Patent:
Austria 503.219
European Union 1.978.949
Eurasia 015.422
USA 9,623,042

For the specific dietary management
of **male fertility disorders**

PROFERTIL®

Product Monograph

for health care professionals

Edition 3 / INT

PROfertil®
also trademarked as PROfortil®

CONTENTS

PART 1:
HEALTH CARE PROFESSIONAL INFORMATION

PRODUCT INFORMATION SUMMARY

Route of Administration	Dosage Form	Clinical Use
Oral	1x2 capsules daily for a period of at least three months in order to optimize each individual phase of spermatogenesis. However, nutritional support with PROfertil® can and should be continued until pregnancy.	Intended for the specific dietary management of male patients with fertility disorders whose distinctive nutritional requirements resulting from this condition cannot be met through a dietary modification alone.

PRODUCT DESCRIPTION

PROfertil® is a food for special medical purposes – a specific food product category which is intended for the dietary management of fertility disorders in men. PROfertil® must be used only under medical supervision. For additional information about food for special medical purpose, please refer to page 3.

PATENTED COMPOSITION

The patented composition of PROfertil® consists of
L-carnitine
L-arginine
Coenzyme Q10
Vitamin E
Zinc
Folic acid
Glutathione
Selenium

Patent registration numbers:
Austria 503.219
European Union 1.978.949
Eurasia 015.422
USA 9,623,042

INDICATION AND CLINICAL/DIETARY USAGE

PROfertil®

- is a nutritional support to improve all parameters in sperm (motility, morphology, count and volume) necessary for successful conception and pregnancy and to reduce DNA fragmentation in sperm cells
- may be used as a nutritional support for persons with reduced sperm quality in case of sub-clinical varicoceles
- increases the possibility of successful conception and pregnancy for primary as well as secondary infertility (2nd child)
- may be used as an assistance for ART treatment options in case of male factor fertility problems

CONTRAINDICATIONS

Hypersensitivity: PROfertil® is contraindicated in patients with a known hypersensitivity to any ingredients contained in the product.
PROfertil® does not contain any ingredients of animal origin and is free of any major food allergens as listed in the EU Food Information for Consumers Regulation (EU FIC).

ADVERSE EFFECTS, PRECAUTIONS, DRUG INTERACTIONS

No adverse events were reported in clinical studies with PROfertil®.

All studies comply with the requirements of the EU regulations on food for special medical purposes that the benefits and safety of these products shall be demonstrated by generally accepted scientific data. This is also reflected in corresponding publications in renowned clinical, peer reviewed medical journals.
Furthermore, from first marketing in 2006 in Austria and subsequently in many countries all over the world up to now, no product related adverse events have been identified. This gives a strong evidence of a long history of safe use for PROfertil®.

No interactions with medications have been observed so far.

DOSAGE AND ADMINISTRATION

PROfertil® is supplied in packs for one month serving (60 capsules) and for three months serving (180 capsules). Two capsules should be taken per day with or after a meal and together with something to drink. The capsules should be taken for a period of at least three months in order to assure complete nutritional support to optimize each individual phase of spermatogenesis.
However, PROfertil® can and should be continued until pregnancy.

FOOD FOR SPECIAL MEDICAL PURPOSES

PROfertil® is a food for special medical purposes and is intended for the dietary management of fertility disorders in men with the desire to have children. Within the European Union, foods for special medical purposes are a specific category of food which are specially processed or formulated and intended for the dietary management of patients and which may be used only under medical supervision. They are intended for the exclusive or partial feeding of patients with limited or impaired capacity to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites; or for patients with other special medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone. This means that in contrast to food supplements the purpose of which is to supplement the normal diet of a healthy person, food for special medical purposes are intended for patients to provide nutritional support which is specifically modified for the management of the special nutrient requirements that result from the specific disease or condition.
The specific medical condition "male fertility disorders" has been scientifically established to result in specific medically-determined nutrient requirements for patients. To manage these specific nutrient requirements a specifically formulated combination of micronutrients, such as those in PROfertil® should be given under medical supervision.

TRADEMARK

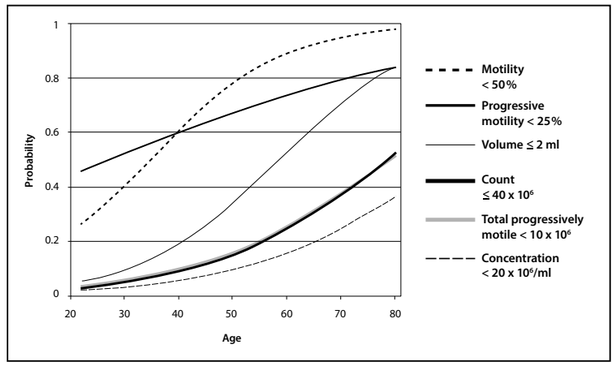
PROfertil® / PROfortil®

PART 2:
SCIENTIFIC INFORMATION

MALE SUBFERTILITY

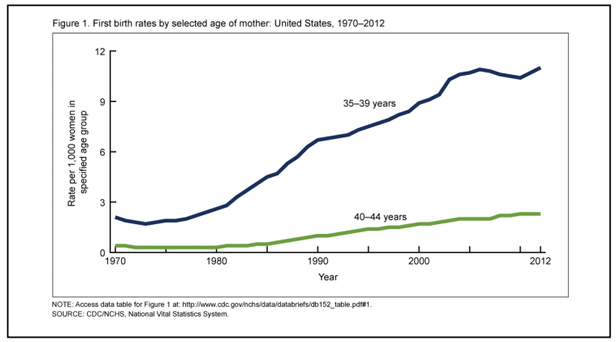
In recent decades, fertility disorders affect a steadily growing number of couples, approximately 15% of them are unable to conceive after one year of unprotected intercourse. In addition to the increased rates of different illnesses and disabilities found in women at childbearing age, postponed childbirth becomes increasingly common in Western countries, especially among groups with higher education qualifications (1). The trend for parenthood at an older age has also been seen in men. Since 1980, the fertility rate for men in their thirties has decreased by 21% and for men in their fourth decade , the rate has decreased nearly 30%. At the same time, the fertility rate in men at an age younger than 30 years has decreased by 15% (2). In addition to the fact that older men usually have older female partners, increasing male age is associated with increased time until pregnancy. The causes are the age-related increase in acquired illnesses, a decline in semen quality, and increasing sperm DNA fragmentation rates. In addition, there is an association between age of the male partner and the incidence of birth defects and chromosomal abnormalities. The male factor is believed to be solely responsible in about 20% of infertile couples and contributory in another 30-40% (3). In approximately half of childless couples the semen analysis parameters lie outside the normal range (4). In 30% to 80% of male subfertility cases, oxidative stress may be the cause of sperm quality decline (5). Small amounts of reactive oxygen species seem to be necessary for spermatozoa to acquire fertilizing capabilities (6, 7). However, an excessive amount of reactive oxygen species may be the cause of lipid-peroxidation-induced damage and pathological changes in sperm DNA (8 -11). The possible use of antioxidants to alleviate oxidative stress in spermatozoa has been proven as a strategy for dietary management (12, 13).

SPERM ABNORMALITY INCREASES WITH AGE



Eskenazi B. et al. The association of age and semen quality in healthy men. Hum. Reprod. 2003;18:447-454.

