

Applied Medical Systems, Inc.
6719 Alvarado Road, Suite 108
San Diego, Ca 92120

September 30, 2003

Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St. SW.
Washington, DC 20204

OCT 10 2003

Re: Notification of claim statements involving "Proceptin"

Attn: Office of Special Nutritionals,

Applied Medical Systems, Inc. has formulated a nutritional product, called ProceptinTM. Its formulation consists of fat-soluble and water-soluble anti-oxidants, amino acids and vitamins. The product is being manufactured by Douglas Laboratories, 600 Boyce Rd., Pittsburgh, PA 15205.

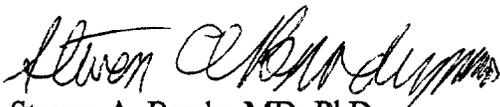
The nutritional supplements in ProceptinTM were chosen on the basis of a careful review of medical and biological research literature regarding supplements which play a supportive role in sperm function and male reproductive function. As a result the following limited structure/function claims are being included in the labeling for ProceptinTM:

- "Designed to provide support for male reproductive function"
- "Support sperm function"
- "Nutritional support for male reproductive function"

I enclose relevant reference material as well as basic marketing material for your records. I certify the information contained in this notice is complete and accurate and that Applied Medical Systems, Inc. has substantiation that the statements are truthful and not misleading.

Thank you for your attention to this matter.

Sincerely,



Steven A. Brody, MD, PhD
President, Applied Medical Systems, Inc.

CC: Natalie Shamitko, Douglas Laboratories

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USAGE:

As a dietary supplement take 1-3 capsules twice daily with meals, or as directed by your qualified health consultant.

Proceptin™
A targeted nutritional formula including fat and water-soluble anti-oxidants and metabolic co-factors

Designed to provide nutritional support for male reproductive function.

Contains no dairy, gluten, yeast, artificial flavorings or coloring.

- GUARANTEED POTENCY
- NO HERBS
- PREMIUM QUALITY
- NO PRESERVATIVES

* These statements have not been evaluated by the Food and Drug Administration

* This product is not intended to diagnose, treat, cure or prevent any disease.

www.Proceptin.com

120 CAPSULES

PROCEPTIN™

SUPPORT SPERM FUNCTION.

High Potency Formula

Anti-oxidants, Vitamins, Co-Factors
Nutritional support for male reproductive function.

Dietary Supplement

Supplement Facts

Serving Size: 3 Capsules
Serving per Container: 40 at 3 per day or 60 at 12 per day

Amount Per Serving	% Daily Value
1. Carnitine	2,500 mg
L-Tyrosine	70 mg
Selenium (Kitchel)	200 mcg
Vitamin B-6	2 mg
Folic Acid	800 mcg
Vitamin B-12 (Methylcobalamin)	1,500 mcg
Vitamin C (Ascorbic Acid)	250 mg
Vitamin E (d-Alpha Tocopherol Succinate)	400 IU
Zinc (Bisulfate)	40 mg
Coenzyme Q-10	10 mg
Ferulic Acid	10 mg
Vitamin A Acetate	250 IU

* Daily Values not established

Other ingredients: A proprietary blend of Acetyl-L-Carnitine, Citric Acid, and Fructose

Distributed Exclusively by:

Applied Medical Systems Inc.
La Jolla CA 92037
1-858-635-1ART

www.Proceptin.com

PROCEPTIN™
SUPPORT SPERM FUNCTION*

Why Proceptin? | FAQ | Male Fertility

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Male Infertility



Proceptin™

A balanced preparation of fat and water-soluble anti-oxidants and metabolic co-factors, each clinically shown to support sperm function. Contains no herbs. Designed to provide nutritional support for male reproductive function.*

- Provides nutritional support for male reproductive function.
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MALE FERTILITY

Infertility is defined as the inability to conceive after at least one year of unprotected intercourse. In general, approximately one out of six couples at any given time has difficulty with conception.

Assisted fertilization is used for cases of severe male factor infertility associated with very low sperm counts, or sperm counts with very low proportions of moving sperm cells. Sperm cells may be placed directly into the egg itself by a process known as intracytoplasmic sperm injection (ICSI). Alternatively, sperm cells may be placed just inside the protective shell surrounding the egg to facilitate fertilization known as sub-zonal insertion (SUZI).

Male infertility is often referred to as male factor infertility; it may be seen in as many as 40 percent of couples trying to conceive. Male factor issues may contribute to a fertility problem even when a clear-cut male factor is not recognizable.

PROCEPTIN™ and MALE FERTILITY

Proceptin™ is a proprietary formulation of fat-soluble and water-soluble antioxidants, amino acid precursors and co-factors related to intermediary metabolism. Proceptin™ has the ability to provide many of the nutrients required to support successful male reproductive function.

Spermatozoa (sperm) comprise a unique group of cells in a man's body. Sperm cells are specialized in their ability to transform nutrients into the energy required for forward movement of the cell. Imagine that the sperm cell is an Apollo space capsule loaded with 18,000 genes. The capsule's job is to carry the man's genes to the woman's egg. In relative terms the distance up the female genital tract is comparable to the sort of journey an Apollo capsule might make to Mars. At the base of the 'capsule' is a propulsion system. Spermatozoa are cells that convert nutrient energy for forward movement. Instead of a blast of burning rocket fuel, the sperm cell is propelled forward by its whip-like tail. Cells that consume large amounts of energy often generate a large quantity of free radicals. Here these free radicals represent a form of oxidative stress on the tissues and organs responsible for reproductive function in the male. Thus, it is useful to use dietary supplements with the appropriate anti-oxidants and metabolic co-factors so that oxidative stress is reduced.

Proceptin™ was formulated as a result of over 60 research studies addressing the role of metabolic intermediaries, anti-oxidants and amino acid precursors in male reproduction.

WHO SHOULD TAKE PROCEPTIN?

Proceptin™ provides nutritional support for the male reproductive function. It is recommended when a couple is trying to have a baby.

In the past it was considered necessary to address the reproductive function of a man only if his sperm count was found to be low. However, subtle abnormalities of sperm function may be seen even with normal sperm counts. Treatment for the male has included lifestyle changes, such as giving up smoking, surgical interventions, such as varicocele repair, and even assisted reproductive technologies involving the injection of sperm cells directly into the wife's egg (ICSI). The use of nutritional therapies may prove useful in improving sperm counts, sperm motility (power to move) and the production of normal sperm.

The use of nutritional supplements is a reasonable approach for men with male factor infertility. Nutritional supplements in men could also be used in cases of female subfertility in which minor decreases in the reproductive function of the wife could potentially be overcome by improving the function of the husband's sperm. For example, in the case of a woman with mild fertility

impairment (due to endometriosis, immune or cervical factors), significant improvements in sperm function might be a critical factor resulting in a successful conception. Nutritional supplements have the potential for helping to avoid more complicated therapies. In most couples experiencing difficulty with conception the problem is subfertility, rather than true infertility. "Subfertility" may be expressed as an inefficiency in the reproductive process rather than "infertility" – the absolute failure to achieve pregnancy over the long haul.

What about Unexplained Infertility?

It should be recognized that a significant number of unexplained infertilities are due to sperm dysfunction. With this type of infertility the failure of the sperm to do its job – traversing the female genital tract and satisfactorily fertilizing the awaiting egg – is unrecognized.

Male infertility is often present in cases where the problem is attributed to the female partner. Therefore, all efforts should be made to achieve optimal sperm function in ALL men desirous of fertility.

In summary, it is recommended that Proceptin™ be taken by all men who, in concert with their partners, are trying to achieve a pregnancy and have a healthy baby.

IS PROCEPTIN™ AN HERBAL PRODUCT?

No. It is our belief that some herbal products should be considered in the same way as pharmaceutical drugs with respect to their effect on the human body.

First, responses to a drug may vary from one person to another in an unpredictable way. Second, there may be adverse interactions with respect to other physiologic processes that happen in the body. For instance, adverse drug interactions could occur in men taking other fertility medications. Third, it should be recognized that herbal products, especially herbal blends, might have a cumulative burden on the liver and other internal organs in the body. This could result in significant metabolic changes over time, particularly if treatment is for six months or more. Ideally, herbal blends should be taken only under the direct supervision of a physician and should never be taken for more than four months at any given time.

WHAT IS THE DOSE OF PROCEPTIN?

It is recommended that Proceptin™ be taken twice daily with food. The standard dose is two capsules twice daily. In men with significant male factor infertility it may be advisable to take three capsules twice daily with food. For men with normal sperm counts and no apparent infertility, a low dose of Proceptin™ – one capsule twice daily – is reasonable. Men taking Proceptin™ are advised not to take any other significant doses of antioxidants with the exception of ascorbic acid (vitamin C), which may be taken in conjunction with Proceptin™ at doses of up to 500-1000 mg per day.

How Long Should a Man Take Proceptin?

Old sperm cells die off and new cells begin to mature at the rate of about one percent each day. Thus, the entire sperm cycle takes approximately 100 days. It is important, therefore, to keep taking Proceptin™ long enough for all new sperm to have been exposed to the benefits of Proceptin™. In addition, it should be remembered that in the biological system of the body it may take several weeks to see an effect from any given nutritional change. Thus, please be patient and recognize that 100 days plus about six weeks – a total of about five months – may be needed to see the beneficial effects of a nutritional intervention.

WHAT CAN A MAN DO TO ENHANCE HIS FERTILITY?

