Effects of Omega-3 Polyunsaturated Fatty Acid Supplementation on Allergic Diseases in Pregnant Women and Infant

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Abstract. In Westernized nations, there has been a notable rise in the incidence of allergic diseases, which has been associated with a shortage serving of omega-3 polyunsaturated fatty acids (n-3 PUFAs) in diet. Supplementing with fish oil during pregnancy is being considered as a potential method to prevent allergic diseases in offspring. It may also help modulate allergic inflammation in pregnant women by influencing the synthesis of associated inflammatory mediators. The potential biological mechanisms underlying the allergic response in pregnant women and the potential protection provided to offspring through maternal supplementation of n-3 PUFAs are complex but crucial for understanding medical interventions and trial settings. The objective of this paper is to summarize the proposed mechanisms of allergic response and the anti-inflammatory pathways executed by n-3 PUFAs in both pregnant women and their offspring, drawing from important research findings. However, the efficacy of early intervention in infants through neonatal absorption of n-3 PUFAs is still unclear. The results suggest that n-3 PUFAs-induced protection covers a wide range of allergens, including those from food, house dust, and pets, as well as asthma. Conversely, the consumption of fish oil during childhood appears to have an insignificant effect on immunological disorders.

Keywords: Omega-3, PUFA, pregnant woman, infant, allergic diseases.

1. Introduction

Numerous studies have uncovered a myriad of health benefits associated with omega-3 polyunsaturated fatty acids (n-3 PUFAs). The first methylene double bond that settles on the third carbon is what distinguishes these essential fatty acids, including DHA, EPA, DPA, SDA, and ALA (Fig. 1). Of these five types of n-3 PUFAs, ALA serves as the parent fatty acid (FA) and is considered an essential FA. This means that the production of n-3 PUFAs by the human body is not possible. According to studies, the liver of lean white fish (like cod) and oily fish (like salmon) both have low amounts of DPA and high amounts of DHA and EPA. However, ALA is predominantly derived from plants, such as seeds, nuts, and vegetable oils. A mere fifteen percent of ALA gets transformed into DHA and EPA. Therefore, obtaining a diverse range of n-3 PUFAs through diet or supplements is essential, as it has demonstrated positive effects in various areas, including cancer prevention, cardiovascular health, cognitive function, immune system, and infant health and development according to numerous studies.

This paper aims to concurrently explore the impacts of early exposure to n-3 PUFAs during the neonatal period on childhood allergic responses and the perform of n-3 PUFAs supplementation by pregnant women on their own allergic responses. It is widely acknowledged that maternal supplementation, health status, and behavior significantly influence the physical and mental health of offspring. For instance, the risk of Vitamin D deficiency-induced depression in offspring is reduced by the intake of folic acid during pregnancy.

Children with allergies, such as asthma, may experience reduced life satisfaction due to a combination of physical activity limitations and mental health challenges. This can place substantial burdens on families and healthcare systems.

The objective of this paper is to summarize and propose whether pre-intervention through maternal supplementation of adequate ω-3 PUFAs is beneficial in establishing a healthier state in infants born with lower risk of developing allergic diseases. This includes examining any potential effects of n-3 PUFAs intake by pregnant women on allergic diseases. This paper will cover the general mechanisms of allergic responses in pregnant women, the impact of maternal n-3 PUFA intake on infant' immune system, the anti-inflammatory results facilitated by n-3 PUFA intake in mothers and unborn children, and the effectiveness of supplementation on allergic responses in both pregnant women and their infants.

