Commentary

The role of food supplements in the treatment of the infertile man

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Abstract

Recently, concerns have been raised about the presumptive increased risk of serious undesirable side effects in children born after IVF and intracytoplasmic sperm injection (ICSI). These treatments must, therefore, be reserved as the ultimate option after evidence-based and cause-directed treatment of the male patient with deficient semen has been exhausted. The present authors found that sperm quality and function improved with the intake of complementary food supplementation using a combination of zinc and folic acid, or the antioxidant astaxanthin (Astacarox®), or an energy-providing combination containing (acyl)-carnitine (Proexed®). Also, double blind trials showed that the latter two substances increase spontaneous or intrauterine insemination- (IU-) assisted conception rates. Extracts of Pinus maritima bark (Pycnogenol®), which inhibits the cyclo-oxygenase enzyme, reducing prostaglandin production and inflammatory reaction, and extracts of the Peruvian plant Lepidium meyenii were shown to improve sperm morphology and concentration, respectively, in uncontrolled trials. Linsed (flaxseed) oil contains alfa-linolenic acid and lignans. The former corrects the deficient intake of omega-3 essential fatty acids, which is correlated with impaired sperm motility among subfertile men. Lignans are precursors of enterolacton, which inhibits aromatase and reduces the ratio of 16-OH over 2-OH oestrogen metabolites. The resulting reduction in oestrogen load may favourably influence Sertoli cell function.

Keywords: antioxidants, food supplementation, male infertility, nutriceuticals

Historical perspective on the management of male infertility

It has been known for a long time that the ejaculate of some men contains too few, or qualitatively inadequate, spermatozoa. However, it is only since 1940–1950 that reliable scientific data have been available regarding the values of the basic sperm variables needed for optimal fertility (MacLeod, 1942; Hellinga, 1976). Also, the role of antibodies against spermatozoa (Rümke, 1965) and biochemical analysis of seminal plasma (Eliasson, 1968) have been highlighted. Many cases of ‘hidden’ male infertility were detected, but only few modalities of treatment were available. Sperm freezing, artificial insemination and the use of donor sperm were developed (Figure 1).

In the 1970s and 1980s, much attention was given to the alleged causes and associations of male infertility. A specific task force of the World Health Organization (WHO) launched large-scale multi-centre trials. These resulted in a diagnostic approach and standardized classification of male infertility (Comhaire et al., 1987) and the publication of manuals for the standardized techniques of semen analysis (WHO, 1980, 1987, 1999).

The best methods for the diagnosis of varicocele were determined (Comhaire et al., 1976), and the efficacy of treatment of this disease was established in a prospective randomized trial (Hargrave, 1995). Placebo-controlled trials did not reveal any benefit in terms of improving the spontaneous conception rate using antibiotic treatment of male accessory gland infection (Comhaire et al., 1986) and of idiopathic oligozoospermia with clomiphene citrate (WHO, 1992) or with mesterolone (Gerris et al., 1991). By contrast, treatment of the latter condition with Tamoxifen has been shown to be effective (Comhaire, 1976, 2000).

The introduction of assisted reproductive technology, namely IVF and intracytoplasmic sperm injection (ICSI) (Palermo et al., 1992), caused a true revolution in reproductive medicine, while also revealing the magnitude of the male factor contributing to couple infertility. Conventional treatment of the infertile male was considered outdated by some, but others have continued unravelling the mechanisms involved in male defective reproductive capacity.

In recent years, concerns have been raised about the economical and ethical aspects (Comhaire, 2000; Katz et al., 2002), and side effects, of assisted reproduction techniques. IVF and ICSI were found to be associated with an increased prevalence of major congenital malformations (Kent-First et al., 1996; van der Ven et al., 1998; Sutcliffe et al., 1999; Koudstaal et al., 2000; Wennerholm et al., 2000; Hansen et al., 2002), impaired development (Stromberg et al., 2002), and increased risk of retinoblastoma (Moll et al., 2003) in the offspring. It seems, therefore, that the wheel has turned full circle, and that clinical andrology will recapture its well-deserved place in the armamentarium for the treatment of couple infertility.
Male infertility: a multifactorial disease

Similar to other diseases, male infertility comes to expression as a result of the synergistic coincidence of four major factors: genetic defects or constitution; lifestyle factors; professional and/or environmental exposure; and diseases of the urogenital region or endocrine system (Figure 2). The latter include the diseases that constitute the traditional interest of the andrologist, such as varicocele, male accessory gland infection, congenital or acquired testicular damage, hypoaandrogenism, immunological factors, etc.

