

Male Subfertility and Efficacy of Fertimax™ Therapy

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Abstract

Objective: Over recent decades, there is a growing concern around the infertility problem in Algeria. In the latest census of the health and populations ministry, the infertility affects approximately 10-12% of the couples and in 30% of these cases and the male is the main associated origin. Thus in this research, we attempt to determine the etiology of reproductive failure in infertile men and to assess the effectiveness therapy of Fertimax™ treatment as combination of a specific micronutrients and antioxidants on their semen quality.

Methods: Thirty six men consulting for infertility spousal in clinic of assisted reproductive techniques “El Bordj”- Algiers were interviewed, examined for clinical signs and their sperm was analyzed, then after, some of them were subjected to Fertimax™ treatment for six months and their sperm was reanalyzed.

Results: The obtained results revealed that Fertimax™ intake for six months can improve significantly all semen parameters including seminal volume and viscosity, spermatozoa number, mobility, vitality and morphology in these patients. Besides, in 33.33% of cases, these treated patients with Fertimax™ have fertilized their partners without recourse to in vitro fertilization process.

Conclusion: This wonderful ameliorating role of Fertimax™ may be related to the particularly potent antioxidant properties of its components and thus we recommend this treatment as remedy for patients suffered from subfertility in both sexes.

Keywords: Male Subfertility; Semen parameters; Fertimax™ treatment; Antioxidants

Introduction

Infertility is defined as the failure to conceive after 12 months of unprotected intercourse with a global prevalence of 9% [1]. Over recent decades, there is a growing concern around the infertility problem in Algeria which affects approximately 10-12% of the couples. In 30% of these cases the male is the main associated origin by a reduction in semen quality under genetic and congenital abnormalities, infection, multi-systemic diseases, varicocele, environmental and lifestyle factors; however, a significant number of cases are idiopathic [2-5]. Sperm quality is one of the most important areas of concern in treatments involving in assisted reproductive technology in patients suffered from an alteration in sperm concentration and/or motility and/or morphology [6]. Many studies have incriminated the sperm oxidative stress as the primary cause in the pathogenesis of men infertility in 30-80% of cases (Figure 1) through sperm DNA damage, membrane peroxidation, membrane defective integrity, decreased motility as well as diminished capacity for sperm-oocyte fusion [7-9].

Oxidative stress is a result of the imbalance between reactive oxygen and nitrogen species (ROS/NOS) and antioxidants defense in the body. Superoxide anion, hydroxyl radical and hydrogen peroxide are major Reactive Oxygen Species (ROS) present in seminal plasma. In normal sperm physiology, low levels of ROS are beneficial and have been shown to stimulate sperm capacitation, enhance zona pellucida binding and promote acrosome reaction, hyperactivation and motility [8,10,11]. Spermatozoa are rich in polyunsaturated fatty acids and it contain low amount of antioxidants within their cytoplasm and in seminal plasma, and, therefore, could be highly susceptible to oxidative stress; thus, high levels of ROS in semen have been correlated with reduced sperm vitality and motility and damage to sperm nuclear DNA and subsequently decline men fertility [12,13].

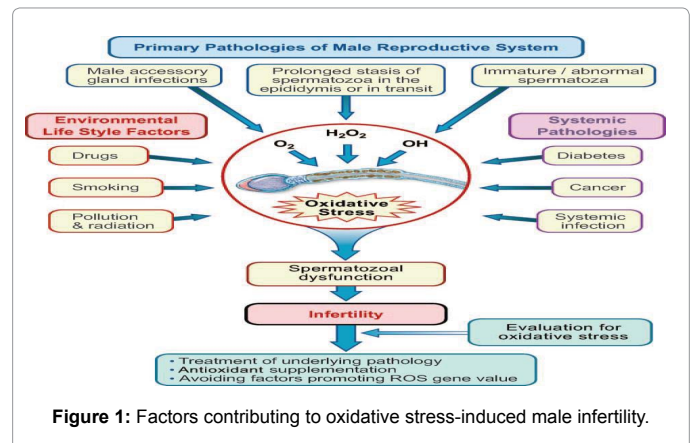


Figure 1: Factors contributing to oxidative stress-induced male infertility.

