Micronutrient Supplementation Increases Sperm Quality in the Sub-fertile Male

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Abstract

Background and Aims: Nearly 50 % of male infertility is idiopathic and to date there is still no proven therapy. We evaluated the effect of a non-prescription nutraceutical containing eight micronutrients on sperm quality in males with idiopathic sub-fertility.
Methods: This open comparative pilot study was carried out at the Fertility Centre IMI, Vienna, Austria. A total of 132 sub-fertile males (active treatment group) were invited to participate and take two daily capsules of the active compound for a three-month period between the first and the follow-up semen analysis. Each capsule contained L-carnitine, L-arginine, zinc, vitamin E, glutathione, selenium, co-enzyme Q10 and folic acid. Sub-fertile men receiving no active treatment served as controls (n=73). The main outcome measure was the standardised semen analysis.
Results: All parameters evaluated by semen analysis significantly increased after three months of treatment with the active compound. 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.
Conclusion: Semen analysis results significantly improved in sub-fertile men after treatment with an active micronutrient compound, leading to pregnancies without any adverse effects.

Keywords

Sperm quality, oligoasthenoteratozoospermia, idiopathic male infertility, sub-fertility

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Birth rates in Western countries are decreasing. Ten per cent to 17 % of all couples experience primary or secondary sub-fertility,[1–4] defined as the failure to conceive after one year of regular, unprotected intercourse with the same partner. Sub-fertility resulting in permanent childlessness may be a very difficult situation for couples.[5,6] In addition, sub-fertile couples try to conceive by all possible means, including assisted reproduction, which obviously does not actually treat the sub-fertility cause.

Male factor accounts for nearly 25–30 % of all infertility causes.[2,7] Several treatable conditions have been identified: hypogonadism, varicocele, gonadotrophin deficiency, genital tract infections and obstructions and sperm autoimmunity. In others cases, sub-fertility can be attributed to known irreversible conditions. However, no specific cause is found in about 50 % of all infertile men with seminal abnormalities seeking treatment. These sperm disorders are the single most common cause of male sub-fertility. Strong associations between sperm quality parameters and pregnancy have been established.[8,9] Thus, low sperm quality has increasingly raised therapeutic interest.[2,10]

The pathogenic mechanisms involved in this form of defective sperm production are unknown;[11] thus, focusing on the development of effective treatments is not easy. Various agents have been used in the attempt to increase the fertility potential of men with decreased semen quality. Nevertheless, studies have rendered heterogeneous results, and the effect of gonadotrophins or anti-oestrogens on pregnancy rates remains controversial.[2] A recent review aimed at searching the rationale for the treatment of idiopathic male factor infertility over the past 20 years concluded that there is no evidence supporting androgen and gonadotrophin use for enhancing male fertility. Evidence regarding anti-oestrogen, aromatase inhibitor and

Table 1: Semen Analysis Data Among Studied Groups (Active Treatment Group and Controls)

	Ejaculatory Volume (ml)		Sperm Cell Density (Million/ml)		Progressive Motility (%)		Total Motility (%)		Normal Morphology (%)	
	Treatment	Control**	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
WHO lower limits	2		20		25		50		30	
Baseline median (IQR)	2.9 (1.5)	3.0 (1.7)	5.0 (6.5)	4.9 (5.8)	30.5 (25)	31 (38.8)	32.5 (23.8)	40.5 (44.8)	29.0 (15.2)	39.0 (38.5)
Median at 3 months (IQR)	3.5 (2.3)	3.2 (1.8)	18.5 (23)	7.5 (9.0)	49 (32)	44.0 (47.2)	47.0 (26.0)	50.0 (40.1)	40.0 (17.5)	35.5 (42.3)
p-value*	0.0001	0.46	0.0001	0.01	0.0001	0.06	0.0001	0.06	0.0001	0.95
Median percentage change from baseline	+33.3 %	+3.7 %†	+215.5 %	+46.4 %†	+83.1 %	+44.0 %†	+36.4 %	+33.9 %†	+23.0 %	-2.4 %†

**p-values when comparing three months with baseline using Wilcoxon rank test. **Controls were sub-fertile men (n=73) who did not receive active compound. † p<0.05 when treatments are compared using Mann Whitney test. Note: Lower-limit values for each semen parameter are provided in accordance with the World Health Organization (WHO).[16] IQR = inter-quartile range.*

antioxidant use was found to be insufficient. No therapeutic drug option was found to clearly benefit idiopathic impaired male fertility in terms of natural conception.[12] To date, there is still no proven therapy for the improvement of semen quality in this large group of men.