The field of genetics is rapidly expanding and includes numerical and structural abnormalities of the chromosomal make-up, as well as microdeletions of the Y chromosome (Tiepolo and Zuffardi, 1976; Ma et al., 1992). Whether or not certain of these minor deletions will cause infertility may depend on the coincidental presence of unfavourable life-style factors or exposure to toxic substances or hormone disrupters. These, and the genital diseases, have been shown to increase the load of reactive oxygen species to the ejaculate and the spermatozoa, resulting in increased chromosome fractionation (Hughes et al., 1998; Irvine et al., 2000) and excessive production of oxidized DNA (8-hydroxy 2-deoxy guanosine) (Fraga et al., 1991).

Oxidative overload also changes the phospholipid composition of the sperm membrane (Alvaraz and Storey, 1995; Zalata et al., 1998), reducing its fluidity and fusogenic capacity as well as the induced acrosome reactivity.

Among lifestyle factors, nutrition, abuse of alcohol, tobacco or recreational drugs, tight clothing and hot baths have been incriminated. Also, men with infertile semen were found to consume less omega-3 fatty acids than fertile men, and a significant correlation was established between the consumption of alfa-linolenic acid (18:3 omega-3) on the one hand and sperm concentration and type a motility on the other hand (Christophe et al., 1998).

Exposure to professional toxicants was proven to impair sperm quality, including heavy metals such as lead (Bonde et al., 2002) and carbon disulphide (Vanhoorne et al., 1994). But it is the exposure to environmental agents with hormone disrupting effects, mainly pseudo- or xeno-oestrogens and anti-androgens, that has caused most concerns recently. The obvious, though regional, deterioration of both sperm variables and fertility, and the parallel increase in the prevalence of testicular cancer, have been linked to an increased internal exposure to artificial chemical substances that mimic or enhance the effects of oestrogens by binding on the human oestrogen receptor or by influencing oestrogen metabolism (for review see Sharpe, 2003).

Inhibin B

Inhibin B is a secretory product of the Sertoli cells that plays an important role in both endocrine feedback, inhibiting the pituitary secretion of FSH, and local regulation of spermatogenesis. Whereas serum inhibin B concentration is significantly related to sperm concentration (for review see Meachem et al., 2001), there is evidence of a direct suppressive effect of inhibin B on spermatogenesis (van Dussel-Emiliain et al., 1989). Both in vitro tests (Depuydt et al., 1999) and in vivo data (Mahmoud et al., 1998, 2000) suggest that oestrogens and certain heavy metals, such as lead, may inappropriately stimulate the secretion of inhibin B by the Sertoli cells. This results in decreased sperm production, in the presence of normal serum concentrations of inhibin B and FSH.

During treatment with the strong antioxidant astaxanthin (see below), the serum concentration of inhibin was reduced, in spite of unchanged sperm concentration, suggesting that reactive oxygen species stimulate inhibin secretion by the Sertoli cells, similar to the effect of oestrogens (Figure 3).

Sub/infertility: a multifactorial disease

<table>
<thead>
<tr>
<th>Genetic defects</th>
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<td>CAVD</td>
<td>Hormone disruptors</td>
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<td>Robertsonian translocations</td>
<td>xeno-oestrogens</td>
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<td>Y-chromosome deletions</td>
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<td>→ CAVE ICSI</td>
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<th>Life-style</th>
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<tr>
<td>Nutrition → obesity</td>
<td>varicocele</td>
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<td>trans PUFA's</td>
<td>MAGI (Chlamydia)</td>
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<td>Tobacco</td>
<td>anti-sperm antibodies</td>
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<td>Alcohol</td>
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<td>Clothing</td>
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Figure 2. The four major contributing factors that act in synergy to cause subfertility or infertility in men – a multifactorial disease. CAVD, congenital absence of the deferent ducts; CAVE ICSI, be cautious about the transmission of genetic defects to the offspring generated by intracytoplasmic sperm injection; PUFA, polyunsaturated fatty acids; Cs₂⁺, carbon disulphide; MAGI, male accessory gland infection.
Decreasing the secretion of inhibin by reducing the oestrogen effect on the Sertoli cells and the exposure to reactive oxygen species may be a target of medical treatment. Indeed, reducing inhibin secretion may counteract the feedback suppression of FSH secretion by the pituitary and thus may directly improve spermatogenesis.

