

# **Impact of preconceptional omega-3-fatty acid supplementation on IVF-success and miscarriage rates in patients of a German fertility center**

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## **Condensed Content**

Based on publications on potential benefits of omega-3-fatty acids an approach of IVF-success modulation by dietary measures was performed in the examined and clearly defined group of patients of a German fertility center.

A group of 52 IVF-patients with a history of at least two miscarriages or unsuccessful fertilization in vitro received periconceptual omega-3-fatty acid supplementation for at time period of at least 3 weeks. The „historical“ control group consisting of 1109 patients without omega-3-fatty acid supplementation was generated out of the fertility center’s patient database. The same inclusion criteria (history of at least two miscarriages or unsuccessful fertilization in vitro) were underlied for both groups. Omega-3-fatty acid supplementation lead to significatly enhanced in vitro fertilization success rates as well as to a significant reduction of miscarriage rates compared to patients in the control group.

The results encourage to conceptualize further age-matched, double-blinded prospective studies in order to verify a positive influence of dietary intervention and life style modification on fertility rates.

**Key Words**

omega-3-fatty acid supplementetation, in vitro fertilization, miscarriage rates

## **Introduction**

Omega-3-fatty acids belong to the group of polyunsaturated fatty acids and naturally occur in seaweed, diverse plants and fish. As they are essential for humans they have to be alimented. Omega-3-fatty acids not only represent important constituents of the cellular membrane, they also serve as basic synthesis compounds for intra- and extracellular signal messengers such as eicosanoids, which are involved in central physiological and pathophysiological processes like f.e. inflammation and tumorigenesis.

Multiple and heterogenous beneficial effects are attributed to omega-3-fatty acid intake such as prevention of cardiac ischemia, stroke, depression and dementia. Also attention deficits shall be diminished as well as intelligence increased in babies of mothers supplemented with these substances. This represents just a small excerpt of the potential benefit spectrum assigned to these supplements in general health magazines. Therefore the readiness for supplementation is broad and en vogue in population, leading to an increased demand in the healthcare market. The question if these benefits are real is a trigger for a diversity of investigative approaches..

As a matter of fact various studies seem to confirm some of these beneficial effects assigned. Omega-3-fatty acids especially lower cardiovascular risks (1,2), they contribute to maintenance of mental health (3), the substances are attributed antiinflammatory advantages (4) and they even are put into context with preventive effects for certain tumor types like f.e. prostate cancer (5).

Beside that, positive associations for a linkage of omega-3-fatty acids with fertility and pregnancy have been published (6,7). Omega-3-fatty acid supplementation enhances uterine blood flow and therefore a successful onset of pregnancy is facilitated, the risk of miscarriages is reduced as well as the durance of pregnancy and the birth weight of the baby is positively influenced (6,8,9).

Beside these effects, an increased consumption of omega-3-fatty acids during pregnancy seems to reduce the risk of a postpartal depression (10). Also positive effects on intelligence quotients of those children are described (11). Recent studies indicate a positive effect of omega-3- and omega-6-fatty acids on the implantation probability with respect to in-vitro fertilization (12,13).

Kernack reports that approximately one in six couple suffers from subfertility. Despite of improvements in artificial reproductive technologies ongoing pregnancy rates per cycle are reported to still remain at ~25% (14). With growing evidence that the periconceptual nutritional status is a key determinant of fertility and long-term health of the offspring, a lucrative market has developed to meet the demand based on these benefits. Routine dietary supplementation of omega-6-fatty acids before and during IVF-treatment has not been

subject to well-powered prospective randomised trials. One of the first prospective intervention trials examining the association of omega-3-fatty acid intake and the likelihood of a pregnancy entry was initiated by Kermack et al. (14). Results of this PREPARE trial are still outstanding.

These approaches encouraged us to use the accessibility of a well defined patient group in a German fertility center for examining the effects of a periconceptional omega-3-fatty acid supplementation on fertility outcome, i.e. likelihood of pregnancy entry and potential prevention of miscarriages in a first preparatory study, being aware that this approach does not meet classical prospective study criteria. For this purpose patients received a minimum of 3 weeks of periconceptional omega-3-fatty acid supplementation. Data for the control group without supplementation were recruited retrospectively from the database of the fertility center.