BIRTH AGE OF WOMAN INCREASES



Mathews TJ and Hamilton BE. First Births to Older Women Continue to Rise. NCHS Data Brief No. 152. May 2014

MICRONUTRIENTS

Dietary management is an important part of the therapy of fertility disorders. Some trace elements, vitamins and other substances, being vitally important for different stages of spermatogenesis, are lacking in sub-/infertile men. L-carnitine is considered to be the energy substrate of spermatozoa. Free L-carnitine positively correlates with sperm count, motility, and motile sperm density (14 -16). L-arginine is the immediate precursor of nitric oxide which may be beneficial for sperm viability and motility (17, 18). Vitamin E may improve sperm motility and common fertilization ability (11, 19). In combination with selenium, vitamin E may increase sperm motility and normal morphology rates (20). Selenium is considered to be an essential component of the enzyme glutathione peroxidase, and is required for the production of this enzyme when glutathione is supplemented. Testicles contain high selenium concentrations, and sperm quantity and quality are decreased in selenium-deficient humans (21, 22). Zinc may be involved in DNA transcription, protein synthesis, testicular development, and sperm maturation, and it is thought to extend functional life span of ejaculated spermatozoa (23). Low seminal zinc levels correlate with decreased fertility potential (24) and zinc supplementation has shown positive effects on sperm parameters (25). Folic acid is required for DNA synthesis and thus may be important for spermatogenesis (26). The supplementation of folic acid with glutathione plays a key role in protein and DNA synthesis. In sub-/infertile men, lower glutathione levels seem to be related to abnormal sperm motility and morphology (27). A positive effect of glutathione intake on sperm motility and morphology has been reported (28, 29). Coenzyme Q10 is deeply involved in body energy metabolism, 95% of all ATP is converted with the aid of coenzyme Q10 (30). Coenzyme Q10 may increase sperm motility in infertile men (31). Taking into account the potential efficacy for the dietary management of male fertility disorders, the eight above mentioned micronutrients have been considered as vitally important for improvement of sperm quality and selected as components of PROfertil®.

CONCLUSION

- Successful natural and/or assisted conception decreases with age in women and men.
- The male factor can be seen as the main or additional cause of infertility in approx. 50% of the cases.
- Dietary factors, oxidative stress, and deficiency of micronutrients may be regarded as the most common causes of male fertility disorders.
- Nutritional support through micronutrient therapy may promote the improvement of sperm quality and increases the likelihood of successful conception and pregnancy, and bearing a healthy child.

The likelihood of conceiving a child decreases with age for women and MEN alike.

CLINICAL STUDIES:
5 STUDIES USING THE PROFERTIL® FORMULATION

Currently, there are 5 studies with 782 patients, showing the efficacy of PROfertil®.

STUDY 1: L-CARNITINE STUDY

Lipovac M., Bodner F., Imhof M., Chedraui P.

Comparison of the effect of a combination of eight micronutrients versus a standard mono preparation on sperm parameters.

Published in Reprod Biol Endocrinol. 2016 Dec 9;14(1):84.

Number of patients: 299 (143 treatment group, 156 L-carnitine group)

Sperm motility is one of the most important sperm parameters in the initial investigation of the male- factor-infertility. The extent of progressively motile spermatozoa in the ejaculate is of biological significance and related to pregnancy rates (32, 33). In several studies, L- carnitine has been investigated in male infertility with the conclusion that it may significantly improve sperm parameters, and has been used for many decades as a monosubstance and in various combined preparations (4, 16, 34, 35). ***This prospective, open-labelled, non-randomized study demonstrated that, in subfertile men treated with PROfertil®, improvement of sperm density, overall progressive and fast progressive motility was significantly better than those in the mono-preparation group.***

STUDY 2: DNA STUDY

Lipovac M., Bodner F., Schütz A., Kurz H., Riedl C., Mair J., Imhof M.

Increased hyaluronan acid binding ability of spermatozoa indicating a better maturity, morphology, and higher DNA integrity after micronutrient supplementation

published in EMJ Urology 2014; 1:60-65e

Number of patients: 107 (67 treatment group, 40 control group)

Conventional sperm quality parameters (volume, count, motility, and morphology) are important for fertility and their assessment is of high value. However, they are poor predictors for reproductive outcome. Although fertile men have higher average sperm parameters, there is a significant overlap between fertile and infertile men (36). Approximately 15% of infertile men have a normal semen analysis (37). Routine sperm parameters do not characterize sperm as a carrier of the paternal genome. However, paternal genetic information, contained in sperm as DNA, is an important pre-condition for fertilization, pregnancy, and birth of healthy offspring, and DNA integrity is its valuable predictor. Sperm DNA integrity can be assessed by hyaluronan-acid-binding assay, which works on live mature sperm and allows a high-quality sperm selection for ART (38). Hyaluronan-acid- bound sperm is viable, has normal morphology, and shows low rates of DNA fragmentation and aneuploidy (38-40). ***This open controlled study demonstrated that, in sub-/infertile men treated with PROfertil®, sperm hyaluronan-acid-binding values may significantly increase.*** *The sperm hyaluronan-acid-binding assay seems to be an appropriate method for an indirect assessment of sperm maturity, which is of importance for enabling natural and ART fertilization, reducing rate of miscarriages and birth defects.*

STUDY 3: CONTROLLED STUDY

Imhof M., Lackner J., Lipovac M., Chedraui P., and Riedl C.

Improvement of sperm quality after micronutrient supplementation

published in e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, December 2011; Europ. Urolog. Review Vol. 6 Issue 6

Number of patients: 205 (132 treatment group, 73 control group)

Based on the positive results of the proof-of-concept pilot study which was performed from 2006 to 2008 on PROfertil® composition, a further controlled study was completed in 2010.
This open comparative study demonstrated improvement of all fertility-relevant sperm quality parameters (count, motility, and morphology) in sub-/infertile men treated with PROfertil® compared to the control group as well as an increase in the number of spontaneous pregnancies in couples in which men were treated with PROfertil® compared to the control group.

STUDY 4: SUBCLINICAL VARICOCELE STUDY

Schauer I., Jost R., Imhof M.

Micronutrients as an alternative to fertility treatment in men with subclinical varicocele

presented at Fortbildungstagung der Österr. Gesellschaft für Urologie und Andrologie, Linz, Austria 2010 and EAU Bratislava 2010

Number of patients: 51

Based on the significance of varicocele in male infertility as well as absence of appropriate drug treatment for subclinical varicocele (41-45) it was proposed that the application of antioxidants and trace elements might be an acceptable option for sub-/infertile men with subclinical varicocele.
This proof-of-concept study demonstrated improvement of all fertility-relevant sperm quality parameters (volume, count, motility, and morphology) in sub-/infertile men with subclinical varicocele receiving PROfertil® as well as an increase in number of spontaneous pregnancies in the respective couples.

STUDY 5: PILOT STUDY

Imhof M., Matthai C., Huber J.C.

The use of the nutraceutical "PROfertil®" – a dietary management of the "male factor" for the improvement of semen quality

presented at EAU Bratislava 2010

Number of patients: 120

Based on results of several studies on dietary intake of antioxidants and trace elements (11, 19, 28, 46-50) it was proposed that a well-balanced combination of eight micronutrients might ameliorate sperm parameters in men with idiopathic infertility.
This proof-of-concept pilot study, performed from 2006 to 2008, demonstrated improvement of all sperm quality parameters (volume, count, motility, and morphology) in sub-/infertile men treated with PROfertil® as well as an increase in number of spontaneous pregnancies in couples in which men were treated with PROfertil®.

STUDY 1 - L-CARNITINE STUDY: PROFERTIL® VS. MONO-PREPARATION

Lipovac M., Bodner F., Imhof M., Chedraui P.