A man wanting fertility should take into account nutritional, environmental and metabolic factors in order to enhance his own fertility. It is recommended that all such men take Proceptin™ on a twice-daily basis. Take at least two capsules daily with food to support all reproductive function, regardless of whether there are any demonstrable abnormalities of sperm function, sperm chromatin or sperm antibodies.

Anti-oxidants may play an important role in helping to absorb and neutralize free radicals through a combination of fat-soluble and water-soluble antioxidants. The proper balance of antioxidants is required to transport the free radicals across the fatty membranes of the cell then circulate them to the liver.

In addition to Proceptin™, a man seeking fertility should eat a low glycemic load diet to reduce circulating levels of insulin. It is also recommended that long-chain essential fatty acids (such as omega-3⁷⁵) be consumed as an additional nutritional supplement. These long-chain fatty acids play a critical role in the energy metabolism of the sperm cell. Remember that a key function of the sperm cell is to convert nutrients into energy for the long swim up the female genital tract. Long-chain essential fatty acids play an important role in the process of oxidation in the cell. Components within Proceptin™ aid the process by facilitating the transport of these fatty acids through the cell membrane.

UNDERSTANDING SPERM

Spermatozoa are unique cells in the human body. A good metaphor to describe the role and function of the sperm cell is to think of it as having the three components of a space craft – capsule, fuel tank and propulsion unit.

The first component on the top of the sperm cell might be an Apollo space capsule. The main function of this capsule is to house the 18,000 genes that each sperm cell has. These genes represent the male's contribution to the DNA make-up of the hoped-for baby. The capsule also has a unique surface feature in its membrane which allows it to burrow through the shell of the woman's egg. Using the enzymes that are built into its surface the sperm cell digests its way through the outer eggshell, called the zona pellucida. The sperm cell is then able to enter the main part of the egg, the ooplasm. As a result successful fertilization may occur.

The second component of the sperm cell is the energy source. Think of this as the rocket's fuel tank. Its sole purpose is to convert nutrients into energy. It is the driving force of the cell.

The third and final component of the sperm cell is the propulsion system. It is the whip-like structure of the sperm tail. It serves the important function of propelling the sperm cell forward with a snake-like motion. It is critical that the sperm move forward and not laterally or in circles. The failure of sperm to move forward is described as an abnormality of sperm motility.

Obviously, men and women are quite different. This is particularly so in their reproductive cells (eggs and sperm). Women are born with a fixed number of eggs. The number of eggs declines month by month, year by year. In a man the opposite occurs. An adult man has billions of sperm cells and every day approximately one percent of these sperm cells die off and are replenished with new cells. The sperm cycle is approximately 100 days. The final 75 days represent a period of maturation for the sperm cell. This final step of sperm maturation, called "spermiogenesis", puts the fuel into the tank and completes the development of the sperm cell (spermatozoon).

Sperm is susceptible to oxidative stress, environmental toxins and metabolic injuries. Thus, it is important to recognize the importance of using a product that provides nutritional support for sperm function. Proceptin™ is a proprietary product that contains nutritional precursors for

cellular metabolism, as well as fat-soluble and water-soluble anti-oxidants.

Proceptin™ is a product that is not intended to treat, cure, prevent or mitigate disease. How this proprietary formulation is based on a large volume of medical research. This research is readily accessible through the National Library of Medicine's website www.PubMed.com.

Try this

Proceptin™ is a product that is not intended to treat, cure, prevent or mitigate disease. How this proprietary formulation is based on a large volume of medical research. A list of research references is available here on the Proceptin™ website.

Altern Med Rev 2000 Feb;5(1):28-38

Related Articles, Links

[Go to Publisher Site](#)**Male infertility: nutritional and environmental considerations.****Sinclair S.**

Green Valley Health, Hagerstown, MD 21742, USA.

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.

J Postgrad Med 2002 Jul-Sep;48(3):186-90

Related Articles, Links

Lipid peroxidation and antioxidant enzymes in male infertility.**Dandekar SP, Nadkarni GD, Kulkarni VS, Punekar S.**

Departments of Biochemistry and Urology, Seth G. S. Medical College, and Radiation Medicine Centre (BARC), Tata Memorial Hospital, Parel, Mumbai - 400 012, India. suchetad@hotmail.com

BACKGROUND AND AIM: Mammalian spermatozoa are rich in polyunsaturated fatty acids and are very susceptible to attack by reactive oxygen species (ROS) and membrane lipid peroxide ion. Normally a balance is maintained between the amount of ROS produced and that scavenged. Cellular damage arises when this equilibrium is disturbed. A shift in the levels of ROS towards pro-oxidants in semen and vaginal secretions can induce an oxidative stress on spermatozoa. The aim was to study lipid peroxidation and antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase (SOD) and to correlate the same, with the 'water test', in male infertility. **SETTINGS:** Experimental study. **SUBJECTS AND METHODS:** Ejaculates from a total of 83 infertile and fertile healthy individuals were obtained. Lipid peroxidation and antioxidant enzyme levels were studied and correlated with water test. **RESULTS:** The results indicate that (i) the antioxidant enzyme catalase showed no significant changes in the various pathological samples, (ii) antioxidant enzymes SOD and glutathione peroxidase correlate positively with asthenozoospermic samples and (iii) the degree of lipid peroxidation also correlates positively with the poorly swollen sperm tails. The increase in SOD and glutathione peroxidase values, in the pathological cases represents an attempt made to overcome the reactive oxygen species. **CONCLUSION:** Water test could be used as a preliminary marker test for sperm tail damage by reactive oxygen species, since it correlates very well with lipid peroxidation and antioxidant enzymes.

Free Radic Biol Med 1997;22(4):581-6

Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE**Effects of ferulic acid on fertile and asthenozoospermic infertile human sperm motility, viability, lipid peroxidation, and cyclic nucleotides.****Zheng RL, Zhang H.**

Department of Biology, Lanzhou University, P.R. China.

The capacity of human sperm fertilization principally depends on sperm motility and membrane integrity. Reactive oxygen species, such as superoxide anion and hydrogen peroxide, are known to impair sperm motility and membrane integrity by inducing membrane lipid peroxidation (LPO). Ferulic acid (FA), an effective constituent in various medicinal herbs, has recently been shown to scavenge oxygen free radicals and increase the intracellular cAMP and cGMP. The aim of this study is to investigate the effects of FA on human sperm motility, viability, lipid peroxidation, and cyclic nucleotides in fertile and asthenozoospermic infertile individuals in vitro. The sperm samples were obtained from 10 fertile volunteers and 10 asthenozoospermic infertile patients. Washed spermatozoa were incubated at 37 degrees C in Ham's F-10 medium with 0, 0.1, 0.2, 0.4, 0.8, or 1.6 mM of FA. Samples were analyzed for viability, determined by eosin-Y dye exclusion method at 0, 1, 2, 3, 5, and 6 h of incubation; motility, determined by the trans-membrane migration method within 2 h of incubation; LPO, determined by thiobarbituric acid (TBA) method at 3 h of incubation and the intracellular cAMP and cGMP, determined, respectively, by 3H-cAMP and 125I-cGMP radioimmunoassay at 3 h of incubation. The results showed: in both fertile and infertile spermatozoa, the viability, trans-membrane migration ratio (TMMR) and the levels of intracellular cAMP and cGMP in FA-treated spermatozoa were significantly higher than those of spermatozoa in control groups, while TBA-reactive substances contents in treated spermatozoa were significantly lower than those in control spermatozoa. The effects of FA on these processes were concentration dependent. These data suggested that FA is beneficial to sperm viability and motility in both fertile and infertile individuals, and that reduction of lipid peroxidative damage to sperm membranes and increase of intracellular cAMP and cGMP may be involved in these benefits. It is possible that FA may be used for cure of asthenozoospermic infertility.

Am J Chin Med 2001;29(1):155-60

Related Articles, Links

Effects of Ginsenoside Rb2 and Rc on inferior human sperm motility in vitro.**Chen JC, Chen LD, Tsauer W, Tsai CC, Chen BC, Chen YJ.**

Research Institute of Chinese Medicine, China Medical College, Taichung, Taiwan.

The purpose of the study was to investigate the effects of two constituents of Panax notoginseng flower extract, Ginsenoside Rb2 and Rc, on human sperm motility and progression in vitro. Semen samples were collected from 20 patients with sperm motility between 20% and 40% of normal. All samples had sperm counts of over 20 million per milliliter, in accordance with the World Health Organization standard. Sperm were separated by a Percoll discontinuous gradient technique, and divided into a Percoll sperm control group, and three Ginsenoside Rb2 experimental groups (0.1, 0.01 and 0.001 mg/ml) and three Ginsenoside Rc experimental groups (0.1, 0.01 and 0.001 mg/ml). The results showed that at concentrations of 0.01 mg/ml and 0.001 mg/ml, Ginsenoside Rc enhanced both sperm motility and sperm progression significantly at the end of the 1st and 2nd hour. However, the three concentrations of Ginsenoside Rb2 did not increase sperm motility at the 1st or 2nd hour, but promoted sperm progression at the 2nd hour, when compared to the Percoll group.

Am J Chin Med 1999;27(1):123-8

Related Articles, Links

Effect of panax notoginseng extracts on inferior sperm motility in vitro.

Chen JC, Xu MX, Chen LD, Chen YN, Chiu TH.

Research Institute of Chinese Medicine, China Medical College, Taichung, Taiwan.

