19(10):819-38.)

Reference 2
Siberian ginseng may be useful in preventing female infertility. Males may experience an increased sperm count. Animal studies indicate that the herb can even boost testosterone levels and thus help reverse certain cases of male impotence. (Salvati G, Genovesi G, Marcellini L, Paolini P, De Nuccio I, Pepe M, Re M. Effects of Panax Ginseng C.A. Meyer saponins on male fertility. Panminerva Med. 1996 Dec;38(4):249-54.)

Reference 3
Scientists have been able to show that Siberian ginseng has a cytotoxic (cell killing) effect on some cancer cell lines in laboratory studies. (Yu CY, Kim SH, Lim JD, Kim MJ, Chung IM. Intraspecific relationship analysis by DNA markers and in vitro cytotoxic and Antioxidant activity in Eleutherococcus senticosus. Toxicol In Vitro. 2003 Apr;17(2):229-36.)

Reference 4
Historically, the Chinese have found Siberian ginseng to be effective in suppressing colds and flu. The herb's immune-enhancing powers may play a role. Recent studies have found that herbal preparations including Siberian ginseng is a helpful adjunctive treatment to conventional therapies for upper respiratory tract infections. Other studies have also shown it to benefit sinusitis. (Narimanian

M, Badalyan M, Panosyan V, Gabrielyan E, Panossian A, Wikman G, Wagner H. Randomized trial of a fixed combination (KanJang) of herbal extracts containing Adhatoda vasica, Echinacea purpurea and Eleutherococcus senticosus in patients with upper respiratory tract infections. Phytomedicine. 2005 Aug;12(8):539-47. Gabrielian ES, Shukarian AK, Goukasova GI, Chandanian GL, Panossian AG, Wikman G, Wagner H. A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. Phytomedicine. 2002 Oct;9(7):589-97.)

Co-enzyme Q10

Reference 1
Supplements of co-enzyme Q10 (CoQ10) may improve the motility and density of sperm in infertile men, according to a new study using Kaneka's ingredient.
The statistically significant but modest results suggest that CoQ10 may have "potential clinical applications in infertile men", wrote Mohammad Reza Safarinejad from Shahid Beheshti University in Tehran, Iran in the peer-reviewed Journal of Urology.
The researcher called for further prospective studies to evaluate if CoQ10 supplementation may play a role in achieving pregnancy in infertile couples.
CoQ10 has properties similar to vitamins, but since it is naturally synthesized in the body it is not classed as such. With chemical structure 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, it is also known as ubiquinone because of its 'ubiquitous' distribution throughout the human body.
The coenzyme is concentrated in the mitochondria - the 'power plants' of the cell - and plays a vital role in the production of chemical energy by participating in the production of adenosince triphosphate (ATP), the body's co-called 'energy currency'.
A role beyond the mitochondria is also acknowledged, with CoQ10 acting as a potent antioxidant. The coenzyme plays an important role in preserving levels of vitamin E and vitamin C.
There is an ever-growing body of scientific data that shows substantial health benefits of CoQ10 supplementation for people suffering from angina, heart attack and hypertension. Clinical trials have also reported benefits for cardiomyopathy and congestive heart failure.

Study details
Sperm quality has been linked to the level of oxidative stress, and in order to test if CoQ10 levels might beneficially effect sperm quality, Safarinejad recruited 212 infertile men and randomly assigned them to receive a daily CoQ10 supplement (300 mg, Kaneka, Japan) or placebo for 26 weeks. This was followed by 30 weeks with no intervention.
The Tehran-based researchers reported a significant improvement in both sperm density and motility following supplements of the coenzyme. A positive association was also found with regards to sperm count. Further analysis showed an increase in the percent of normal forms of sperm, added Safarinejad.
Finally, an increase in the acrosome reaction of over 100 per cent was observed in the CoQ10 group, compared to a 1 per cent increase in the placebo group. The acrosome reaction aids in egg penetration, and subsequently fertilisation.
"Coenzyme Q10 supplementation resulted in a statistically significant improvement in certain semen parameters," wrote Safarinejad. "However, further studies are needed to draw a final conclusion and evaluate the effect of coenzyme Q10 supplementation on the pregnancy rate." (Source: The Journal of Urology, Volume 182, Issue 1, Pages 237-248 "Efficacy of Coenzyme Q10 on Semen Parameters, Sperm Function and Reproductive Hormones in Infertile Men" Authors: M.R. Safarinejad)

Reference 2
Coenzyme Q10 (CoQ10) is a nutrient used by the body in the production of energy. While its exact role in the formation of sperm is unknown, there is evidence that as little as 10 mg per day (over a two-week period) will increase sperm count and motility. (Tanimura J. Studies on arginine in human semen. Part III. The influences of several drugs on male infertility. *Bull Osaka Med School* 1967;13:90–100.)

L-Carnitine Tartrate

Reference 1
There is a statistically significant, positive correlation between L-carnitine and the number of spermatozoa and the percentage of motile spermatozoa in the human male.' (Matalliotakis I, et al, L-carnitine levels in the seminal plasma of fertile and infertile men: correlation with sperm quality, Department of Obstetrics and Gynecology, University Hospital, Heraklion, Crete, Greece.)

Reference 2
L-carnitine is a substance made in the body and also found in supplements and some foods (such as meat). It appears to be necessary for normal functioning of sperm cells. In preliminary studies, supplementing with 3–4 grams per day for four months helped to normalize sperm motility in men with low sperm quality. (Costa M, Canale D, Filicori M, et al. L-carnitine in idiopathic asthenozoospermia: a multicenter study. *Andrologia* 1994;26:155–9. Vitali G, Parente R, Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. *Drugs Exp Clin Res* 1995;21:157–9.)

Reference 3
Carnitine is concentrated within the epididymis and contributes directly to the energy supply required by sperm for maturation and motility. (Sinclair S. Male infertility: nutritional and environmental considerations. *Altern Med Rev.* 2000;5:28–38.)

Reference 4
Treatment with carnitine or acetylcarnitine (1.0–2.0 g/day) increases the number and motility of sperm, and the number of spontaneous pregnancies. (Agarwal A, Nallella KP, Allamaneni SS, Said TM. Role of antioxidants in treatment of male infertility: an overview of the literature. *Reprod Biomed Online*. 2004;8:616–627.)