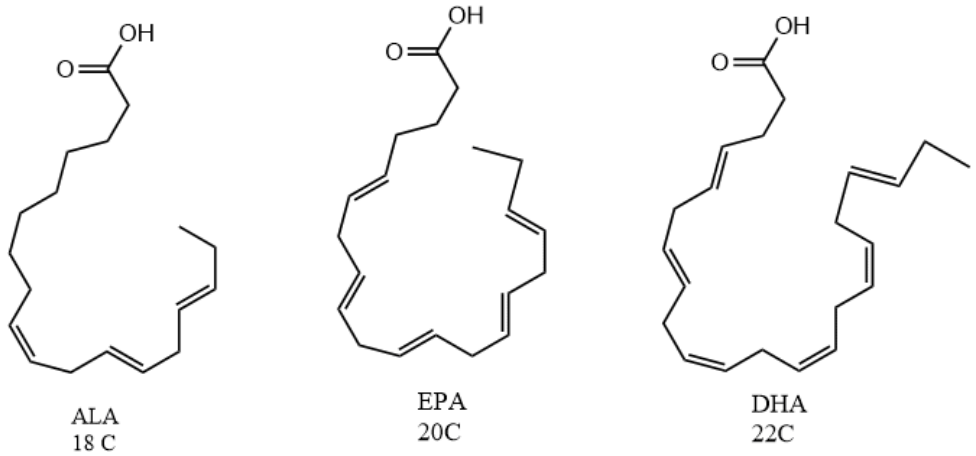

Figure 1. The structure of ALA, EPA and DHA.

2. General Mechanism of Allergic Response

2.1. Mechanism of Allergic Response in Pregnant Woman in General

Because immune responses are highly similar, studies on the mechanisms of allergic reactions in adults can be applied to allergic reactions in pregnant women.

IgE is an antibody strongly correlated with allergic response, mostly in early-phase allergic reactions. A study demonstrated a linear positive correlation between the logarithm of IgE serum level in blood and asthma incidence, this phenomenon also includes patients who has non-allergic asthma [1]. Allergic reaction occurs by bounding of the allergens cross-link IgE to the FcεRI on the mast cells, which is a highly specialized cells, largely reside in epithelial and mucosal tissues of small blood vessels and post-capillary venues. FcεRI is a type of high-affinity receptor located on the mast cells, which transmit activation signals after being activated by bounding of IgE, secretion of chemical mediators will then undergo to initiate the local inflammatory response, this process is known as degranulation. There are a range of inflammatory mediators that are stored in the mast cells basophilic granules.

When degranulation take place, there are two possible pathways to follow. Firstly, inflammation response induced by secreting toxic mediators (histamines), enzyme (tryptase) from granules and synthesizing cytokines (IL-4, IL-3, TNF-α), chemokine (MIP-1α) and lipid mediator (Leukotrienes, Platelet-activating factor) after activation. The blood flow and vessel permeability both increased locally due to release of histamine into the blood stream; increased number of inflammatory lymphocytes and leukocytes presented in the blood stream occur due to release of TNF-α from the granules, which will aggravate inflammation. All mediators released from the granules will promote both the chronic and acute inflammatory response. Secondly, degranulation triggers a late-phase response by recruiting other effector cells, which plays vital role in a sustained inflammation process in allergic response.

High level of IgE is found in patients with allergic diseases, lead to a significant increase in FcεRI on the surface of the mast cells, therefore, sensitivity towards specific antigens is enhanced, which

means minute amount of the antigens is adequate for activation and releasing of the IgE-dependent mediators and cytokines [2].

2.2. How Can Intake of the Fish Oil Potentially Alleviate the Inflammation Caused by Allergic Disease in Pregnant Woman

The vital connection between the PUFAs to the allergic response is regard with the eicosanoid synthesis. Eicosanoid, a type of lipid mediator, include leukotrienes, prostaglandins, and thromboxanes, they are synthesized from 20C PUFAs that released from the membrane phospholipids under stimulation of the cell. Immune cells usually include high proportion of n-6 PUFAs (AA) to n-3 PUFAs (EPA), therefore it is the AA that dominates the synthesis. Some eicosanoid is involved in increasing sensitization to allergens such as PGE2, and some is taking part in the inflammation, epithelial and smooth muscle cells.