The purpose of this study was to investigate the effects of Panax notoginseng extracts on inferior sperm motility in vitro. Semen samples were collected from 23 patients with sperm motility between 20% and 40%. The sperm count was over 20×10^6 /ml in accordance with the World Health Organization standard. 1.0 mg/ml and 2.0 mg/ml of Panax notoginseng extracts including aqueous extract, n-butanol extract, and polysaccharide fraction on sperm motility and progression were evaluated by computer assisted semen analysis. The results demonstrated that sperm motility as well as progression on inferior sperm motility were enhanced at 1 hour and 2 hours after incubation with all three types of extracts.

Hinyokika Kyo 1984 Apr;30(4):581-6

Related Articles, Links

[Clinical experience with methylcobalamin (CH3-B12) for male infertility]

[Article in Japanese]

Isoyama R, Kawai S, Shimizu Y, Harada H, Takihara H, Baba Y, Sakatoku J.

CH3-B12 was administered daily (1,500 micrograms/day, for 4 to 24 weeks) to 26 infertile male patients who visited our clinic from January to December, 1982. It was not administered, however, to patients with azoospermia. Semen analysis was conducted from 8 weeks after the administration of CH3-B12. Sperm concentration increased in 10 cases (38.4%), total sperm counts increased in 14 cases (53.8%), sperm motility increased in 13 cases (50.0%) and total motile sperm count increased in 13 cases (50.0%). Semen volume, however, could not be evaluated due to wide variation. Serum LH, FSH and testosterone were unchanged. Judging by our criteria, 11 cases (42.3%) improved, 11 cases (42.3%) were unchanged and the remaining 4 cases (15.4%) had aggravated.

Fertil Steril 1993 Oct;60(4):698-701

Related Articles, Links

Folinic acid in the treatment of human male infertility.**Bentivoglio G, Melica F, Cristoforoni P.**

Istituto di Clinica Ostetrica e Ginecologica, Universita di Genova, Italy.

OBJECTIVE: To investigate the clinical and histologic effects of folinic acid in the treatment of round cell idiopathic syndrome. **DESIGN:** Sixty-five males of infertile couples have been treated with folinic acid alone (15 mg one time per day) for a 3-month period. Various sperm parameters (spermatozoa number and motility, round cell number) have been evaluated before and after the therapy. Moreover, to investigate the histologic patterns of the testis induced by the administration of folinic acid, an experimental animal model has been designed on rats previously treated with chemotherapy drugs. **RESULTS:** All the investigated human seminal parameters presented significant variations after the treatment. An improvement in spermatozoa number and motility and a decrease in round cell number have constantly been noticed; the significance of the changes was particularly impressive in those men whose partners became pregnant later on. A consistent improvement in the histologic structure of the rat tubular epithelium was also detected. **CONCLUSION:** Folinic acid appears to be a valuable approach for the treatment of round cell idiopathic syndrome.

Andrologia 1994 May-Jun;26(3):155-9

Related Articles, Links

L-carnitine in idiopathic asthenozoospermia: a multicenter study. Italian Study Group on Carnitine and Male Infertility.**Costa M, Canale D, Filicori M, D'Iddio S, Lenzi A.**

Institute of Obstetrics and Gynecology, University of Genova, Italy.

The aim of the study described here was to evaluate any possible effect of L-carnitine on spermatozoal motility in a group of patients with unexplained asthenozoospermia in four different infertility centres. One hundred patients received 3 g d⁻¹ of oral L-carnitine for 4 months. Sperm parameters were studied before, during and after this treatment. Motility was also studied by means of a computer-assisted sperm analysis. The results of the study indicate that L-carnitine is able to increase spermatozoal motility, both in a quantitative and in a qualitative manner (per cent motile spermatozoa increased from 26.9 +/- 1.1% to 37.7 +/- 1.1% [P < 0.001]; per cent spermatozoa with rapid linear progression increased from 10.8 +/- 0.6% to 18.0 +/- 0.9% [P < 0.001]; mean velocity increased from 28.4 +/- 0.6 microns s⁻¹ to 32.5 +/- 0.8 microns s⁻¹ [P < 0.001]; linearity index increased from 3.7 +/- 0.1 to 4.1 +/- 0.1 [P < 0.001], especially in the subgroup of patients with poor rapid linear progression of spermatozoa (per cent of motile spermatozoa increased from 19.3 +/- 1.9% to 40.9 +/- 1.4% [P < 0.001], and per cent of spermatozoa with rapid linear progression increased from 3.1 +/- 0.4% to 20.3 +/- 1.6% [P < 0.001]) An increase in spermatozoal output was also observed (total number of ejaculated spermatozoa increased from 142.4 +/- 10.3 10⁶ to 163.3 +/- 11.0 x 10⁶) [P < 0.001]. The authors conclude that oral administration of L-carnitine may improve sperm quality at least in patients with idiopathic asthenozoospermia

from count
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Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial.

Wong WY, Merkus HM, Thomas CM, Menkveld R, Zielhuis GA, Steegers-Theunissen RP.

Department of Obstetrics and Gynecology, University Medical Centre Nijmegen, Nijmegen, The Netherlands.

OBJECTIVE: To study the effects of folic acid and zinc sulfate treatment on semen variables in fertile and subfertile men. **DESIGN:** Double-blind, placebo-controlled interventional study. **SETTING:** Two outpatient fertility clinics and nine midwifery practices in The Netherlands. **PARTICIPANT(S):** One hundred eight fertile and 103 subfertile men. **INTERVENTION(S):** Both groups were randomly assigned to receive one of four treatments for 26 weeks: folic acid and placebo, zinc sulfate and placebo, zinc sulfate and folic acid, and two placebos. Folic acid was given at a daily dose of 5 mg, and zinc sulfate was given at a daily dose of 66 mg. **MAIN OUTCOME MEASURE(S):** Before and after treatment, standardized semen and blood samples were obtained for determinations of sperm concentration, motility, and morphology according to World Health Organization guidelines; semen morphology according to strict criteria; and blood folate and zinc concentrations. Effects of the four interventions were evaluated separately in subfertile and fertile men. **RESULT(S):** Subfertile men demonstrated a significant 74% increase in total normal sperm count and a minor increase of 4% abnormal spermatozoa. A similar trend was observed in fertile men. Pre-intervention concentrations of folate and zinc in blood and seminal plasma did not significantly differ between fertile and subfertile men. **CONCLUSION(S):** Total normal sperm count increases after combined zinc sulfate and folic acid treatment in both subfertile and fertile men. Although the beneficial effect on fertility remains to be established, this finding opens avenues of future fertility research and treatment and may affect public health.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 11872201 [PubMed - indexed for MEDLINE]

sperm count E supplement

The effect of oral selenium supplementation on human sperm motility.

Scott R, MacPherson A, Yates RW, Hussain B, Dixon J.

Department of Urology, Glasgow Royal Infirmary, UK.

OBJECTIVES: To determine whether the decline in selenium intake and selenium status in men in the West of Scotland might be a contributory factor to male subfertility. PATIENTS AND METHODS: Two semen samples were collected from patients attending a subfertility clinic and those patients with samples showing reduced motility were invited to participate in an ethically approved double-blind clinically controlled trial with informed consent. Sixty-nine patients were recruited and received either placebo, selenium alone or selenium plus vitamins A, C and E daily for 3 months. A further semen sample was collected at the end of the trial. Plasma selenium status was determined at the beginning and end of the trial period, as was total sperm density and motility. RESULTS: Plasma selenium concentrations were significantly ($P < 0.001$) higher in both selenium-treated groups than in controls. No significant effect of treatment on sperm density was recorded. Sperm motility increased in both selenium-treated groups, in contrast to a slight decline in the placebo group, but the difference was not significant. However, as the provision of additional vitamins had no effect on any variable measured it was considered justified to combine the two selenium-treated groups and compare them with the placebo treatment. On this basis, selenium treatment significantly ($P < 0.002$) increased plasma selenium concentrations and sperm motility ($P = 0.023$) but sperm density was again unaffected. Five men (11%) achieved paternity in the treatment group, in contrast to none in the placebo group. CONCLUSION: This trial confirms the result of an earlier study, that selenium supplementation in subfertile men with low selenium status can improve sperm motility and the chance of successful conception. However, not all patients responded; 56% showed a positive response to treatment. The low selenium status of patients not supplemented again highlights the inadequate provision of this essential element in the Scottish diet.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

*Br J Urol - July 1998
82 : 76-80*

Hum Reprod 1999 Apr;14(4):1028-33

Related Articles, Links

Comment in:

- Hum Reprod. 1999 Dec;14(12):3149-50.

Full text article at
humrep.oupjournals.org

Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study.

Rolf C, Cooper TG, Yeung CH, Nieschlag E.

Institute of Reproductive Medicine of the University, Munster, Germany.

In a randomized, placebo-controlled, double-blind study we investigated whether high-dose oral treatment with vitamins C and E for 56 days was able to improve semen parameters of infertile men. Ejaculate parameters included semen volume, sperm concentration and motility, and sperm count and viability. Thirty-one patients without genital infection but with asthenozoospermia (< 50% motile spermatozoa) and normal or only moderately reduced sperm concentration ($> 7 \times 10^6$ spermatozoa/ml) (according to WHO criteria) were examined. To investigate the influence of the epididymal storage period on semen parameters, the patients were asked to deliver two semen samples with abstinence times of 2 and 7 days both before and at the end of vitamin treatment. After randomization, the patients received either 1000 mg vitamin C and 800 mg vitamin E ($n = 15$) or identical placebo capsules ($n = 16$). No changes in semen parameters were observed during treatment, and no pregnancies were initiated during the treatment period. Combined high-dose antioxidative treatment with vitamins C and E did not improve conventional semen parameters or the 24-h sperm survival rate. Prolonged abstinence time increased ejaculate volume ($P < 0.05$), sperm count ($P < 0.05$), sperm concentration ($P < 0.05$) and the total number of motile spermatozoa ($P < 0.05$).