## **Material and Methods**

### **Patients**

Patients with a history of at least two miscarriages or unsuccessful fertilization in vitro (IVF)-treatments were recruited for the trial in a German Fertility Center (Interdisciplinary IVF-Center, Düsseldorf, Germany), leading to a selected patient group with poor prerequisites for successful fertility treatment. Patients with prednisolone intake and patients unwilling to have their data passed on were excluded from the trial group.

The same criteria were applied for the generation of a retrospective, „historical“ control group out of the fertility center database.

Overall a group of 52 patients with omega-3-fatty acid substitution was compared with a „historical“ control group of 1109 patients, having received no dietary supplementation.

### **Omega-3-fatty acid substitution**

Patients received omega-3-fatty acid substitution during the IVF-treatment concept. The dietary supplement was „OMEGAVEN Fresenius Emulsion“, administered intravenously (1 ml per kg body weight per day) over at least 3 weeks. The product information reveals a content of 1.25-2.82 g eicosapentaenoic acid, 1.44-3.09 g docosahexaenoic acid, 0.015-0.0296 g  $\alpha$ -tocopherol and 2.5 g glycerol per 100 ml emulsion. First controls with respect to IVF-success were performed average 4-6 weeks after supplementation, the minimum interval was 3 weeks.

## **Statistics**

Statistical analysis was performed by IBM SPSS Statistics (version 22). For descriptive analysis mean values and standard deviations were calculated. Stochastic independence of IVF-success rates and dietary omega-3-fatty acid supplementation were checked by means of the chi-square test of independence.

## **Results**

### **Influence of omega-3-fatty acid supplementation on IVF-success rates**

The likelihood of pregnancy entry in 52 patients receiving a minimum of 3 weeks of periconceptional omega-3-fatty acid supplementation was compared with that of a „historical“ control group of 1109 patients (tab.1).

36 patients (69.2%) of the supplemented trial branch (total 52) became pregnant after IVF-treatment at the end the observation period of 4-6 weeks (minimum 3 weeks). One of these 36 patients had an miscarriage later during pregnancy.

The „historical“ control group of 1109 patients, receiving no omega-3-fatty acid supplementation, revealed a pregnancy success rate of 33.3% (369 patients). The difference was statistically significant ( $p < 0.001$ ).

### **Impact of omega-3-fatty acid supplementation on miscarriage rates**

After successful IVF-treatment 1 of 36 patients (2.8%) in the omega-3-fatty acid substituted group and 74 out of 369 patients in the „historical“ control group (20.1%) suffered from a miscarriage earlier than week 12 of pregnancy (tab. 2). The difference was statistically significant ( $p = 0.010$ ).

## **Discussion**

Goal of this study was to determine if there are first hints for a positive effect of omega-3-fatty acid supplementation on success of IVF-treatment and on a consecutive reduction of miscarriage rates. This led to a study design with a prospective study group and a „historical“ retrospective control group using the availability of the well defined patient collective of a German fertility center.

For this preliminary approach the study group included 52 patients, whereas the control group with 1109 patients was nearly 20-fold larger. The substantial differences in numbers between study and control group are due to this specific study concept and of course limit conclusions.

In the interventional branch of the study successful pregnancy rates in IVF-patients periconceptionally treated with omega-3-fatty acids nearly doubled compared to the rate in the control group, which received IVF-treatment alone.

This promising result is in accordance with several recent studies. Jungheim and coworkers described a positive influence on success rates of fertilization in vitro by modification of omega-6- to omega-3-fatty acid-ratios (13). In animal experiments the quality of male sperms could be reduced by reduction of omega-3-fatty acid content in feed of freshwater guppies (15). These findings give space to the hypothesis, that with reduced dietary amounts of naturally occurring omega-3-fatty acids in industrialized countries also males in couples with fertilization problems may profit from supplementation. Further findings from the veterinary sector substantiate the hypothesis of positive effects of omega-3-fatty acids on fertility. Beside guppies, supplementation of omega-3 and omega-6 fatty acids in a special species of carp fish leads to improved maturation of gonads, breeding performance and spawn (16). Prepubescent sheep react on an increased supply with omega-3-fatty acids with increased release of reproductive hormones and increased fertility (17). Adding eicosapentaenoic acid to dairy cow feed improved folliculogenesis and the success rate of artificial fertilization (18).

