UNIVERSITAT ROVIRA I VIRGILI

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FINAL MASTER'S PROJECT

BENEFITS OF OMEGA 3 FATTY ACIDS IN CONDITIONS RELATED TO INFERTILITY IN MEN AND WOMEN

INTER-UNIVERSITY MASTER'S DEGREE IN NUTRITION AND METABOLISM

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1. Abstract

Introduction: Infertility is a serious health problem that is on the rise, and the causes for it are still unclear. The role of antioxidants in fertility problems has been gaining attention for some time now. Intake of omega 3 polyunsaturated fatty acids (PUFAs) has been found to improve semen and embryo quality among infertile men and women, respectively.

Objective: The aim of this study was to identify the potential benefits of omega 3 fatty acids in patients with conditions related to infertility.

Methodology: A comprehensive literature search of randomized clinical trials in English and Spanish from 2010 to date was carried out using the scientific data bases: PubMed, Science Direct, and Cochrane Library. The full texts of 9 articles were included in this systematic review.

Results: Omega 3 had a beneficial effect on sperm count, concentration, motility, and morphology; however, this was not a significant effect. Serum concentrations of omega 3 PUFAs, ratio of follicle / retrieved oocyte, injected oocytes and fertilization rate were increased, as well as a significant improvement in embryo quality and pregnancy outcomes.

Conclusion: Omega 3 fatty acids have a beneficial effect on fertility markers both in men and women; however, the results obtained in the meta-analysis of studies with men are not statistically significant. More research on the topic is needed to provide evidence for an adequate diagnosis and treatment for this condition.

Key words: Fertility, DHA, Omega 3, Polyunsaturated fatty acids, Infertility.

2. Introduction

2.1. Background

Infertility is defined as the inability to get pregnant after 12 months or more of unprotected intercourse. This condition affects about 1 in 6 people, representing about 17.5% of adults worldwide. It has been seen that environmental and lifestyle factors such as smoking, obesity, alcohol, and exposure to environmental pollutants among others, have been linked to lower fertility rates (1). It is estimated that 50% of factors that affect the pregnancy rates are linked to female issues, 20-30% are linked to male factors, and 20-30% are linked to both sexes (2). In Europe, about 15% of couples and 7.5% of men are reported to be infertile; while in Spain, this number increased to 43.2% of couples seeking treatment for this condition (3).

The social impact of this problem is important because most countries can-not guarantee the availability of quality treatment against infertility since this condition is not seen as a priority in demographic policies and the health system does not usually finance it. In addition, the cost of the treatments is quite high, there are not always adequate materials or qualified personnel in these matters to address this health problem. For this matter, infertility can have negative social repercussions in the lives of affected couples such as depression, anxiety, stress, low self-esteem, social rejection, and they may be more likely to suffer violent behavior or divorce for this reason (4).

A Dutch study found that 91% of the interviewed participants considered that fertility problems were an unacceptable health condition. Fertility is an important aspect of a normal healthy life, but treatments are sometimes seen as unnecessary or of low priority. In many countries, accessibility to fertility treatments is limited. In the Netherlands, couples can get a maximum of 3 In-Vitro Fertilization (IVF), or Intra-Cytoplasmic Sperm Injections (ICSI) attempts as part of their healthcare system. In Austria, about 70% of treatment and drug costs are reimbursed under certain circumstances, while in the USA, most couples pay for their own treatment (5).

Among the main causes of infertility is that, lately, both men and women have decided to postpone the age at which they want a pregnancy, with the average age being 35 years, age at which fertility is already declining. Another important factor is the alteration in the quality of the semen, mainly due to the abuse of toxic substances such as alcohol and tobacco. In addition, there has been a change in sexual behavior, increasing the number of sexual partners, which exposes couples to a greater possibility of contracting a sexually transmitted infection with important consequences for fertility. Infertility may also be caused by anomalies in sperm motility / morphology or in the reproductive system, problems in semen ejaculation, and absence or low quantity of sperm (6). These sperm characteristics are typical of patients undergoing idiopathic male infertility, which is still an unknown disease hard to diagnose and treat. Oxidative stress could lead to abnormal sperm parameters and high levels of sperm fragmentation (7). About 30-80% of male infertility is due to the negative impacts of oxidative stress on the sperm (8). More than 20% of normozoospermic males have a DNA fragmentation index >27%, resulting in decreased chances of conception after intrauterine insemination (9).

Another main cause of infertility is anovulation. Chronic anovulation is distinguished by irregular menstrual cycles, abnormal uterine bleeding, or amenorrhea. Some possible causes of this anovulation are hypothalamic amenorrhea, polycystic ovary syndrome, hyperprolactinemia, thyroid dysfunction, and premature ovarian failure. In ovarian failure, ovarian follicles are depleted, generating an elevation of gonadotropins, which influences female fertility (10).

Within the therapeutic options, the basis of treatment is to treat the primary cause of ovulatory dysfunction. Once the cause is corrected, if the alterations persist, ovulation induction should be indicated by various methods such as: anti-estrogens, aromatase inhibitors, gonadotrophins, or a combination of drugs (11).