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Biol Trace Elem Res 1996 Summer;53(1-3):65-83

Related Articles, Links

Selenium-vitamin E supplementation in infertile men. Effects on semen parameters and micronutrient levels and distribution.**Vezina D, Mauffette F, Roberts KD, Bleau G.**

Department of Obstetrics and Gynecology, University of Montreal, Canada.

In order to verify the hypothesis that selenium (Se) and vitamin E (Vit E) could improve male fertility, nine oligoasthenoteratozoospermic men were supplemented for a period of 6 mo with Se and Vit E. Compared to the baseline period (presupplementation) of 4 mo, statistically significant increases were observed for Se and Vit E levels, sperm motility, percent live, and percent normal spermatozoa. These improvements are likely to be "supplementation-dependent," since all of the parameters returned to baseline values during the posttreatment period. None of the couples reported a pregnancy during the study. The HPLC analysis conducted on the serum of one of the patients showed the existence of at least six different Se-containing peaks, whose Se content was affected by supplementation. The mechanism(s) involved in these improvements of semen parameters is presently under investigation.

Fertil Steril 1992 Nov;58(5):1034-9

Related Articles, Links

Effect of ascorbic acid supplementation on the sperm quality of smokers.VTC
Smoker**Dawson EB, Harris WA, Teter MC, Powell LC.**

Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston 77555.

OBJECTIVE: To determine the effect of ascorbic acid supplementation on the sperm quality of heavy smokers. **DESIGN:** Microscopic examination of semen for 1 month during supplementation with placebo or ascorbic acid at dose levels of 200 or 1,000 mg/d. **SETTING:** Department of Obstetrics and Gynecology, The University of Texas Medical Branch. **PARTICIPANTS:** Seventy-five men (20 to 35 years old) randomly divided into one of three supplementation groups: placebo, 200 mg and 1,000 mg of ascorbic acid. **MAIN OUTCOME:** Improvement in sperm quality as compared with presupplementation levels and between the three treatment groups. **RESULTS:** The placebo group showed no improvement in sperm quality. The groups receiving ascorbic acid showed improvement in sperm quality with most improvement in the 1,000-mg group. Pearson's correlation showed statistically significant relationships between the weekly group means of serum and seminal plasma ascorbic acid levels and sperm qualities. **CONCLUSIONS:** Ascorbic acid supplementation of heavy smokers in excess of 200 mg/d results in improved sperm quality

Contraception 1986 Sep;34(3):295-302

Related Articles, Links

Spermicidal effect in vitro by the active principle of garlic.**Qian YX, Shen PJ, Xu RY, Liu GM, Yang HQ, Lu YS, Sun P, Zhang RW, Qi LM, Lu QH.**

The in vitro spermicidal effect of Allitridum, an active principle of garlic, was investigated. The data showed that sperm motility was inhibited with various concentrations of Allitridum at different intervals ranging from 20 seconds-200 minutes as compared to control. An obvious immobilization of spermatozoa occurred at 7.5 mg/ml of Allitridum. The effects on sperm motility appeared to be dose-dependent.

Khirurgiia (Sofia) 1989;42(6):49-52

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[The treatment of male infertility with the preparation vitaton]

[Article in Bulgarian]

Tsvetkov D.

Thirty men with fertility disorders, 21 to 42 years of age (mean 29 years) and mean duration of sterile matrimony 4 years 7 months received Vitaton treatment. The patients were divided in three groups: 8 with cryptorchidism, 12 having undergone resection of v. testicularis interna sin for varicocele and 10 with idiopathic oligospermia. In the first group of patients with bilateral cryptorchidism and azoospermia the control spermatograms showed persistence of azoospermia, i.e. in none of these patients was fertility reestablished. The second group of patients who had been operated for idiopathic varicocele experiences significant improvement in spermatozoid motility. In the third group (with idiopathic oligospermia) spermatozoid viability was improved--more than 50 per cent motility and more than 10 mu/sec speed of the spermatozoa. Application of Vitaton in andrologic practice gives justifiable hopes for improvement of spermatozoid motility and speed, which are the most important parameters for male inseminating capacity.

Andrologia 2002 Apr;34(2):107-11

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Online**Coenzyme Q10 levels in idiopathic and varicocele-associated asthenozoospermia.****Balercia G, Arnaldi G, Fazioli F, Serresi M, Alleva R, Mancini A, Mosca F, Lamonica GR, Mantero F, Littarru GP.**Division of Endocrinology, School of Medicine, University of Ancona, Italy. clendo@popcsi.unian.it

Levels of coenzyme Q10 (CoQ10) and of its reduced and oxidized forms (ubiquinol, QH2, and ubiquinone, Qox) have been determined in sperm cells and seminal plasma of idiopathic (IDA) and varicocele-associated (VARA) asthenozoospermic patients and of controls. The results have shown significantly lower levels of coenzyme Q10 and of its reduced form, QH2, in semen samples from patients with asthenospermia; furthermore, the coenzyme Q10 content was mainly associated with spermatozoa. Interestingly, sperm cells from IDA patients exhibited significantly lower levels of CoQ10 and QH2 when compared to VARA ones. The QH2/Qox ratio was significantly lower in sperm cells from IDA patients and in seminal plasma from IDA and VARA patients when compared with the control group. The present data suggest that the QH2/Qox ratio may be an index of oxidative stress and its reduction, a risk factor for semen quality. Therefore, the present data could suggest that sperm cells, characterized by low motility and abnormal morphology, have low levels of coenzyme Q10. As a consequence, they could be less capable in dealing with oxidative stress which could lead to a reduced QH2/Qox ratio. Furthermore, the significantly lower levels of CoQ10 and QH2 levels in sperm cells from IDA patients, when compared to VARA ones, enable us to hypothesize a pathogenetic role of antioxidant impairment, at least as a cofactor, in idiopathic forms of asthenozoospermia.

The effect of coenzyme Q10 on sperm motility and function.

Lewin A, Lavon H.

Department of Obstetrics and Gynecology, Hadassah-Hebrew University Medical School, Jerusalem, Israel.

In sperm cells, the majority of coenzyme Q10 (CoQ10) an energy promoting agent and antioxidant, is concentrated in the mitochondria of the midpiece, so that the energy for movement and all other energy-dependent processes in the sperm cell also depend on the availability of CoQ10. The reduced form of CoQ10-ubiquinol also acts as an antioxidant, preventing lipid peroxidation in sperm membranes. The objective of the study was to evaluate the effect of CoQ10 on sperm motility *in vitro*, after incubation with 38 samples of asthenospermic and normal motility sperm, and to evaluate the effect of CoQ10 administration *in vivo* in 17 patients with low fertilization rates after *in vitro* fertilization with intracytoplasmic sperm injection (ICSI) for male factor infertility. All 38 sperm samples from patients registered in our infertility clinic had normal concentrations and morphology. Of these, 16 patients had normal motility (mean 47.5%) and 22 patients were asthenospermic (mean motility 19.1%). Sperm samples were divided into four equal parts and incubated for 24 h in: HAM's medium alone, in HAM's medium with 1% DMSO and HAM's with 5 microM or 50 microM CoQ10. While no significant change in motility after incubation was observed in the samples with initial normal motility, a significant increase in motility was observed in the 50 microM CoQ10 subgroup of sperm from asthenospermic men, with a motility rate of 35.7 +/- 19.5%, as compared to 19.1 +/- 9.3% in the controls ($P < 0.05$). The 17 patients with low fertilization rates after ICSI were treated with oral CoQ10, 60 mg/day, for a mean of 103 days before the next ICSI treatment. No significant change was noted in most sperm parameters, but a significant improvement was noted in fertilization rates, from a mean of 10.3 +/- 10.5% in their previous cycles, to 26.3 +/- 22.8% after CoQ10 ($P < 0.05$). In conclusion, the administration of CoQ10 may result in improvement in sperm functions in selective patients. Further investigation into the mechanisms related to these effects is needed.

J Androl 1995 Sep-Oct;16(5):441-7

Related Articles, Links

Selenium supplementation enhances the element concentration in blood and seminal fluid but does not change the spermatozoal quality characteristics in subfertile men.**Iwanier K, Zachara BA.**

Municipal Hospital, Grudziadz, Poland.

The objective of this study was to evaluate the effect of selenium (Se) supplementation on Se concentration and glutathione peroxidase (GSH-Px) activity in blood components and seminal fluid and on spermatozoal quality characteristics in subfertile men. Thirty-three men were supplemented for 12 weeks with 200 micrograms Se/day in the form of yeast-rich Se (group I, n = 16) or sodium selenite (group II, n = 17). Blood samples and sperm were collected at the start of the study and after 2, 4, 8, and 12 weeks following Se supplementation. Se concentration in whole blood and plasma and GSH-Px activity in red cells and plasma increased significantly during the study, but in the group supplemented with yeast-Se the effect was more pronounced. Se concentration in seminal fluid also increased in both groups, but the effect of yeast-Se was markedly higher than that of selenite. In both groups statistically significant correlations were found between Se concentration in plasma and seminal fluid. GSH-Px activity in seminal fluid in the yeast-Se group increased significantly and reached a plateau after 2 weeks, whereas in the selenite group the activity did not change throughout the whole study period. Weak correlations between Se concentrations and GSH-Px activities in seminal fluid were seen, but only in the yeast-Se group were the relations statistically significant. The subjects in both groups showed no response in sperm count, motility, and morphology. In conclusion, we can ascertain that the supplementation of subfertile men with yeast-rich Se showed a more pronounced effect on Se concentrations and GSH-Px activities in blood components and seminal fluid than selenite did. Se supplementation did not improve the spermatozoal quality characteristics of sperm count, motility and, morphology.