Reference 5
Growing, if not entirely consistent evidence, suggests that various forms of the supplement L-carnitine may improve sperm function and thereby provide benefit in male infertility (Loumbakis P, Anezinis P, Evangeliou A, et al. Effect of L-carnitine in patients with asthenospermia [abstract]. *Eur Urol.* 1996;30(suppl 2):255. Muller-Tyl E, Lohninger A, Fischl F, et al. The effect of carnitine on sperm count and sperm motility [translated from German]. *Fertilitat.* 1988;4:1-4. Micic S, Lalic N, Nale DJ, et al. Effects of L-carnitine on sperm motility and number in infertile men [abstract]. *Fertil Steril.* 1998;70(3 suppl 1):S12. Vicari E. Effectiveness of a short-term anti-oxidative high-dose therapy on IVF program outcome in infertile male patients with previous excessive sperm Radical Oxygen Species production persistent even following antimicrobials administered for epididymitis: preliminary results. In: International Meeting on Infertility and Assisted Reproductive Technology; June 11-14, 1997; Porto Cervo, Italy. Vicari E, Cerri L, Cataldo T, et al. Effectiveness of single and combined antioxidant therapy in patients with astheno-necrozoospermia from non-bacterial epididymitis: effects after acetyl-carnitine or carnitine-acetyl-carnitine. Presented at: 12th National Conference, Italian Andrology Association; June 9-12, 1999; Copanello, Italy. Campaniello E, Petrarolo N, Meriggiola MC, et al. Carnitine administration in asthenospermia. Presented at: 4th International Congress of Andrology; May 14-18, 1989; Florence, Italy. Costa M, Canale D, Filicori M, et al. L-carnitine in idiopathic asthenozoospermia: a multicenter study. *Andrologia.* 1994;26:155-159. Vitali G, Parente R, Melotti C. Carnitine supplementation in human idiopathic asthenospermia: clinical results. *Drugs Exp Clin Res.* 1995;21:157-159. Moncada ML, Vicari E, Cimino C, et al. Effect of acetylcarnitine treatment in oligoasthenospermic patients. *Acta Eur Fertil.* 1992;23:221-224.)

Reference 6
In one double-blind study, 60 men with abnormal sperm function were given either carnitine (as L-carnitine 2 g/day and acetyl-L-carnitine 1 g/day) or placebo for 6 months.[34] The results showed significant improvement in sperm function in the treated group as compared to the placebo group. (Lenzi A, Sgro P, Salacone P, et al. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. *Fertil Steril.* 2004;81:1578-1584.)

Citrus Bioflavonoids

Reference 1
Basic life processes are affected by flavonoids such as immune mechanisms, inflammation, cancer cellular differentiation, atherosclerosis, metabolism, heat shock protein synthesis and possibly aging. There is a body of evidence that the flavonoids possess potentially health promoting effects.*(Pharmaceutical News, p.6-8, Vol. 1, No. 3, 1994)*

Reference 2
Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Over 4000 different flavonoids have been described. It is estimated that humans ingest a few hundred milligrams per day. The intake of flavonols and flavones, which are subclasses of flavonoids, has been inversely associated with subsequent coronary heart disease in most prospective studies. *(P.C. Hollman, et al, Food Chem Toxicol 1999 Sep-Oct;37(9-10):937-42)*

Reference 3
Flavonoids are a group of phenolic compounds found in fruit and vegetables, which are known to have antioxidant properties. *(L. Yochum, et al, Am J Epidemiology 1999 May 15;149(10):943-9)*

Reference 4
A standardized extract composed of a mixture of flavonoids has strong free radical-scavenging activity against reactive oxygen and nitrogen species, and is able to protect endogenous vitamin E and glutathione from oxidative stress. It is also able to modulate the metabolism of nitric oxide, which suggests potential applications in immune and circulatory disorders as well as in neurodegnerative disease. It can bind to proteins, altering their structure and thereby modulating the activity of key enzymes and proteins involved in metabolic pathways. Finally, it has been reported to have cardiovascular benefits, such as vasorelaxant activity, angiotensin-converting enzyme inhibiting activity, and the ability to enhance the microcirculation by increasing capillary permeability. *(L. Packer, et al, Free Radic Biol Med 1999 Sep;27(5-6):704-24)*

Vitamin A (2500 IU)

Reference 1
Urinary excretion of norepinephrine and epinephrine significantly increased in vitamin A depleted rats. It also caused a significant increase in norepinephrine turnover in heart and spleen. (K. Nakano, et al, J Nutr Sci Vitaminol (Tokyo) 1984 Apr30(2):163-70)

Reference 2
Study results suggest that vitamin A depletion causes derangement of the neurosympathetic system in rats, making them unable to respond appropriately to stress. Alternately, vitamin A depletion may itself be a stress so that the animals are already in a state of maximal response. (R. Mizutani, et al, J Nutr 1982 Dec;112(12):2205-11)

Reference 3
Vitamin A, its analogues and its metabolites function in vision, cell differentiation, embryogenesis, the immune response, reproduction and growth. (JS Garrow, WPT James, A Ralph, Human Nutrition and Dietetics, 10th Edition, Chapter 13 p230-231, Churchill Livingstone.)

Reference 4
In vitamin A deficiency, both specific and non-specific protective mechanisms are impaired, namely: the humoral response to bacterial, parasitic and viral infections; cell-mediated immunity; mucosal immunity, natural killer cell activity and phagocytosis. The immune responses to certain antigens in vitamin A depleted children are enhanced by vitamin a supplementation. (A C Ross, U G Hammerling. Retinoids and the immune system (1994). In Sporn M B, Roberts A B, Goodman D S (eds) The retinoids: biology, chemistry and medicine, 2nd edition Raven Press, New York, pp 521-543)

Reference 5
Vitamin A was termed the ‘anti-infective’ vitamin based on the increased number of infections noted in

vitamin A deficient animals and humans. (A Sommer, K P West Jr, Vitamin A deficiency-health, survival and vision. Oxford University Press, Oxford 1996)

Reference 6
Another major function of Vitamin A is in cell differentiation. The recent discovery of two sets of retinoic acid receptors, the RAR and RXR, has clarified in large part the molecular action of vitamin A in this process. (P Chambon FASEB Journal (1996) 10:940-954 and D J Mangelsdorf et al. The retinoid receptors. In Sporn M B, Roberts A B, Goodman D S (eds) The retinoids: biology, chemistry and medicine, 2nd edition Raven Press, New York, pp 319-349.