Treatment and management of infertility include several pharmaceutical, non-pharmaceutical and surgical interventions. The primary clinical treatments include antioxidants, L-carnitine, and other drugs. Non-pharmaceutical treatments like lifestyle interventions can improve sperm motility, morphology, and quality (8).

Among other treatments, many couples now a days have been testing Artificial Reproductive Techniques (ART), to conceive; however, these techniques do not cure the causes of infertility but rather overcome some obstacles. Dietary supplements, like antioxidants, may be beneficial to enhance fertility since they have an important role in the regulation of fertilization. One of them are Polyunsaturated fatty acids (PUFAs), which are part of the composition of cell membranes of both the sperm and the oocyte and can influence prostaglandin synthesis and creation of steroid hormones (12).

Couples that underwent Assisted Reproductive Technology (ART) and received emotional support had a beneficial effect on infertility duration, as it was associated with a lower level of depression and higher levels of life purpose in both partners (13).

The outcome of the treatment can also have an impact on relationship quality. A study evaluated the relationship’s wellbeing before and after Testicular Sperm Extraction (TESE) and they saw that men with viable sperm reported a significant improvement in overall self-esteem and family-related self-esteem after the procedure. Also, the impact of infertility can be seen in couple separation, being the main reason for discontinuation of fertility treatments (14).

2.2. Context

Various studies highlight the importance of nutrition in fertility. In most of them, they talk about factors that could have a detrimental effect on fertility, such as an excessive intake of saturated fats, trans fats, and proteins of animal origin. In the same way, a beneficial effect has been related to the consumption of fiber, complex carbohydrates, omega 3 fatty acids (ω-3FAs) and monounsaturated fats. Several dietary patterns can influence spermatogenesis because of the content of ω-3FAs and antioxidants (15).

Dietary behavior has been associated with semen quality parameters; there are certain diets that can have negative effects on semen quality. One of them is the Western diet, that has been recently one of the most common diets and includes a high amount of saturated fats, trans fats, industrially processed food, animal protein, simple carbohydrate and is low in fiber and monounsaturated fat. This type of diet could lead to certain micronutrient deficiencies because of the lack of fruits and vegetables included, or to several diseases like obesity, diabetes, hypertension, and infertility through changes in hormonal levels, sperm function and gamete composition (16).

On the other hand, the Mediterranean diet has been linked to an increase in sperm number and quality as an improvement in the chances of conceiving. This diet consists of the intake of high amounts of antioxidants, vitamins, omega 3 fatty acids and carotenoids, which are linked to higher sperm counts. Also, a higher intake of fruits, vegetables and cereals were related to sperm concentration and motility (17).

There is evidence that certain type of foods and nutrients help to improve semen quality parameters like antioxidants and ω-3FAs. An overall healthy diet including fish and seafood was found to be associated with increased semen quality parameters.

Increased fatty acid intake is beneficial to fertility since spermatozoa membrane structure is essential for fertilization, membrane lipids are involved in acrosome reaction and sperm-oocyte fusion. Also, sperm motility, morphology and concentration are positively associated with levels of DHA. Fatty acid concentrations are different between infertile and fertile men, as levels of DHA and EPA are reduced in infertile men. Men with higher intake of omega 3 were less likely to develop asthenozoospermia, which is reduced sperm motility, compared to men with lower intake of omega 3 (18).

It has been seen that a diet high in saturated fats and trans fats is associated with an alteration in the quality and quantity of spermatozoa, as well as alterations in ovulation due to an increase in insulin resistance caused by this high intake. Intake of Polyunsaturated Fatty Acids (PUFAs), specially ω-3FAs is beneficial for improving both male and female fertility since it helps regulate certain hormones like progesterone and testosterone to successfully have a pregnancy. Likewise, omega 3 supplementation has had benefits in terms of improvement in insulin resistance in women with polycystic ovarian syndrome (PCOS), improvement in sperm quality and greater efficacy in assisted reproduction treatments (19).

Omega 3 fatty acids act as energy substrates during oocyte maturation and embryo development, as well as precursors for prostaglandins and steroid synthesis, necessary for pregnancy maintenance. Also, several studies have seen a significant association between the intake of PUFAs, estradiol levels, embryo morphology and the number of follicles. The type and amount of PUFA is important to have a positive effect in ovarian steroid synthesis, correct oocyte maturation and a pregnancy outcome. These effects are due to steroidogenesis and prostaglandin synthesis (20). EPA and DHA are an essential part of the cell membrane, which helps stabilize individual cells (21). Omega 3 fatty acids have shown to increase sperm concentration due to the anti-inflammatory and antioxidant properties it has, helping to protect the function and composition of cell membranes (7).

The mechanism by which omega 3 PUFAs can affect spermatogenesis is their incorporation into the spermatozoa cell membrane; successful fertilization depends on the lipid composition of the spermatozoa membrane (22).