Hinyokika Kyo 1984 Feb;30(2):265-73

Related Articles, Links

[The effect of Chinese drug therapy on the patients with male infertility. 1. Concomitant administration of ninjinto and hachimijiogan on patients with male infertility]

[Article in Japanese]

Nishizawa Y.

Ten patients (age range, 28 to 36 years with a mean of 32.3 years) with male infertility were orally given Ninjinto and Hachimijiogan concomitantly at a daily dose of 7.5 g each for 96 to 182 days (mean 116.8 days). Ten percent of these patients showed remarkable improvement in their volume of semen, 10% showed improvement and 80.0% showed no improvement. Thirty percent of these patients showed remarkable improvement in the number of sperm, 10.0% showed improvement, and 60.0% showed no improvement. Twenty percent of these patients showed remarkable improvement in their sperm mobility, 30.0% showed improvement and 50.0% showed no improvement. The fertility index was improved markedly in 60.0%, improved in 20.0% and not improved in 20.0%. The spouses of 2 patients became pregnant. Side effects were seen in only 30.0% (epigastralgia) of these patients. Laboratory examination of these patients revealed no significant change. These results suggested that concomitant administration of Ninjinto and Hachimijiogan is effective on patients with male infertility.

Hinyokika Kyo 1984 Nov;30(11):1685-9

Related Articles, Links

[Clinical effects of goshajinkigan for male infertility]

[Article in Japanese]

Takayama H, Konishi T, Kounami T, Wakabayashi Y, Watanabe J, Hayashida H, Tomoyoshi T.

No study has been reported of the effects of Goshajinkigan on male infertility. Thirty infertile male patients were orally given Goshajinkigan at a daily dose of 5.0 g for three months or more. Sixteen of these patients showed significant improvement in sperm motility. Ten cases showed effective increase in sperm count. Only one patients became pregnant during the period of administration of this drug. Laboratory examination showed no significant change in serum LH, serum FSH or prostaglandin E in seminal fluid. These results suggest that administration of TSUMURA-Goshajinkigan is effective as therapy for male infertility, but how this drug may be involved in promoting fertility should be investigated in future.

Hinyokika Kyo 1984 Jan;30(1):97-102

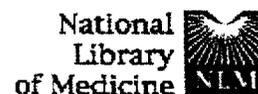
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[Clinical experience of Hachimijiogan for male infertility patients]

[Article in Japanese]

Miura K, Matsubashi M, Maki A, Takanami M, Fujio K, Nakayama K, Shirai M, Ando K.

We treated 53 patients for male infertility with TSUMURA - Hachimijiogan given as a daily dose of 7.5 g for 144 days on the average. The sperm density was improved by administration to $10 \times 10^6/\text{ml}$ or more in 22 patients (41.5%) and lowered to $10 \times 10^6/\text{ml}$ or more in only 2 patients (3.8%). The sperm motility was improved by 10% or over in 29 patients (54.7%) as compared with 5 patients (9.4%) in whom it was lowered by 10% or more. The sperm motile efficiency index (SMEI) was improved in 40 (75.5%) of the 53 patients. Statistically significant differences were noted in the improvement in sperm density, sperm motility and SMEI. By contrast, there was no difference in semen volume, sperm morphology or sperm agglutination between the pre- and post- treatment periods. During the period of treatment, the wives of 4 patients (7.5%) conceived children. These results suggest that TSUMURA - Hachimijiogan is effective for male infertility to a certain extent and that clinical trials on its use for male infertility may be meaningful.



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1: Prostaglandins Leukot Essent Fatty Acids 2000 Sep;63(3):159-65 Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

The effects of combined conventional treatment, oral antioxidants and essential fatty acids on sperm biology in subfertile men.

Comhaire FH, Christophe AB, Zalata AA, Dhooge WS, Mahmoud AM, Depuydt CE.

Department of Internal Medicine, Section Endocrinology, University Hospital Ghent, De Pintelaan 185, B 9000 Ghent, Belgium. frank.comhaire@rug.ac.be

We evaluated the effects of combined conventional treatment, oral antioxidants (N-acetyl-cysteine or vitamins A plus E) and essential fatty acids (FA) on sperm biology in an open prospective study including 27 infertile men. The evaluation included sperm characteristics, seminal reactive oxygen species (ROS), FA of sperm membrane phospholipids, sperm oxidized DNA (8-OH-dG), and induced acrosome reaction (AR). Treatment did not improve sperm motility and morphology, nor decrease the concentration of round cells and white blood cells in semen. Sperm concentration increased in oligozoospermic men (7.4+/-1.3 to 12.5+/-1.9 million/ml). Treatment significantly reduced ROS (mean+/-SEM) (775.3+/-372.2 to 150.3+/-105.2 x 10(3) counts/10 second) and 8-OH-dG (45.3+/-10.4 to 16.8+/-3.3 fmol/microg DNA). Treatment increased the AR (55.1+/-2.2 to 71.6+/-2.2%), the proportion of polyunsaturated FA of the phospholipids, and sperm membrane fluidity. The overall pregnancy rate was 4.5% in 134 months. The per month pregnancy rate tended to be higher in partners of (ex)-smokers (7.15%, n=14,70 months) than in never-smokers (1.6%, n=13,64 months) (OR:4.57, 95% CI:0.55-38.1). Copyright 2000 Harcourt Publishers Ltd.

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Mar 17 2003 10:44:01

Male Infertility: Nutritional and Environmental Considerations

by Steven Sinclair, ND, LAc

Abstract

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. (Altern Med Rev 2000;5 (1):28-38.)

Introduction

An estimated six percent of adult males are thought to be infertile.¹ Infertility is defined by most authorities as the inability to achieve a pregnancy after one year of unprotected intercourse. Conception is normally achieved within 12 months in 80-85 percent of couples using no contraceptive measures; thus an estimated 15 percent of couples attempting their first pregnancy will have difficulty conceiving. While certain cases of male infertility are due to anatomical abnormalities such as varicoceles, ductal obstructions, or ejaculatory disorders, an estimated 40-90 percent of cases are due to deficient sperm production of unidentifiable origin.²

Diagnosis and Evaluation

While the focus of this article is on specific nutritional and environmental factors, there are other important diagnostic considerations when evaluating male infertility. These include endocrine abnormalities, such as hyper- and hypothyroidism or hypogonadism. Prescription drugs, including phenytoin, glucocorticoids, sulfasalazine, and nitrofurantoin all may have detrimental effects on sperm production and motility.² A detailed history of exposure to occupational and environmental toxins, recreational drugs and alcohol, excessive heat or radiation, and previous genitourinary infections should be elicited. Concurrent pathologies may also affect sperm production. Hepatic cirrhosis is associated with increased endogenous estrogens, which can suppress pituitary gonadotropin secretion and affect spermatogenesis. In addition, an estimated 80 percent of men with hemochromatosis have some degree of testicular dysfunction. Scrotal temperature is highly regulated by the body, and sperm production is greatly reduced at temperatures above 96° F. Men attempting to improve their fertility should not wear tight fitting pants or underwear (boxer shorts instead of briefs), and should avoid strenuous exercise, hot tubs, and baths.

Semen Analysis

A normal semen sample should have a volume of 1.5-5.0 ml, with greater than 20 million sperm/ml. The number of abnormal sperm should be less than 40 percent, with greater than 30 percent of the sperm sample demonstrating proper motility. Unfortunately, conventional semen analysis is not a highly accurate predictor of fertility. Purvis et al reported, after surveying infertility clinics, that 52 percent of men with a sperm count below 20 million/ml were able to impregnate their partners and 40 percent of men with a sperm count below 10 million/ml were also able to conceive.¹ Conventional semen analysis often fails to identify infertile males with "normal" samples and conversely fails to identify fertile males with subnormal semen parameters.³ Another confounding factor is variations in sperm density, motility, and morphology among multiple samples from the same subject.

More sensitive tests are available, including the post-coital test, which measures the ability of sperm to penetrate cervical mucus, and the hamster-egg penetration test, which measures the in vitro ability of sperm to penetrate hamster eggs. This test predicts fertility in an estimated 66 percent of cases, in comparison to 30 percent with conventional sperm analysis.¹

Infection

The role of infection in idiopathic male infertility has been underestimated, in particular chronic asymptomatic chlamydial infections.¹ Chlamydia can reside in the epididymis and vas deferens, affecting sperm development and fertility. One study suggests approximately 28-71 percent of infertile men have evidence of a chlamydial infection.⁴ The presence of anti-sperm antibodies may indicate an undiagnosed infection, and is estimated to be a relative cause of infertility in 3-7 percent of cases. In a study designed to examine the effects of antioxidants on anti-sperm antibodies, there was a significant correlation between beta carotene levels and antibody titers, suggesting dietary antioxidants are involved in mediating immune function in the male reproductive system.⁵

Declining Sperm Counts

There is a growing body of scientific evidence supporting the idea that sperm counts have declined considerably over the last 50 years. Carlsen et al analyzed a total of 61 studies including 14,947 men from the years 1938 to 1991, for mean sperm density and mean seminal volume. Their results show a significant decline in mean sperm density from 113 million/ml in 1940 to 66 million/ml in 1990 ($p < 0.0001$). Seminal volume decreased from an average of 3.40 ml to 2.75 ml ($p = 0.027$).^{6,7} This demonstrates a 20-percent drop in volume and a substantial 58-percent decline in sperm production in the last 50 years. Three other recent reports also found semen quality has declined among donors over the last 20 years.⁸⁻¹⁰ Because the decline in sperm production is relatively recent, one must suspect a combination of environmental, lifestyle, and dietary factors might be interfering with spermatogenesis.