BioMed Central
Reproductive Biology and Endocrinology

Comparison of the effect of a combination of eight micronutrients versus a standard mono preparation on sperm parameters

Published in Reprod Biol Endocrinol. 2016 Dec 9;14(1):84.

Number of patients: 299 (143 treatment group, 156 L-carnitine group)

Study Setting	PROfertil® group	L-carnitine group
Inclusion criteria	Subfertile men (≥ 1 year) between 20 and 60 years of age, with at least one recent (≤ 3 months) pathological semen analysis (WHO 1999)	
Exclusion criteria	Azoospermia, aspermia, varicocele, recent urogenital infections, and hormonal disorders	
Parameter	143 subfertile men, age 20 to 60	156 subfertile men, age 20 to 60
Treatment	2 capsules/day PROfertil® for 3 months	500 mg L-carnitine twice a day for 3 months

INTRODUCTION

10–15% of couples trying to achieve pregnancy remain childless (51). Male factor accounts for nearly half of cases of infertility presenting an abnormal semen analysis. In 45% of sub-/infertile men, this disorder is of unexplained (unidentified) origin (4, 52). In a Cochrane review, it has been reported that antioxidant supplementation in sub-fertile males may improve the outcomes of live birth and pregnancy rate for sub-fertile couples undergoing ART cycles (53). The suspected mechanism of action is the improvement of sperm quality through the alleviation of the nutrient deficiency as well as the reduction of oxidative stress (11).

AIM OF THE STUDY

The aim of this prospective, open-labelled, non-randomized study was to compare the short term effect of a combination of eight micronutrients (including L-carnitine) vs. a standard mono-substance (L-carnitine alone) on sperm parameters.

MATERIALS AND METHODS

Patients received 3 months treatment either with a mono-substance (L-carnitine 1000 mg) or a combined compound (L-carnitine 440 mg, L-arginine 250 mg, zinc 40 mg, vitamin E 120 mg, glutathione 80 mg, selenium 60 µg, coenzyme Q10 15 mg, and folic acid 800 µg; PROfertil®, Lenus Pharma, Seeboeckgasse 59, 1160 Vienna, Austria).

PATIENTS & STUDY DESIGN

From 2005 to 2014, 299 patients of the IMI Fertility Center and the Med19 Study Center of Vienna, Austria, were enrolled in the study. Patients met inclusion criteria: 20 to 60 years of age, suffering from at least 1 year of subfertility and had at least one recent pathological semen analysis result (up to 3 months, considered baseline, according to WHO guidelines (4th edition). 156 subfertile men received treatment with a mono-substance (control group) and 143 the combined preparation (treatment group). The following sperm parameters were analysed at baseline and after treatment: sperm volume (ml) and density (mio/ml), overall, fast and slow progressive motility (expressed as %), and % of sperm with normal morphology.

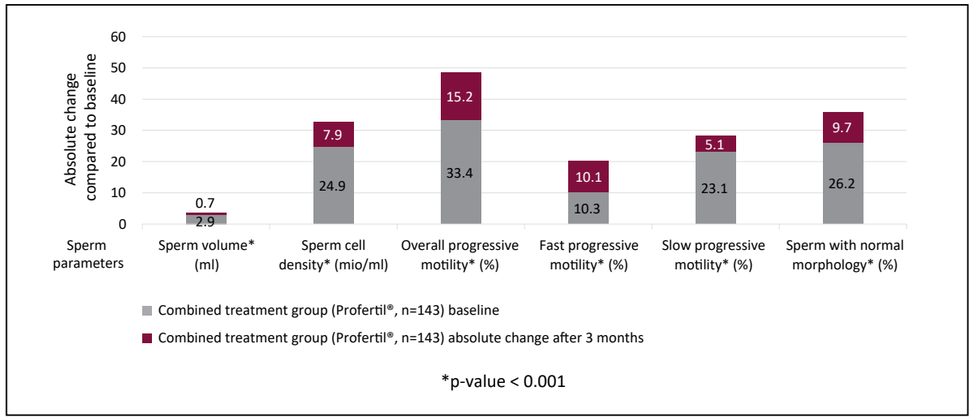
STATISTICAL ANALYSIS

Statistical analysis was performed with the Statistical Package for the Social Sciences version 22.0 (IBM SPSS, Armonk, NY, USA). All data are presented as mean ± standard deviations. The Kolmogorov Smirnov test was used to assess the normality of data distribution. For each measured variable and each case changes from baseline (increase, decrease or none) were calculated as absolute (subtraction of 3rd month value minus baseline) or relative values (the percent expression of each calculated absolute value). Paired Student's T test was used for intragroup comparisons. Non paired Student's T test or the Mann Whitney U test was used for intergroup comparisons. A p value of <0.05 was considered as statistically significant.

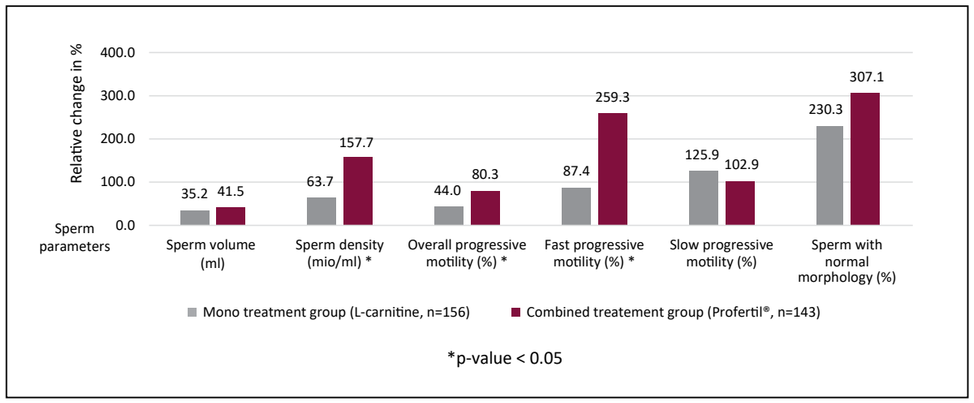
RESULTS

All studied sperm parameters (volume, density, overall progressive motility [including slow and fast motility]) and % of sperm with normal morphology significantly improved after 3 months of treatment in both groups as compared to baseline (p<0.001). However, ***relative change (expressed as % increase of absolute values) for sperm density and overall progressive motility (including fast motility) was found to be higher for the combined micronutrient treatment group as compared to the mono-treatment group using L-carnitine alone (p<0.05).***

IMPROVEMENT OF SPERM PARAMETERS AFTER 3 MONTHS OF PROFERTIL® INTAKE



RELATIVE CHANGE OF SPERM PARAMETERS AFTER 3 MONTHS TREATMENT (PROFERTIL® GROUP COMPARED TO MONOSUBSTANCE GROUP)



DISCUSSION

The effect of the administered mono-substance composed of the hydrophile molecule L-carnitine can be ascribed to its properties as a radical catcher in the mitochondrial membrane. By substitution anti-oxidative capacity in the seminal plasma increases significantly (15). Moreover, studies in animals have shown that the molecule has protective effects on testicular tissue which has been exposed to ionising radiation (54, 55). This realisation can have a relevant effect on sperm quality in certain daily situations. Both effects serve as an explanation model for the positive influence of L-carnitine on sperm concentration, motility and morphology (16, 56, 57). Consistent with these studies, our study found that L-carnitine alone or in combination with seven other micronutrients displayed short term improvement of all studied sperm parameters. Nevertheless, the combined preparation showed better results through a higher percent increase for sperm density and overall progressive motility (including fast motility) as compared to L-carnitine alone. To the best of our knowledge this research may be the first to prospectively compare the short-term effects of a mono treatment versus a combined product on sperm parameters.
L-carnitine seems not the sole actor in sperm production. As already mentioned, the combined compound displayed a better improvement of sperm density and overall progressive motility. This is important because motility seems to be a key parameter of male fertility. The effect of the combination substance is to be seen as the sum of the partly augmentative effects of each component. The diverse target points for eight micronutrients and their partially synergistic cooperation in different body compartments serve as an explanatory model for its selective superiority as compared to the mono-therapy with L-carnitine alone.

