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Effect of Fish Oil on the Level of Interferon Gamma on the Breast Milk of Atopic Mothers: A Randomized Clinical Trial

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ABSTRACT

Background: The prevalence of allergic diseases is increasing worldwide. The effective role of omega-3 fatty acids in the maturation of immune system and protection against atopic diseases has been well discussed. However, previous studies revealed conflicting results. This study was conducted to investigate the effect of fish oil consumption by nursing atopic mothers on the level of interferon gamma (IFN-γ) in their breast milk and incidence of allergic disease in their infants.

Methods: This randomized clinical trial was conducted on 94 atopic mothers, who were assigned to two equal groups receiving either 1000 mg fish oil capsules or placebo for 60 days after delivery. The breast milk was collected 120 days after delivery, and IFN-γ level was measured. The history of the symptoms of atopic disease in infants was collected from their mothers through ISAAC questionnaire; in addition, the infants' growth was evaluated.

***Results*:** Sixty mother-infant pairs completed the trial. The mean values of IFN-γ in breast milk was higher in the fish oil group (1.11±1.15 Pg/ml) than in the placebo group (0.81±0.86 Pg/ml), but the difference was not significant (P=0.288). In addition, the incidence of allergic symptoms of infants was not significantly different between the two groups (P=0.84).

Conclusion: In this trial, the consumption of fish oil by lactating mothers did not have a significant effect on IFN-γ level in their breast milk and the incidence of allergic symptoms in their infants. Future studies with longer follow-ups are necessary in this regard.

Keywords: Allergy, Fish oil, Lactation, Prevention

Introduction

The prevalence of allergic diseases had an escalating trend during the last few decades, particularly in industrial countries and among young age groups (1, 2). Environmental factors, including early infant nutrition, are effective in the occurrence of these diseases (3). Dietary omega-3(*n–3*) fatty acids (FAs) might have an effect on the development of the neonatal immune system before the establishment of allergic responses (4). The three types of omega-3 FAs in human physiology are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). The ALA is found in the plant oils, while the EPA and DHA are commonly found in marine oils (5).

It is well established that the dietary FA composition can alter the milk FA composition (6). The most widely available dietary sources of EPA and DHA are oily fish (5), which are known to reduce allergic inflammation (7, 8). Unfortunately,

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the per capita fish consumption in Iran is less than the world's average (9, 10). One of the concerns about fish consumption is the potential health risk caused by the presence of heavy metals and fat-soluble contamination, especially for women of childbearing age (11).

Some studies found that the intake of *n*−6 polyunsaturated fatty acid (PUFA) may lead to allergic diseases, but *n*−3 PUFAs act conversely and might protect against atopic sensitization and clinical manifestations (12). However, the results of the studies investigating the effect of the PUFAs of fish oil on allergic diseases are inconsistent (4, 13-17). Atopic individuals respond to allergen exposure with a rapid expansion of type 2 T helper (Th2) cells secreting cytokines, including interleukins IL-4, IL-5, and IL-13.

The immune system is immature in newborns and involves Th2 polarization. Immune maturation process occurs during the infancy period and seems to be characterized by Th1 polarization and the production of cytokines, such as gamma interferon (IFN-γ) (4). The IFN-γ inhibits the Th2 cytokines, such as IL-4 or IL-13 (18). Aberrant IFN-γ expression is associated with a number of autoinflammatory and autoimmune diseases (19). It is demonstrated that IFN-γ is effective in the treatment of moderate to severe atopic dermatitis (20-22).

On the other hand, a fraction of the immune response to allergens would result in the proliferation of type 1 T helper (Th1) cells. This is important because Th1 cytokines, such as IFN-γ, can potentiate the function of the allergic inflammatory effector cells, such as eosinophils; therefore, it might contribute to the disease severity (1). These inconclusive results, in addition to the high prevalence of allergic diseases in Iran, especially in industrial cities, and low per capita seafood consumption among the Iranians, have encouraged us to investigate the effect of fish oil on allergy prevention among the children living in Isfahan, an industrial city in Iran.

The aim of this study was to determine the effect of fish oil supplementation on the level of IFN-γ in the breast milk of atopic mothers and its effect on reducing the incidence of allergic diseases in their infants. As a secondary objective, we assessed the effect of fish oil on infants' growth.

Methods

This double-blind, randomized clinical trial was conducted from March to September 2016 in Isfahan, Iran. Ninety four atopic women within the age range of 18-40 years who had delivered their neonates within 48 h prior to the study in the teaching hospitals (i.e., Al-Zahra and Shahid Beheshti hospitals) affiliated to the Isfahan University of Medical Sciences, Isfahan, Iran, were enrolled in the study. These hospitals are the two major centers of Gynecology/Obstetrics and Neonatology in Isfahan city.