Vitamin D3 (as D3 600 IU)

Reference 1
We performed experiments to determine whether treatment with vitamin D or 1,25-dihydroxycholecalciferol could reverse male infertility caused by vitamin D deficiency. Additionally, an attempt was made to distinguish between a direct and an indirect effect of 1,25-dihydroxycholecalciferol on reproductive tissue. Vitamin D-deficient male rats with impaired fertility were treated with vitamin D and 1,25-dihydroxycholecalciferol for 3 wk, then mated. Secondly, vitamin D-deficient male rats were made normocalcemic by increasing dietary calcium, and their fertility was compared with that of vitamin D-deficient, hypocalcemic rats. The fertility of male rats was restored by treatment with either vitamin D or 1,25-dihydroxycholecalciferol. However, fertility was also restored in vitamin D-deficient animals by feeding them a diet supplemented with high levels of calcium. These results indicate that the influence of vitamin D and its active metabolite, 1,25-dihydroxycholecalciferol, on male fertility is indirect. Vitamin D and 1,25-dihydroxycholecalciferol seemed to influence male fertility by acting on classic target tissues and regulating levels of calcium in reproductive tissues. (Uhland, A M : Kwiecinski, G G : DeLuca, H F. Normalization of serum calcium restores fertility in vitamin D-deficient male rats. J-Nutr. 1992 Jun; 122(6): 1338-44)

Reference 2
Researchers at Fertility First, in Sydney, Australia, were studying sperm to see which ones and how many had damaged DNA, in the hope that it may shed light on why the 800 men enrolled, could not impregnate their partners.

Reference 3
All the men had undergone blood testing, and it was noticed purely by chance that a third of the men had vitamin D and folate deficiencies. A substance known as homocysteine, an amino acid which occurs when the body is toxic through lack of folate and vitamins, was present in the blood. The medical profession already know how important vitamin D and folic acid is to women, and that a lack of these can cause infertility, which is one of the reasons why women are encouraged to take folic acid supplements for three months prior to trying for a baby, but until now they didn't know that the same was true for men. (Vitamin D Deficiency And Infertility Low Vitamin and Folate Levels Have Been Observed In Infertile Men. Joanna Karpasea-Jones Nov 5, 2008)

Reference 4
Objectives
Several animal studies have suggested that vitamin D and the vitamin D receptor (VDR) play a role in male fertility. The mechanism of action in the testis and the interaction with sperm is unknown. The presence of the VDR on sperm has never been demonstrated. The objective of this pilot study was to investigate the presence of the VDR on human sperm.
Methods
A prospective study of sperm collected from 10 fertile men, mean age 33.7 ± 2.2 years, was undertaken. Qualitative analysis for VDR was performed by immunohistochemistry using a monoclonal antibody to human VDR. For comparison of the spatial relationship of the receptor, qualitative analysis of the androgen receptor on sperm was performed. Immunoprecipitation and immunoblotting of total sperm protein lysate using VDR antibodies further characterized the VDR.
Results

Immunohistochemistry demonstrated that the VDR was located predominantly on the head/nucleus of the sperm and mid-piece. Immunoblotting confirmed the presence of the VDR with a molecular weight of 50 kDa in all subjects.
Conclusions
Our results have demonstrated the presence of the VDR on human sperm for what we believe to be the first time. (Vitamin D receptor found in human sperm, Volume 68, Issue 6, December 2006, Pages 1345-1349)

Reference 5

Spermatozoa are vulnerable to oxidative stress because of their inherent reduced antioxidant defence and DNA repair mechanisms. Polyunsaturated fatty acids in sperm plasma membrane break down to cytotoxic lipid aldehyde, 4-Hydroxynonenal, whereas 3-Nitrotyrosine is generated by peroxynitrite induced tyrosine nitration. Both oxidative stress markers contribute to altered sperm function and infertility. Vitamin D, a membrane antioxidant, has a potential scavenger capacity. We compared oxidative stress markers and vitamin D in male subjects with normal and altered sperm parameters and explored association of these markers: 4-Hydroxynonenal and 3-Nitrotyrosine with Vitamin D. Higher 4-Hydroxynonenal levels in altered sperm parameter group and a negative correlation with sperm count, motility and morphology ($p < 0.001$) was observed. Vitamin D serum concentration in altered sperm parameters was less ($p = 0.016$) showing a significant positive correlation with sperm count and morphology. 4-Hydroxynonenal was significantly higher in altered sperm parameters showing negative correlation with vitamin D. Highest serum concentrations of 4-Hydroxynonenal were observed in vitamin D-deficient subjects. Significantly higher concentration of 4-Hydroxynonenal was estimated in altered sperm parameters of vitamin D sufficient group ($p < 0.001$). This suggests 4-Hydroxynonenal as an oxidative stress marker leading to altered sperm function and infertility with some association with vitamin D; needs to be explored.
Shahid, M. et al. (2021), *Male Infertility: Role of vitamin D and oxidative stress markers,* Andrologia, 53:8, pp: e14147

Vitamin E

Reference 1
Vitamin E has shown to increase the motility of sperm and may have a substantial benefit on improved sperm motility and potential increase in fertilization in asthenospermic subjects (men with reduced spermatozoon motility in the semen). In a study of patients with asthenospermia treated with oral vitamin E, eleven out of the 52 treated patients (21%) impregnated their spouses; nine of the spouses successfully ended with normal term deliveries, whereas the other two aborted in the first trimester. No pregnancies were reported in the spouses of the placebo-treated patients. (S. A. Suleiman et al, Lipid Peroxidation and Human Sperm Motility: Protective Role of Vitamin E, Journal of Andrology, 1996; vol. 17, No. 5; 530-537)

Reference 2
In a double-blind, placebo-controlled study of 110 men whose sperm showed subnormal activity, daily treatment with 100 IU of vitamin E resulted in improved sperm activity and increased rate of pregnancy in their partners. (Suleiman SA, Elamin Ali M, Zaki ZMS, et al. Lipid peroxidation and human sperm motility: protective role of vitamin E. *J Androl.* 1996;17:530-537.)

Reference 3
Vitamin E deficiency in animals leads to infertility. (Thiessen DD, Ondrusek G, Coleman RV. Vitamin E and sex behavior in mice. *Nutr Metab* 1975;18:116–9.)

Reference 4
In a preliminary human trial, 100–200 IU of vitamin E given daily to both partners of infertile couples led to a significant increase in fertility. (Bayer R. Treatment of infertility with vitamin E. *Int J Fertil* 1960;5:70–8.)

Reference 5
In a preliminary study, men with low fertilization rates in previous attempts at *in vitro* fertilization were given 200 IU of vitamin E per day for three months.[43] After one month of supplementation, fertilization rates increased significantly, and the amount of oxidative stress on sperm cells decreased. (Geva E, Bartoov B, Zabludovsky N, et al. The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. *Fertil Steril* 1996;66:430–4.)