CONCLUSION

- Overall effect on sperm parameters was similar in both analyzed groups.
- In the PROfertil® group improvement of sperm density, overall and fast progressive motility was significantly better than those in the mono-preparation group.

PRACTICAL BENEFITS:

In subfertile men, nutritional support with PROfertil® may
- significantly improve standard sperm parameters,
- improve sperm density significantly more effective than mono-preparation alone,
- improve overall progressive sperm motility significantly more effective than mono-preparation alone,
- improve fast progressive sperm motility significantly more effective than mono-preparation alone, and, thus,
- increase the likelihood of successful natural and/or assisted conception, pregnancy, and offspring health.

i

Therapy with the PROfertil® combination showed significantly better improvement of sperm density, overall and fast progressive motility as compared to mono-substance alone.

STUDY 2 – DNA STUDY: DNA FRAGMENTATION IN SUBFERTILE MEN

M. Lipovac, F. Bodner, A. Schütz, H. Kurz, C. Riedl, J. Mair, M. Imhof

EMJ EUROPEAN MEDICAL JOURNAL

Increased hyaluronan acid binding ability of spermatozoa indicating a better maturity, morphology, and higher DNA integrity after micronutrient supplementation

published in EMJ Urology 2014; 1:60-65e

Number of patients: 107 (67 treatment group, 40 control group)

Study Setting	PROfertil® group	Control group
Inclusion criteria	Infertile men (> 1 year) with 2 pathological semen analyses	
Exclusion criteria	Varicocele, aspermia, azoospemia and recent urogenital infections	
Parameter	67 men, mean age 34 (18-43)	40 men, mean age 38 (22-52)
Treatment	2 capsules/day PROfertil® for 3 months	Dietary plan for 3 months

INTRODUCTION

There is growing evidence highlighting the role of sperm nuclear DNA integrity in male factor sub-/infertility. Reports indicate that a higher amount of DNA damage is associated with a negative effect on fertility potential (25, 58, 59). While sub-/infertile men with poor semen parameters tend to have high levels of sperm DNA damage, increased DNA fragmentation can also be seen in 8% of men with normal semen analysis (59). Sperm DNA integrity can be estimated by various methods, the sperm hyaluronan binding assay (SHBA) is one option. Only sperm which has gone through all stages of development is able to recognize hyaluronan as a component of the human zona pellucida. For this reason, DNA integrity is higher in hyaluronan-recognizing mature sperm. This is believed to be the main reason for the significant correlation between high SHBA values, good embryonic quality, and lower miscarriage rates.
Various agents have been used in an attempt to increase the fertility potential of men with decreased semen quality. To date there is still no proven therapy for the improvement of semen quality in this large group of men (60). Most of the essential compounds required for DNA synthesis and spermatogenesis are derived from the diet. Therefore, the concentration of required nutrients and other relevant factors may have substantial effects on sperm quality and reproduction (26, 61). A number of nutrients such as trace elements, vitamins, amino acids, and other agents involved in spermatogenesis have been examined and advocated as a way of optimizing sperm production and quality. A Cochrane review stated that antioxidant supplementation in sub-/ infertile men may improve reproductive outcomes (i.e. live births and pregnancy rates) among couples undergoing ART cycles (53). Studies examining the effect of a combination of several of the aforementioned elements and their effect over SHBA are still lacking.

AIM OF THE STUDY

The aim of the study was to evaluate the effect of a non-prescription nutraceutical containing eight micronutrients on values indicated by the SHBA (maturity, strict morphology, high DNA integrity, and reduced chromosomal aneuploidies) among males with idiopathic sub-/infertility.

MATERIALS & METHODS

Nutrient combination: 2 capsules per day containing L-carnitine 440 mg, L-arginine 250 mg, zinc 40 mg, vitamin E 120 mg, glutathione 80 mg, selenium 60 µg, coenzyme Q10 15 mg, and folic acid 800 µg.
(PROfertil®, Lenus Pharma, Seeboeckgasse 59, 1160 Vienna, Austria)
Assay: Sperm-HBA (Sperm-Hyaluronan Binding Assay Biocoat, Inc., 211 Witmer Road, Horsham, PA 19044, USA)

PATIENTS & STUDY DESIGN

A total of 67 sub-/infertile males (active treatment group) attending the Fertility Center IMI, Vienna, Austria were invited to participate and to take two capsules per day of the nutrient combination for a three-month period between the first and the follow-up semen analysis. Sub-/infertile men receiving no active treatment served as controls (n=40). The main outcome measure was the change in Sperm-HBA value indicating DNA fragmentation index after 3 months.

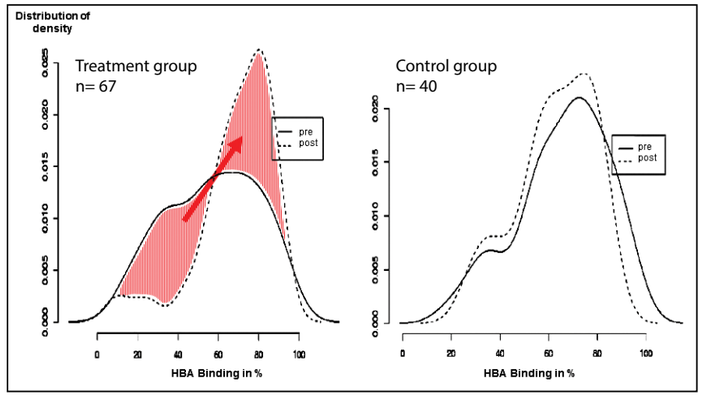
STATISTICAL ANALYSIS

There was no significant difference in patient age between test and control group. Analysis was performed by Kolmogorov Smirnov test (normality of data distribution), Mann Whitney test (continuous non parametric data), chi-square test (percentages) and Wilcoxon rank test.
A p-value <0.05 was considered as statistically significant.