Oily fish is an excellent supplier of EPA and DHA, containing 1.5-3.5 g per serving. Most prevalent fish oil capsule supplement contains 30% EPA+DHA, therefore 1 g of fish oil supplement contain 300 mg of EPA+DHA. The amount of DHA and EPA inserted in the phospholipids of immune cell membrane is increased by extra consumption of fish oils, thus, the ratio of AA: EPA is reduced [3]. While the AA-derived eicosanoid synthesized lessen, the EPA-derived eicosanoid is shown to own about 10-100-fold less potent than that synthesized from AA. In addition, specialized pro-resolving mediators (SPMs), a type of lipid mediators, includes E-resolvins and D-resolvins, are produced from EPA and DHA respectively, this type of mediators possess capability of inflammation resolving and anti-inflammation, however, the resolution program is very complex, involving multi-factorial tissue level [4]. The SPM does not resemble the structure nor the function of common eicosanoids [4]. Multiple studies suggest higher intake of EPA and DHA than n-6 PUFAs is more effective to prevent and mitigate allergic diseases via SPMs. A Randomized Controlled Trial (RCT) suggested that taking 2.7g n-3 PUFAs supplements in the third trimester may reduce some immunological reactions associated with allergic inflammation in pregnant woman. In detailed, they found out among participants who received n-3 PUFA treatment, the reduction in LPS-induced PGE2 release was more evident in nonatopic mothers [5]. This means decrease the synthesis level of PGE2 will lessen the inflammation associated with related disease.

3. The Potential Mechanism Connect with the Foetus Genetic Towards Allergic Disease During Pregnancy

3.1. The Anti-Inflammatory Mechanism

Pro-inflammatory cytokines and those that are anti-inflammatory but stimulate allergic reactions can be functionally separated into two groups. Cytokines are primarily produced from T cells, which have antigen-specific receptors located on their cell surface to recognize allergens or pathogens. T cells can then be subdivided into 2 groups, TH1 (cell-mediated pathway) and TH2 (humoral pathway), the cytokines produced are called Th1 and Th2-type cytokines correspondingly.

The Th1-type cytokines often result in pro-inflammatory reactions that are necessary for eliminating pathogens or allergens and maintaining autoimmune responses. There must be a mechanism to prevent uncontrolled tissue damage from excessive pro-inflammatory reactions, which is Th2 responses. The Th2 type cytokines which induce anti-inflammatory response include interleukin 4, 5, 10, and 13. Therefore, the ideal situation for the immunological reaction is to create a balanced Th1 and Th2 response in human body. Cell mediated immune responses is suppressed by n-3 PUFAs consumed, therefore restrain the production of Th1-type cytokines that will cause inflammation [6].

3.2. PUFAs Intake by Maternal Affecting the Foetus Future Allergic Response

According to a number of research, maternal fish oil supplementation alters immunological markers in umbilical cord blood, and therefore allergic sensitization and the allergic diseases risk can be alternate as well [7]. Several EPA and/or DHA maternal supplementation-controlled trials suggested there is an association with DNA methylation levels of genes that code for inflammatory mediators in offspring. This means that pregnant women who take n-3 PUFA3 can transfer DHA and EPA to the fetus and modulate its immunology, therefore lowering the likelihood of child allergies.

Fish Oil supplementation during gestation period result in lower mRNA levels of TH2-related molecules and natural killer (NK) cells in the developing fetus, reduced number of inflammatory cytokines in the mother is also observed. This study group hypothesize that TGF-β is the mediator for these effects, due to the mRNA levels of TGF-β elevate in maternal cord blood and peripheral blood. Moreover, the TGF-β levels in fetus also elevated, the regulatory T cells which produce this cytokine suppress both NK cell activity and responses to self-antigens [8].

Several studies stated that pregnancy supplementation of increased n-3 PUFAs in diets contributes to a long-term benefit in preventing or impairing allergic diseases. For example, a significant effect of reduced allergic asthma in offspring was observed in fish oil group that consume 4 g/d (32%EPA, 23%DHA) in comparison to olive oil group, the follow-up age is up to 16 years old with 99.1% completed rate [9]. Another recent study also suggests that less asthma medical intervention made on the fish oil group that intake 4 g/d (32%EPA, 23%DHA) as well, 2 years follow-up is completed after the delivery with 98.0% completed rate [10]. Both trials started intervention from 30 weeks of pregnancy until delivery. Moreover, a recent study noticed a drastic decline in the risk of sensitization to peanut and egg is possible by n-3 PUFA intake from the start of the pregnancy [11].