Reference 6
A double-blind, randomized, cross-over controlled study by Kessopoulou *et al.* examined 30 men with high ROS production. 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. (Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russel JM, Cooke ID and Barratt CLR (1995) A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. *Fertil Steril*. 64(4): 825-831.)

Reference 7
A double-blind, randomized study by Suleiman *et al*. in 1996 looked at a group of 87 men with decreased sperm motility (asthenozoospermia). 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. 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 ($p<0.01$). Furthermore, 21% of treated patients impregnated their partners while no pregnancies were reported in the placebo group. (Suleiman SA, Ali ME, Zaki ZMS, El-Malik EMA and Nasr MA (1996) Lipid peroxidation and human sperm motility: protective role of vitamin E. *J Androl*. 17: 530-537.)

Reference 8
There is some evidence that suggests a relationship between daily antioxidant intake and better semen quality among healthy men. Semen analysis was performed on 97 healthy male volunteers and results were correlated with the results of a dietary assessment questionnaire. Higher levels of vitamin E intake were associated with higher levels of progressive sperm motility. (Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G and Wyrobek AJ (2005)
Antioxidant intake is associated with semen quality in healthy men. *Hum Reprod*. 20(4): 1006-1012.)

Reference 9
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. 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). (Geva E, Bartoov B, Zabludovsky N, Lessing JB, Lerner-Geva Liat and Amit A
(1996) The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. *Fertil Steril*. 66(3): 430-434.)

Reference 10
Since studies have found that only 8% of US men consume sufficient amounts of vitamin E, it is reasonable to encourage infertile males to maintain adequate dietary intakes of vitamin E through diet or supplements. (Maras JE, Bermudez OI, Qiao N, Bakun PJ, Boody-Alter EL and Tucker KL (2004) Intake of alpha-tocopherol is limited among US adults. *J Am Diet Assoc*. 104(4): 567-75.)

Vitamin C

Reference 1
Vitamin C - a high concentration of the antioxidant vitamin C in semen plays a key role in maintaining the genetic integrity of sperm cells, by preventing oxidative damage to sperm DNA. This might affect sperm quality and increase risk of genetic defects, particularly in populations with low ascorbic acid, such as smokers. In a study of 75 heavy smokers given 200 or 1000 mg vitamin C or placebo daily for one month, treated groups showed improvement in sperm quality. (C.D. Hunt, et al, Am J Clin Nutr 1992;56/1:148-157)

Reference 2
Preliminary studies suggest that vitamin C may improve sperm count and function. (Dawson EB, Harris WA, Rankin WE, et al. Effect of ascorbic acid on male fertility. *Ann N Y Acad Sci.* 1987;498:312-323)

Reference 3
Vitamin C protects sperm from oxidative damage. (Fraga CG, Motchnik PA, Shigenaga MK, et al. Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. *Proc Natl Acad Sci* 1991;88:11003–6.)

Reference 4
Supplementing vitamin C improves the quality of sperm in smokers. (Dawson EB, Harris WA, Teter MC, Powell LC. Effect of ascorbic acid supplementation on the sperm quality of smokers. *Fertil Steril* 1992;58:1034–9.)

Reference 5
When sperm stick together (a condition called agglutination), fertility is reduced. Vitamin C reduces sperm agglutination, and supplementation with 200–1,000 mg per day increased the fertility of men with this condition in a controlled study. (Dawson EB, Harris WA, McGanity WJ. Effect of ascorbic acid on sperm fertility. *Fed Proc* 1983;42:531 [abstr 31403]. Dawson EB, Harris WA, Powell LC. Relationship between ascorbic acid and male fertility. In: Aspects of Some Vitamins, Minerals and Enzymes in Health and Disease, ed. GH Bourne. *World Rev Nutr Diet* 1990;62:1–26 [review]. Dawson EB, Harris WA, Rankin WE, et al. Effect of ascorbic acid on male fertility. *Ann N Y Acad Sci* 1987;498:312–23.)

Thiamin (Vitamin B1)

Reference 1
A mouse model of thiamin-responsive megaloblastic anemia (diabetes mellitus, deafness, megaloblastic anemia) lacking functional Slc19a2 has been generated and unexpectedly found to have a male-specific sterility phenotype. We describe here the characterization of the testis-specific effects of absence of the high-affinity thiamin transporter, Tht1. Null males were found to have hypoplastic testes secondary to germ cell depletion. Morphologic and expression analysis revealed that under conditions of standard thiamin intake, tissues affected in the syndrome (pancreatic beta-cell, hematopoietic cells, auditory nerve) maintained normal function but pachytene stage spermatocytes underwent apoptosis. Under conditions of thiamin challenge, the apoptotic cell loss extended to earlier stages of germ cells but spared Sertoli cells and Leydig cells. Injection of high-dose thiamin was effective in reversing the spermatogenic failure, suggesting that the absence of the thiamin carrier could be overcome by diffusion-mediated transport at supranormal thiamin concentrations. These observations demonstrated that male germ cells, particularly those with high thiamin transporter expression beyond the blood-testis barrier, were more susceptible to apoptosis triggered by intracellular thiamin deficiency than any other tissue type. The findings described here highlight an unexpected and critical role for thiamin transport and metabolism in spermatogenesis. (Male infertility due to germ cell apoptosis in mice lacking the thiamin carrier, Tht1. A new insight into the critical role of thiamin in spermatogenesis)

Reference 2
"Those on high carbohydrate intakes (high in sugar and starch) require higher intakes of thiamin, as do those with a high intake of alcohol, smokers and those subject to excessive stress". (S Davies and

A Stewart (1987); Nutritional Medicine: A Drug-Free Guide to Better Family Health; Pan Books; London).