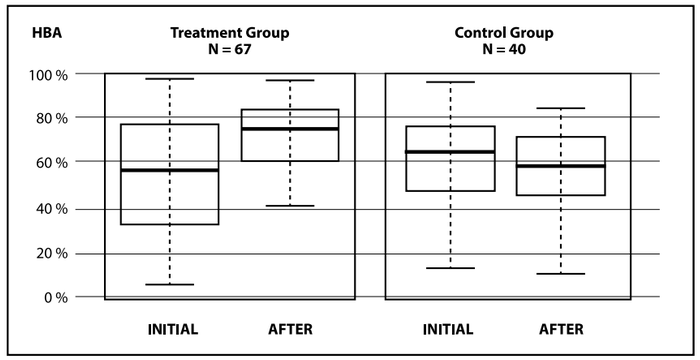
RESULTS

SHBA value significantly increased in the active group after 3 months of treatment with the nutrient combination, from a median baseline value of 56.0-74.0% (p<0.05). This represented a 19.7% increase compared to baseline, which was significantly higher than the 2.1% decrease observed in the control group. ***The rate of subjects displaying an increase in SHBA values after 3 months was significantly higher in the active group (74.6% versus 30.0%, p=0.0001).***

DATA BEFORE AND AFTER TREATMENT, COMPARED TO CONTROL



DATA BEFORE AND AFTER TREATMENT, COMPARED TO CONTROL



Parameter	Treatment group n=67	Control group n=40	p value*
Percent of sperm-hyaluronan binding at baseline	56.0 [41.0]	69.5 [23.3]	0.02
Percent of sperm-hyaluronan binding after 3 months	74.0 [21.0] **p=0.0001	64.5 [20.8] **p=0.03	0.01
Median percent change compared to baseline	19.7 [64.8]	-2.1 [7.6]	0.0001
Increase after 3 months n (%)	50 (74.6)	12 (30.0)	0.0001
Neutral after 3 months n (%)	2 (3.0)	2 (5)	0.99
Decrease after 3 months n (%)	15 (22.4)	26 (65.0)	0.0001

Data are presented as medians [interquartile ranges] and frequencies n (%).
* p value after comparing groups using the Mann Whitney test or the chi-square test.
** p value when compared to baseline (intragroup comparison) using the Wilcoxon rank test. :

DISCUSSION

The investigated nutrient combination was designed to treat idiopathic male sub-/infertility through the supplementation of several vitamins, enzymes, and trace elements required for optimal sperm cell metabolism, DNA synthesis during spermatogenesis, proliferation, and antioxidative protection. In consideration of their biochemical function, these ingredients are of great significance for male reproduction. A deficiency of these nutrients may result in male fertility disturbances.
To date, no study has reported on the use of a combination of eight of these nutrients (as performed in this study) and its effect on sperm hyaluronan-acid binding values. Yagci et al. (62) demonstrated that hyaluronan acid shows a high degree of selectivity for sperm with high DNA integrity. As Breznik et al. (63) stated, the HBA-slide is found to be useful in predicting the ability of spermatozoa to fertilize oocytes in IVF and is helpful in distinguishing semen samples suitable for IVF and intra-cytoplasmic sperm injection. These studies indeed demonstrate that the SHBA can be used for indirect measurement of sperm DNA integrity. An increase of hyaluronan acid-binding ability means that more motile and morphologically normal sperm with high DNA integrity are binding, which means a higher possibility of achieving an effective fertilization and a subsequent normal pregnancy. This seems to be an important approach in treating sub-/infertile couples as low DNA integrity values are associated with a lower probability of natural conception, a lower fertilizing potential of sperm used in AR techniques, a higher rate of disrupted embryonic development and miscarriages, and a higher probability of diseases in newborns (13). The examined nutrient combination was well tolerated by all participants and no adverse reactions appeared. All ingredients have been thoroughly examined for decades and toxicological data show that they exert no negative health effects or potential hazards, even at higher dosages than those used in the present study.

CONCLUSION

- Sperm HBA value significantly increased after 3 months of treatment with the active compound (p<0.05).
- The rate of subjects displaying an increase in SHBA values after 3 months was significantly higher in the active group (74.6% versus 30.0%, p=0.0001).
- In hyaluronan-acid-bound spermatozoa, the frequency of chromosomal disomy and diploidy was reduced 4- to 6-fold compared with morphologically selected sperm fractions (37, 38).
- The investigated combination seems to be a promising therapeutic approach for improving hyaluronan acid binding ability of spermatozoa in order to enable natural conception among couples with idiopathic male sub-/infertility.
- Hyaluronic acid-binding ability of spermatozoa is improved in sub-/infertile men after treatment with the nutrient combination without any adverse effects.

PRACTICAL BENEFITS

Nutritional support with PROfertil® may
improve sperm DNA integrity and thus improve spermatozoa maturity which may

- increase the probability of natural conception and pregnancy
- increase the likelihood of a successful conception and pregnancy in ART treatment
- reduce paternal genetic defects load and prevent recurrent miscarriages
- reduce paternal genetic defects load and the risk of birth defects

The investigated combination seems to be a promising therapeutic approach for improving hyaluronan acid binding ability of spermatozoa in order to enable natural conception among couples with idiopathic male sub-/infertility.

STUDY 3 – CONTROLLED STUDY: IMPROVED SPERM QUALITY

Imhof M., Lackner J., Lipovac M., Chedraui P., Riedl C.

e-SPEN Journal, Volume 7, Issue 1, February 2012

Improvement of sperm quality after micronutrient supplementation

published in e-SPEN, the European e-Journal of Clin. Nutrition and Metabolism, December 2011; Europ. Urolog. Review Vol. 6 Issue 6

Number of patients: 205 (132 treatment group, 73 control group)

Study Setting	PROfertil® group	Control group
Inclusion criteria	Infertile men (> 1 year) with 2 pathological semen analyses	
Exclusion criteria	Varicocele, aspermia, azoospemia and recent urogenital infections	
Parameter	132 men, mean age 34 (18-43)	73 men, mean age 38 (22-52)
Treatment	2 capsules/day PROfertil® for 3 months	Dietary plan for 3 months

INTRODUCTION

Nearly 50% of male infertility is idiopathic and to date there is still no proven therapy.

AIM OF THE STUDY

The effect of a non-prescription nutraceutical was evaluated containing eight micronutrients on sperm quality in males with idiopathic subfertility.

MATERIALS & METHODS

Nutrient combination: 2 capsules per day containing L-carnitine 440 mg, L-arginine 250 mg, zinc 40 mg, vitamin E 120 mg, glutathione 80 mg, selenium 60 µg, coenzyme Q10 15 mg, and folic acid 800 µg. (PROfertil®, Lenus Pharma, Seeboeckgasse 59, 1160 Vienna, Austria)

PATIENTS & STUDY DESIGN

This open comparative study was carried out at the Fertility Centre IMI, Vienna, Austria. A total of 132 subfertile males (active treatment group) were invited to participate and to take two capsules per day of PROfertil® for a three-month period between the first and the follow-up semen analysis. Subfertile men receiving no active treatment served as controls (n=73). The main outcome measure was the standardized semen analysis.

STATISTICAL ANALYSIS

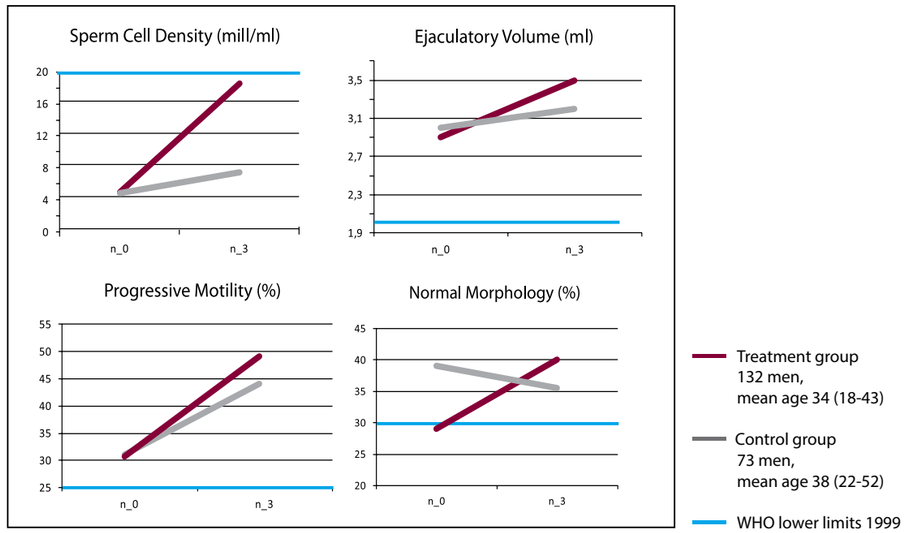
Statistical analysis was performed using SPSS® software package (Version 10.0 for Windows, SPSS Inc., Chicago, Illinois, US). Data are presented as means (minimum/maximum values), medians, inter-quartile ranges and percentages. The Kolmogorov Smirnov test was used to determine the normality of data distribution. According to this, differences between groups were analyzed with the Mann–Whitney test (continuous non-parametric data) whereas changes within each studied group were evaluated with the Wilcoxon rank test. A p-value <0.05 was considered as statistically significant.