In recent years, recourse to the use of micronutrients and vitamins as antioxidants treatment in infertile men has been strongly recommended. So, several reviews of clinical studies addressing the effect of oral antioxidants supplementation (vitamins C, B₁₂ and E, zinc, selenium, magnesium, arginine folate, carnitine and carotenoids) on sperm quality and pregnancy rate in infertile men have been published recently [14-17]. It found that a woman was more likely to have a

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pregnancy or live birth if her male partner took certain vitamins or other antioxidants [18]. These micronutrients and vitamins can neutralize free radicals, prevent ROS production and DNA fragmentation in spermatozoa, improve outcomes of live birth, pregnancy rates and semen quality among couples undergoing assisted reproduction cycles and stimulate spermatogenesis and androgen synthesis and secretion by several mechanisms [17,19,20].

Many articles researches and reviews have been reported the efficacy of micronutrients and vitamins supplementation each alone to treat infertility and improve reproductive outcomes in patients with azoospermia, oligospermia, asthenospermia and unexplained subfertility [14,21-24]. However, studies on the effectiveness of different combinations of these microelements in the treatment of men infertility are still very limited.

Fertimax™ is one of the new formulations based on the combination of numerous antioxidant vitamins (Vitamin E, C, B₉ and B₁₂) and micronutrients (Zinc, Selenium and L-Carnitine). To date no study has reported on the use of this combination as performed in this pilot study, hence we attempt here to investigate the efficacy of Fertimax™ as therapeutic tools in men infertility through assisted reproductive technology IVF and/ or ICSI.

Materials and Methods

Patients selection

The current prospective study was conducted at the Clinic of Assisted Reproductive Technologies (ATR) “El Bordj” Algiers, in collaboration with the reproductive toxicology unit, department of Biology, University of Boumerdes, Algeria. A total of thirty six patients consulting for infertility spousal at least one year aged from 28 to 54 years and who did not receive any treatment before were used, interrogated about socio-demographic characteristics (age, race, and education), occupation, possible occupational exposures, medical and reproductive histories and lifestyle habits and then examined for the clinical signs. The patients exhibiting abnormal semen characteristics for 3 consecutive semen analysis and who did not receive any treatment before were recruited in this study, the exclusion criteria were azoospermia, aspermia, varicocele and recent urogenital infections as well as who have already received some antioxidants.

These patients were divided into untreated and treated groups. Untreated group (n=26), did not receive any treatment and treated group (n=10) received a new combination of micronutrients and multivitamins « Fertimax™ » treatment for six months, after which a follow-up semen analysis was performed (Figure 2).

Fertimax™ composition

Fertimax is a new combination consisted of micronutrients (Zinc, Selenium, L-tartrate de L-carnitine) and multivitamins (Vitamines C, E, B₉ and B₁₂) (Table 1).

Semen collection and analysis

Semen samples were obtained by masturbation into a sterile collection container after abstinence of 3–5 days. After 30 min of liquefaction at room temperature, each sample was immediately analyzed macroscopically and microscopically for conventional semen quality including liquefaction, aspect, PH, viscosity, sperm volume, sperm number, motility, viability and morphology followed by Sperm Migration Test (SMT) according to WHO protocols [25]. Briefly, the