Reference 3
In a study of rats fed diets with differing amounts of protein, and sucrose content inversely related to protein content, protein malnutrition did not alter tissue thiamin concentrations, but decreased transketolase activity in the brain, indicating functional thiamin deficiency. (S.M. Ahmed, et al, J Am Coll Nutr 1988 Jun;7(3):215-21)

Reference 4
Thiamin is a co-factor for enzymes key in bridging aerobic and anaerobic metabolism. One such enzyme, transketolase, catalyzes two of three reactions for entry into a major source of chemical reducing power. Thus, thiamin deprivation is considered a classic model of systemic oxidative stress and is linked with degenerative diseases. In rats, thiamin deficiency produces neurodegeneration with Alzheimer's disease characteristics. (P.H. Frederikse, et al, Biochem Biophys Res Commun 1999 May 19;258(3):703-7)

Reference 5
A study in rats fed ethanol, together with thiamin at a dose equivalent to 15.47mg thiamin daily in humans, for 20 weeks concluded that thiamin megavitamin therapy supports a neuron's carbohydrate metabolism and therefore could be able to prevent or reduce alcohol-induced damages to certain cells in the central nervous system. (S. Wenisch, et al, Z Ernahrungswiss 1996 Sep;35(3):266-72)

Reference 6
Scientific literature confirms that thiamin deficiency can be both predisposing to, and be a consequence of, increased alcohol consumption. In one study, the activity of a marker of a thiamin dependent enzyme decreased 61-79% in the blood, liver and brain of rats fed 15% ethanol as their only source of drinking fluid for 6 months. Another study showed that thiamin deficiency leads to a prolonged increase of the preferential intake of ethanol solutions in rats. (S.M. Zimatkin, et al, Alcohol Alcohol 1996 Jul;31(4):421-7)

Reference 7
A survey of first-time blood donors in Australia in 1995 revealed a significant prevalence of low red blood cell thiamin concentrations (13%). (C.K. Booth, et al, Am J Clin Nutr 1998 Nov;68(5):1075-80)

Riboflavin (Vitamin B2)

Reference 1
In a study of 6 sedentary to moderately active men with previous biochemical signs of riboflavin deficiency (improved at the start of the study), additional exercise for 18 days between two periods of habitual activity resulted in a significant deterioration in riboflavin status, suggesting an increased demand for the vitamin for selective biochemical functions during exercise. (M.J. Soares, e tal, Br J Nutr 1993 Mar69(2):541-51)

Reference 2
In a study on rats after exercise for 6 or 8 weeks, total riboflavin retention increased in gastrocnemius and soleus muscles. (K.E. Hunter, et al, J Nutr 1987 Feb;117(2):298-304)

Reference 3
In a study of 132 healthy vegetarians age range 25-57 years who had been practicing vegetarianism for 1-22 years, compared to 68 healthy non-vegetarian controls, 24.2% of vegetarians were deficient in vitamin B2, as well as 22.2% of controls. (N. Vudhivai, et al, J Med Assoc Thai 1991 Oct;74(10):465-70)

Reference 4
In a study of young rats fed a diet deficient in folic acid and vitamin B2, haemoglobin concentration as well as haemocrit value and red blood cell count were highest in rats which received replenishing supplementation with the full dosage of both vitamins. (D.Y. Dako, et al, Int J Vitam Nutr Res 1980;50(3):254-60)

Niacin (Vitamin B3)

Reference 1
A study of patients with high-density lipoprotein less than 35 mg/dl and without hypertriglyceridemia showed that niacin supplementation could increase high-density lipoprotein ('good' cholesterol) levels by 16%. (A.C. Sposito, et al, Am J Cardiol 1999 Jan 1;83(1):98-100, A8)

Reference 2
Niacin is effective therapy for lipoprotein regulation and cardiovascular risk reduction. (D.M. Capuzzi, et al, Am J Cardiol 1998 Dec 17;82(12A):74U-81U;discussion 85U-86U)

Reference 3
Niacin is a useful lipid-modifying nutrient because it decreases low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and lipoprotein(a), while at the same time increasing high-density lipoprotein (HDL) cholesterol. (A.C. Goldberg, Am J Cardiol 1998 Dec 17;82(12A):35U-38U;discussion 39U-41U)

Reference 4
Niacin manifests beneficial effects in cardiovascular disease with respect to dyslipidemic states. It lowers low-density lipoprotien (LDL) cholesterol, triglycerides, lipoprotein(a) and increases high-density lipoprotein (HDL). (J.M. Morgan, et al, Am J Cardiol 1998 Dec 17;82(12A):29U-34U;discussion 39U-41U)

Reference 5
Study results demonstrate that niacin supplementation decreases plasma fibrinogen and low-density lipoprotein cholesterol in subjects with peripheral vascular disease. (C.S. Philipp, et al, Am J Cardiol 1998 Sep 1;82(5):697-9,A9)

Reference 6
Niacin has been used for many years to treat hyperlipidemia. It has been shown to reduce coronary death and non-fatal myocardial infarction and, in separate analysis of long-term (15 year) follow-up, all cause mortality. It reduces total cholesterol, low-density lipoprotein cholesterol and triglycerides and increases high density lipoprotein cholesterol. (J.R. Crouse 3rd, Coron Artery Dis 1996 Apr;7(4):321-6)

Vitamin B6

Reference 1
Needed for the production of red blood cells and antibodies, coenzyme in protein, fat and carbohydrate metabolism. Vitamin B6 also plays a vital role in both humeral and cell mediated immunity. *(J. Nat. Cancer Inst. 1987:5, 951)*

Reference 2
Vitamin B6 may play a role in attenuating the rise in plasma growth hormone during exercise. (M.M. Manore, et al, Int J Sport Nutr 1994 Jun;4(2):89-103) In a study of 13 endurance athletes, there was a mean loss of about 1 mg vitamin B6 as a result of a marathon race. (L. Rokitzki, et al, Int J Sport Nutr 1994 Jun; 4(2):154-65)

Reference 3
Studies of norepinephrine content in the brains of rats exposed to stress suggest an antistress effect of vitamin B6. (J.G. Henrotte, et al, Ann Nutr Metab 1992; 36(5-6):313-7)

Reference 4
In a study on monkeys, pretreatment with vitamin B6 resulted in a 20% enhancement of the rate of serotonin formation in the brain, indicating the regulatory role of vitamin B6 on the synthesis of neurotransmitter in vivo, and that vitamin B6 may be important in diseases with deficiencies in

neurotransmitter function. (P. Hartvig, et al, J Neural Transm Gen Sect 1995;102(2):91-7)

Reference 5
In a study on 1,149 patients with various peripheral nervous system diseases, after three weeks of treatment with a vitamin B preparation, a positive effect on pain in particular was observed in 69% of the cases. Similar observations were also made for parasthesias and muscular weakness in the legs. (M. Eckert, et al, Fortschr Med 1992 Oct 20;110(29):544-8)

Folacin (Folic Acid)

Reference 1
Increasing folic acid intake for fathering men, may be advantageous in reducing the risk of chromosomal anomalies in their offspring. A study in the association of folate, zinc and antioxidant intake with sperm aneuploidy (abnormal number of chromosomes) in healthy non-smoking men, found that men with high folate intake had lower overall frequencies of several types of aneuploid sperm. (S.S. Young et al, The association of folate, zinc and antioxidant intake with sperm aneuploidy in healthy non-smoking men, Human Reproduction 2008 23(5):1014-1022)

Vitamin B12

Reference 1
Vitamin B12 is needed to maintain fertility. Vitamin B12 injections have increased sperm counts for men with low numbers of sperm. (Sandler B, Faragher B. Treatment of oligospermia with vitamin B12. *Infertility* 1984;7:133–8.)