RESULTS

All parameters evaluated by semen analysis significantly increased after three months of treatment with the nutrient combination. Median ejaculatory volume, sperm cell density, sperm motility (progressive and total) and normal morphology rate increased by 33.3, 215.5, 83.1, 36.4 and 23.0 %, respectively. These increments were significantly higher than those observed among controls. ***In the active treatment group no side effects were encountered and a total of 34 pregnancies were reported after six months follow-up,*** whereas 11 were reported in the control group.

Improvement in % after 3 months	PROfertil® group	Control group
Ejaculatory Volume (ml)	+ 33.3 %	+ 3.7 %
Sperm Cell Density (mill/ml)	+ 215.5 %	+ 46.4 %
Progressive Motility (%)	+ 83.1 %	+ 44.0 %
Total Motility (%)	+ 36.4 %	+ 33.9 %
Normal Morphology (%)	+ 23.0 %	-2.4 %

IMPROVEMENT OF SPERM QUALITY AFTER MICRONUTRIENT SUPPLEMENTATION (TREATMENT GROUP VS. CONTROL GROUP)



CONCLUSION

- Semen analysis results significantly improved in subfertile men after treatment with a nutrient combination, leading to pregnancies without any adverse effects.

PRACTICAL BENEFITS

Nutritional support with PROfertil® may

- ameliorate sperm quality (volume, density, motility and morphology) in subfertile men
- increase the likelihood of successful natural conception and clinical pregnancy rate

In the active treatment group no side effects were encountered and a total of 34 pregnancies were reported after six months follow-up.

STUDY 4 – SUBCLINICAL VARICOCELE STUDY: IMPROVED SPERM QUALITY

Schauer I., Jost R., Imhof M.

Micronutrients as an alternative to fertility treatment in men with subclinical varicocele

presented at Fortbildungstagung der Österr. Gesellschaft für Urologie und Andrologie, Linz, Austria 2010; EAU Bratislava 2010

Numbers of patient: 51

Study Setting	PROfertil® group
Inclusion criteria	Infertile men (> 2 years), >=1 pathological semen analysis and subclinical varicocele
Exclusion criteria	Infections, aspermia and hormonal disorders
Parameter	51 men, mean age 32 (18-43)
Treatment	2 capsules/day PROfertil® for 3 months

INTRODUCTION

Treatment with micronutrients represents another, substantially newer form of the sub- or infertility treatment of varicocele patients. While micronutrients and antioxidants are already used regularly in men with idiopathic fertility disorder and with predominantly positive results, this therapy option for men with varicoceles is still relatively unexplored, particularly compared with surgical or interventional radiological forms of treatment. Building on the theory that varicoceles lead to an increasingly inflammatory altered environment burdened by oxidative stress, studies that used anti-inflammatory drugs (NSARs such as e.g. Cinnoxicam) and antioxidant substances (Vitamin E, Glutathione, Coenzyme Q10 etc.) observed predominantly positive results (31, 64). Even the use of L-carnitine or L-acetylcarnitine to transport substances essential to fatty acids seems to hold therapeutic potential on its own or in combination with an anti-inflammatory drug (65). The therapeutic use of micronutrients such as zinc, selenium, folic acid, etc., has to date been investigated very little in connection with varicoceles, but it has brought significant improvements as a combination preparation with antioxidants (66).

MATERIALS & METHODS

Nutrient combination: 2 capsules per day containing L-carnitine 440 mg, L-arginine 250 mg, zinc 40 mg, vitamin E 120 mg, glutathione 80 mg, selenium 60 µg, coenzyme Q10 15 mg, and folic acid 800 µg. (PROfertil®, Lenus Pharma, Seeboeckgasse 59, 1160 Vienna, Austria)

PATIENTS & STUDY DESIGN

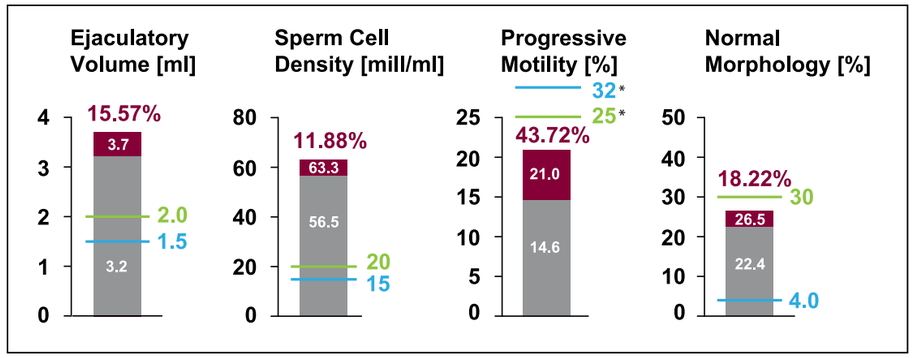
In the context of this study, after the exclusion of infections, aspermia and hormonal disorders, 55 men (age: 18-43; avg. 32 years) with subclinical varicocele (WHO classification 0.1), two pathological semen analyses (at least one month apart) and an unfulfilled desire for children for more than 2 years (avg. 2.7 years) took 2 capsules of PROfertil® per day over a period of three months.

RESULTS

The post-treatment evaluation resulted in an improvement of all sperm parameters and the ***occurrence of a pregnancy in 41.18%.***

Improvement in % after 3 months	
Ejaculatory Volume (ml)	+ 15.57 %
Sperm Cell Density (mill/ml)	+ 11.88 %
Progressive Motility (%)	+ 43.72 %
Total Motility (%)	+ 15.99 %
Normal Morphology (%)	+ 18.22 %

IMPROVEMENT OF SPERM QUALITY AFTER MICRONUTRIENT SUPPLEMENTATION (PRE-TREATMENT DATA COMPARED TO POST-TREATMENT DATA)



* The assessment of progressive motility according to grades, as recommended by the WHO 1987-1999 manuals, was replaced by categorizing motile sperm as being 'progressive' or 'non-progressive'. WHO 1999 ≥ 25% (grade a); WHO 2010 32% (a + b)

CONCLUSION

- The post-treatment evaluation resulted in improvement of all sperm parameters and the occurrence of pregnancy in 41.18%
- Treatment with micronutrients seems to offer a possibility of improving sperm quality and thus fertility particularly for men with subclinical and low-grade varicoceles, for whom a surgical or interventional cure is not indicated or holds more risk than benefit
- No adverse effects

PRACTICAL BENEFITS

Nutritional support with PROfertil® may

- improve sperm quality in infertile men with subclinical varicocele and no indication or contraindication for surgery
- improve spontaneous pregnancy rate
- optimize the varicocelectomy outcome as a concomitant therapy

The post-treatment evaluation resulted in an improvement of all sperm parameters and the occurrence of a pregnancy in 41.18%.

STUDY 5 – PILOT STUDY: PILOT STUDY ON COMPOSITION

Imhof M., Matthai C., Huber J.C.