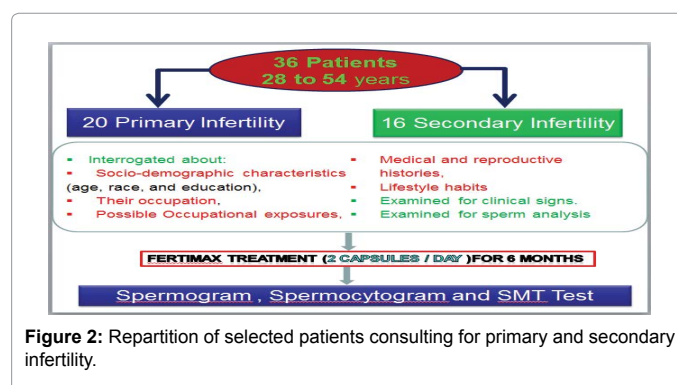


Figure 2: Repartition of selected patients consulting for primary and secondary infertility.

Fertimax composition per 1capsule	quantity 1 capsule	quantity (mg) per 2 capsules
Vitamine C (ascorbic acid)	90 mg	180 mg
Vitamine E (α-tocopherol)	15 mg	30 mg
Vitamine B12(cobalamin)	1 µg	2 µg
Vitamine B9 (folic acid)	100 µg	200 µg
Zinc	7.5 mg	15 mg
Selenium	25 µg	50 µg
L-tartrate de L-Carnitine	200 mg	400 mg

Table 1: Fertimax™ composition.

liquefaction usually occurs within 15 to 30 minutes at room temperature, if complete liquefaction does not occur within 60 minutes, this should be recorded. The color, normal sperm have grey-opalescent appearance, red-brown when red blood cells are present (haemospermia), or yellow in a man with jaundice. The sperm volume was measured directly by aspirating the complete sample into graduate pipette (0.1 ml accuracy) from the container; while viscosity was estimated by the manner that sperm dropped from the pipette, a normal sample leaves the pipette in small discrete drops, if viscosity is abnormal; the drop will form a thread more than 2 cm long. For sperm, leucocytes (leucospermia) and round cells count, 20 µl of an aliquot was taken in Malassez haemocytometer chamber after an appropriate dilution (1: 20 or 1:50) and examined with phase-contrast microscope at × 200 magnification. To determine sperm motility, one drop of the aliquot was placed on a slide, covered by a coverslip, and evaluated under a phase contrast microscope at x200 magnification. The sperm were categorized on the basis of their motility as “motile” or “immotile” and four different grades (a,b,c,d). To examine the sperm cells morphology, smear was prepared from the samples, stained and investigated by Papanicolaou method and evaluated according to the criteria by Kruger et al. [26] at ×1000 magnification with oil immersion. Sperm viability is reflected in the proportion of spermatozoa that are “alive”. The eosin-nigrosin staining technique is based on the principle that dead cells will take up the eosin and as a result stain red. The nigrosin provides a dark background, which makes it easier to assess the slides. Finally, sperm migration test (washing swim-up (WSU)) method was performed to select a concentrate of high quality (morphology and viability); it is based on spermatozoa self-propelled active movement from a single centrifuged, pre-washed cell pellet, into an overlaying medium which serves as a hospitable environment for healthy sperm [25].

Statistical analysis

Data are expressed as mean values ± SD and analyzed by using SPSS (version 14.0) for Windows. Paired samples t-test was used to compare

between the data of the control (before treatment) and those of after treatment. A p value of <0.05 was considered statistically significant (*p<0.05, **p<0.01).

Results

Etiology and frequency of infertility problems

The obtained results were presented in the (Figures 3-6).

As shown in Figures 3 and 4, infertility problem was frequently affected the population between 36-44 years old in 50% of cases, in addition, the patients of the selected population suffered from primary and secondary infertility represent 56% and 44% of cases respectively.

Also, according of the jobs (Figure 5), the security officers, traders and administrative officers are the most affected persons by infertility with incidence of 11.11%, 25% and 27.78% respectively, followed by engineers and teachers with 8.33%, medical practices, drivers and welders with 5.56% and the agricultures with low prevalence of 2.58%.