Reference 2
A group of infertile men were given oral vitamin B12 supplements (1,500 mcg per day of methylcobalamin) for 2 to 13 months. Approximately 60% of those taking the supplement experienced improved sperm counts. (Isoyama R, Baba Y, Harada H, et al. Clinical experience of methyl-cobalamin (CH3-B12)/clomiphene citrate combined treatment in male infertility. *Hinyokika Kiyo* 1986;32:1177–83 [in Japanese].)

Reference 3
Abnormalities of motor conduction are part of the changes in vitamin B12 deficiency in addition to the involvement of the sensory nerves. (M.A. Carvalho, et al, Electromyogr Clin Neurophysiol 1996 Jul-Aug;36:163-91)

Reference 4
Vitamin B12 deficiency causes a deficient remethylation of homocysteine and therefore probably contributes to increased homocysteine levels. (B. Regland, et al, Scand J Rheumatol 1997;26(4):301-7)

Reference 5
A study of 6 women and 14 men treated for 14 days with 3 mg vitamin B12 or methylcobalamin (a coenzyme derived from vitamin B12), found that changes in “sleep quality”, “concentration” and “feeling refreshed” showed significant correlation with vitamin B12 plasma levels. It was concluded that vitamin B12 exerts a direct influence on melatonin. Methylcobalamin also had an alerting affect, with a distribution of the sleep-wake cycle toward sleep reduction. (G. Mayer, et al, Neuropsychopharmacology 1996 Nov;15(5):456-64)

Reference 6
A study of patients with normal serum vitamin B12 levels given injections of vitamin B12 found that with higher serum vitamin B12 levels, the patterns of a Multiphasic Personality Inventory test (an objective computerized psychological test to indicate feelings of well-being) were at or closer to ‘normal’. With lower serum vitamin B12 levels, test patterns showed much more emotional distress. (H.L. Newbold, Med Hypotheses 1989 Mar;28(3):155-64)

Biotin

Reference 1
Biotin is a water-soluble vitamin that acts as an essential step in intermediary metabolism. In humans, biotin deficiency causes hair loss and a scaly, erythematous dermatitis around body orifices. (D.M. Mock, et al, Semin Dermatol 1991 Dec;10(4):296-302)

Reference 2
Studies in animals show vitamins such as biotin are essential in the metabolism of the keratinizing epidermal cells and therefore form part of the link between nutrition and hoof [nail] quality. (C.K. Mulling, et al, Anat Histol Embryol 1999 May;28(2):103-8)

Reference 3
A study on ponies found that animals supplemented with biotin for five months had a 15% greater growth rate for hoofs and hoof than control animals. (J.D. Reilly, et al, Equine Vet J Suppl 1998 Sep;(26):51-7)

Reference 4
A study of 108 horses with brittle hoof horn or chipped hooves over 1 to 6 years, found that horses supplemented with 5 mg biotin per 100 to 150 kg body weight, per os, daily, improved the condition of their hooves after 8 to 15 months supplementation. The improvement was not seen in controls. (H. Geyer, et al, Schweiz Arch Tierheilkd 1994;136(4):137-49)

Reference 5
Microscopic observations of claw horns of pigs supplemented with biotin showed that there was an increase in the density of horn tubules and that they were more clearly defined, horny squames were more tightly packed, and there were alterations in the structure of the coronary skin. (S.A. Kempson, et al, Vet Rec 1989 Jan 14;124(2):37-40)

Reference 6
Molecular studies show that biotin directly stimulates the differentiation of epidermal cells. Biotin definciency in animals also causes pathological changes of the skin and its appendages including excessive peeling and dryness (exfoliative dermatitis), depigmentation, and hair loss. The hooves of biotoin deficient swine are weak and brittle. Biotin supplementation noticeably improves hoof quality of horses, cattle and swine even when there is no apparent biotin deficiency. (A. Friysche, et al, Schweiz Arch Tierheilkd 1991;133(6):277-83)

Reference 7
Addition of biotin to cells cultured in a biotin deficient medium results in enhanced protein synthesis, DNA synthesis and cell growth. (R.P. Bhullar, et al, J Cell Physiol 1985 Jun;123(3):425-30)

Pantothenic Acid

Reference 1
Pantothenic acid, also called vitamin B5, is a water-soluble vitamin involved in the Kreb's cycle of energy production and is needed to make the neurotransmitter acetylcholine. It is also essential in producing, transporting, and releasing energy from fats. Synthesis of cholesterol (needed to manufacture vitamin D and steroid hormones) depends on pantothenic acid. Pantothenic acid also activates the adrenal glands. (Fidanza A. Therapeutic action of pantothenic acid. *Int J Vitam Nutr Res* 1983;suppl 24:53–67).

Reference 2
In a prospective, double-blind randomized study of 49 patients undergoing surgery for tattoos, of whom 18 were supplemented with 1 g ascorbic acid and 0.2 g pantothenic acid daily for 21 days, results suggested supplementation may benefit wound healing through variations in trace element content of skin and scars. Trace elements are correlated to mechanical properties of scars. (F. Vaxman, et al, Eur Surg Res 1995;27(3):158-66)

Reference 3
A study in animals found that supplementation with pantothenic acid induced an accelerated effect of the normal healing process. The mechanism responsible for this improvement seemed to be an increase in cellular multiplication. (M. Aprahamian, et al, Am J Clin Nutr 1985 Mar;41(3):578-89)

Magnesium

Reference 1
Data from the CARDIA study, involving 2643 black and 2472 white men and women aged 18-30 years found that insulin was positively correlated with serum glucose and negatively correlated with magnesium intake. (T.A. Manolio, et al, J Clin Epidemiol 1991;44(6):571-8)

Reference 2
Rats fed a magnesium deficient diet have a lower endurance capacity than rats fed a control diet. This result is probably due to multiple factors affected by dietary magnesium intake, including changes in insulin levels, calcium concentrations in plasma and gastrocnemius muscle, trace element concentrations in tissue, and alterations in body composition. (P. Lowney, et al, Biol Trace Elem Res 1988 Jun;16(1):1-18)