### Food supplementation

#### Fatty acids

Since there is a positive correlation between the intake of alfa-linolenic acid and sperm concentration and motility, and since the food intake of essential fatty acids of the omega-3 group was found to be sub-optimal among subfertile men (Christophe et al., 1998), it seems logical to supplement these patients with a source of 18:3 omega-3, namely linseed oil (also called flaxseed oil). When given in association with the co-factors zinc and vitamin B6, which enhance the elongase and desaturase enzymes, the alfa-linolenic acid will be converted into the long-chain, highly unsaturated omega fatty acids, namely eicosapentaenoic acid and docosahexaenoic acid. The latter increase the fluidity of the sperm membrane, improving the induced acrosome reaction and fusogenic capacity of the spermatozoa (Comhaire et al., 2000).

Alternatively, fish oil supplements can be a source of eicosapentaenoic acid and docosahexaenoic acid. These fatty acids are, however, highly susceptible to oxidative damage, which initiates an undesirable chain reaction of lipo-oxidation. If fish oil is given for food supplementation, it is mandatory to ascertain a favourable antioxidant internal environment at the same time.

#### Antioxidants

The resistance of LDL-cholesterol in serum to an in-vitro oxidative challenge reflects the oxidant-antioxidant balance of a particular person. The time lag before the initiation of LDL-cholesterol oxidation and the occurrence of conjugated dienes is a measure of oxidative stress, being higher if the time lag is shorter and vice versa. Subfertile patients were found to present a significantly shorter time lag than fertile men, indicating an imbalance between excessive oxidative stress and a reduced antioxidant capacity (Christophe et al., 1998). The present authors have demonstrated that food supplementation with an antioxidant preparation can significantly and persistently increase the time lag (Bernard et al., 2003). Also, it has been shown that treatment with either acetylcysteine (600 mg per day orally) or an antioxidant mixture of β-carotene (30 mg per day orally) and α-tocopherol (180 mg per day orally) significantly reduces the level of reactive oxygen species in semen (Comhaire et al., 2000). In combination with fish oil intake, providing 1 g of docosahexaenoic acid per day, antioxidant treatment increases sperm concentration and significantly reduces the concentration of oxidized DNA (8-hydroxy-2-deoxyguanosine) in spermatozoa of subfertile men. At the same time, the fatty acid composition of the phospholipids of the sperm membrane shift toward the long-chain highly polyunsaturated eicosapentaenoic acid and docosahexaenoic acid, increasing membrane fluidity. This then results in an increased calcium ionophore-induced, but not spontaneous, acrosome reactivity.

Figure 3. Endogenously produced as well as exogenous xenostrogens act in concert inhibiting the secretion of gonadotrophins by the hypothalamo-pituitary unit, and stimulating the secretion of inhibin B by Sertoli cells. This effect can be counteracted by the administration of a specific anti-oestrogen. Oxidative overload also seems to increase inhibin B production by Sertoli cells, which directly suppresses spermatogenesis and decreases the secretion of FSH by the pituitary. The oxidative overload can be balanced by the administration of anti-oxidant(s).

This agrees with the finding that vitamin E supplementation improves the in-vitro function of spermatozoa in the zona-free hamster oocyte test (Kessopoulou et al., 1995). In the present trial, the spontaneous pregnancy rate during the treatment period was 7.2% per month in the partners of (ex)-smokers, but remained at baseline among the partners of non-smokers (1.6%) (OR: 4.57, not significant).

Supplementation with vitamin C among smokers with abnormal sperm quality was reported to improve semen quality (Dawson et al., 1992), whereas no such effect was seen in another trial using high-dose vitamin C (Rolf et al., 1999). The latter may be related to the known pro-oxidative effect of high-dose vitamin C (Fraga et al., 1991), particularly in men with the haptoglobin type 1–2 or 2–2 (Bernard et al., 2003).

The oxido-reductase ubiquinone Q10 increased sperm motility in cases of asthenozoospermia, when added in vitro or given orally (Lewin and Lavon, 1997). Also other antioxidants such as selenium (Scott et al., 1998) and glutathione (Lenzi et al., 1993) were found to improve sperm motility in subgroups of patients.