Concludingly it can be postulated from human and animal data that supplementation of omega-3-fatty acids in male as well as in female may positively influence the overall reproductive success.

The influence of omega-3-fatty acid supplementation on miscarriage rates in patients after successful IVF-therapy revealed also first encouraging data. Out of the 36 patients comprising omega-3-fatty acid-supplemented group which became successfully pregnant, just 1 patient suffered from a miscarriage later during pregnancy (2.8%), whereas in 20.1% of the non-supplemented control group miscarriage occurred. Although this ratio is significantly higher it is of limited validity and explanatory power due to the small size of both study branches well as their relation in size.

Nevertheless preventive effects of omega-3-fatty acid on miscarriage rates have been described before. Lazzarin published data for supplemented women formerly having miscarriages due to bad uterine blood circulation. These showed a significant improvement of arterial uterine blood supply (19).

Even patients with antiphospholipid syndrome responded to omega-3-fatty acid supplementation with a reduced incidence of miscarriages (20).

Supplementing vitamins, omega-3- fatty acids and minerals was described to reduce the risk of pre-eclampsia, premature births, gestation diabetes and miscarriages (21).

Veterinary data indicate halving of miscarriage rates in milk cows by adding of omega-3- fatty acids enriched linseed (22).

Our results in combination with results of human and veterinarian origin as described above reveal encouraging aspects with respect to a preventive effect of omega-3-fatty acid supplementation on as well IVF-success rates as a reduction of miscarriage rates.

A unique strength of our study is the fact that the study group, even with the relatively small number of 52 patients, is extremely well defined as well as clinically monitored during a long period and therefore strongly delineated to general female population. It also is composed by a patient collective preselected by poor prerequisites with respect to successful pregnancy (either unsuccessful fertilization in vitro (IVF)-treatment or at least two miscarriages in the past). Positive impact of dietary measures in such a negatively preselected group heavily outweighs against normal female population and gives rise to further studies. Our results are weakened by the fact, that the study could not be concipated as classical intervention study. All patients received omega-3-fatty acid supplementation and the effect with respect to influence on IVF-success rates and miscarriage rates was compared to a „historical“ control group out of the same German fertility center. Study group and control group differ significantly in size, potentially influencing p-values already by stochastical fluctuations. Additionally age distribution in both groups could not be considered in this approach.

Promising first results of our study taking into account potential improvements described above and data already published before encourage in planning a new age-matched, placebo-controlled double-blinded study design. The meaningfulness of such an approach is suggested by the currently performed PREPARE trial study (14). This randomized, placebo-controlled dietary intervention study is based on a six-week duration olive oil containing alimentation combined with vitamin D and omega-3- fatty acid intake in the interventional branch and a six-week duration sunflower oil containing diet without vitamin D and omega-3-fatty acid supplementation in the control group. Goal is the evaluation of dietary intervention on early stages of embryonal development.



## **Conclusions**

First positive effects of at least 3-week-preconceptional omega-3-fatty acid supplementation on reduction of miscarriage rates and on success of IVF-treatment could be shown in patients of a German fertility center, which encourage to conceive larger prospective studies in such well defined patient groups.

This approach of life style modification may be a low-cost mosaique block which is simple to realize improving the outcome of fertility treatment.

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## Tables

**Table 1:** Comparison of IVF-success rates between 52 omega-3-fatty acid supplemented and 1109 non-supplemented patients in a German fertility center

	supplementation group		„historical“control group		total	
	absolute no.	percentage	absolute no.	percentage	absolute no.	percentage
<b>IVF successful</b>	36	69.2***	369	33.3	405	34.9
<b>IVF not successful</b>	16	30.8	740	66.7	756	66.1
<b>total</b>	52	100	1109	100	1161	100

\*\*\* p< 0.001

**Table 2:** Comparison of miscarriage rates between 36 omega-3-fatty acid supplemented and 369 non-supplemented patients after successful IVF-treatment in a German fertility center

	supplementation group		„historical“control group		total	
	absolute no.	percentage	absolute no.	percentage	absolute no.	percentage
<b>miscarriage rate</b>	1	2.8***	74	20.1	75	18.5
<b>completed pregnancy</b>	35	97.2	295	79.9	330	81.5
<b>total</b>	36	100	369	100	405	100

\*\*\* p=0.001