Reference 3
In young, apparently healthy trained Israeli men, strenuous effort gave rise to persistent magnesium deficiency. (G. Stendig-Lindberg, J Basic Clin Physiol Pharmacol 1992 Apr Jun;3(2):139-51)

Reference 4
The central nervous system concentration of magnesium appears to have a critical level below which neurologic dysfunction occurs. (W.F. Langley, et al, Arch Intern Med 1991 Mar; 151 (3): 593-6)

Iron

Reference 1
Short-term moderate iron deficiency was accompanied by decreased platelet concentrations, increased activity of serum enzymes indicative of cell damage, and increased liver copper concentrations in rats. (G.I. Stangl, et al, Z Ernahrungswiss 1998 Sep;37(3):260-8)

Reference 2
Iron deficiency selectively affects the integrity of the blood-brain barrier for insulin, glucose, and valine transport. (D. Ben-Shachar, et al, J Neurochem 1988 May; 50(5):1434-7)

Reference 3
Iron is an integral part of many proteins and enzymes that maintain good health. In humans, iron is an essential component of proteins involved in oxygen transport. (Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. Washington, DC: National Academy Press, 2001. Dallman PR. Biochemical basis for the manifestations of iron deficiency. Annu Rev Nutr 1986;6:13-40.)

Reference 4
A deficiency of iron limits oxygen delivery to cells, resulting in fatigue, poor work performance, and decreased immunity. (Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr 2001;131:691S-6S. Bhaskaram P. Immunobiology of mild micronutrient deficiencies. Br J Nutr 2001;85:S75-80.)

Zinc

Reference 1
Zinc is necessary in the regulation of male hormones (testosterone) and is an important mineral in prostate gland function and sperm production. Zinc deficiency can lead to a depletion of testosterone and inhibition of spermatozoa production. Zinc is also thought to help extend the functional life span of the ejaculated spermatozoa. In a study of 53 infertile men, zinc was positively correlated with the concentration of moving sperm in the group of middling sperm motility. H. Ota, Jap Journal Fertility & Sterility 1995;40/1:78-82

Reference 2
Zinc and folic acid may help increase sperm count. In a double-blind randomised placebo-controlled trial, of 108 fertile and 103 sub-fertile men, taking zinc and folic acid supplements, the total normal sperm count increased after combined zinc sulphate and folic acid treatment in both the sub-fertile and fertile men. Results were significantly high in the sub-fertile group, demonstrating a 74% increase in total normal sperm count. (Wai Yee Wong et al, Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial, Fertility and Sterility, March 2002, Vol 77, Issue 3, Pages 491-498)

Reference 3
A daily intake of zinc is required to maintain a steady state because the body has no specialized zinc storage system. (Rink L, Gabriel P. Zinc and the immune system. Proc Nutr Soc 2000;59:541-52. [PubMed abstract])

Reference 4
Zinc deficiency is characterized by growth retardation, loss of appetite, and impaired immune function. In more severe cases, zinc deficiency causes hair loss, diarrhea, delayed sexual maturation, impotence, hypogonadism in males, and eye and skin lesions. (Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press, 2001.)

Reference 5
A 26-week, double-blind, placebo-controlled trial compared the effects of treatment with zinc (66 mg of zinc sulfate, supplying 15 mg of zinc), folate (5 mg), and zinc plus folate against placebo.[22] A total of 108 fertile men and 103 men with impaired fertility ("subfertile men") participated in the study. The two supplements combined significantly improved the sperm count and the percentage of healthy sperm in the subfertile men. (Wong WY, Merkus HM, Thomas CM, et al. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. *Fertil Steril.* 2002;77:491-498.)

Reference 6
Zinc deficiency leads to reduced numbers of sperm and impotence in men. (Prasad AS, Cossack ZT. Zinc supplementation and growth in sickle cell disease. *Ann Intern Med* 1984;100:367–71.)

Reference 7
The correlation between blood levels of zinc and sperm quality remains controversial. Infertile men have been reported to have lower levels of zinc in their semen, than do men with normal fertility. (Kvist U, Kjellberg S, Bjorndahl L, et al. Seminal fluid from men with agenesis of the Wolffian ducts: zinc-binding properties and effects on sperm chromatin stability. *Int J Androl* 1990;13:245–52.)

Reference 8
Men with normal sperm density tend to have higher amounts of zinc in their semen, than do men with low sperm counts. (Saaranen M, Suistomaa U, Kantola M, et al. Lead, magnesium, selenium and zinc in human seminal fluid: comparison with semen parameters and fertility. *Hum Reprod* 1987;2:475–9.)

Reference 9
A few studies have shown that oral zinc supplementation improves both sperm count motility, and the physical characteristics of sperm in some groups of infertile men. (Stankovic H, Mikac-Devic D. Zinc and copper in human semen. *Clin Chim Acta* 1976;70:123–6. Hartoma TR, Nahoul K, Netter A. Zinc, plasma androgens and male sterility. *Lancet* 1977;2:1125–6. Stankovic H, Mikac-Devic D. Zinc and

copper in human semen. *Clin Chim Acta* 1976;70:123–6. Kynaston HG, Lewis-Jones DI, Lynch RV, Desmond AD. Changes in seminal quality following oral zinc therapy. *Andrologia* 1988;20:21–2.)

Reference 10
For infertile men with low semen zinc levels, a preliminary trial found that zinc supplements (240 mg per day) increased sperm counts and possibly contributed to successful impregnation by 3 of the 11 men. (Marmar JL, Katz S, Praiss DE, DeBenedictis TJ. Semen zinc levels in infertile and postvasectomy patients and patients with prostatitis. *Fertil Steril* 1975:26:1057–63.)

Reference 11
In a controlled trial, 100 men with low sperm motility received either 57 mg of zinc twice daily or a placebo. After three months, there was significant improvement in sperm quality, sperm count, sperm motility, and fertilizing capacity of the sperm. (Omu AE, Dashti H, Al-Othman S. Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. *Eur J Obstet Gynecol Reprod Biol* 1998;79:179–84.)