So, the tobacco habits are one of the men infertility factors, which affect 61% of the selected population (Figure 6).

Effects of Fertimax on semen analysis

Results concerning the effects of fertimax on semen analysis were summarized in (Figures 7-11) and (Tables 2-4). In these patients, fertimax therapy at least for 6 months of treatment showed an evidence ameliorating role in the semen characteristics pronounced by an increase (P<0.05) in sperm volume (Figure 7), number (Figure 8), motility (Figure 9) and viability (Figure 10), meanwhile, a decrease in sperm viscosity (Table 2) and abnormalities (Figure 11) (P<0.01) as well as number of round cells (Table 3) and sperm leucocytes (Table 4).

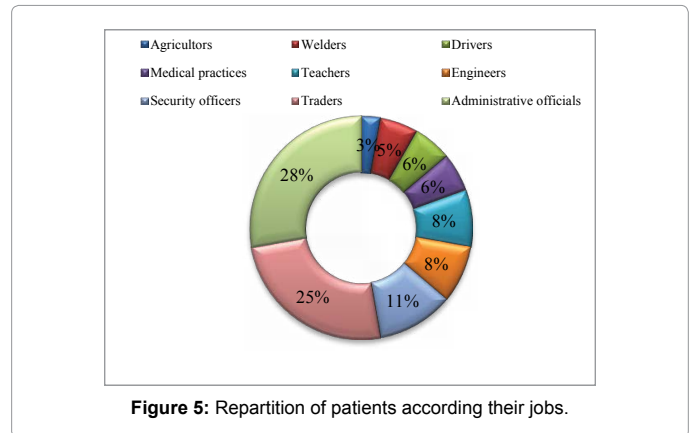


Figure 5: Repartition of patients according their jobs.

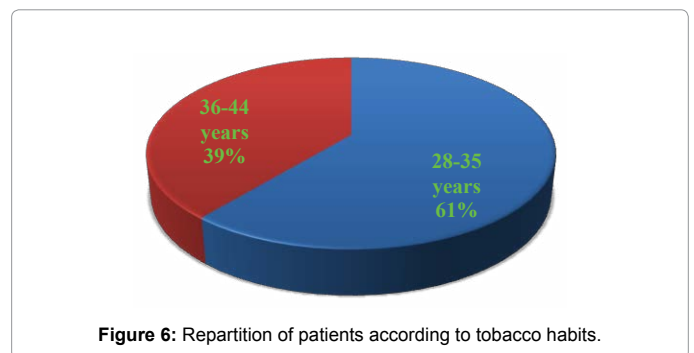


Figure 6: Repartition of patients according to tobacco habits.

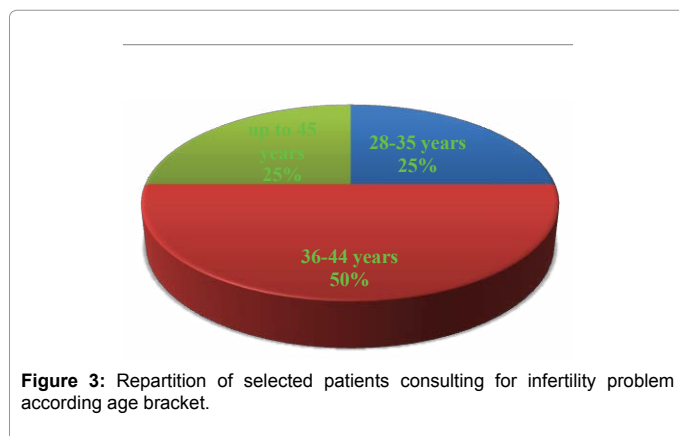


Figure 3: Repartition of selected patients consulting for infertility problem according age bracket.