The use of the nutraceutical "PROfertil®" – a dietary management of the "male factor" for the improvement of semen quality

presented at EAU Bratislava 2010

Number of patients: 120

Study Setting	PROfertil® group
Inclusion criter	Infertile men (> 2 years) with 2 pathological semen analyses
Exclusion criteria	Varicocele, infections, aspermia and hormonal disorders
Parameter	120 men, mean age of 35.9 (23-58) years
Treatment	2 capsules/day PROfertil® for 3 months

INTRODUCTION

The reason for infertility may be ascribed equally to both men ("male" factor) and women ("female" factor). There has been a steady rise during the last decade concerning the number of pathologic semen analysis. Until today there is no proven therapy for the improvement of semen quality.

AIM OF THE STUDY

The aim of this study is to administer a nutrient combination comprising 8 substances, which are all known to improve semen quality. The hypothesis is that the effect of the single substances accumulates and therefore ensures a stronger response.

MATERIALS & METHODS

Nutrient combination: 2 capsules per day containing L-carnitine 440 mg, L-arginine 250 mg, zinc 40 mg, vitamin E 120 mg, glutathione 80 mg, selenium 60 µg, coenzyme Q10 15 mg, and folic acid 800 µg. (PROfertil®, Lenus Pharma, Seeboeckgasse 59, 1160 Vienna, Austria)

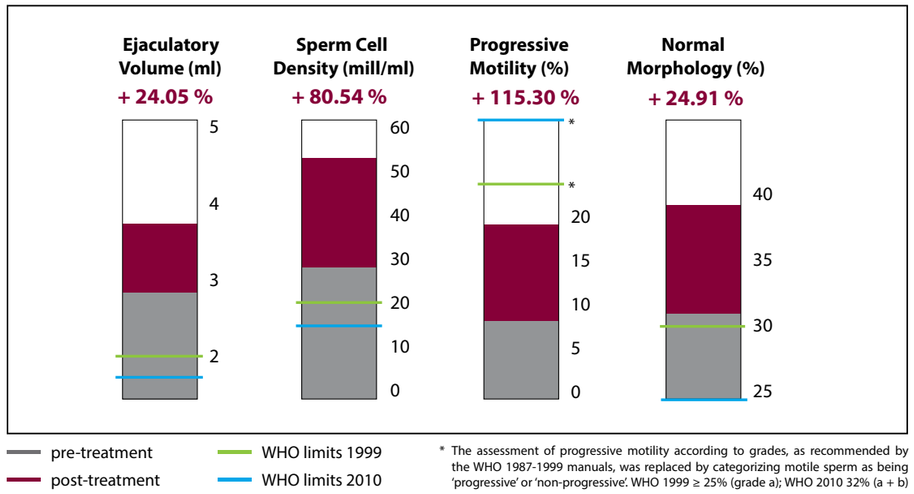
PATIENTS & STUDY DESIGN

The study collective contains 120 men, on average 35.9 years old (23-58), long-term childlessness (> 2 years) and at least 2 pathologic semen analyses in their anamnesis. Patients with azoospermia, aspermia, varicosis of the testes and urogenital infections were excluded. The patients took 2 capsules of PROfertil® per day for a period of 3 months. After the period of 3 months a control semen analysis was performed.

RESULTS

The sperm cell density increased on average from 29.46 million/ml to 53.19 million/ml (+ 80.54%), with an average 23.73 million increase in sperm density per millilitre. The ejaculate volume increased from 2.91 ml to 3.61 ml (+ 24.05%). The number of progressively motile sperm increased from 8.95% to 19.27% (+115.3%) on average. Total motility (excluding static sperm) showed a cumulative increase from 33.13% to 49.27% (+ 48.71%). The number of sperm with normal morphology improved from 31.14% to 38.90% (+24.91%). 30 of 120 subjects achieved a normal sperm count without any abnormalities. 21 pregnancies have been reported.

Improvement in % after 3 months	
Ejaculatory Volume (ml)	+ 24.05 %
Sperm Cell Density (mill/ml)	+ 80.54 %
Progressive Motility (%)	+ 115.30 %
Total Motility (%)	+ 48.71 %
Normal Morphology (%)	+ 24.91 %



* The assessment of progressive motility according to grades, as recommended by the WHO 1987-1999 manuals, was replaced by categorizing motile sperm as being 'progressive' or 'non-progressive'. WHO 1999 ≥ 25% (grade a); WHO 2010 32% (a + b)

CONCLUSION

- 30 of 120 subjects achieved a normal sperm count without any abnormalities
- 21 pregnancies have been reported
- These results confirm the hypothesis that the combination of individual substances as described in literature shows significantly better results than the sum of the effects of single administration

PRACTICAL BENEFITS

Nutritional support with PROfertil® may

- ameliorate sperm quality in subfertile men
- improve all sperm fertility-relevant parameters
- increase the likelihood of successful natural conception and clinical pregnancy rate
- no adverse effects

30 of 120 subjects achieved a normal sperm count without any abnormalities. 21 pregnancies have been reported.