Drug dosage is crucial in treating disease, same drugs with different dosage can lead to varies effects, includes n-3 PUFA. To discover the optimum dosage that exert its effectiveness, it is necessary to find the lowest limit of fish oil intake that is purportless and insignificant, and to what level of overdose that can cause fatty liver of the mother. A previous study reported that ≥2000 mg/d of n-3 PUFAs supplied can result in statistically significantly decreased in the risk of pediatric asthma, moreover, the study suggested that the change is more dramatic in trials conducted in Europe among other regions [12]. In a dose-response analysis model of another study, suggested increasing the additional dose of n-3 LC-PUFAs by 100 mg per day can reduce the incidence of asthma by 2% [13].

Multiple contrary studies reported that their result oppose their initial hypothesis, demonstrated that there is no revealing difference between the neonatal exposure of fish oil groups and the control groups. For example, a research group with 84 pairs of mothers and infants who finished the RCTs with total 57 of them receiving DHA-rich fish oil capsule (900 mg DHA with 180 mg EPA), EPA-rich capsule (1060 mg EPA with 274 mg DHA), and the rest 27 of them receiving soy oil placebo that is n-6 PUFAs enriched. The final model with adjustments in the potential risk factors showed that the risk of eczema developed in 36 months child was 8 time greater for the EPA and 9 time greater for the DHA fish oil groups contrasted to the control group. They suggested the contradictory outcome may be due to the unvaried dose, length, timing of supplementation, limited trial scales, participants' historical allergic disease, location of the study take place, under-consideration of the potential protective effect of n-6 PUFAs in soy oil [14]. These thinking is also applied to all the other trials that gained results deviated from the estimated model.

The timing of intervention effect on the offspring allergic response is also an important factor to be included in the discussion. However, as mentioned above, this trial includes multiple factors intertwined, thus trials started at the same gestation age (GA) may result in different observations. For instance, 2 trials conducted both start intervention from 20 weeks of GA, one study suggested infants were 3-fold less likely to develop allergic reaction towards eggs and observed a statistically significant reduction in cytokine responses (IL-10) of infants towards cat after maternal supplementation of 3.7 g/d n-3 PUFAs [7]. The other study claimed consumption of 2 portions of salmon (3.45 g EPA+DHA) each week result in a decreased response of IL-2, 4,5,10, and TNF-α to phytohemagglutinin that exist in wide range of beans [15].

This means that the outcomes of this type of trials depend on varies complex factors and inevitable bias is included during the RCTs.

3.3. Consequences of N-3 PUFA Supplementation on Pediatric Immunological Disorders

The optimum type of omega-3 for newborns is DHA, which should be given in doses of 10-12 mg/kg of body weight, according to the WHO. The recommended daily intake for older children should combined DHA and EPA, and adjust the dose with age, ranging from 100 to 250mg. Obtaining needed nutrition from healthy home-cooked food is always a better choice than taking supplements. Supplementing with fish oil after birth enhanced the n-3 levels of the baby but did not stop allergy illness in children [16]. The results of n-3 PUFAs supplementation trials in individuals (adults and children) with established asthma have also been largely unsatisfactory. This may mean that it may be too late for this type of intervention when allergic immune responses are developed, especially opposed to food allergies and sensitization like egg and peanuts.