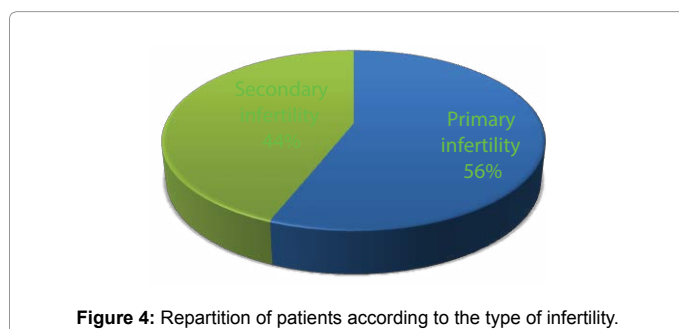


Figure 4: Repartition of patients according to the type of infertility.

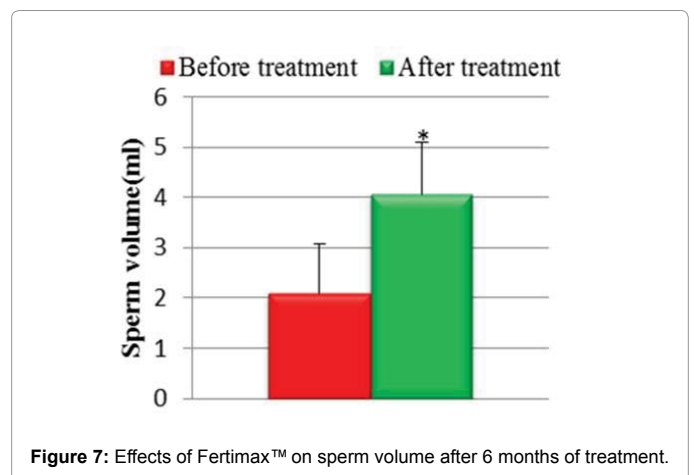


Figure 7: Effects of Fertimax™ on sperm volume after 6 months of treatment.

Thus, overall altered sperm parameters were obviously improved and/or adjusted to the normal range of WHO when patients were subjected to fertimax treatment upper 6 months.

Discussion

Regarding to the etiology of the male infertility in the last decade, there is a growing concern about the association between male infertility and environmental and occupational pollutants, changes in lifestyles, exposure to toxic agents, and changes in dietary habits [27,28]. Support to the alteration of all sperm parameters in these patients consulted for male infertility spousal, the environmental toxicants are reported

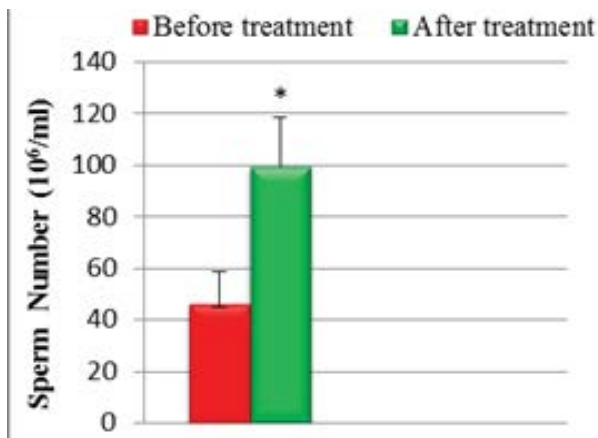


Figure 8: Effects of Fertimax™ on number after 6 months of treatment.

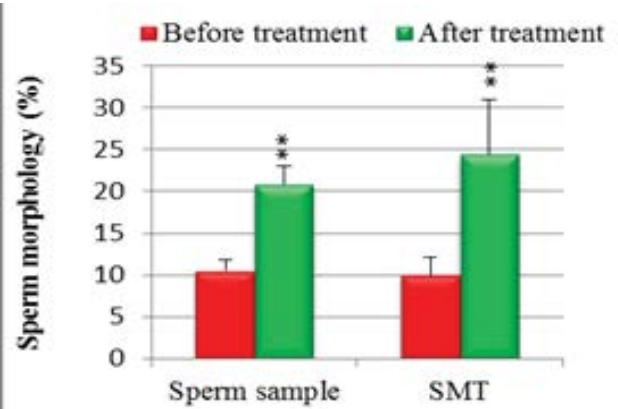


Figure 11: Effects of Fertimax™ on sperm viability in sperm morphology and SMT after 6 months of treatment.

