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Omega-3 polyunsaturated fatty acids and IVF treatment

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ABSTRACT

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids, derived mostly from fish oil, that have a significant anti-inflammatory effect. Data from animal studies support their role in the reproductive mechanism, and recent human studies suggest a positive effect on sperm quality and natural conception. Their general role in human fertility, and specifically in IVF treatment, however, is not clear. A few small, prospective cohort studies have examined the relationship between serum PUFAs and outcome measures and success in IVF, with conflicting results. Some have demonstrated a better chance of live birth with increased levels of serum omega-3 PUFAs, whereas others have failed to show such a correlation, and the reasons for such differences are not clear. Moreover, no well-designed, published studies have assessing whether the administration of omega-3 PUFAs before IVF treatment can improve clinical pregnancy and live birth rates. The development of safe and well-tolerated pharmaceutical forms of the active omega-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), mean that assessment of this question is now possible and future studies are warranted.

INTRODUCTION

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids, i.e. they cannot be made by the human body and must be obtained from dietary sources, primarily cold water-dwelling, oily fish. The two main omega-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), exert anti-inflammatory effects through a variety of mechanisms involving the eicosanoid metabolites, thromboxane, prostaglandins, leukotriene and prostacyclin, as well as by inhibiting genes that start the inflammatory process. They can be administered in pharmaceutical form for many different therapeutic purposes, such as approved treatment of hyperlipidaemia and after myocardial infarction; they are also in development and have been used experimentally for chronic inflammatory diseases, such as asthma, ulcerative colitis and Crohn's disease (*Scaioli et al., 2018*).

In general, fat comprises 30–40% of the body's daily energy consumption in the form of saturated and unsaturated fatty acids. The association between fatty acid, specifically omega-3 PUFAs, and fertility has not been studied extensively.

In-vitro and animal studies have shown that omega-3 PUFAs are important substrates in early reproductive events, including improved fecundity, oocyte maturation and embryo implantation (*Nehra et al., 2012; Gaskins and Chavarro, 2017*), and restored fertility and spermatogenesis in male rodents (*Roqueta-Rivera et al., 2010*). On the contrary, *Wakefield et al. (2008)* found that, despite normal fertilization and development *in vitro* after IVF in the mouse, exposure of oocytes to an environment high in *n*-3 PUFAs during IVF adversely affected the morphological appearance of the embryo and decreased developmental ability to the blastocyst stage. The association of PUFAs, and specifically omega-3 PUFAs, and fertility, however, has not been studied extensively in humans.

OMEGA-3 PUFAS AND NATURAL FERTILITY

Chavarro et al. (2007) studied a large cohort of 18,555 premenopausal women without a history of infertility who attempted a pregnancy or became

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pregnant over a period of 8 years. They found that trans-fatty acid intake was associated with a greater risk of self-reported ovulatory infertility, whereas intake of saturated fatty acids, monounsaturated fatty acids, total PUFAs, omega-3 PUFAs and omega-6 PUFAS was not associated with ovulatory infertility. *Mumford et al. (2016)* studied the associations between total and specific types of dietary fat intake, hormone concentrations and the risk of sporadic anovulation in a cohort of 259 regularly menstruating women. They found that total fat intake, and intake of PUFAs in particular, was associated with small increases in testosterone concentrations in healthy women, and that PUFAs and DHA were associated with increased progesterone concentrations and a decreased risk of anovulation. Others have shown that women with high omega-3 PUFA intake had a decreased risk of endometriosis (*Missmer et al., 2010; Hopeman et al., 2015*).

In a recent study, *Wise et al. (2018)* assessed the association between dietary fat consumption and fecundity or time to pregnancy among women participating in preconception cohort studies in Denmark (*n* = 1126) and in the USA (*n* = 1290). Women were included if they were trying to conceive for less than 6 months and had completed the specially designed food frequency intake online questionnaire. They found that, in the USA, omega-3 fatty acid intake was associated with higher fecundity, but no dose-response relationship; no such association was found in Danish women, however, probably because low intake of omega-3 PUFAs was rare. The investigators concluded that high trans-fatty acid intake and low omega-3 fatty acid intake were associated with reduced fecundity. In a recent prospective, cohort study with preconception enrolment and daily follow-up for up to 1 year of couples planning for pregnancy, seafood intake in both partners was associated with a higher frequency of sexual intercourse and fecundity. Specifically, the daily odds of sexual intercourse were 39% higher when both partners consumed seafood on the same day, and couples in which both partners consumed eight or more seafood servings per cycle had 61% higher fecundity and a 13% lower absolute difference in incidence of infertility compared with couples consuming less seafood (*Gaskins et al., 2018*).