However, more studies are needed to determine the efficacy of ω-3FAs, and which population of infertile people will benefit from them, since there are still few Randomized Controlled Trials (RCTs) on this topic, with a low number of participants, different doses, and duration of the supplementation (23).

Given the evidence about infertility and nutrition is still limited to this day and there are not enough articles about this topic, this review aims to identify how ω-3FAs can influence fertility both in men and women to contribute to the prevention and improvement of infertility through applied nutrition.

3. Hypothesis

Since infertility is related to inflammatory markers, nutrients with anti-inflammatory properties, such as omega 3 fatty acids, have a protective role against this condition.

4. Objective

4.1. General objective

The aim of this study was to understand and identify the potential benefits of omega 3 fatty acids in patients with conditions related to infertility.

4.2. Specific objectives

- Identify the risk factors for infertility in men and women.
- Determine if PUFAs have a protective role against infertility in men and women.

5. Methodology

Search strategy

The literature search was carried out in June 2023 using the scientific data bases: PubMed, Science Direct, and Cochrane Library. The PRISMA statement was carried out to make this systematic review. For the quality of the studies, the Study Quality Assessment Tool for controlled clinical trials was used.

The search strategy included the following terms “fertility”, “infertility” followed by the Boolean operator “AND” and the terms “PUFAs”, “Polyunsaturated fatty acids”, “DHA”, “Omega 3”.

Eligibility criteria

Randomized clinical trials in English and Spanish from 2010 to date, were analyzed for the present review. Studies that evaluated if PUFAs were associated to the improvement of male and female fertility were included.

Studies including animals, adolescents, people > 60 years old, with a high risk of bias (articles that are not double-blinded), and articles that were not available for full text were excluded from the search.

Of the 1,145 studies found in the search from scientific literature (PubMed (n = 71), Cochrane library (n = 64), and Science Direct (n = 1,010), the full texts of 9 articles were read, after the removal of duplicates and screening of the title and abstract. Studies were imported to Mendeley, and duplicates were identified and eliminated before reading the full article (Fig. 1).

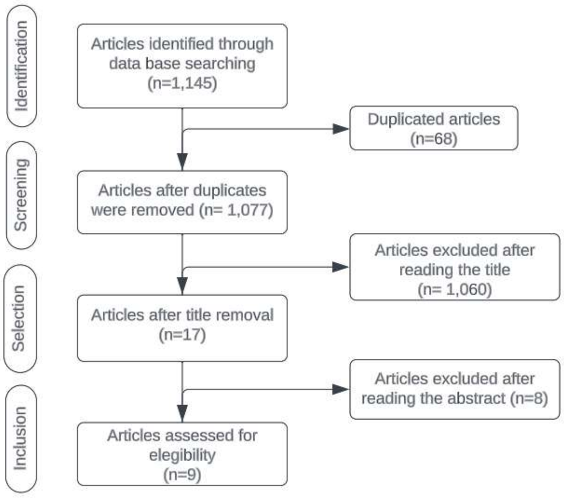

Figure 1: Flow diagram of the selection of studies for their subsequent inclusion in the meta-analysis.

Quality assessment and risk of bias

Study quality was assessed using the National Institutes of Health (NIH) "Study Quality Assessment Tool" for controlled clinical trials, which consists of 14 questions (24). In the Annexes section, Table 3 reports the results obtained. The studies included in the review had a mean score of 11,8 out of 14 points.

Data extraction

The data extracted from the studies included in this review, is summarized in Table 1 and collects the following information: Author, year of publication, country, journal, objective of the study, sample size, characterization of the study population, methods, analyzed variables, intervention, and outcomes.

Table 1: Characteristics and summary of the selected studies included in the systematic review