4. Conclusion

This paper compiles the mechanisms underlying allergic responses in individuals, the inflammatory processes in pregnant women influenced by n-3 PUFAs intake, and the plausible mechanisms of maternal supplementation with n-3 PUFAs on infants. When considering these collective findings, it becomes evident that the additional feeding of n-3 PUFAs in pregnant women could potentially reduce the risk of allergic diseases in children, potentially extending its effects to a certain age. However, the results have shown inconsistency. The concept of additional supply of n-3 PUFAs by mothers does indeed exert beneficial effect on the offspring's immune system with regard to allergic diseases is confirmed by certain studies. Nevertheless, the statistically significant results varied in relation to specific allergens. The variations in trial outcomes can be attributed to the multifaceted nature of RCTs conducted in different countries, with participants having varying baseline status of n-3 PUFAs and different group sizes. Additionally, several studies indicated that the fish oil uptake by children themselves has a lesser effect on their allergic manifestation and sensitization, particularly for children with already established allergic diseases. This highlights the need for further in-depth research on this controversial yet significant topic.

References

[1] Rosenwasser Lanny J. Mechanisms of IgE Inflammation. Current Allergy and Asthma Reports, 2011, 11 (2): 178 - 183.

[2] Charles A Janeway Jr, Paul Travers, Mark Walport, and Mark J Shlomchik. Effector mechanisms in allergic reactions. Immunobiology: The Immune System in Health and Disease 5th edition. Newyork. 2001.

[3] Yaqoob P., Pala H. S., Cortina-Borja M., et al. Encapsulated fish oil enriched in alpha-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. Eur J Clin Invest, 2000, 30 (3): 260 - 274.

[4] Bannenberg Gerard, Serhan Charles N. Specialized pro-resolving lipid mediators in the inflammatory response: An update. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 2010, 1801 (12): 1260 - 1273.

[5] Warstedt K., Furuhjelm C., Duchén K., et al. The effects of omega-3 fatty acid supplementation in pregnancy on maternal eicosanoid, cytokine, and chemokine secretion. Pediatr Res, 2009, 66 (2): 212 - 217.

[6] Simopoulos Artemis P. Omega-3 Fatty Acids in Inflammation and Autoimmune Diseases. Journal of the American College of Nutrition, 2002, 21 (6): 495 - 505.

[7] Dunstan J. A., Mori T. A., Barden A., et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol, 2003, 112 (6): 1178 - 1184.

[8] Krauss-Etschmann S., Hartl D., Rzehak P., et al. Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. J Allergy Clin Immunol, 2008, 121 (2): 464 - 470.e6.

[9] Olsen Sjurdur F., Østerdal Marie Louise, Salvig Jannie Dalby, et al. Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial1. The American Journal of Clinical Nutrition, 2008, 88 (1): 167 - 175.

[10] Hansen S., Strøm M., Maslova E., et al. Fish oil supplementation during pregnancy and allergic respiratory disease in the adult offspring. J Allergy Clin Immunol, 2017, 139 (1): 104 - 111.e4.

[11] Venter C., Agostoni C., Arshad S. H., et al. Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology. Pediatr Allergy Immunol, 2020, 31 (8): 889 - 912.

[12] Lin Jilei, Zhang Yin, Zhu Xiaohong, et al. Effects of supplementation with omega-3 fatty acids during pregnancy on asthma or wheeze of children: a systematic review and meta-analysis. The Journal of Maternal-Fetal & Neonatal Medicine, 2020, 33 (10): 1792 - 1801.

[13] Jia Yin, Huang Yafang, Wang Huili, et al. A dose-response meta-analysis of the association between the maternal omega-3 long-chain polyunsaturated fatty acids supplement and risk of asthma/wheeze in offspring. BMC Pediatrics, 2022, 22 (1): 422.

[14] Berman D., Clinton C., Limb R., et al. Prenatal Omega-3 Supplementation and Eczema Risk among Offspring at Age 36 Months. Insights Allergy Asthma Bronchitis, 2016, 2 (1): 1.

[15] Nciri N., Cho N., El Mhamdi F., et al. Toxicity Assessment of Common Beans (Phaseolus vulgaris L.) Widely Consumed by Tunisian Population. J Med Food, 2015, 18 (9): 1049 - 1064.

[16] D'Vaz N., Meldrum S.J., Dunstan J.A., et al. Postnatal Fish Oil Supplementation in High-Risk Infants to Prevent Allergy: Randomized Controlled Trial. Pediatrics, 2012, 130 (4): 674 - 682.