History of allergic diseases, including allergic rhinitis, asthma, eczema, urticaria, and lifetime food allergy, were considered as atopic diseases. The data were collected based on the International Study of Asthma and Allergies in Childhood (ISAAC) standard questionnaire (23). The inclusion criteria for atopic mothers were the age of 18-40 years, gestational age of more than 37 weeks, and having a healthy singleton neonate with a birth weight of more than 2,500 g.

Those with a history of smoking, history of using anti-inflammatory medications during pregnancy, inflammatory and autoimmune diseases, and consumption of fish and seafood more than twice a week during pregnancy were not included in the study. The other exclusion criteria were feeding the infant with formula or any supplementary food during the study (the first 4 months of life), using anti-inflammatory drugs during the study, clinical manifestations of allergy to fish in mothers, drug reaction in mothers, and low compliance to continue the study.

The trial was conducted according to the Helsinki declaration for clinical trials. Ethical approval was obtained from the Ethics Committee of Isfahan University of Medical Sciences (code: 394652). The trial was registered in the Iranian Registry of Clinical Trials, which is an international registry of the World Health Organization (IRCT code: IRCT2017052234082N1).

The mothers who participated in the study were asked to read and sign an informed consent. Then, by using random allocation software (Randomizer, 2016.6.0.56), they were assigned into two groups of equal members (47 in each).

A pediatric resident physician completed the checklists, which consisted of mother's demographic characteristics (e.g., age, educational level, gestational age, parity, delivery method, and gender of the neonate), clinical manifestations of atopy in mother, father, and siblings, and history of medication use for allergy. Furthermore, the height, weight, and head circumference of the neonates were measured and recorded at the birth time. We also documented the intake amount of food and supplements, containing omega-3, by mothers during the last month of pregnancy. The data were entered into the

Nutritionist-4 software (Nutritionist-4 modified for Iranian foods) and analyzed by a nutritionist.

Each 1,000 mg omega-3 softgel contained 180 mg EPA and 120 mg DHA and was mercury-free, produced by Dana Pharmaceutical Company (OMEGA-REX, Tabriz, Iran). Each placebo capsule contained 70% amylum and 30% dicalcium phosphate (prepared in the School of Pharmacy of Isfahan University of Medical Sciences). Omega-3 and placebo capsules were packed in similar boxes and labeled by a person who was not involved in the study.

While the investigator and subjects were blind to the intervention and placebo groups, 47 mothers received a 1000-mg omega-3 softgel per day for 60 days, and the other 47 mothers consumed 500 mg placebo capsules in a similar schedule. Drug compliance was reassured by regular phone call follow-ups to mothers. The mothers were asked to be visited in our clinic again 60 and 120 days after the beginning of the study (i.e., immediately and 60 days after the last day of medication use).

On the 60th day after birth, a pediatric resident measured the infants' height, weight, and head circumference. On day 120, in addition to collecting data related to infants' growth, breast milk sampling was conducted. At the end of the study, in the fish oil group, 21 mothers came for breast milk sampling, and 7 mothers did not attend for sampling, so only the growth data of their infants were collected (totally 28 infants). In the placebo group, these numbers were 22 and 10, respectively (totally 32 infants).

In the case group, one of the excluded mothers had skin rash after using fish oil. The rash disappeared after drug withdrawal. Another mother stopped taking the medication because her neonate showed an allergic reaction that was eliminated after drug discontinuation. The CONSORT algorithm of the trial is shown in Figure 1.

When the mothers came for breast milk sampling, they were asked to clean their breasts with a cotton piece soaked in normal saline; then, they expressed 20 cc breast milk by hand into a sterile 50-cc falcon tube. The fat was separated from the residue of milk by keeping these tubes in a refrigerator at 4ºC for 24 h. When the fat was separated, the residual liquid was stored in microtubes and kept frozen at -20ºC. The remaining fat was removed by centrifuging the frozen samples using a refrigerated centrifuge at