Reference	Country	Participants	Intervention	Variables evaluated	Outcomes
Steinberg et al., 2023	Israel	34 women between 25-38 years old with anovulation/ oligovulation PCOS related infertility who underwent ovulation induction.	50 mg of clomiphene citrate on day 12 of the cycle + 3 x 600 mg capsules of omega 3 supplement (360 mg EPA and 240 mg DHA) vs 3 placebo capsules of sunflower oil daily until they conceived or completed two cycles of clomiphene	Mean diameter of the follicle and full endometrial thickness, luteinizing hormone, follicle-stimulating hormone, total testosterone, free androgen index, androstenedione levels	8/30 pregnancies with omega 3 supplement vs 4/30 with placebo capsules. Omega 3, lower BMI, and a higher value of endometrium's thickness increased the odds of becoming pregnant.
Mohammadi et al., 2022	Iran	92 participants between 20- and 50-years old working in a manufacturing plant were randomly assigned to 4 different groups	1st group: 100 mg vitamin E + placebo 2nd group: 180 mg EPA + 120 mg DHA + placebo 3rd group: 100 mg vitamin E + 180 mg EPA + 120 mg DHA 4th group: placebo + placebo for 3 months	Semen parameters (sperm count, motility, morphology) and sex hormone levels were analyzed	Consumption of vitamin E and omega 3 had a significant effect on sperm motility and morphology
Eslamian et al., 2020	Iran	180 idiopathic asthenozoospermic men aged 20 - 45 years old with normal endocrine function were randomly assigned to 4 different groups	1st group: 465 mg DHA + 600 UI vitamin E (DE) 2nd group: 465 mg DHA + placebo (DP) 3rd group: 600 UI vitamin E + placebo (EP) 4th group: two placebo capsules (PP) for 12 weeks	Sperm characteristics (sperm count, motility, morphology), oxidative stress of seminal plasma, serum, and sperm membrane fatty acids	Sperm progressive motility, sperm count, and concentration were greater in the DE group than the other 3 groups. Serum concentrations of n-3 PUFAs were greater in the DE and DP groups.
Kermack et al., 2020	UK	111 couples with infertility undergoing IVF and ICSI were randomly assigned to 2 groups	55 couples received omega 3 fatty acid + vitamin D + olive oil + olive oil -based spread vs 56 couples that received the control intervention with placebo + sunflower oil + sunflower oil – based spread	The endpoints were the time taken for completion of the second, third and fourth cycles (CC2, CC3 and CC4), the synchrony of the second and third cycles (S2 and S3) and the day 3 and day 5 of Known Implantation Data Scores (KIDS)	There was no difference in CC2 between the two groups; however, CC4 was accelerated in the study group compared to the control group, as well as a shortened S3 and an increase on KIDS on day 3, indicating improved embryo quality.
González et al., 2018.	Spain	60 infertile patients between 18 and 50 years old with a previous history of infertility were randomly assigned to 4 different groups	DHA (0.5, 1 or 2 g) vs placebo for 1 and 3 months	Macroscopic and microscopic sperm parameters, oxidative stress, apoptosis, lipid peroxidation, mitochondrial membrane potential and DNA fragmentation	A significant increase in progressive sperm motility was seen after 1 or 2 g of DHA ingestion during the first month and after 3 months with 0,5 g. No differences were found in molecular semen parameters except for oxidative stress, in which a slight benefit was observed after DHA treatment.
Alousi et al., 2018	Iraq	120 sub fertile women between 20- and 40-years old undergoing ICSI treatment	2 groups: 60 women in the intervention group with 1000 mg omega 3 and 60 women in the placebo group taking liquid paraffin 500 mg for 8 weeks	The variables were number of follicles, number of oocytes, fertilization rates and embryonic quality.	The ratio of follicle / retrieved oocyte, number of metaphase II oocytes, fertilization rate and grade I embryo were increased in the intervention group compared to the placebo group.
Nouri et al., 2016	Austria	100 women between 19- and 42-years old undergoing IVF / ICSI treatment	2 groups: 50 women in the control group, receiving 400 mcg of folic acid and 50 women in the intervention group,	Embryo quality on day 3 after oocyte retrieval and clinical pregnancy rate	A higher rate of women with at least one good quality embryo was found in the study group compared to

			receiving the multi-nutrient supplement which contained: 1 capsule with 800 mcg folic acid, 70 mg selenium, 30 mg vitamin E, 4 mg catechins, 12 mg glycyrrhizin, 32 mg diosgenin, 90 mg damiana and one soft gel with 500 mg omega 3 fatty acid		the placebo group, demonstrating beneficial effects in terms of embryo quality.
Martínez et al., 2016	Spain	57 men over 18 years old who were undergoing evaluation for infertility were randomized into 2 groups	Placebo (1,500 mg sunflower oil) vs intervention group (1,500 mg of DHA-enriched oil) for 10 weeks	Sperm concentration, motility, vitality, count, morphology, semen volume, total antioxidant capacity, deoxyribonucleic acid fragmentation and fatty acid composition	An increase in DHA seminal plasma, improvement in antioxidant status and a reduction in the percentage of spermatozoa with deoxyribonucleic acid damage was observed in the DHA intervention group.
Safarinejad et al., 2010	Iran	230 infertile men between 23 and 41 years old with idiopathic oligoasthenoteratospermia were randomized into 2 groups	Intervention group received 1.12 g of EPA and 0.72 g of DHA vs control group that received 4 capsules of placebo for 32 weeks	Sperm concentration, motility, count, morphology, EPA and DHA concentrations, antioxidant status of seminal plasma	A significant improvement of sperm count and concentration was observed in the intervention group. Superoxide dismutase-like and catalase-like activity were positively correlated with seminal parameters.

PCOS: Polycystic ovary syndrome, EPA: eicosapentanoid acid, DHA: docosahexaenoic acid, BMI: Body Mass Index, PUFAs: Polyunsaturated Fatty Acids, IVF: In Vitro Fertilization, ICSI: intracytoplasmic sperm injection, DNA: Deoxyribonucleic acid

6. Results

Studies evaluating parameters in men

Four studies about sperm parameters were analyzed for the meta-analysis and the main results were heterogeneous. In some of them, there was an improvement in sperm count, concentration, motility, and morphology; however, the results were not statistically significant in the meta-analysis. Serum concentrations of omega 3 PUFAs were increased in the intervention groups, and a reduction in oxidative stress was observed (25–27,29). In Martínez et al. study (27), an increase in DHA seminal plasma, an improvement in antioxidant status and a reduction in the percentage of spermatozoa with deoxyribonucleic acid was observed.