Environmental Risk Factors

Current evidence suggests there may be environmental reasons for deteriorating sperm quality, including occupational exposure to various chemicals, heat, radiation, and heavy metals.^{11,12} In addition, exposure to environmental estrogens and pesticides has been linked to alterations in spermatogenesis. Lifestyle risk factors are

also significant, including cigarette smoking, alcohol consumption, chronic stress, and nutritional deficiencies.¹³

Xeno-Estrogens and Pesticides

Increased exposure to estrogens is thought to be responsible for not only prenatal testicular damage, but may also contribute to post-natal depression of testicular function and spermatogenesis. Exogenous estrogens impact fetal development by inhibiting the development of Sertoli cells, which determine the lifelong capacity for sperm production.

Circulating estrogens also inhibit enzymes involved in testosterone synthesis and may directly affect testosterone production.

The synthetic estrogen, diethylstilbestrol (DES), is a well-documented example of this problem. DES was prescribed from 1945 to 1971 to millions of women during pregnancy. Male offspring from those women had a higher incidence of developmental problems of the reproductive tract, as well as diminished sperm volume and sperm count.⁵

Synthetic estrogens are still widely used in the livestock, poultry, and dairy industries. Men wishing to improve their fertility and sperm quality probably should avoid hormone-containing dairy products and meats and opt instead for organic or hormone-free foods.

Many commonly-used pesticides, such as organochloride compounds, have estrogenic effects within the body. Chemicals such as dioxin, DDT, and PCBs are known to interfere with spermatogenesis. One study which examined the effect of DDT on male rat sexual development found low levels of DDT caused degeneration in sperm production, a decrease in the total number of sperm, and a reduced number of Leydig cells. The authors hypothesize that DDT acts as an hormonal disrupter, damaging the seminiferous epithelium and lowering local testosterone levels.¹⁴

Dietary and Lifestyle Factors

In addition to avoiding exogenous estrogens and pesticides, there are other dietary factors to consider. Adequate intake of essential fatty acids is important to ensure proper membrane fluidity and energy production in sperm cells. High dietary intake of hydrogenated oils, particularly cottonseed oil, has been shown to have a negative impact on sperm cell function. Not only does cottonseed oil contain toxic pesticide residues, it also contains high levels of the chemical gossypol, which can interfere with spermatogenesis.¹⁵

In Nigeria, a randomized, controlled trial was designed to evaluate the effect of dietary aflatoxin on infertile men. Forty percent of the 50 infertile men in the study had aflatoxin in their semen samples, compared to eight percent of the fertile control group. Infertile men exposed to dietary aflatoxin had a 50-percent higher number of abnormal sperm than controls.¹⁶

Heavy Metals

Another environmental concern with infertility is the toxic effects of heavy metals on sperm quality and

production. In Hong Kong, infertile males were found to have approximately 40-percent higher hair mercury levels than fertile males of similar age.¹⁷ Occupational exposure to lead has been shown to cause a significant decrease in male fertility.¹⁸ Considering the occupational and environmental prevalence of heavy metals and their potentially negative interactions with the neuroendocrine system, a hair analysis should be included in the diagnostic work-up of idiopathic male infertility.

Cigarette Smoking

Cigarette smoking has been associated with decreased sperm count, alterations in motility, and an overall increase in the number of abnormal sperm.¹⁹ A study designed to evaluate seminal zinc levels in smokers and non-smokers found that although smokers did not have significantly lower zinc levels than non-smokers, seminal cadmium levels were significantly increased, especially in those smoking more than one pack per day.²⁰ Experimental evidence also suggests nicotine can alter the function of the hypothalamic-pituitary axis, affecting growth hormone, cortisol, vasopressin, and oxytocin release, which then inhibits the release of luteinizing hormone (LH) and prolactin.²¹ Cigarette smokers were also shown to have higher levels of circulating estradiol and decreased levels of LH, follicle-stimulating hormone (FSH), and prolactin than non-smokers, all of which potentially impact spermatogenesis. Smokers with low prolactin levels also demonstrated defects in sperm motility.²²

Nutritional Therapies

Carnitine

The main function of carnitine in the epididymis is to provide an energetic substrate for spermatozoa. Carnitine contributes directly to sperm motility and may be involved in the successful maturation of sperm.²³ This is especially important since epididymal sperm use fatty acid oxidation as their main source of energy metabolism, and thus tend to concentrate carnitine while in the epididymis, as carnitine is necessary for transport of fatty acids into the mitochondria.²⁴ Low levels of carnitine reduce fatty acid concentrations within the mitochondria, leading to decreased energy production and potential alterations in sperm motility.

In a study involving 124 infertile patients, a direct correlation between semen carnitine content and sperm motility was found. The results also show a positive correlation between free L-carnitine and both sperm count and the number of motile sperm per milliliter ($P < 0.01$)²⁵

In one multi-center trial, 100 patients received 3 g/day of oral L-carnitine for four months. Sperm parameters were assessed before, during, and after the study. Motility was determined by computer-assisted sperm analysis. The results clearly demonstrate carnitine has a positive effect on sperm motility. The percentage of motile spermatozoa increased from 26.9 ± 1.1 to 37.7 ± 1.1 percent. The percent of sperm with rapid linear progression increased from a baseline of 10.8 percent to 18.0 percent. Not only did carnitine significantly affect sperm motility, but the total number of spermatozoa per ejaculate also increased.²⁶

Another clinical study reported similar results with 3 g carnitine given daily for three months. Thirty-seven of the 47 participants had increases in sperm motility, rapid linear progression, and total number of sperm.²⁷

In a related study, 20 men with idiopathic asthenospermia (defective sperm motility) were given acetylcarnitine, 4

g/day for 60 days. While acetylcarnitine did not affect sperm density or total motility, it did significantly increase progressive linear sperm motility. It is interesting to note that gains in sperm motility were sustained in 12 of the subjects during the four-month follow-up period. Five pregnancies occurred during treatment, with two more occurring during the four months following the trial.²⁸

Arginine

The amino acid arginine is a biochemical precursor in the synthesis of putrescine, spermidine, and spermine, which are thought to be essential to sperm motility. In 1973, Schachter et al published a study in which arginine was given to 178 men with low sperm count. Seventy-four percent of the subjects had significant improvement in sperm count and motility after taking 4 g/day for three months.²⁹

More recently, researchers in Italy evaluated the clinical efficacy of arginine in 40 infertile men. All the men had a normal number of sperm (> 20 million/ml) but had decreased motility which was not due to immunological disorders or infections. Subjects were given 80 ml of a 10-percent arginine HCl solution for six months. Arginine supplementation significantly improved sperm motility without any side effects.³⁰

Zinc

Zinc is a trace mineral essential for normal functioning of the male reproductive system. Numerous biochemical mechanisms are zinc dependent, including more than 200 enzymes in the body.³¹ Zinc deficiency is associated with decreased testosterone levels and sperm count. An adequate amount of zinc ensures proper sperm motility and production. Zinc levels are generally lower in infertile men with diminished sperm count, and several studies have found supplemental zinc may prove helpful in treating male infertility.³²

In one trial, the effect of zinc supplementation on testosterone, dihydrotestosterone, and sperm count was studied. Thirty-seven patients with idiopathic infertility of more than five-years duration and diminished sperm count received 24 mg elemental zinc from zinc sulfate for 45-50 days. The results were dramatic in the 22 subjects with initially low testosterone levels; a significant increase in testosterone levels and sperm count (from 8 to 20 million/ml) was noted, along with nine resulting pregnancies.³³

Fourteen infertile males with idiopathic oligospermia were supplemented with 89 mg zinc from oral zinc sulfate for four months. Serum zinc levels were unaffected, but seminal zinc levels significantly increased. There were also improvements in sperm count and in the number of progressively motile and normal sperm. Three pregnancies occurred during the study.³⁴

Zinc supplementation appears warranted in the treatment of male infertility, especially in cases of low sperm count or decreased testosterone levels.

Antioxidants

Polyunsaturated fatty acids and phospholipids are key constituents in the sperm cell membrane and are highly susceptible to oxidative damage. Sperm produce controlled concentrations of reactive oxygen species, such as the

superoxide anion, hydrogen peroxide, and nitric oxide, which are needed for fertilization; however, high concentrations of these free radicals can directly damage sperm cells.³⁵ Disruption of this delicate balance has been proposed as one of the possible etiologies of idiopathic male infertility.