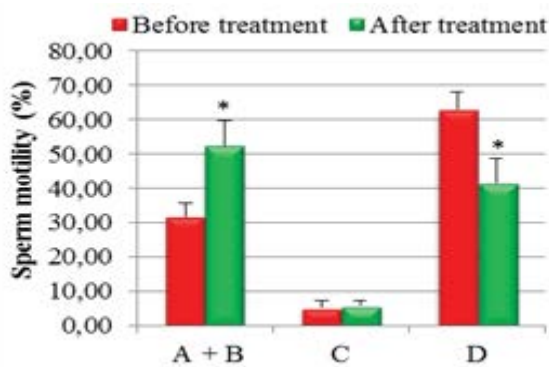


Figure 9: Effects of Fertimax™ on sperm motility after 6 months of treatment.

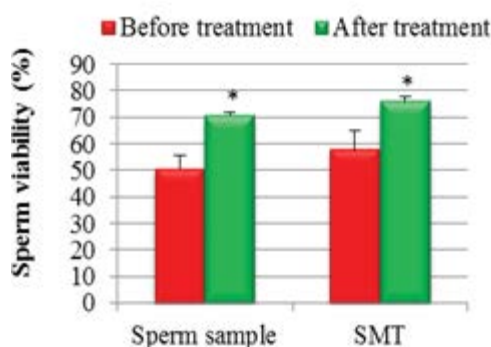


Figure 10: Effects of Fertimax™ on sperm viability in sperm sample and SMT after 6 months of treatment.

to cause oxidative stress in the testis with decreased spermatogenesis and fertility [29]. Although, low physiologic levels of ROS produced by the germ cells are needed to regulate sperm capacitation, acrosome reaction, hyperactivation, motility, and fertilization [21], evidence now suggests that Reactive Oxygen Species (ROS)-mediated damage

Patients	Before treatment	After treatment
P1	N	N
P2	-H-	N
P3	+F-	N
P4	N	N
P5	+	N
P6	N	N
P7	+	N
P8	-F-	N
P9	N	N
P10	N	N

N: Normal, +: Low viscosity, ++: Medium viscosity, +++: High viscosity.

Table 2: Effects of Fertimax™ on sperm viscosity after 6 months of treatment.

Patients	Before treatment	After treatment
P1	>im	<1M
P2	<1M	<1M
P3	<1M	<1M
P4	<1M	<1M
P5	> 3M	<1M
P6	> 1M	<1M
P7	> 1M	<1M
PS	<1M	<1M
P9	<1M	<1M
P10	>im	<1M

Table 3: Effects of Fertimax™ on the number of round cells (10⁶/ml) after 6 months of treatment

to sperm is a significant contributing pathology in 30–80% of cases by two mechanisms. First, ROS damage the sperm membrane which in turn reduces the sperm's motility and ability to fuse with the oocyte. Secondly, ROS directly damage sperm DNA, compromising the paternal genomic contribution to the embryo [30]. The main sources of high levels of ROS in human ejaculates are pathological (endogenous ROS) from immature, morphologically abnormal spermatozoa and seminal leukocytes (polynuclear 50-60%, macrophages 20-30% from prostate and seminal vesicles) and environmental (exogenous ROS) stressors [31]. Under these conditions, leukocytes number increased in response to infection and inflammation of various stimuli; these activated leukocytes can produce up to 100-fold higher amounts of

Parameter	Before treatment	After treatment
Number of leucocytes (10 ⁶ /m1)	<1 million/50% of cases >1million/50% of cases	100°0

Table 4: Effects of Fertimax™ on the number of leucocytes (10⁶/ml) after 6 months of treatment.

