

RESEARCH HIGHLIGHT

The roles of omega-3 and omega-6 fatty acids in idiopathic male infertility

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Omega-3 fatty acids found in some foods have a wide-range of health benefits. The omega-3 supplementation results in higher antioxidant activity in human seminal fluid and enhanced sperm count, sperm motility, and sperm morphology. Considerable number of infertile men with idiopathic oligoasthenoteratozoospermia might be benefit from omega-3 fatty acids administration.

Infertility caused by idiopathic oligoasthenoteratozoospermia (OAT) syndrome without any female factor represents one of the biggest patients group in the daily practice of urologists. Despite great advances in the field of infertility, still many cases of male infertility are diagnosed as idiopathic and remained untreated. In low-income communities where health service resources are restricted and basic health needs are unmet, health resources are not used to provide expensive technologies for the treatment of infertility. Social and family consequences of infertility, especially in developing and under developed communities are devastating. A decrease in male fertility has been occurred over the years.¹ Sperm density had fallen by 40% over the past 50 years.² One of the reasons for the impaired semen parameters over the years is dietary factors.^{3,4} The significant effects of dietary fatty acids (FAs) on male fertility have been well documented both in animal and human studies.^{5,6} There are three types of natural FAs: saturated, monounsaturated and polyunsaturated. Polyunsaturated fatty acids (PUFAs) are essential FAs, because they cannot be synthesized by the human body. Docosahexanoic acid (DHA), eicosapentanoic acid (EPA) and α -linolenic acid are the main omega-3 PUFAs.

Linoleic acid, γ -linolenic acid and arachidonic acid (AA) are the main omega-6 PUFAs. The first mechanism by which omega-3 and omega-6 PUFAs affect spermatogenesis, is by the incorporation into spermatozoa cell membrane. Omega-3 and omega-6 PUFAs are structural components of cell membranes.⁷ The lipid bilayer of cellular membranes is maintained by the presence of these PUFAs.⁸ The successful fertilization of spermatozoa depends on the lipids of the spermatozoa membrane.⁹ Deleterious health effects of increased dietary omega-6/omega-3 ratios have been documented in many studies.¹⁰ The ideal ratio is 1:1. During the past 100 years, omega-6 PUFAs of Western diets have increased dramatically. This has resulted in an omega-6/omega-3 ratio of 25:1 to 40:1.¹¹ Increased omega-6/omega-3 ratio in spermatozoa has also been implicated in impaired semen quality in oligozoospermic and/or asthenozoospermic men.¹² Spermatozoa from asthenozoospermic and oligozoospermic men exhibit decreased concentrations of DHA compared with those from normozoospermic men. Conquer *et al.*¹³ demonstrated that, compared with normozoospermic men, spermatozoa from asthenozoospermic men have diminished concentrations of DHA and higher concentrations of oleic acid. Safarinejad *et al.*¹⁴ investigated PUFA composition of the blood plasma and spermatozoa in men with idiopathic OAT. They found that, fertile men had higher blood and spermatozoa levels of omega-3 PUFAs compared with the infertile counterparts. Also, the serum omega-6/omega-3 PUFAs ratio was significantly higher in infertile men. These findings have also been replicated in human clinical trials. Attaman *et al.*¹⁵ evaluated the relation between dietary fats and semen quality in 99 men. They concluded that, higher intake of omega-3 PUFAs was positively correlated with sperm morphology. In another randomized clinical

trial, 238 infertile men with idiopathic OAT were randomized to EPA and DHA, 1.84 g day⁻¹ or placebo for 32 weeks.¹⁶ A significant improvement in total sperm count and sperm cell density was observed in the omega-3 group. The second mechanism by which omega-3 PUFAs improve semen quality, involves anti-oxidant activity. Oxidative stress is one of the main issues associated with male infertility. Reactive oxygen species (ROS) significantly and adversely affect sperm function at high concentrations. Imbalance between antioxidant capacity in seminal plasma and the production of ROS results in oxidative stress. The seminal plasma anti-oxidant capacity plays an important role in sperm function. Balanced seminal plasma antioxidant activity prevents the oxidation of various macromolecules such as DNA, proteins and lipids.⁷ Omega-3 PUFAs are among important antioxidants. In a study by Safarinejad *et al.*,¹⁴ seminal plasma enzymatic antioxidant levels of catalase, and superoxide dismutase (SOD) were measured. Significantly lower levels of catalase- and SOD-like activities were found in infertile men compared with fertile men. In addition, catalase- and SOD-like activities were significantly positively correlated with sperm density, sperm motility and sperm morphology.

The omega-6/omega-3 ratio in spermatozoa cell membrane has utmost importance in maintaining normal sperm integrity and function. Oxidative stress to sperm DNA can result in increased DNA fragmentation. In humans, there is a positive strong correlation between sperm motility and sperm membrane DHA concentrations. Infertile men have higher mean AA/DHA ratio and AA/EPA ratio than fertile men.¹⁴

Also, other supplements with anti-oxidant activities such as selenium,¹⁷ coenzyme Q₁₀,¹⁸ and pentoxifylline¹⁹ have demonstrated favorable efficacy in infertile men with

idiopathic OAT. Recently supplementation with omega-3 PUFAs has received great attention in the course of psychiatric, neurologic and cardiovascular diseases.²⁰ The incorporation of omega-3 PUFAs, including ALA, EPA and DHA, into the diets has also beneficial effects on fertility. As omega-3 PUFAs have excellent safety profiles, are widely available and cost effective, and have had beneficial effects on spermatogenesis in human studies, they might be considered as nutritional supplementation to improve semen quality. We frequently treat infertile men with idiopathic OAT who were candidate for assisted reproductive techniques (ARTs) using above mentioned supplementations. The cost of ART protocols is high. Selection of infertility treatment often inter-related to different issues such as efficacy, cost, mode of administration and its potential side effects. Legal, cultural, social, economical and religious inquiries have considerably restricted the available choices in some countries. Each community has own concerns. In some communities use of donor sperms or oocytes is not acceptable, and in poor-resource areas ART protocols have not been resulted in improvement of quality of infertility care. The prevalence of infertility is highest in countries that experience the severe conditions of war, poverty, and starvation. In developing and underdeveloped areas, if infertility occurs, it is the female partner who is frustrated, disinherited, and ostracized and suffers from unstable marriages, divorce, polygamy, domestic violence and economic deprivation, and may even endure life-threatening medical intervention. In some

communities, female partners are discerned as a source of evil, subjected to physical and psychological violence and are even killed. We urgently need effective, inexpensive, and safe medications for dealing with OAT in idiopathic infertile men.

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