The use of antioxidants supplements has a beneficial effect on fertility, especially when there are combined as seen in two of the studies where, when DHA was combined with vitamin E, the effect on fertility was much more improved than in the groups that only received DHA or vitamin E alone. Sperm count, concentration and progressive motility were higher in the intervention group consuming vitamin E plus DHA in comparison to the other groups. A significant difference was observed in the percentage of sperm with normal morphology after the treatment in the intervention group with DHA and vitamin D vs the group of vitamin E and DHA alone, that also showed an improvement but not as significant as the DHA + Vitamin E one (25,26).

The only parameter that showed a significant improvement with the use of omega 3 in all the studies evaluated in men was motility, while in women it was embryo quality.

For the realization of the meta-analysis, 4 studies about infertility in men were included, where the main variables analyzed were sperm count, sperm motility and sperm morphology in the study and the placebo groups after the intervention with omega 3. The results of the meta-analysis are shown in Figure 2, 3 and 4 in the forest plots.

The effect in the 3 variables is not statistically significant, conclusions about the effects of omega 3 in infertility can-not be made due to the heterogeneity of the studies.

Egger's regression is not significant, which means that there is no risk of publication bias. I^2 has a high value in the 3 forest plots, which means that the results of the study are heterogeneous, so more studies are needed to get to a solid conclusion.

Random-Effects Model (k = 4)

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	−0.744	0.746	−0.997	0.319	−2.207	0.719
	.	.	.	.	.	.

Note. Tau² Estimator: Restricted Maximum-Likelihood

[3]

Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
1.472	2.1672 (SE= 1.8191)	97.53%	40.532	.	3.000	154.120	< .001

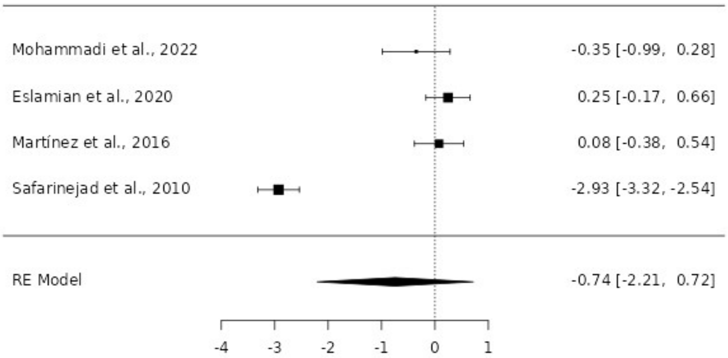

Figure 2: Meta-analysis of the effect of an intervention with omega 3 vs placebo in sperm count in infertile men.

Random-Effects Model (k = 4)

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	−0.275	1.13	−0.244	0.807	−2.483	1.933
	.	.	.	.	.	.

Note. Tau² Estimator: Restricted Maximum-Likelihood

[3]

Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
2.237	5.0063 (SE= 4.1443)	98.75%	80.139	.	3.000	269.252	< .001

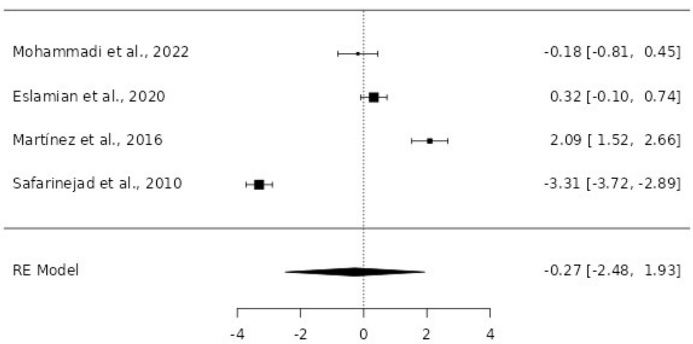

Figure 3: Meta-analysis of the effect of an intervention with omega 3 vs placebo in sperm motility in infertile men.

Random-Effects Model (k = 4)

	Estimate	se	Z	p	CI Lower Bound	CI Upper Bound
Intercept	−0.0119	0.884	−0.0135	0.989	−1.744	1.720

Note. Tau² Estimator: Restricted Maximum-Likelihood

[3]

Heterogeneity Statistics

Tau	Tau²	I²	H²	R²	df	Q	p
1.749	3.0581 (SE= 2.5514)	98.19%	55.320	.	3.000	170.350	< .001

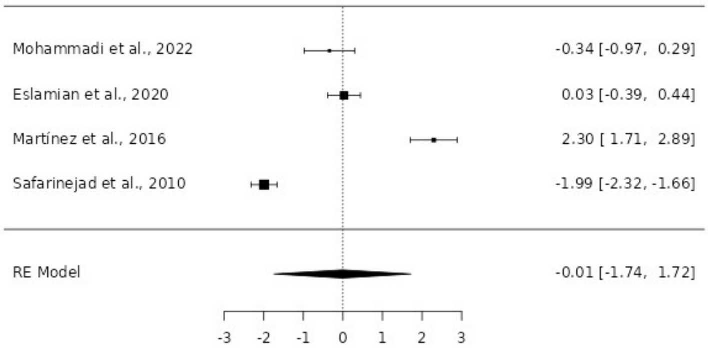

Figure 4: Meta-analysis of the effect of an intervention with omega 3 vs placebo in sperm morphology in infertile men.

