



# The Omega-3 Polyunsaturated Fatty Acid Supplementation and Female Infertility

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Some reasons such as achieving high economic status before deciding to have children, having an education degree and waiting for starting a professional career cause women to delay their pregnancy decisions until late reproductive ages (1). It is known that advancing age is associated with decreased ovarian reserve (1). Today, no adjuvant therapy exists for the women with decreased ovarian reserve. Androgens and dehydroepiandrosteron are used in women with decreased ovarian reserve, but the available evidence is not strong (2,3). It was shown in polycystic ovary induced rats that omega-3 improves the ultrastructural changes in follicle cell-oocyte associations and reduces malondialdehyde levels (4,5). Omega-3 fatty acid supplementation in experimental models have been shown to improve folliculogenesis, oocyte maturation, and embryo quality (6). But the data about omega-3 polyunsaturated fatty acids and ovarian reserve is limited and Omega-3 polyunsaturated fatty acids supplementation merits further investigation in women with diminished ovarian reserve (7).

Reactive oxygen species (ROS) and antioxidants are in balance in a healthy body (4). Increasing the level of ROS and decreasing antioxidant systems leads to cellular oxidative damage, including a decrease in the number of ovarian follicles (8). The inflammation has a potential role in diminished ovarian function (9). Omega-3 plays an active role in the regulation of the antioxidant system and omega-3 fatty acids are thought to have positive effects on ovulation and implantation (10). Omega-3 long chain polyunsaturated fatty acids ( $\omega$ -3 LC-PUFA) are compounds that have a double bond at the third carbon atom from the methyl end of the carbon chain. Some of these, especially alpha-linoleic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have very important physiological functions, and their main sources are fish and seafood (10). Omega-3 derivatives have anti-inflammatory activity (11).

On the other hand; it was declared that there is limited evidence in support of supplemental oral antioxidants for subfertile women in 2020 (12). Also, it was declared

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in a recent study that omega-3 serum levels are not associated with natural fertility in human (13). Stanhiser et al reported that mean omega-3, omega-6 and omega-6:omega-3 ratios did not significantly differ between the fertile, subfertile and infertile women  $\geq 30$  years of age (13). There were no associations (all fecundability ratios  $\sim 1.0$ ) between pregnancy and individual omega-3 fatty acid concentrations, including alpha-linolenic acid, eicosapentaenoic acid and DHA, or omega-6 fatty acids, including linoleic acid, dihomo- $\gamma$ -linolenic acid and arachidonic acid (13). In some animal studies, an elevated inflammatory status (14), and reductions in the count of primordial, primary, secondary, and antral follicles were found following exposure to a high-fat diet (15-17). Jenkinson et al highlighted that high levels of omega-3 intake with diet may cause oxidative stress, which is harmful to gametes and embryos, because lipids are hypersensitive to oxidation (18).

A recent study investigated the relationship between nutrition and reproduction with a focus on factors that cause aging, including oxidation, glycation, and chronic inflammation and the results showed that care should be taken to achieve proper intake of omega-3 fatty acids (19). Women taking omega-3 supplementation were found more likely to be younger, thinner, nulligravid, white and taking vitamin D, and multivitamins compared to women not taking omega-3s (20). After adjusting for age, obesity, race, previous pregnancy, vitamin D and multivitamin use in this study, women taking omega-3 supplements were 1.51 (95% CI 1.12, 2.04) times more probable to conceive compared to women not taking omega-3s (20). Couples

Received 10 February 2022, Accepted 17 April 2022, Available online 21 April 2022

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awaiting in vitro fertilization were given the 6-week treatment intervention of olive oil for cooking, an olive oil-based spread, and a daily supplement drink enriched with vitamin D and the marine omega-3 fatty acids DHA and EPA (21). The follicular fluid of women in the treatment group contained significantly higher amounts of EPA and DHA (21).

The results about the omega-3 fatty acid supplementation and female fertility is not yet consistent. The participants used multiple types and brands with varying dosages of omega-3 fatty acids in studies (20). Most of the studies reported the type of supplement they were taking but not the concentration of omega-3s in that supplement, so it is not possible to compare dosing or a dose-response relationship (20). Oral Omega-3 supplementation alters intrafollicular fatty acids concentrations but further research is required to determine whether this intervention improves oocyte quality (21). There are few clinical trails encouraging omega 3 supplementation for restoring ovarian reserve parameters (7,22). But, the median age of the women is <35 in these studies and the number of the participants is very low (7,22).

The prevalence of diminished ovarian reserve increases in many countries and the actual problem is to improve the ovarian function. Omega 3 fatty acid supplementation is far away from this purpose now. New prospective randomized studies conducted in women with diminished ovarian reserve are needed to clarify the real effect of omega 3 fatty acid supplementation.

#### Ethical Issues

Not applicable.

#### Conflict of Interests

The author has no conflicts of interest to disclose.