Vitamin C

Studies have shown the concentration of ascorbic acid in seminal plasma directly reflects dietary intake, and lower levels of vitamin C may lead to infertility and increased damage to the sperm's genetic material.³⁶ Fraga et al demonstrated this by reducing ascorbic acid intake in healthy men from 250 mg to 5 mg per day. Seminal plasma levels of vitamin C decreased by 50 percent, with a concomitant 91-percent increase in sperm with DNA damage.³⁷

Cigarette smoking has been documented as having deleterious effects on sperm quality. In a University of Texas study on vitamin C and sperm quality in heavy smokers, 75 men were divided into three supplementation groups; one was given placebo, the other groups received 200 mg or 1000 mg ascorbic acid. While the placebo group showed no improvement, the ascorbic acid groups showed significant improvement in sperm quality, with the greatest improvement occurring in the 1000 mg group.³⁸

In perhaps one of the best studies on vitamin C and male infertility, 30 infertile but otherwise healthy men were given a placebo, 200 mg, or 1000 mg vitamin C daily. After one week, the group receiving 1000 mg/day had a 140-percent increase in sperm count, while there was no change in the placebo group. The 200 mg/day group had a 112-percent increase in sperm count, while both groups demonstrated significant reductions in the number of agglutinated sperm. Most importantly, by the end of the 60-day study every participant in the vitamin C group had impregnated their partner, while no pregnancies occurred in the placebo group.³⁹

Vitamin E

Vitamin E is a well-documented antioxidant and has been shown to inhibit free-radical-induced damage to sensitive cell membranes.⁴⁰ In one study, lipid peroxidation in the seminal plasma and spermatozoa was estimated by malondialdehyde (MDA) concentrations. Oral supplementation with vitamin E significantly decreased MDA concentration and improved sperm motility, resulting in a 21-percent pregnancy occurrence during the study.⁴¹

In one randomized, cross-over, controlled trial, 600 mg/day vitamin E improved sperm function in the zona binding assay, therefore enhancing the ability of the sperm to penetrate the egg in vitro.⁴²

Nine men with low sperm count and alterations in sperm motility were given vitamin E with the antioxidant trace mineral selenium for six months. Compared to the baseline pre-supplementation period of four months, the combination of vitamin E and selenium significantly increased sperm motility and the overall percentage of normal spermatozoa.⁴³

Glutathione/Selenium

Glutathione is vital to sperm antioxidant defenses and has demonstrated a positive effect on sperm motility.⁴⁴⁻⁴⁶ Selenium and glutathione are essential to the formation of phospholipid hydroperoxide glutathione peroxidase, an

enzyme present in spermatids which becomes a structural protein comprising over 50 percent of the mitochondrial capsule in the mid-piece of mature spermatozoa. Deficiencies of either substance can lead to instability of the mid-piece, resulting in defective motility.^{47,48}

Glutathione therapy was used in a two-month, placebo-controlled, double-blind, cross-over trial of 20 infertile men. The subjects were given either a daily 600 mg intramuscular injection of glutathione or an equal volume of placebo. Glutathione demonstrated a statistically significant effect on sperm motility, especially increasing the percentage of forward motility.⁴⁹

Sixty-nine infertile Scottish men were given either placebo, selenium, or selenium in combination with vitamins A, C, and E for three months. At the end of the trial, both selenium-treated groups had significant improvements in sperm motility; however, sperm density was unaffected. Eleven percent of the participants in the treatment groups impregnated their partner during the course of the study.⁵⁰

Another study compared the effects of selenium supplementation in 33 infertile men. They were given either a 200 mcg/day dose of selenium from sodium selenite or a selenium-rich yeast for 12 weeks. While selenium concentration in seminal fluid was increased in both groups, it was markedly higher in the yeast-Se group. Yeast-Se significantly increased glutathione peroxidase activity in the seminal fluid, but failed to produce any improvements in sperm count, motility, or morphology.⁵¹

Coenzyme Q-10

In sperm cells, coenzyme Q10 (CoQ10) is concentrated in the mitochondrial mid-piece, where it is involved in energy production. It also functions as an antioxidant, preventing lipid peroxidation of sperm membranes. When sperm samples from 22 asthenospermic men were incubated in vitro with 50 microM CoQ10, significant increases in motility were observed. CoQ10 (60 mg) was given to 17 infertile patients for a mean 103 days, and although there were no significant changes in standard sperm parameters, there was a significant improvement in fertilization rate ($p < 0.05$).⁵²

In another study, 10 mg/day of coenzyme Q7 (an analog of CoQ10) was given to infertile men, with resulting increases in sperm count and motility.⁵³

Clearly, additional studies will be needed to evaluate the possible role of coenzyme Q10 in the treatment of male infertility.

Vitamin B12

Vitamin B12, in its various forms, has been studied for its effect on male infertility. Vitamin B12 is important in cellular replication, especially for the synthesis of RNA and DNA, and deficiency states have been associated with decreased sperm count and motility.

Methylcobalamin (1,500 mcg/day) was given to a group of infertile men for a period of 8-60 weeks. They were evaluated periodically by semen analysis, and standard sperm parameters were increased by 60 percent.⁵⁴ In another methylcobalamin study, 1,500 mcg/day was given to 26 infertile men for a period of 4-24 weeks. Sperm analysis was conducted eight weeks into the study. Sperm concentration increased in 38.4 percent of the cases and

total sperm count increased in 53.8 percent of the men. Sperm motility increased in 50 percent of the participants. Serum LH, FSH, and testosterone levels were unchanged.⁵⁵ When 6000 mcg/day was given to men with low sperm count, it resulted in a 57-percent improvement.⁵⁶ Vitamin B-12 (1000 mcg/day) was administered to men with a sperm count less than 20 million/ml. By the end of the study, 27 percent of the men had a sperm count over 100 million/ml.⁵⁷

Acupuncture and Botanical Medicine

Several studies have investigated the use of acupuncture as a therapy for male infertility. In one prospective controlled study, 16 infertile males were treated with acupuncture twice per week for five weeks. Compared to the control group, patients receiving acupuncture had increases in total functional sperm fraction, percentage of viability, total motile sperm per ejaculation, and overall integrity of the axonema ($p < 0.05$).⁵⁸

An additional study reported when acupuncture was performed on 28 infertile men, all sperm parameters significantly improved, with the exception of ejaculate volume.⁵⁹

Ginseng has historically been used in Chinese medicine as a male Qi tonic. *Panax ginseng* and *Eleutherococcus senticosus* (Siberian ginseng) have a long history of traditional use and were commonly prescribed to enhance male virility and fertility.

Ginseng, an adaptogenic herb, has a multitude of physiological effects within the body. Chen et al found extracts of *Panax notoginseng* were capable of significantly enhancing in vitro sperm motility.⁶⁰ Other studies have shown that *Panax ginseng* promotes increased sperm formation and testosterone levels in animals.^{61,62}

Researchers in Korea have recently determined that administering *Panax ginseng* extract to animals can enhance erectile capacity and protect against atrophy and testicular damage induced by dioxin.^{63,64}

When 18 water extracts of Chinese medicinal herbs were evaluated for their effect on sperm motility, *Astragalus* was the only herb with a significant stimulatory effect. At 10 ml/mg, in vitro sperm motility was increased 146.6 ± 22.6 percent compared to control.⁶⁵

The herb *Pygeum africanum* may also be an effective therapy for male infertility, especially in cases of diminished prostatic secretions. *Pygeum* extracts have been shown to increase alkaline phosphatase activity, which helps maintain the appropriate pH of seminal fluid, and increases total prostatic secretions. Sperm motility is partly determined by the pH of the prostatic fluid. If *Pygeum* can raise the pH of prostatic fluid, it may have a role in promoting and maintaining optimal sperm motility.⁶⁶⁻⁶⁸

Conclusion

Male infertility is a multifactorial disease process with a number of potential contributing causes. Considering the majority of male infertility cases are due to deficient sperm production of unknown origin, environmental and nutritional factors must be evaluated. Occupational risk factors, including exposure to heat, chemicals, and heavy metals needs to be examined. Lifestyle and dietary choices, pesticide residues, and xeno-estrogens all may adversely affect spermatogenesis.

Various nutritional strategies have been presented which have a beneficial impact on sperm count, motility, and ultimately, fertility. Spermatogenesis is an energetically-demanding process which requires an optimal intake of antioxidants, minerals, and nutrients.

Is it purely coincidence that sperm quality has diminished over the last 50 years, while ever increasing amounts of synthetic chemicals and hormones have been introduced to the environment and food supply? Perhaps we should consider decreased fertility in men as a physiological early warning system, a "canary in the coal mine," so to speak, which is acting as a sensitive indicator of environmental disruptions and nutritional imbalances.

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Improvement in Sperm Quality and Function with French Maritime Pine Tree Bark Extract

Scott J. Roseff, M.D.

OBJECTIVE: To determine the effects of Pycnogenol® (French maritime pine tree bark extract) on sperm parameters and function in subfertile men.

STUDY DESIGN: Prospective, nonrandomized, clinical study in a private infertility practice. Nineteen subfertile men were given 200 mg Pycnogenol® daily orally for 90 days. Semen samples were analyzed before and after treatment for sperm count, motility score and strict morphology before and after capacitation, and mannose receptor binding.

RESULTS: The mean sperm morphology following Ham's F-10 capacitation increased by 38% following Pycnogenol® treatment, and the mannose receptor binding assay scores improved by 19%.