Copper

Reference 1
Copper - the activity of copper and zinc containing superoxide dismutase is higher in seminal plasma with spermatozoa of good motility than low motility. In a study of 18 fertile and 172 infertile men, sperm concentration, percentage progressive motility and normal morphology were significantly correlated with copper concentrations in semen. (F. Jockenhovel, et al, Andrologia 1990 Nov-Dec;22(6):503-11)

Reference 2
In a study of 41 trained male athletes and 24 controls, runners had lower serum copper concentrations than controls. (A. Resina, et al, Int J Sports Med 1990 Feb;11 (1):58-60)

Reference 3
Copper-zinc superoxide dismutase is believed to play a major role in the first line of antioxidant defense. (Y.S. Ho, et al, J Biol Chem 1998 Mar 27;273(13):7765-9)

Reference 4
Men and women fed diets close to 1 mg of copper per day, amounts quite frequent in the US, responded similarly to deficient animals with reversible, potentially harmful changes in blood pressure control, cholesterol and glucose metabolism and electrocardiograms. (L.M. Klevay, J Am Coll Nutr 1998 aug;17(4):322-6)

Reference 5
Copper is an essential trace metal which plays a fundamental role in the biochemistry of the human nervous system. Recent studies have also implicated copper in the pathogenesis of neuronal injury in Alzheimer's disease. (D.J. Waggoner, et al, Neurobiol Dis 1999 Aug;6(4):221-30)

Reference 6
Activity of the antioxidant enzyme superoxide dismutase was significantly reduced in the livers of rats consuming a copper deficient diet. (S.I. Dashti, et al, Nutrition 1995 Sep-Oct;11(5 Suppl):564-7)

Manganese

Reference 1
High physical exertion produced an increased excretion of iron, copper, manganese, and zinc from qualified skiers. Results suggest that the diet of athletes be enriched with trace elements, especially with iron in the course of rehabilitation after intensive training and competitions. (V.I.a Rusin, et al,

Vopr Pitan 1980 Jul-Aug; (4):15-9)

Reference 2
Administration of therpeutic doses of iron raises copper and manganese excretion from the body. (V. V. Nasolodin, et al, Ter Arkh 1984; 56(9): 116-9)

Reference 3
The optic nerve needs manganese for the maintenance of its cell structure. (H. Gong, et al, Exp Eye Res 1999 Mar; 68(3):313-20)

Reference 4
Biotic doses of trace elements iron, copper, and manganese exert a favourable effect on working capacity of athletes. (K.L. Vlasenko, et al, Vopr Pitan 1980 Jul-Aug; (4): 9-22)

Selenium

Reference 1
Selenium appears to be essential for normal spermatozoa development. In a study of semen samples from 184 men attending a clinic for fertility investigation, a significant positive correlation was obtained between seminal plasma selenium concentrations and concentrations of spermatozoa in ejaculate. (N.B. Oldereid, et al, Hum Reprod 1998 Aug;13(8):2172-6)

Reference 2
Another study to determine whether the decline in selenium intake and status in men in the West of Scotland might be a contributory factor to male sub-fertility had the same outcome – that selenium supplementation can improve sperm motility and the chance of successful conception. (Scott R et al, The effect of oral selenium supplementation on human sperm motility Br J Urol, 1998 Jul;82(1):76-80)

Reference 3
In a double-blind study of infertile men with reduced sperm motility, supplementation with selenium (100 mcg per day for three months) significantly increased sperm motility, but had no effect on sperm count. Eleven percent of 46 men receiving selenium achieved paternity, compared with none of 18 men receiving a placebo. (Scott R, MacPherson A, Yates RWS, et al. The effect of oral selenium supplementation on human sperm motility. *Br J Urol* 1998;82:76–80.)

Reference 4
Currently, biomedical research is showing interest in the anti-oxidant activity of selenium. This could be due to compelling evidence that reported that oxidative damage to cells and cell membranes is one of the causative agents in the pathogenesis of many disease states including male infertility. Selenium is a trace element which may be found in soil, water and some foods and is considered to be an essential element which plays an active role in several metabolic pathways and is believed to perform several important roles in the human body. These roles include anti-oxidative activities at cellular level and participating in different enzyme systems. Selenium also serves as a vital component in the maintenance of muscle cell and red blood cell integrity, playing a role in the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It has also been reported that selenium is essential in the detoxification of toxic metals in the human system, foetal respiration and energy transfer reactions as well as in the production of sperm cells. It is thought that male infertility can be the result of a selenium deficiency as the absence of selenium in the testicular tissues induces degeneration which results in the active impairment of sperm motility as the first indication of impending infertility. (Selenium: its potential role in male infertility, Pak J Med Sci April - June 2009 Vol. 25 No. 2 332-337)

Reference 5
Selenium is needed for immune, thyroid, and liver function. It also acts as an antioxidant and may prevent the formation of certain cancers, like that of the prostate. (Clark LC et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. Br J Urol 1998;81:730-734.)

Reference 6

Abstract

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 ≤ 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.**

PMID: 21403799 (Int J Gen Med. 2011 Jan 23;4:99-104. Selenium-vitamin E supplementation in infertile men: effects on semen parameters and pregnancy rate. Moslemi MK, Tavanbakhsh S. Highly Specialized Jihad Daneshgahi Infertility Center, Qom Branch (ACECR), Qom, Iran.)

Chromium

Reference 1

Chromium has become a popular supplement for carbohydrate metabolism, and for good reason. Chromium is part of the glucose tolerance factor. It has been shown to reduce blood glucose, hemoglobin A1c levels, and serum cholesterol. (Evans GW et al. Cholesterol and glucose lowering effect of chromium picolinate. FASEB 1989;3:A761.)

Reference 2

Chromium is an essential nutrient involved in the regulation of carbohydrate and lipid metabolism. Normal dietary intake of chromium in humans and farm animals is often suboptimal. In addition to its effects on glucose, insulin, and lipid metabolism, chromium has been reported to increase lean body mass and decrease percentage body fat, which may lead to weight loss in humans. These effects are supported by animal studies. There have been no confirmed negative effects of chromium in nutritional studies. (R.A. Anderson, et al, Nutr Rev 1998 Sep;56(9):266-70)

Reference 3

It is estimated that most individuals are not ingesting sufficient amounts of chromium in their diets. Chromium deficiency is thought to contribute to glucose intolerance and unhealthy blood lipid profiles. The primary function of chromium is to potentiate the effects of insulin, and thereby alter glucose, amino acid and fat metabolism. (P.M. Clarkson, et al, Sports Med 1997 Jun;23(6):341-9)

Reference 4

Most diets contain less than 60% of the minimum suggested intake of 50 mcg chromium. Insufficient

dietary intake of chromium leads to signs and symptoms similar to those observed for diabetes and cardiovascular disease. Trivalent chromium has a very large safety range and there have been no documented signs of chromium toxicity in any of the nutritional studies at levels up to 1 mg per day. (R.A. Anderson, Regul Toxicol Pharmacol 1997 Aug;26(1 Pt 2):S35-41)