Although the aetiology of oligoasthenoteratozoospermia is generally poorly understood and most of the precise mechanisms are far from being known, idiopathic sub-fertility may be considered a multifactorial disorder in which many genetic, environmental and lifestyle-related factors act together. Unfavourable conditions of any origin can interfere with spermatogenesis and reduce sperm quality and production.

A key factor of major therapeutic interest is nutrition. Most of the essential compounds required for DNA synthesis and spermatogenesis are derived from the diet. Therefore, concentration of required nutrients and other relevant factors may have substantial effects on sperm quality and reproduction.[13,14] Even more importantly, male factor sub-fertility due to nutritional deficiencies is easily amenable to the curative and preventative actions of supplementation. A multi-faceted therapeutic approach to improve male fertility should compensate for underlying nutritional imbalances in order to support optimal sperm production and function.

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 optimising sperm production and quality. A recent Cochrane review stated that antioxidant supplementation in sub-fertile men may improve outcomes of live birth and pregnancy rates among couples undergoing assisted reproduction cycles.[15]

The aim of the present pilot study was to evaluate the effect of a non-prescription nutraceutical containing eight micronutrients on sperm quality in males with idiopathic sub-fertility. Micronutrients included in the preparation were L-carnitine, L-arginine, zinc, vitamin E, glutathione, selenium, co-enzyme Q10 (CoQ10) and folic acid. The treatment time of three months was selected according to the period of 74 days for spermatogenesis and the common interval between first and usual follow-up semen analysis.

Materials and Methods

Study Design and Subjects

The present open comparative pilot study was performed from January 2006 to October 2010 at the out-patient Fertility Centre IMI, Vienna, Austria. Men with at least one year of sub-fertility and at least one prior and one recent abnormal semen analysis were invited to participate and take two daily capsules of the proposed nutraceutical for three months, after which a follow-up semen analysis was performed (active treatment group). Exclusion criteria were azoospermia, aspermia, varicocele and recent urogenital infections. Participants in the active treatment group were requested to give signed consent after being informed of the study, its aims and methodology. Sub-fertile men attending the Department of Urology of the Medical University of Vienna, Austria, who did not take the active compound during the study period, served as controls.

Preparation (Nutraceutical)

Each capsule of the active compound (PROfertil®) contained: L-carnitine (440 mg), L-arginine (250 mg), zinc (40 mg), vitamin E (120 mg), glutathione (80 mg), selenium (60 µg), CoQ10 (15 mg) and folic acid (800 µg) and was provided by LENUS Pharma GmbH, Vienna, Austria.

Primary Outcome Assessment – Semen Analysis

A semen analysis was performed at baseline and after three months in the active treatment group. These data were compared with those provided by sub-fertile controls who did not receive treatment and had two semen analyses three months apart (baseline and confirmatory). In addition, participants of the active treatment group were instructed to report pregnancies occurring within the six months after treatment. Pregnancies in the control group were assessed by a retrospective telephone survey.

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 analysed 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

During the study period, a total of 141 eligible sub-fertile men attending the Fertility Clinic IMI, Vienna, Austria were enrolled and took the active compound. Nine men withdrew from study participation, leaving 132 subjects who completed three months of treatment and provided data for full analysis. The control group included 73 sub-fertile men. Mean age of men taking the active compound was 34 years (min/max: 18–43 years) whereas in the control group this was 38 years (min/max: 22–52 years).

Semen analysis data from studied groups (active treatment and controls) are depicted in *Table 1*. Lower-limit values for each semen analysis parameter according to the World Health Organization (WHO) are also provided.[16] All parameters evaluated within the semen analysis significantly increased after three months of treatment with the active compound, compared with the baseline values. Median ejaculatory volume, sperm cell density, sperm motility (progressive and total) and rate of normal morphology 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 (25.8 %) pregnancies were reported after six-month follow-up. Only 11 (15.0 %) were reported in the control group.

Discussion

The investigated nutrient combination was designed to treat idiopathic male 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. The studied composition was based on the rationale that each ingredient has been shown to improve sperm factors that may contribute to fertility.