ROS compared with non-activated leukocytes and this is mediated by an increase in NADPH production via the hexose monophosphate shunt [32].

Oxidative stress affects the testicular function by disrupting germinal cell epithelial division, differentiation [33] and also induces germ cell apoptosis [34] and subsequently decrease spermatogenesis, sperm count, mobility, viability and morphology [29]. The main proposed mechanism that high levels of ROS disrupt the inner and outer mitochondrial membranes, inducing the release of the cytochrome-C protein and activating the caspases 9 and 3 and Apoptosis Inducing Factor (AIF), which directly interacts with the DNA and leads to DNA fragmentation, axonemal damage and apoptosis. Apoptosis in sperm also may be initiated by ROS-independent pathways involving the cell surface protein Fas [35].

In the ordinary conditions, to contrary this oxidative stress in the organism, there are three different antioxidant protection systems: 1) enzymatic antioxidants such as Superoxide Dismutase (SOD), catalase, and Glutathione Peroxidase/Glutathione Reductase (GPX/GRD), 2) non enzymatic antioxidants by way of ascorbate, urate, vitamin E, pyruvate, glutathione, albumin, vitamin A, ubiquinol, taurine, and hypotaurine, 3) dietary antioxidants: vitamin C, vitamin E, beta-carotenes, carotenoids and flavonoids. In several times, overwhelm of ROS generation exceeds endogenous antioxidants defenses capacities, thus recourse to antioxidants supplementation is highly recommended. It is presumable that the free radical scavenging effect of the antioxidants used in the treatment of infertility decreased the oxidative stress, prevents DNA damage and restored the spermatogenesis and spermiogenesis [36-38].

Thereby, vitamin E and C enhance the activity of a range of antioxidant enzymes involved in scavenging free radicals and improve motility and fertilization or pregnancy rates in infertile men with high ROS by influencing the expression of genes involved in the intracellular redox pathways [16,39]. Vitamin B₉ (Folic acid) is necessary for red blood cells production, cell division and growth [40], maintenance of DNA synthesis and methylation, and consequently chromatin structure and gene expression [41]. Vitamin B₁₂ is important in cellular replication especially for the synthesis of RNA and DNA [42]. Zinc (Zn) is a trace element essential to maintain optimal functional levels of antioxidant enzymes, cell proliferation and differentiation, immune function, DNA replication and transcription as well as for reproduction due to its fundamental role in germ cell development and expression of steroid receptors for spermatogenesis [43]. Selenium (Se) is a micronutrient plays an important antioxidant role against oxidative sperm DNA damage and is necessary for testicular development, spermatogenesis, sperm motility and for the biosynthesis of testosterone [44,45]. L-carnitine protects cell membranes and DNA from damage caused by free oxygen radicals. It is also crucial to transport fatty acids into mitochondria matrix within spermatozoa for utilization in metabolism and energy production through β -oxidation and subsequently contributes directly to sperm metabolism, nutrition, maturation, count and motility [21,46].

Looking to our results, it seems that Fertimax treatment in this population of infertile men can restores partially or completely all altered sperm parameters (sperm volume, count, motility, morphology, viscosity and leucospermia) to the normal range and subsequently improves semen quality and pregnancy rates. These beneficial roles may be due to the ability and synergic effects of their multivitamins and micronutrients antioxidants components in scavenging free radicals, promoting sperm enzymatic and or non-enzymatic antioxidants defense and thereby prevent DNA damage and membrane peroxidation that will reduce its fusogenic capacity, rendering fertilization less probable. So, because our study is preliminary to test the efficacy of Fertimax as therapy in men subfertility, the limitation of the study was that we could not perform the complimentary semen tests such as immunologic and genetic tests (antisperm antibodies, karyotype, Y chromosome micro-deletion test, motile sperm organelle morphology examination). In some cases, infertility might be associated to these factors and suppose the Fertimax antioxidant properties can correct the resulting abnormalities.