Studies evaluating parameters in women

In women, 4 studies using an omega 3 supplement were analyzed for the systematic review, and the results were an improvement in pregnancy outcomes, an increase in the ratio of follicle / retrieved oocyte, injected oocyte, and fertilization rate, as well as an improvement in embryo quality (30–33). However, a meta-analysis could not be produced due to a lack of studies measuring the same parameters. Some studies had analyzed that a lower Body Mass Index (BMI), a higher value of endometrial thickness and supplementation with omega 3, increased clinical pregnancy rates.

7. Discussion

Lately, infertility has been an issue in several countries around the world, increasing the numbers year by year and affecting approximately 15% of couples worldwide. The causes for infertility are still unknown but several studies have observed some risk factors that can interfere with the correct functioning of sex hormones, sperm parameters or oocyte quality. Among the main risk factors for infertility are PCOS, sperm damage, exposure to chemicals or contaminants, oxidative stress, and lifestyle. Recently, several antioxidants have been studied to prove if they have an effect in the improvement of fertility and pregnancy outcomes (25–27,30,32,34).

In this review, the association of omega 3 polyunsaturated fatty acids with semen parameters and oocyte quality has been addressed. In the literature, there are few reviews that discuss the effect of omega 3 in the improvement of fertility in both men and women. It is important to take into consideration the dietary pattern and use of supplements in both parts of the couple to have a successful fertilization.

In the study of Mohammadi et al. (25), participants were randomized into 4 different groups and were prescribed with their respective supplements for 3 months: vitamin E + omega 3, omega 3 + placebo, vitamin E + placebo or placebo + placebo. Sex hormone levels were measured before and after the intervention, where they found that after the intervention, mean testosterone levels were increased in the three supplement groups. The lowest testosterone level before the intervention was found in the group vitamin E + omega 3, while the lowest level after the intervention was found in the placebo group. The other sex hormones did not have a statistically significant change before and after the treatment. Sperm characteristics were also measured, where mean sperm count and sperm with full motility increased after the treatment in the intervention groups. In the vitamin E + Omega 3 group and the Vitamin E + placebo group, a significant difference was observed in the percentage of sperm with normal morphology after the treatment. Also, the mean percentage of immotile sperm was lower after intervention in the supplement groups.

Eslamian et al. (26), measured the efficacy of consumption of DHA and Vitamin E in sperm characteristics on men with asthenospermia. Men were divided into 4 different groups: DE (DHA + Vitamin E), EP (Vitamin E + Placebo), DP (DHA + Placebo) and PP (Placebo + Placebo) group. As is shown in the study, total sperm count, concentration, motility, grade a motility and progressive motility were significantly increased in the DE, EP, DP groups compared to the PP group. The effect of DHA + Vitamin E was significant in sperm concentration, count, motility, and progressive motility.

In Martínez, et al. study (27), seminal parameters, total antioxidant capacity, lipid composition and deoxyribonucleic acid fragmentation were measured in 57 subjects assigned to two groups: intervention or placebo. Supplementation of DHA for 10 weeks induced an increase in total antioxidant capacity, an increase in the percentage of DHA in seminal plasma, a reduction in the percentage of spermatozoa with DNA damage, a reduction in the ratio omega 6: omega 3 PUFAs, a higher proportion of omega 3 PUFAs and a reduction in DNA fragmentation. While in the placebo group, no seminal parameter or fatty acid composition was identified.

González et al. (28) performed a double-blind, randomized, placebo-controlled intervention trial where sperm parameters, lipid peroxidation, oxidative stress, and DNA fragmentation were analyzed before and after the supplementation of DHA in doses of 0.5, 1- or 2-grams vs placebo for 1 and 3 months in 60 infertile patients. The results confirmed that there was a significant increase in the percentage of normal morphology in the placebo group and the 0.5 g DHA group after 3 months, while the same increased was observed in the 1 and 2 g DHA group after 1 and 3 months. Also, sperm motility was significantly increased in the 0.5 g DHA group after 3 months of treatment; while in the 2 g DHA group, the progressive motility was increased after 1 month of treatment.

In another study, 238 infertile men with idiopathic oligoasthenoteratospermia were randomized to the intervention group receiving 1.84 grams of omega 3 or to the placebo group to determine if the administration of omega 3 resulted in an improvement of semen parameters. The results indicated that there was a significant improvement in sperm total count, motility, morphology, and concentration in the omega 3 group. Antioxidant status of seminal plasma was also evaluated, and the results indicated that superoxide dismutase-like and catalase-like activity were positively correlated with sperm count, motility, and morphology (29).