CONCLUSION: Pycnogenol® therapy resulted in improved capacitated sperm morphology and mannose receptor binding. The increase in morphologically and functionally normal sperm may allow couples diagnosed with teratozoospermia to forgo in vitro fertilization and either experience improved natural fertility or undergo less invasive and less expensive fertility-promoting procedures, such as intrauterine insemination. (J Reprod Med 2002;47:821-824)

Keywords: infertility, male; antioxidants; sperm

count; sperm motility; sperm capacitation; Pycnogenol®.

Up to 60% of infertile couples have difficulty conceiving due to "male factor" subfertility, meaning that one or more sperm parameters are abnormal. The production of abnormal quantities of reactive oxygen species (ROS) is thought to be involved in many facets of human male infertility.¹ Sperm exposed to superoxide an-

ions are apparently rendered dysfunctional by lipid peroxidation and altered membrane function, along with impaired metabolism, morphology and motility.²⁻⁴ The formation of reactive oxygen species has been associated with decreased sperm-egg interaction and reduced fertility.⁵

Vitamin C has been given to infertile men for years, as it has anecdotally proven to be efficacious in improving sperm parameters. More recently, studies have documented the efficacy of antioxidant treatment on human spermatozoa and fertilization rates, especially in the setting of *in vitro* fertilization (IVF). Indeed, improvements in IVF rates have been demonstrated after vitamin E therapy.^{6,7}

One of the richest natural sources of bioavailable

The increase in morphologically and functionally normal sperm may allow infertile couples diagnosed with teratozoospermia to forgo IVF and donor sperm insemination....

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and bioactive antioxidant compounds known is found in the bark of the *Pinus maritima* tree; the proprietary name of the extract is Pycnogenol[®] (Horphag Research, Ltd., Geneva, Switzerland). The biologic precursors of the oligomeric procyanidins, such as catechin and taxifoline, are effective and well-known free-radical scavengers. Pycnogenol[®] counteracts redox-sensitive NF κ B-regulated gene expression of various inflammatory mediators, such as endothelial adhesion molecules and cytokines TNF- α and IL-1 β .³

Pycnogenol[®] has been found to be many times more potent than other known antioxidants, like vitamin C and E.⁹ The objective of this prospective study was to evaluate the possible influence of Pycnogenol[®], one of the most potent known antioxidants, on human sperm parameters, including the ability of sperm to bind to α -D-mannose receptors *in vitro*.

Materials and Methods

Following institutional review board approval, 19 subfertile men with abnormal baseline sperm testing were enrolled. Each patient received Pycnogenol[®] tablets, 200 mg orally per day, for 90 days. Supplementation with vitamins, minerals and other antioxidants was prohibited.

Men eligible for participation in the study were required to have one or more abnormalities previously demonstrated in their semen analysis (precapacitation or postcapacitation) and/or sperm capacity to bind to mannose receptors. All patients signed an informed consent form after the nature of the study had been fully explained.

Patients were not eligible for the study if they exhibited one or more of the following: (1) sperm antibodies; (2) current drug, tobacco, or alcohol abuse; (3) exposure to antioxidants or medication containing hormones within 90 days prior to the study; and (4) therapy to improve sperm parameters within 90 days prior to admission into this study.

After two to seven days of sexual abstinence, a semen sample was collected by masturbation into a sterile container. Semen analysis, sperm capacitation, sperm antibody testing and the mannose receptor binding assay were carried out per usual protocols. Briefly, the semen analysis consisted of sperm count, motility score and strict morphology. The sperm count (normal ≥ 20 million/mL) was manually done via a Makler Counting Chamber (Sefi-Medical Instruments, Haifa, Israel). The motility score (normal ≥ 150) and strict sperm morpholo-

gy (normal ≥ 14) were calculated according to previously described methods.¹⁰ Direct sperm antibodies were tested via a commercially available immunobead kit (ImmunoSpheres[®], Bioscreen Inc New York, New York). Capacitation was performed by the standard swim-up method utilizing Ham's F-10 solution. Finally, the mannose receptor binding assay (normal $\geq 36\%$), which measures sperm's potential to bind to glycoproteins similar to those found on the zona pellucida of human oocytes, was completed using a standardized test kit (Mannose Binding Assay[™] [MBA], Embryotech Laboratories, Inc., Wilmington, Massachusetts).

A 90-day supply of Pycnogenol[®] was given to each patient who entered the study, and each participant took 200 mg/d by mouth for 90 days. A "target" date was set for termination of the study, at which time the patient produced a second masturbated specimen in order to repeat the sperm testing.

Individual percent changes (from baseline) in sperm parameters were calculated, and the mean of the percent changes was utilized for data analysis. Data were statistically analyzed by paired *t* testing. $P < .05$ was considered significant.

Results

None of the patients tested positive for direct sperm antibodies. The pretreatment and posttreatment mean sperm parameters analyzed in the 19 subjects are listed in Table I. As compared to pretreatment the mean percent change from baseline sperm count after Pycnogenol[®] therapy decreased not significantly by 10%. There was also a nonsignificant decline in the mean Ham's F-10 capacitated motility score (4%). The mean change from baseline morphology increased by 33%, but this improvement was not statistically significant.

After Ham's F-10 capacitation, the mean percent changes in strict morphology and the mannose receptor binding assay revealed significant improvements following Pycnogenol[®] treatment ($38 \pm 0.6\%$, $P < .001$, and $19 \pm 1.5\%$, $P < .005$, respectively). There were no adverse effects reported by the men during the test period.

Discussion

We have known for over 30 years that the human sperm plasma membrane has a high content phospholipid-bound polyunsaturated fatty acids (PUFA).¹¹ This high PUFA content of sperm membranes has drawn attention to their susceptibility to peroxidative changes. Most of the sperm men

Table 1 Sperm Parameters in 19 Subfertile Men Before and After 90 Days of Treatment with Pycnogenol®

Pycnogenol® treatment	Baseline count	Baseline motility score	Baseline morphology	Capacitated count	Capacitated motility	Capacitated morphology	Mannose binding
Before	118.0 ± 17.2	145.8 ± 11.5	4.3 ± 0.6	87.8 ± 11.0	248.3 ± 5.9	8.9 ± 0.8	32.9 ± 1.8
After	92.0 ± 10.5	132.6 ± 14.3	4.9 ± 0.6	89.7 ± 9.7	238.4 ± 15.7	11.4* ± 0.9	37.8** ± 1.1

Values are mean ± SEM.

Normal ranges: count 20 million/mL, motility score ≥ 150, morphology ≥ 14%, mannose binding ≥ 36%.

*P = .001.

**P < .005.

brane's polyunsaturated fatty acids contain carbon atoms with five and six double bonds. PUFA containing two or more double bonds are readily attacked by oxygen radicals, so sperm lipids that are very enriched in fatty acids possessing five or six double bonds are particularly vulnerable to peroxidation.¹¹

When sperm membrane proteins are damaged, the membranes become "leaky," and eventually the membrane breaks down completely, leading to the functional impairment of sperm.¹² Altered sperm structure and function due to ROS may be evidenced by loss of sperm motility,¹³ midpiece abnormalities,¹⁴ decreased sperm and oocyte fusion (binding),⁵ and abnormal morphology.²

Normally, the seminal fluid surrounding sperm contains antioxidant factors (glutathione, urate, ascorbate, α -tocopherol, taurine, etc.), protecting them from oxidative damage.¹¹ In many subfertile men, however, for poorly understood reasons, the seminal fluid may either lack sufficient protective elements or the man's body may be so overloaded with ROS so as to overwhelm the normal inherent antioxidative mechanisms. Increased levels of ROS may be generated internally from damaged or defective sperm as well as from leukocytes in seminal plasma.¹⁵ High levels of circulating ROS may result from external sources, such as air/water pollution and common environmental toxin exposures, for which it has been widely suggested that we all take daily antioxidant supplements.

Iwasaki¹⁶ detected ROS formation in 40% of semen specimens from men attending an infertility clinic. Mazilli and coworkers¹⁷ found significantly elevated levels of superoxide anion in 87% of infertile patients.

It is common knowledge that severe defects in sperm morphology render sperm dysfunctional and greatly reduce a couple's chances of pregnancy with either coitus or intrauterine insemination. In-

fertile couples may therefore need to resort to donor sperm inseminations or costly advanced assisted reproductive techniques, such as IVF. Many couples reject the notion of donor sperm insemination, as they prefer to pass the male partner's genes on to their offspring. Other patients are unable to undergo IVF due to either religious beliefs or cost restrictions.

A number of glycoproteins on the oocyte's zona pellucida play a role in the binding of human sperm to the egg. The predominant sugar residue in this glycoprotein is mannose. Mannose residues are hypothesized to interact with a sperm surface enzyme as part of the recognition mechanism leading to sperm/oocyte binding. This sperm surface enzyme is expressed on a percentage of normal sperm following capacitation.^{18,19}

The MBA allows measurement of the ability of sperm to bind to α -D-mannose. Although a normal MBA does not guarantee fertilization or fertility, as it tests only the first step in the complex of sperm/egg interactions, data show that normal MBA levels correlate with normal fertilization *in vitro*.^{20,21}

This study demonstrated a 38% mean improvement in capacitated sperm morphology following three months of Pycnogenol® therapy in a group of subfertile men. Additionally, a significant mean increase, 19%, in the MBA after Pycnogenol® treatment was found. The increase in morphologically and functionally normal sperm may allow infertile couples diagnosed with teratozoospermia to forgo IVF and donor sperm insemination and thereby undergo less stressful, invasive and expensive fertility-enhancing procedures, such as intrauterine insemination with the male partner's sperm.

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