The benefit of fish oil consumption in improving fecundity might be alarmingly hampered by long-term exposure to fish contaminated with persistent organochlorine compounds, e.g., polychlorinated biphenyls and dioxins, which are known to affect reproductive outcomes in humans. Buck *et al*. (2002) found that maternal, but not paternal, consumption of contaminated fish from Lake Ontario may reduce fecundity among couples attempting pregnancy (*Buck et al., 2000*). In contrast, another group did not find any evidence of reduced fertility in women assumed to have a high lifetime consumption of contaminated fatty fish from the Baltic Sea (*Axmon et al., 2002*).

OMEGA-3 PUFAS AND SPERM QUALITY

The lipid composition of the sperm membrane has a significant effect on the functional characteristics of spermatozoa. Most researchers have indicated that DHA is a major PUFA in human spermatozoa, and its deficiency in spermatozoa is a typical sign of subfertile or infertile men (*Esmaeili et al., 2015*). In humans, sperm motility is strongly correlated with sperm membrane DHA; decreased amounts of DHA and EPA, and increased omega-6/omega-3 PUFAs, were reported in semen of men with oligozoospermia, asthenozoospermia, or both (*Safarinejad et al., 2010*). Moreover, total n-3 PUFA of normozoospermia was significantly higher than in men with oligozoospermia, asthenozoospermia and oligoasthenozoospermia (OAT). *Esmaeili et al. (2015)* conducted a subsequent large-scale study for a relatively long duration of 32 weeks, in which 266 infertile men with idiopathic OAT were randomly assigned to fish oil capsules that contained EPA and DHA at doses of 1.84 g per day or placebo capsules containing corn oil. In the fish oil group, EPA and DHA levels in red blood cells and seminal plasma showed a statistically significant correlation with those in the spermatozoa, and a significant improvement of sperm cell total count and sperm cell concentration was observed (*Safarinejad, 2011*).

A few studies assessing the effect of a diet enriched with omega-3 PUFAs, either as a standalone parameter or as part of a 'prudent' or 'healthy' diet (such as the Mediterranean diet), on sperm quality have been conducted. These studies demonstrated a positive correlation with total sperm count (*Afeiche et al., 2014; Karayiannis et al., 2017*), morphology (*Attaman et al., 2012; Afeiche et al., 2014; Karayiannis et al., 2017*), higher progressive sperm motility (*Eslamian et al., 2012; Gaskins et al., 2012; Karayiannis et al., 2017*) and less sperm DNA fragmentation (*Vujkovic et al., 2009*). No studies have assessed clinical outcome and chance of pregnancy in couples with male infertility, in relation to a diet enriched with omega-3 PUFAs.

OMEGA-3 PUFAS IN ASSISTED REPRODUCTIVE TECHNOLOGIES

We identified five studies from the USA and one from Iran, all of them prospective cohort studies, which investigated the association between serum fatty acid concentrations at a single point before or during ovarian stimulation and outcome parameters of IVF (TABLE 1).

Hammiche et al. (2011) investigated 235 women who self-recorded their dietary intake of omega-3 PUFAs over the 4 weeks preceding stimulation for IVF (*Hammiche et al., 2011*). On the basis of a web questionnaire, the investigators calculated the daily intake of PUFAs and the main eicosanoids. They found that high intake of the omega-3 PUFA, alpha-linolenic acid (ALA), increased baseline oestradiol concentrations. High intakes of EPA and DHA reduced oestradiol response and number of follicles after ovarian stimulation, but this milder response had a positive effect by improving embryo morphology, in particular associated with intake of ALA and DHA. The study was too small and underpowered to estimate the effect on clinical pregnancy rate, and it was not reported. Serum level of the fatty acids in this study was not measured.

Jungheim et al. (2011) found that elevated levels of ALA were associated with a decreased chance of pregnancy in women undergoing IVF. No significant correlation was identified between serum ALA levels and ovarian response to gonadotrophin, peak serum oestradiol level, or per cent of high-quality oocytes among participants. A weak negative correlation was detected between serum ALA levels and embryo implantation. It was not clear whether the effect was caused by excess ALA intake, impaired ALA metabolism, or both.