In Kermack et al. study (30), 111 couples undergoing IVF or ICSI participated in the study where they were randomized into the intervention group and the control group. The intervention group received a supplement enriched with omega 3 and vitamin D plus olive oil and olive oil- based spread. The results demonstrated that the fourth cell cycle was accelerated, and the Known Implantation Data Score on day 3 was increased in the study group compared to the control group. These findings indicate improved embryo quality in the study group, demonstrating that a short period of supplementation helps to improve the rate of embryo cleavage. Further studies are required to fully determine the optimal duration of a pre-conceptional dietary intervention.

Regarding women, in another study, number of follicles, number of oocytes, fertilization rates and embryonic quality was evaluated in 120 infertile women between 20- and 40-years old undergoing ICSI treatment. These women were divided into two groups: intervention and placebo; the number of follicles and injected oocytes were higher in the omega 3 group compared with the placebo group, though the difference was not statistically significant. The total number of embryos was higher in the omega 3 group than in the placebo one and the embryo quality was also significantly improved (31).

Trop-Steinberg et al. (32), investigated the effects of omega 3 supplements during ovulation induction treatment in women with Polycystic Ovarian Syndrome (PCOS) – related infertility. 34 women were randomly assigned to the intervention group, receiving an omega 3 supplement or the placebo group, receiving placebo capsules. In the total of 30 ovulatory cycles, there were 8 pregnancies in women who were in the intervention group compared to 4 pregnancies in women who were in the placebo group. Among the findings, the study demonstrated that omega 3 fatty acids increased the chances of becoming pregnant, as well as the factor of the increase in endometrial thickness was taken into consideration for increasing the odds of becoming pregnant. Thus, increases in BMI reduced the odds of having a pregnancy, supplementation with omega 3 helped improved those chances; 29,6% of pregnancies in the omega 3 group compared to 5,3% of pregnancies in the placebo group.

In Nouri et al. study (33), the impact of a standardized multi-nutrient supplement was tested to analyze outcomes like embryo quality and clinical pregnancy rate in one hundred women who underwent IVF and ICSI. Women were divided into two groups; one with the intervention of the supplement, which included folic acid, selenium, vitamin E, omega 3, damiana, diosgenin and glycyrrhizin, while the control group received folic acid only. The results of the study demonstrated that 58% of women in the study group had at least one embryo of good quality compared with 36% in the control group, showing the benefits of the supplement in terms of embryo quality.

In table 2, the risk factors for infertility and their mechanisms identified in the articles are described. The reasons for infertility are still unknown but several authors have investigated several risk factors that can contribute to this pathology like exposure to electromagnetic fields, which can lead to a reduction in testosterone levels by affecting membrane polarization in testicle's cells (25). Diet also plays an especially important role in determining if fertilization can be successful. Both men and women need to have a good peri-conceptional nutrition status to have more changes of having a pregnancy. Weight-loss diets and excessive red meat consumption are related to a decreased chance of blastocyst formation according Kermack et al (30). There are several conditions that can be related with infertility like Polycystic Ovary Syndrome (PCOS), which causes anovulation, hyperandrogenism and smaller oocytes, affecting fertility outcomes in women who suffer from this condition (32). Another risk factor is structural defects in the sperm flagellum, caused by several reasons which can lead to reduced or absent sperm motility. Free radicals and oxidative stress also play a major risk factor for infertility since the imbalance of oxidants and antioxidants can make changes in sex hormone levels, promote impaired sperm function by inducing DNA sperm damage and lipid peroxidation, contributing to diminished sperm quality and motility, making it difficult to the sperm to fertilize the egg (26,27).

Table 2: Risk factors for infertility and their mechanisms

Reference	Country	Journal	Risk factor	Mechanism
Trop-Steinberg et al., 2023	Israel	Israel Medical Association Journal	Polycystic ovary syndrome (PCOS)	Chronic anovulation, hyperandrogenism, and smaller oocytes affect fertility outcomes in women with PCOS
Mohammadi et al., 2022	Iran	Male Sexual and Reproductive Health	Exposure to electromagnetic fields	Exposure to electromagnetic fields can lead to a reduction in reproductive indices such as testosterone levels by affecting the membrane polarization of the Leydig cells in the testicles.
Eslamian et al., 2020	Iran	American Journal of Clinical Nutrition	Structural defects in the sperm flagellum	Reduced or absent sperm motility
Eslamian et al., 2020	Iran	American Journal of Clinical Nutrition	Free radicals	Oxidants can make changes in levels of sex hormones that can lead to sterility having a negative effect in sperm quality and motility. Seminal oxidative stress can promote impaired sperm function.
Kermack et al., 2020	UK	Fertility and Sterility	Peri-conceptional nutritional status	Weight-loss diet and high consumption of red meat is associated with a decreased chance of blastocyst formation.
Martínez et al., 2016	Spain	Systems biology in Reproductive Medicine	Oxidative stress	Induction of DNA sperm damage by reactive oxygen species and lipid peroxidation.