Astaxanthin is a lipophilic carotenoid produced by the alga Haematococcus pluvialis, and it has a strong antioxidant capacity (Iwamoto et al., 2000; Goto et al., 2001). In a pilot double-blind randomized trial, 16 mg per day of the natural astaxanthin (AstaCarox, Astacarotene AB, Gustavsberg, Sweden) was given to the male partners of 20 infertile couples, whose semen characteristics were below the WHO recommended reference values. This food supplementation resulted in a significant reduction of seminal reactive oxygen species and serum inhibit B concentration among treated cases, but not in the placebo controls. Rapid linear progressive motility significantly increased, and sperm morphology presented an insignificant increase in the astaxanthin group, but sperm concentration remained unchanged. In the treated group, the total and monthly pregnancy rates were 54.5% and 23.1%, respectively, compared with 11.1% and 3.6% in the placebo group (OR: 9.6, $P = 0.08$) (Comhaire et al., submitted).
Carnitine

L-carnitine plays a pivotal role in the transport mechanisms necessary for the translocation of longer-chain-length fatty acids from the cellular cytosol into the mitochondrial matrix, where these can be oxidized and generate energy (Wildman and Medeiros, 2000) and stimulate respiratory chain complexes (Ruiz-Pesini et al., 2001). Free carnitine and acetyl-L-carnitine play an important role in the post-gonadal maturation of mammalian spermatozoa (Jeulin and Lewin, 1996), and the ratio of acetyl carnitine/carnitine was different in extracts of sperm with good or poor motility (Golan et al., 1984; Bartellini et al., 1987). Acetyl-L-carnitine is the prominent carnitine in spermatozoa, and its concentration is reduced in the semen of infertile men (Kohengkul et al., 1977; Soufir et al., 1984). The free carnitine concentration in seminal plasma is significantly correlated with sperm concentration and motility (P < 0.01) (Menchini-Fabris et al., 1984), and sperm motility can be stimulated by the addition of acetyl carnitine in vitro (Tanphaichit, 1977).

Treatment with a food supplement containing a combination of L-carnitine (2 g per day) and acetyl-L-carnitine (1 g per day) together with fructose and citric acid (Proseed, Sigma-Tau Health Science, Rome, Italy), was found to significantly increase sperm concentration and forward progressive motility (by 40% or more, P < 0.001) in both open label trials (Moncada et al., 1992; Costa et al., 1994; Vitali et al., 1995) and a double-blind crossover trial (P < 0.01) (Lenzi et al., 2003). In the open label trial, a total spontaneous pregnancy rate of 6.7% in 3 months was registered (Voliani et al., 2001). There are no data on the pregnancy rate in the placebo-controlled trial.

Folic acid and zinc

Folic acid (5 mg per day) and zinc sulphate (66 mg per day) have been given orally both to men with normal sperm quality and to patients with moderate oligozoospermia in a placebo-controlled trial (Wong et al., 2002). This combination was found to significantly increase sperm concentration (by an average of 60%, P < 0.05) and morphology in the sub fertile men. These changes occurred in spite of the absence of deficient blood levels of folic acid or zinc before supplementation in the sub fertile men. It was hypothesized that the supplementation with lower, physiological doses of micronutrients may even have a larger beneficial effect, since these have a stronger influence on absorption, transport and metabolic processes. It remains, however, to be established whether the administration of the combination of folic acid and zinc will result in improvement of fertility.

Seed oil and lignans

Aside from alpha-linolenic acid (see above), linseed or flaxseed oil contains several lignans, which are converted in the intestine into enterodiol and enterolactone. These are phytoestrogens with weak and short-lasting oestrogenic effects. However, enterolactone is a rather strong aromatase inhibitor. Thanks to this inhibitory effect, enterolactone reduces the conversion of androgens (androstenedione and testosterone) into the potent oestrogens oestrone and oestriadiol (Adlercreutz et al., 1993; Wang et al., 1994). Hence, food supplementation with linseed oil will decrease the level of endogenous oestrogens, which were commonly found to be increased in men combining oligozoospermia with normal serum concentrations of FSH and inhibin B (Mahmoud et al., 1998).