TABLE 1 STUDIES ASSESSING CORRELATION OF OMEGA-3 POLYUNSATURATED FATTY ACIDS IN IVF CYCLES

Study and location	Number of cycles	Correlation assessed	Clinical outcome of IVF	Main findings
Hammiche *et al*., 2011, USA	235	Dietary intake of fatty acids by self-reported questionnaires over 4 weeks before cycle	No	High EPA and DHA intake decreased oestradiol response and number of follicles, and high total omega-3 PUFA intake improved embryo morphology.
Jungheim *et al*., 2011, USA	91	Serum level of fatty acides on day of oocyte retrieval	Yes	Increased level of ALA was associated with decreased chance of pregnancy.
Jungheim *et al*., 2013, USA	200	Serum level of fatty acid on day of oocyte retrieval	Yes	No individual PUFA was correlated with pregnancy; increased ratio of linoleic acid–ALA was associated with higher chance of pregnancy and embryo implantation.
Eskew *et al*., 2017,USA	60	Serum level of fatty acid on day 8 of stimulation	Yes	No correlation between omega-3 PUFA index and IVF outcomes.
Mirabi *et al*., 2017), Iran	105	Serum level of fatty acid	Yes	EPA serum level was significantly higher in pregnant women.
Chiu *et al*., 2018, USA	100	Serum level of fatty acid on days 3–9 of stimulation	Yes	High levels of total omega-3 PUFAs and EPA are associated with higher probability of pregnancy and live birth.

ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsatured fatty acid.

In a follow-up study of 200 women undergoing IVF, the same group found that no single PUFA was correlated with chance to conceive; however, women with increased linoleic acid –ALA ratios had a higher chance of pregnancy compared with women with lower linoleic acid–ALA ratios (Jungheim et al., 2013).

No correlation between omega-3 PUFA index and IVF outcomes, such as number of oocytes retrieved, embryo grade or clinical pregnancy, was found in another small study (*n* = 60) (Eskew et al., 2017).

Mirabi et al. (2017) measured serum and follicular fluid level of fatty acids in 105 women undergoing IVF. They found that EPA levels were significantly higher in pregnant than non-pregnant women (*P* = 0.006), and following adjustment for age and body mass index (BMI), total fatty acids was correlated with high-quality oocytes.

Recently, Chiu et al. (2018) sampled 100 women from a prospective cohort study (EARTH) who underwent 136 assisted reproductive technology cycles within 1 year of blood collection. In total, 62 cycles (46%) resulted in a clinical pregnancy and 47 cycles (35%) ended in a live birth. The investigators found that omega-3 PUFA concentrations were associated with a higher probability of clinical pregnancy and live birth, and these associations were mainly driven by EPA. Moreover, the probability of clinical pregnancy and live birth increased by 8% for every 1% increase in serum omega-3 PUFA levels. Serum linoleic acid and omega-6 to omega-3 PUFA ratio were inversely associated with specific preclinical end-points, such as peak oestradiol concentration and oocyte yield, but this did not translate into differences in clinical outcomes.

Overall, these studies in a limited number of patients found inconsistent and conflicting results on the relationship between omega-3 PUFA intake and IVF outcome. No large-scale studies on the effect of prospectively administrating an omega-3 PUFA-rich diet before IVF treatment have been published. We are aware of only a single published study from Australia, in which overweight and obese women undergoing IVF were randomized to a PUFA-enriched diet plus physical activity (intervention) or standard care (control). After adjustment for BMI and smoking status, women who became pregnant had higher PUFA intake, specifically omega-6 PUFAs and linoleic acid, with a trend for an elevated intake of omega-3 PUFAs. No dietary differences were identified for women who did or did not have a live birth. This study, however, was conducted in a small cohort of patients (*n* = 46) (Moran et al., 2016).

Currently, no prospective randomized clinical trial has assessed the effects of dietary enrichment with specific PUFAs before IVF or during the periconception period. Also, no studies have reported on the effect of PUFAs in intrauterine inseminations.

DISCUSSION

Omega-3 PUFAs have a significant effect on animal and human reproduction. The main PUFAs, EPA and DHA are important for sperm motility and normal morphology, and recent studies have demonstrated the correlation of a diet enriched with omega-3 PUFAs and sperm quality. Only a single randomized controlled trial investigating administration of omega-3 PUFA-containing capsules versus placebo in men with OAT showed significantly improved sperm quality in the treatment group; however, this study did not assess clinical outcome of treatment (Safarinejad, 2011). No other studies have tested the effect of consuming omega-3 PUFA on clinical pregnancies in male infertility. In a recent prospective cohort study, Gaskins et al. (2018) demonstrated that, among couples trying to conceive naturally, those in which the men consumed a high level of fish oil had a higher fecundity rate with increased sexual drive and reduced time to pregnancy (Gaskins et al., 2018); however, no data are available on sperm parameters before or at any time of the study, nor whether there was any male factor infertility. Similarly, recent data showed a positive association between a diet enriched with omega-3 PUFAs consumed by women (Wise et al., 2018), or by either or both partners (Gaskins et al., 2018), and natural fecundity and time to pregnancy among couples trying to conceive naturally; however, no randomized controlled trials have evaluated the effect of omega-3 PUFAs on natural conception, in couples with or without infertility. Therefore, emerging data show positive correlations between omega-3 PUFAs and sperm quality and natural conception; however, it is currently impossible to assess their clinical effect in the context of male and female infertility.