Supporting to our finding, several studies were reviewed the use of oral antioxidants supplementation in the treatment of male infertility [16,18]. In the same way, Singh et al. [47], have conducted a subsequent nonrandomized study on azoospermic men with maturation arrest (n=24), these patients were received a mixture of multivitamins, micronutrients, and co-enzyme Q10 for three months, the results revealed a significant increases in motility and morphology (p<0.05) and two pregnancies. Also, the intra-gastric administration of micronutrient mixture of vitamin A, vitamin C, vitamin E, Zinc, and selenium for four weeks in infertile male rats induced by adenine caused a significant increase in testis index, sperm counts and motility, while a decrease in sperm malformation and recovering in LH and testosterone levels were observed [20].

Furthermore, Imhof et al. [48] have carried out a pilot study at the Fertility Centre IMI, Vienna, Austria. So, a total of 132 sub-fertile males (active treatment group) were invited to participate and take two daily capsules of the active compound of (PROfertil®) for a three-month period between the first and the follow-up semen analysis. Each capsule (PROfertil®) contained L-carnitine (440 mg), L-arginine (250 mg), zinc (40 mg), vitamin E (120 mg), glutathione (80 mg), selenium (60 μ g), CoQ10 (15 mg) and folic acid (800 μ g). The results showed a wonderful ameliorating effect of PROfertil® on sperm characteristics.

Similarly, Buhling and Laakmann [38] have reported a significant increase in sperm quality and pregnancy rates when the infertile men were supplemented by specific vitamins and micronutrients. So, in recent prospective randomized control study, azoospermic patients with primary infertility when subjected to a twice daily doses supplementation for 6 months to a combination of multivitamins and micronutrients (Tablet A to Z contents :Vitamin C (40 mg), Vitamin B3 (16 mg), Vitamin E (15 mg), Vitamin B5 (5 mg), Vitamin B6 (2 mg) ,Vitamin B2 (2.4 mg), Vitamin B1 (1.2 mg),Vitamin A (600 mcg), Folic acid (100 mcg), Methylcobalamine (1 mcg), Zinc (10 mg) , Manganese (2 mg), Copper (0.9 mg) and Selenium (55 mcg). Their sperm count and motility were significantly (P<0.05) improved after treatment [49].

Likewise in other recent study, patients with idiopathic oligo/astheno and oligiasthenospermia were subject to a cap Doxycycline 100 mg twice daily for 1 month and tablet Oligocare (Meyer Organic Pvt Ltd, India) 1 tab twice daily for 2 months. Each oligocare tablet contains : Vit A (375 mg) ,Vit C (75 mg), Vit E (12.5 mg), Vit D3 (12.5 mcg),

Methylcobalamine (750 mg), Co-Enzyme Q 10 (2.5 mg), Lycopene (2 mg), Folic acid (1.5 mg), L-Arginine (10 mg), L-Carnitine tartarate (50 mg), Iron (5 mg), Zink (7.5 mg), Copper (1 mg), Manganese (2 mg), Selenium (100 mcg), Pyridoxyl hydrochloride (5 mg), Glutathionine (2.5 mg). Results show a significant improvement in sperm count and in total and progressive motility in 79% of patients under Oligocare treatment that based on the use of a mixture of multivitamins and micronutrients as basic antioxidant elements [17].

In conclusion, in this study we investigated the effectiveness of a new combination of multivitamins and micronutrients « Fertimax » on semen quality in randomized population of infertile men; we conclude that Fertimax treatment for 6 months leads to a significant improvement of semen parameters and ability to help achieving pregnancy in some couples without recourse to ART process. We suggest further investigations on the effect of this combination in azoospermic patients with large sample sizes and genetic tests.

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