This review has several strengths, being one of them the type of design of the studies: all the studies included were randomized, double-blind, placebo-controlled trials which included the information about the dose and type of omega 3 that was given to the participants. The characteristics of the participants of the studies were all similar between them, being infertile men and women between the ages of 18 and 50 years old who were undergoing evaluation for infertility or were in a treatment of IVF or ICSI.

The variables evaluated were similar between the studies: in men, sperm characteristics (sperm count, motility, morphology, concentration, vitality), oxidative stress, antioxidant capacity of seminal plasma, EPA and DHA serum concentrations, DNA fragmentation, and sperm fatty acid composition were analyzed. While in women, embryo quality, clinical pregnancy rate, level of sexual hormones, number of follicles, endometrial thickness, and number of retrieved oocytes were analyzed. Regarding the methodology, it was similar between studies except for the amount of omega 3 used and the time of the intervention. All studies used an adequate method of randomization, the treatments were concealed (so that assignments could not be predicted), the groups were similar at baseline (so that important characteristics like demographics, risk factors or co-morbid conditions could not affect outcomes in the study), the background treatments were similar, there was a high adherence to the interventions, and outcomes were assessed using valid measures.

The limitations of this review were that although the articles were of quality, the number of included RCTs was limited enough to make a solid conclusion about the use of omega 3 in the treatment of infertility. Also, the timing of intake of the supplement of DHA and EPA was different between trials, and some studies had a small number of participants to make conclusions for the general population.

The dosage used in each study was different; in one study the timing of the intervention needed to be longer to observe a positive correlation if the dosage was smaller than in another study that had a beneficial effect using a bigger dose. The search was limited to articles from 2010 to present since there was limited evidence that compared interventions with DHA vs placebo in infertile patients that analyzed the variables of sperm parameters and oocyte quality to observe if there was an improvement in fertility markers.

8. Conclusion

Anti-inflammatory nutrients like omega 3 fatty acids can help to improve certain fertility markers in individuals with related conditions. In this systematic review, evidence of omega 3 fatty acids was analyzed to reach information about the effect of PUFAs on infertility. 9 studies were included where patients with infertility took omega 3 fatty acids or placebo to determine if there was an association of PUFAs with fertility.

The studies included in the meta-analysis showed different results regarding sperm count, motility, morphology and concentration in men; so, a significant effect was not found. However, there is a tendency of improvement of fertility with supplementation of omega 3. Studies regarding the effect of omega 3 in women's fertility are scarce, therefore, a meta-analysis could not be produced. Still, evidence shows that omega 3 might have a beneficial effect on fertility. The literature in women show that PUFAs had a positive effect on the ratio of follicles / retrieved oocytes, increased injected oocytes, fertilization rates, embryo quality and pregnancy outcomes. Also, serum concentrations of omega 3 are improved in both men and women, influencing the process of fertilization.

The use of omega 3 for fertility problems is being used with more frequency than before; however, we need more evidence since the root causes of infertility are still unclear and it is a complex pathology. There are many factors that can affect fertility like age, diet, smoking, family history of infertility, PCOS, exposure to electromagnetic fields, an imbalance between oxidants and antioxidants, free radicals, oxidative stress, structural defects in the sperm flagellum, among other factors. Some factors cannot be controlled, but diet and the use of supplements can help couples to a large degree.

Adequately statistical powered, high-quality, long-term randomized controlled trials are needed to provide enough information about the use of omega 3 fatty acids in infertility treatments. Evidence is hopeful for this condition.

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10. Anexes

Table 3: Analysis of the quality of the studies included in the systematic review

Study	**Quality criteria**														**Total**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Steinberg et al., 2023	1	1	1	1	1	1	1	1	NM	1	1	0	1	1	12
Mohammadi et al., 2022	1	1	1	1	NM	1	1	1	NM	1	1	NM	1	1	11
Eslamian et al., 2020	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14
Kermack et al., 2020	1	1	1	1	NM	1	1	1	0	1	1	1	1	1	12
González et al., 2018.	1	1	1	1	NM	1	1	1	NM	1	1	0	1	1	11
Alousi et al., 2018	1	1	1	1	NM	1	1	1	NM	1	1	NM	1	1	11
Martínez et al., 2016	1	1	1	1	1	1	0	0	NM	1	1	NM	1	1	10
Nouri et al., 2016	1	1	1	1	1	1	1	1	NM	1	1	0	1	1	12
Safarinejad et al., 2010	1	1	1	1	1	1	1	1	1	1	1	1	1	1	14

0: no, 1: yes NM: Not Mentioned

The questions are the following:

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?
3. Was the treatment allocation concealed (so that assignments could not be predicted)?
4. Were study participants and providers blinded to treatment group assignment?
5. Were the people assessing the outcomes blinded to the participants' group assignments?

6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?
9. Was there high adherence to the intervention protocols for each treatment group?
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?