Plant extracts

Using immune histochemical techniques, Mayerhofer et al. (2002) have recently demonstrated that the cyclo-oxygenase iso-enzyme 2, which converts arachidonic acid (20:4 omega-6) into the inflammatory prostaglandin E2, is present in the testicular interstitial tissue of patients with idiopathic oligozoospermia, but not in men with normal spermatogenesis. Extracts of Pinus maritima bark (Pycnogenol; SiberHegner, PO Box 888, CH-8034 Zurich, Switzerland) contain substances that inhibit the cyclo-oxygenase enzyme (Baumann et al., 1980; Rohdewald, 2002), reduce the mRNA of the inflammatory cytokine interleukin-1β (Cho et al., 2001), and protect the effects of vitamin E on endothelial cells (Virgili et al., 1998). In an open label study including four sub fertile men, oral administration of 200 mg per day of this extract improved sperm morphology by an average of 99% (Rossef and Galati, 1999).

Extracts of Lepidium meyenii (maca), a plant growing in the central Andean region of Peru between 4000 and 4500 m altitude, increases sexual function of male mice and rats (Zheng et al., 2000) and invigorates spermatogenesis at the mitotic stages (Gonzales et al., 2001b). When given to eight men with normal spermatogenesis, this extract significantly increased sperm production (+85%, P < 0.05) and motility (+15%) without interfering with endocrine regulation (Gonzales et al., 2001a).

Though these plant extracts may show promise for the future, complementary studies are needed before they can be recommended for the treatment of male infertility.

Miscellaneous substances

For several years, arginine (De Aloysio et al., 1982; Aydin et al., 1995) and kallikrein (Schill et al., 1979) have been promoted for the treatment of men with oligozoospermia, but the alleged favourable effects of these supplements have been questioned (Pryor et al., 1978; Comhaire and Vermeulen, 1983).

Discussion

Several controlled and well-validated trials provide evidence that food supplementation with particular substances can improve semen quality and function in sub fertile men. These substances include carnitine, zinc, folic acid, tocoopherol and astaxanthin. There is evidence to suggest that certain of these supplements, when given as a complement to the WHO recommended conventional treatment (Rowe et al., 2000; Tournaye, 2003), can improve male fertility.

On a deductive basis, but without convincing data from clinical trials, certain other food supplements such as linseed oil and plant extracts may favourably influence sperm quality.
Although the exact mechanisms of action of these supplements on spermatogenesis and sperm function remain to be unravelled, a direct effect on the Sertoli cells (Figure 3) and via epididymal function seems conceivable.

It makes sense to further explore the therapeutic potential of food supplementation in the management of couple infertility due to the male factor.

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International calls to ban reproductive cloning

The body called the Inter-Academy Panel on International Issues plans to try to ban reproductive cloning worldwide. It plans to present a statement to the UN Ad Hoc Committee involving an International Convention against the Reproductive Cloning of Human Beings. This is to be done on 29 September 2003, at UN Headquarters in New York. There has apparently been some discord on obtaining a clear agreement among members. One divisive question is whether the ban should extend to both reproductive and therapeutic cloning. Many of the world's leading Academies of Science have joined in this protest, a total of more than 50 being listed. They include the Chinese, Third World, US and French Academies, and Lord Robert May, President of the UK Royal Society, signed the agreement of this Society at a Press conference in London on 22 September 2003. Thirty countries have joined this effort, still a minority.

Reported comments from Lord May included 'Recent reports about attempts by unscrupulous scientists to clone human beings have concerned the scientific society' and 'Attempts at human cloning seem reckless and grossly irresponsible'. He also commented that opinions of therapeutic cloning were divided, and it is notable that few countries (e.g. UK and Sweden) have legislated this procedure into practice.

Meanwhile, an Act is being introduced in the USA to ban somatic cell nuclear transfer (SCNT), making it a crime with up to 10 years in prison and fines of $US1 million or three times any profit made by using it for patients, whichever is highest. The reporter (Tipton, 2003) comments that 'Therapeutic cloning is vital to the development of new therapies that could assist millions of Americans. Weldon's bill criminalizes the very biomedical research that may provide the best hope for finding cures for Alzheimer disease, amyotrophic lateral sclerosis, diabetes, various cancers, strokes, Parkinson's disease, traumatic brain injuries, and spinal cord injuries'.

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