#### References

- Podfigurna A, Lukaszuk K, Czyzyka A, et al. Testing ovarian reserve in pre-menopausal women: why, whom and how? *Maturitas*. 2018;109:112-117. doi:10.1016/j.maturitas.2017.11.014
- Montoya-Botero P, Rodriguez-Purata J, Polyzos NP. Androgen supplementation in assisted reproduction: where are we in 2019? *Curr Opin Obstet Gynecol*. 2019;31(3):188-194. doi: 10.1097/GCO.0000000000000532.
- Dragojević Dikić S, Vasiljević M, Jovanović A, et al. Premature ovarian insufficiency - novel hormonal approaches in optimizing fertility. *Gynecol Endocrinol*. 2020;36:162-165. doi: 10.1080/09513590.2019.1640203.
- Ouladsahebmadarek E, Khaki A. Ultra-structural Study by Transmission Electron Microscopy: Effect of Omega-3 on Ovary Cell Organelles after Experimental Induced Poly Cystic Ovary Syndrome. *Int J Womes Health Reproduction Sci*. 2014;2(3):186-194.
- Ouladsahebmadarek E, Khaki A, Khanahmadi S, Ahmadi Ashtiani H, Paknejad P, Ayubi MR. Hormonal and metabolic effects of polyunsaturated fatty acid (omega-3) on polycystic ovary syndrome induced rats under diet. *Iran J Basic Med Sci*. 2014;17(2):123-127.
- Stanhiser J, Jukic AMZ, McConaughy DR, Steiner AZ. Omega-3 fatty acid supplementation and fecundability. *Hum Reprod*. 2022 Feb 11:deac027. doi: 10.1093/humrep/deac027
- Bauer JL, Kuhn K, Bradford AP, et al. Reduction in FSH throughout the menstrual cycle after omega-3 fatty acid supplementation in young normal weight but not obese women. *Reprod Sci*. 2019;26(8):1025-1033.
- Shi L, Zhang J, Lai Z, et al. Long-term moderate oxidative stress decreased ovarian reproductive function by reducing follicle quality and progesterone production. *PLoS One*. 2016;27:11 e0162194. doi: 10.1371/journal.pone.0162194
- Huang Y, Hu C, Ye H, et al. Inflamm-Aging: A New Mechanism Affecting Premature Ovarian Insufficiency. *J Immunol Res* 2019;2019:8069898. doi: 10.1155/2019/8069898
- Burchakov DI, Kuznetsova IV, Uspenskaya YB. Omega-3 long-chain polyunsaturated fatty acids and preeclampsia: trials say "no," but is it the final word? *Nutrients*. 2017;9(12):1364.
- Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: agonists of resolution. *Curr Opin Pharmacol*. 2013;13:632-640.
- Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. *Cochrane Database Syst Rev*. 2020;8(8):CD007807. doi: 10.1002/14651858.CD007807.pub4.
- Stanhiser J, Jukic AMZ, Steiner AZ. Serum omega-3 and omega-6 fatty acid concentrations and natural fertility. *Hum Reprod*. 2020;35(4):950-957. doi: 10.1093/humrep/dez305
- Skaznik-Wikiel ME, Swindle DC, Allshouse AA, Polotsky AJ, McManaman JL. High-fat diet causes subfertility and compromised ovarian function independent of obesity in mice. *Biol Reprod*. 2016;94(5):108. doi: 10.1095/biolreprod.115.137414
- Sohrabi M, Mohammadi Roushandeh A, et al. The Role of Anti-müllerian hormone (AMH) in assessing ovarian reserve. *J Clin Endocrinol Metab*. 2011;96:3609-3614.
- Wang N, Luo L-L, Xu J-J, et al. Obesity accelerates ovarian follicle development and follicle loss in rats. *Metabolism*. 2014;63(1):94-103. doi: 10.1016/j.metabol.2013.09.001
- Ma X, Hayes E, Prizant H, Srivastava RK, Hammes SR, Sen A. Leptin-Induced CART (Cocaine- and Amphetamine-Regulated Transcript) Is a Novel Intraovarian Mediator of Obesity-Related Infertility in Females. *Endocrinology*. 2016;157(3):1248-57. doi: 10.1210/en.2015-1750
- Jenkinson A, Franklin MF, Wahle H, Duthie GG. Dietary intakes of polyunsaturated fatty acids and indices of oxidative stress in human volunteers. *Eur J Clin Nutr*. 1999;53(7):523-8. doi: 10.1038/sj.ejcn.1600783
- Koga F, Kitagami S, Izumi A, Uemura T, Takayama O, Koga T, Mizoguchi T. Relationship between nutrition and reproduction. *Reprod Med Biol*. 2020;19(3):254-264. doi: 10.1002/rmb2.12332.
- Stanhiser J, Jukic AMZ, McConaughy DR, Steiner AZ. Omega-3 fatty acid supplementation and fecundability. *Hum Reprod*. 2022:deac027. doi: 10.1093/humrep/deac027
- Kermack AJ, Wellstead SJ, Fisk HL, et al. The fatty acid composition of human follicular fluid is altered by a 6-week dietary intervention that includes marine omega-3 fatty acids. *Lipids*. 2021;56(2):201-209. doi: 10.1002/lipd.12288
- Al-Safi ZA, Liu H, Carlson NE, et al. Omega-3 fatty acid supplementation lowers serum FSH in normal weight but not obese women. *J Clin Endocrinol Metab*. 2016;101(1):324-333. doi: 10.1210/jc.2015-2913