REFERENCES

1. Lampic C et al. Fertility awareness, intentions concerning childbearing, and attitudes towards parenthood among female and male academics. Hum Reprod. 2005;21:558–564.
2. Martin JA et al. Births: final data for 2006. National Vital Statistics Reports.2009;57:1–101.
3. Thonneau P et al. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988-1989). Hum Reprod 1991; 6:811.
4. Cavallini G. Male idiopathic oligoasthenoteratozoospermia. Asian J. Androl. 2006; 8 (2), 143–57.
5. Gharagozloo P, Aitken RJ. The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy. Hum Reprod. 2011 Jul;26(7):1628-40.
6. Aitken RJ: Molecular mechanisms regulating human sperm function. Mol Hum Reprod 1997; 3:169–173.
7. Gagnon C et al. Reactive oxygen species and human spermatozoa. Ann N Y Acad Sci 1991; 637:436–444.
8. Wang X et al. Oxidative stress is associated with increased apoptosis leading to spermatozoa DNA damage in patients with male factor infertility. Fertil Steri. 2003;80:531-5.
9. Alvarez JG et al. Increased DNA damage in sperm from leukocytospermic semen samples as determined by the sperm chromatin structure assay. Fertil Steril. 2002 Aug;78(2):319-29.
10. Saleh RA et al. Negative effects of increased sperm DNA damage in relation to seminal oxidative stress in men with idiopathic and male factor infertility. Fertil Steril. 2003 Jun;79 Suppl 3:1597-605.
11. Suleiman SA et al. Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl. 1996 Sep-Oct;17(5):530-7.
12. Sharma RK, Agarwal A. Role of reactive oxygen species in male infertility. Urology. 1996 Dec;48(6):835-50.
13. Aitken RJ, De Iuliis GN. On the possible origins of DNA damage in human spermatozoa. Mol Hum Reprod. 2010; 16:3-13.
14. Menchini-Fabris GF et al. Free L-carnitine in human semen: its variability in different andrologic pathologies. Fertil Steril. 1984;42:263-7.
15. Balercia G et al. Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. Fertil Steril. 2005;84:662-71.
16. Lenzi A, Lombardo F, Sgro P, et al. Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. Fertil Steril. 2003 Feb;79(2):292-300.
17. Zhang H, Zheng RL. Possible role of nitric oxide on fertile and asthenozoospermic infertile human sperm functions. Free Rad Res. 1996;25:347-54.
18. Scibona M et al. L-arginine and male infertility. Minerva Urol Nefrol. 1994;46:251-3.
19. Kessopoulou E et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril. 1995;64:825-31.
20. Vezina D et al. Selenium-vitamin E supplementation in infertile men. Effects on semen parameters and micronutrient levels and distribution. Biol Trace Elem Res. 1996;53:65-83.
21. Oldereid NB et al. Selenium in human male reproductive organs. Hum Reprod. 1998;13:2172-6.
22. Scott R et al. The effect of oral selenium supplementation on human sperm motility. Br J Urol. 1998;82:76-80.
23. Kvist U 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.
24. Omu AE et al. Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. Eur J Obstet Gynecol Reprod Biol. 1998;79:179-84.
25. Venkatesh S et al. Clinical significance of sperm DNA damage threshold value in the assessment of male infertility. Reprod Sci. 2011;18:1005-13.
26. Wong WY et al. Male factor subfertility: possible causes and the impact of nutritional factors. Fertil Steril. 2000;73:435-42.
27. Raijmakers MT et al. Glutathione and glutathione S-transferases A1-1 and P1-1 in seminal plasma may play a role in protecting against oxidative damage to spermatozoa. Fertil Steril. 2003;79: 169-72.
28. Lenzi A et al. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod. 1993;8:1657-62.
29. Favilli F et al. Effect of orally administered glutathione on glutathione levels in some organs of rats: role of specific transporters. Br J Nutr. 1997;78:293-300.
30. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. 1995;1271:195-204.
31. Mancini A et al. Coenzyme Q10 evaluation in pituitary-adrenal axis disease: preliminary data. Biofactors. 2005;25:197–199.
32. Jouannet P et al., 1988; Male factors and the likehood of pregnancy in infertile couples. I. Study of sperm characteristics. International Journal of Andrology, 11, 379-384.
33. Larsen L et al. Computer-assisted semen analysis parameters as predictors for fertility of men from the general population. Hum. Reprod. (2000) 15 (7): 1562-1567.
34. Khademi A et al. The effects of L-carnitine on sperm parameters in smoker and non-smoker patients with idiopathic sperm abnormalities. J Assist Reprod Genet. 2005 Dec;22(11-12):395-9.
35. Costa M et al. L-carnitine in idiopathic asthenozoospermia: a multicenter study. Italian Study Group on Carnitine and Male Infertility. Andrologia. 1994 May-Jun;26(3):155-9.
36. Guzick DS et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med. 2001 Nov 8;345(19):1388-93.
37. Guzick DS et al. Efficacy of treatment for unexplained infertility. Fertil Steril. 1998 Aug;70(2):207-13.
38. Jakab A et al. Intracytoplasmic sperm injection: a novel selection method for sperm with normal frequency of chromosomal aneuploidies.Fertil Steril. 2005;84:1665–1673.
39. Huszar G et al. Fertility testing and ICSI sperm selection by hyaluronic acid binding: clinical and genetic aspects. Reprod Biomed Oline.2007;14:650–663.
40. Huszar G et al. Hyaluronic acid binding by human sperm indicates cellular maturity, viability, and unreacted acrosomal status. Fertil Steril. 2003;79:1616–1624.
41. Dubin L, Amelar RD. Etiologic factors in 1294 consecutive cases of male infertility. Fertil Steril. 1971;22:469–74.
42. Naughton CK et al. Pathophysiology of varicoceles in male infertility. Hum Reprod Update. 2001;7:473–81.
43. Witt MA, Lipshultz LI. Varicocele: a progressive or static lesion? Urology. 1993;42:541–3.
44. World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. Fertil Steril. 1992;57:1289–1293.
45. Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. Fertil Steril. 1993;59:613–616.
46. Eskenazi B et al. (2005) The association of age and semen quality in healthy men. Hum Reprod 18,447–454.
47. Apgar J (1985) Zinc and reproduction. Annu Rev Nutr 5,43–68.
48. Hunt CD et al. (1992) Effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations, and sperm morphology in young men. Am J Clin Nutr 56, 148–157.
49. H. Fuse, T. Kazama, S. Ohta, Y. Fujiuchi. Relationship between Zinc Concentrations in Seminal Plasma and Various Sperm Parameters. International Urology and Nephrology May 1999, Volume 31, Issue 3, pp 401-408.
50. Wallock LM, Tamura T, Mayr CA, Johnstin KE, Ames BN, Jacob RA. Low seminal plasma folate concentrations are associated with low sperm density and count in male smokers and nonsmokers. Fertil Steril. 2001;75(2):252-9.
51. Breckwoldt M, Kaufmann M, Pfleiderer A (Hg.). Gynäkologie und Geburtshilfe. 2008. Stuttgart:Georg Thieme Verlag.
52. Hancke K, Denschlag D, Gitsch G, Keck C. Therapeutische Ansätze bei idiopathischer Infertilität des Mannes. Geburtshilfe und Frauenheilkunde. 2006 Januar;(1):26–33.
53. Showell MG et al. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD007411.
54. Ahmed MM, Ibrahim ZS, Alkafafy M, El-Shazly SA. L-carnitine protects against testicular dysfunction caused by gamma irradiation in mice. Acta Histochem. 2014;116:1046–55.
55. Topcu-Tarladacalisir Y, Kanter M, Uzal MC. Role of L-carnitine in the prevention of seminiferous tubules damage induced by gamma radiation: a light and electron microscopic study. Arch Toxicol. 2009;83:735–46.
56. Lenzi A, Sgrò P, Salacone P, Paoli D, Gilio B, Lombardo F, 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;81:1578–84.
57. Ahmed SD, Karira KA, Jagdesh, Ahsan S. Role of L-carnitine in male infertility. J Pak Med Assoc. 2011;61:732–6.
58. Zini A et al. Biologic variability of sperm DNA denaturation in infertile men. Urology. 2001;58:258-61.
59. Zini A et al. Correlations between two markers of sperm DNA integrity, DNA denaturation and DNA fragmentation, in fertile and infertile men. Fertil Steril. 2001;75:674-7.
60. Baker HW. Management of male infertility. Baillieres Best Pract Res Clin Endocrinol Metab. 2000;14:409-22.
61. Ebisch IM et al. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. Hum Reprod Update. 2007;13:163-74.
62. Yagci A et al. Spermatozoa bound to solid state hyaluronic acid show chromatin structure with high DNA chain intergrity: an acridine orange fluorescence study. J Androl. 2010;31(6):566-72.
63. Pregl Breznik B et al. Are sperm DNA fragmentation, hyperactivation, and hyaluronan-binding ability predictive for fertilization and embryo development in in vitro fertilization and intracytoplasmic sperm injection? Fertil Steril. 2013;99(5):1233-41.
64. Cavallini G et al. Medical therapy of oligoasthenospermia associated with left varicocele. BJU International Volume 91, Issue 6, pages 513–518, January 2003.
65. Cavallini G et al. Cinnoxicam and L-carnitine/acetyl-L-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. J Androl. 2004 Sep-Oct;25(5):761-70; discussion 771-2.
66. Imhof M (2009); Mikronährstoffe In Der Fertilitätsbehandlung: Klinische Ergebnisse. Fortbildungsveranstaltung der österreichischen Gesellschaft Urologie und Andrologie.Linz, Redoutensäle 6.-7. Nov. 2009.

PROFERTIL®

11-02-INT.05/17

Lenus Pharma GesmbH
Seeböckgasse 59, 1160 Vienna / Austria
Phone: +43 1 405 14 19-0 | Fax: -20
www.lenuspharma.com, office@lenuspharma.com

A product of
LENUSPHARMA
innovative medicine