L-carnitine is the energy substrate of spermatozoa. Free L-carnitine is positively correlated with sperm count, motility and motile sperm density.[17] Although several controlled trials have reported positive effects on each of these parameters,[18–20] a recent study on men with idiopathic asthenospermia found no significant effect on sperm motility or total motile sperm counts.[21]

Reports indicate that nitric oxide (NO) is beneficial to sperm viability and motility in both fertile and infertile individuals.[22] Arginine is the immediate precursor of NO. L-arginine improved sperm motility in infertile men with normal cell counts[23] and displayed a beneficial *in vitro* effect on the sperm motility of asthenozoospermic men.[24]

Vitamin E improved sperm motility, enabled fertility in asthenospermic men[25] and significantly improved the *in vitro* function of human spermatozoa in single studies.[26] In combination with selenium, vitamin E increased sperm motility and normal morphology rates.[27,28] Selenium is an essential component of the enzyme glutathione peroxidase, and is necessary 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.[29,30] Despite this, selenium supplementation data are conflictive. Indeed, increased,[31] unchanged[32] and even decreased sperm motility have been reported after selenium use.[33]

Zinc is involved in DNA transcription, protein synthesis, testicular development and sperm maturation, and it is thought to extend the functional lifespan of ejaculated spermatozoa.[34] Low seminal zinc levels have been correlated with decreased fertility potential.[35,36] Zinc supplementation has shown positive effects on sperm counts and other measures.[37–39] Combined treatment with zinc and folic acid has rendered diverging results: sperm count and density improvement,[40] sperm concentration increase alone[41] and no effect after controlling for covariates.[42] Folic acid is required for DNA synthesis[43] and thus is important for spermatogenesis.[13] Nevertheless, the underlying mechanisms of folic acid in spermatogenesis are still unknown.

The supplementation of folic acid alone failed to show beneficial effects on sperm concentration in normo- and oligozoospermic men.[44]

Glutathione plays a key role in protein and DNA synthesis. Lower glutathione levels have been reported in sub-fertile men and related to abnormal sperm motility and morphology.[45] Three studies have reported positive effects of glutathione supplementation on sperm motility and morphology.[46–48] CoQ10 is deeply involved in body energy metabolism. Ninety-five percent of all adenosine triphosphate (ATP) is converted with the aid of CoQ10.[49] This defines a role for CoQ10 in male infertility[50] that has been confirmed by increased sperm motility in asthenospermic men.[51,52] Spermatozoa are particularly sensitive to oxidative and electrophilic stress. Moreover, reactive oxygen species (ROS) have been implicated in both male and female reproductive functions.[53,54] Despite this, the role of antioxidants in sperm quality improvement is still controversial, mainly due to the low quality of most studies and the use of different combinations, doses and durations of antioxidants. Pregnancy, the most relevant outcome, was reported in only one study.[55]

As extensively described above, each micronutrient alone or in combination has reported positive effects on semen parameters in sub-fertile men. However, to date no study has reported on the use of a combination of eight of these nutrients as performed in this pilot study. Baseline semen parameters among the studied subjects were sub-fertile in relation to limits proposed by the WHO.[16]

After three months of treatment with the active compound, all semen parameters significantly increased compared with baseline. Net increase was significantly higher than that observed for controls. Although controls displayed an increase in all parameters, this was only significant for sperm cell density. This could be related to the recognition of sub-fertility, resulting in a change of lifestyle habits, such as a reduction in nicotine consumption and nutrition quality improvement.

The examined preparation was well tolerated by all participants and no adverse reactions appeared. All micronutrients have been thoroughly examined for decades and toxicological as well as pharmacodynamic data show that they exert no negative health effects or potential hazards, even at higher dosages than those used in the present study. Finally, we recognise the non-randomised, placebo-controlled design of our study as a limitation. However, a double blind, randomised, placebo-controlled study is currently on the way to support these preliminary results. Thirty-four pregnancies were reported after six months of active compound treatment. A telephone survey among 59 of the 73 controls revealed only 11 pregnancies (18.7 %). Comparing pregnancy rates may also be seen as a limitation; however, pregnancy was not the primary end-point of the study. Despite mentioned limitations and in light of the fact that therapies for sub-fertile men are still missing, the investigated compound is a promising therapeutic approach, improving sperm parameters and enabling natural conception for couples with idiopathic male infertility.

Conclusion

In conclusion, semen analysis results significantly improved in sub-fertile men after treatment with the active micronutrient compound, leading to pregnancies without any adverse effects. More research is warranted in this regard. ■

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