It is unclear why studies in IVF have yielded conflicting results on the relationship between PUFA intake and IVF outcomes, but it may be due, in part, to the combination of a small number of cycles in each study and the variability of studies. In total, five studies (556 cycles) reported a clinical outcome of IVF: two studies showed a positive effect of omega-3 PUFAs, especially EPA, on clinical pregnancy (Mirabi et al., 2017; Chiu et al., 2018), one found no correlation (Eskew et al., 2017), and one found a negative effect of ALA (Jungheim et al., 2011); however, in a larger follow-up study from the same group, no detrimental effect was found nor was a correlation found between PUFAs and the chance of becoming pregnant, although a higher ratio of linoleic acid–ALA increased this chance (Jungheim et al., 2013). Marked differences exist between the studies. For example, time of blood sampling ranged from days 3–9 of stimulation (Chiu et al., 2018), day 8 (Eskew et al., 2017), day of oocyte retrieval (Jungheim et al., 2013) or was not specified (Mirabi et al., 2017). Differences in patient characteristics were present between studies, e.g., in BMI (27.7 versus 24.4 kg/m^2) (Jungheim et al., 2013; Chiu et al., 2018), and analytical approaches also differed, especially for assessment of linoleic acid–ALA ratios (Chiu et al., 2018).

At the periconception period and during early pregnancy, PUFA metabolism, including genetic variation and the balance between omega-3 and omega-6 PUFAs, is complex and not clearly understood (Wathes et al., 2007). Animal studies have suggested at least three areas of female reproduction that may be affected by PUFA intake and metabolism: direct effects on oocyte and embryo quality, steroidogenesis and embryo implantation in the uterus.

A direct effect on oocytes is supported by Nehra et al. (2012), who demonstrated that a diet rich in omega-3 PUFAs resulted in improved fecundity and oocyte quality in ageing mice. Others, however, have found contradicting results of poorer embryo morphology and developmental competence among mice fed a diet rich in omega-3 PUFAs (Gaskins and Chavarro, 2017).

Omega-3 PUFAs are sources of cholesterol, the precursor molecule for all steroid hormones, and may have direct and indirect effects on steroid biosynthesis through regulation of enzymes and prostaglandins; in this process, a fine balance is reached between omega-3 and omega-6 PUFAs, although no strong evidence has validated this speculation.

It is likely that PUFA metabolites affect embryo implantation. Omega-3 PUFAs promote the generation of 3-series prostaglandins (such as PGE3 and PGF3α), which are generally categorized as anti-inflammatory, whereas omega-6 PUFAs are precursors to the pro-inflammatory prostaglandins (such as PGE2). Prostaglandin composition within the uterine environment is thought to be critical for successful implantation (Salleh, 2014), but reports on which prostaglandins enhance implantation, and which are detrimental, are conflicting. For example, Biondi et al. (2006) argued that PGE2 inhibits trophoblast invasion, whereas a more recent concept is that PGF2α stimulates conceptus–maternal interactions and angiogenesis in the endometrium (Waclawik et al., 2017). Prostaglandins and prostacyclin (PGI2, another metabolite of PUFAs) are involved in all stages of embryo implantation: increased vascular permeability and angiogenesis at the implantation site, decidualization, extracellular matrix remodelling, embryo transport, blastocyst growth and development, and trophoblast invasion (Salleh, 2014).

In conclusion, emerging data suggest, on balance, that high intake and increased serum levels of omega-3 PUFAs have a positive effect on IVF and intracytoplasmic sperm injection. Because of the anecdotal, sparse and sometimes conflicting animal and human data, however, it is difficult to conclude whether omega-3 PUFAs have a substantial beneficial effect on female fertility and, in particular, as a prophylactic treatment before IVF. With the development and availability of highly purified omega-3 PUFA products, either in EPA form or as a combination of EPA and DHA, and their safe long-term use in other indications, it is now warranted to prospectively assess in well-designed randomized controlled trials whether omega-3 PUFA administration before IVF treatment can improve clinical pregnancy and live birth rates.

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