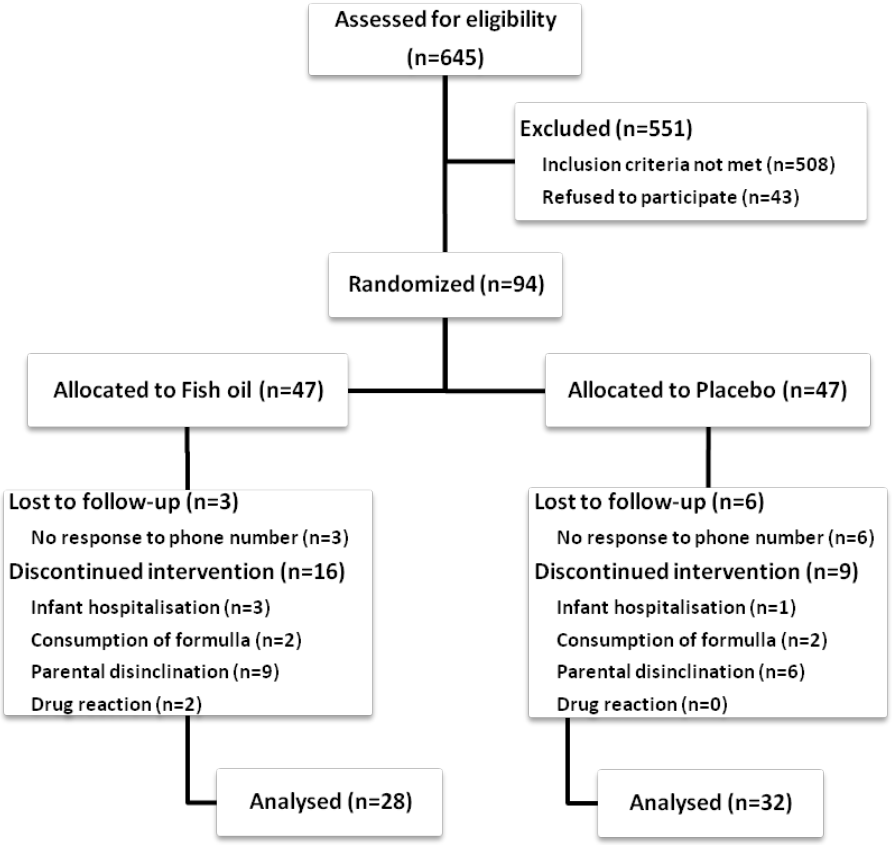

Figure 1. CONSORT algorithm of the trial

5000 rpm for 15 min before the enzyme-linked immunosorbent assay (ELISA) procedure started.

All steps of ELISA procedure were followed as suggested by the protocol of "human IFN-γ ELISA MAX standard set" (BioLegend, San Diego, CA, USA). The history of atopic disease symptoms (e.g., atopic dermatitis, food allergy, eczema, or prolonged cough) in the infants was enquired from their mothers through ISAAC questionnaire.

Statistical analysis

The data were analyzed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The significance level was set at less than 0.05. Pearson Chi-square and Fisher's exact tests were run to determine the relationships between dependent and independent variables. The t-test was used to compare the quantitative data.

Results

Out of the 94 mother-infant pairs included in this study, 60 pairs (i.e., 28 and 32 pairs in the case and control groups, respectively) completed the research (Figure 1). Table 1 presents the

Table 1. Demographic characteristics and prevalence of allergy in parents and family of the case and control groups

	Total (n=60)	Control (n=32)	Case (n=28)	P-value
Mother's age (years)¶	30.18 (5.11)	28.63 (4.50)	31.96 (5.26)	0.010 *[a]
Mother's education				
Middle school and lower	15 (25.0)	9 (28.1)	6 (21.4)	
High school diploma	31 (51.7)	16 (50.0)	15 (53.6)	0.83 [b]
Undergraduate and higher	14 (23.3)	7 (21.9)	7 (25.0)	
Number of gravidity				
1st	22 (36.7)	15 (46.9)	7 (25.0)	
2nd	17 (28.3)	11 (34.4)	6 (21.4)	0.01 *[b]
3rd and more	21 (35.0)	6 (18.8)	15 (53.6)	
Type of delivery				
NVD	15 (25.0)	7 (21.9)	8 (28.6)	0.55 [b]
C/S	45 (75.0)	25 (78.1)	20 (71.4)	
Type of mother allergy				
Urticaria	5 (8.3)	2 (6.3)	3 (10.7)	
Eczema	4 (6.7)	4 (12.5)	0 (0.0)	
Rhinitis	35 (58.3)	14 (43.8)	21 (75.0)	
Asthma	4 (6.7)	4 (12.5)	0 (0.0)	
Food allergy	1 (1.7)	1 (3.1)	0 (0.0)	
Drug allergy	1 (1.7)	1 (3.1)	0 (0.0)	
Rhinitis and drug allergy	1 (1.7)	1 (3.1)	0 (0.0)	0.13 [b]
Rhinitis and food allergy	2 (3.3)	1 (3.1)	1 (3.6)	
Rhinitis and asthma	2 (3.3)	2 (6.3)	0 (0.0)	
Rhinitis and urticaria	2 (3.3)	1 (3.1)	1 (3.6)	
Drug and food allergy	1 (1.7)	0 (0.0)	1 (3.6)	
Urticaria and eczema	1 (1.7)	0 (0.0)	1 (3.6)	
Asthma and eczema	1 (1.7)	1 (3.1)	0 (0.0)	
Name of drug that mother uses				
No drug	19 (31.7)	13 (40.6)	6 (21.4)	
Antihistamine	28 (46.7)	10 (31.3)	18 (64.3)	0.03 *[b]
Other drugs	13 (21.7)	9 (28.1)	4 (14.3)	
Father's allergy				
No	45 (75.0)	25 (78.1)	20 (71.4)	0.55 [b]
Yes	15 (25.0)	7 (21.9)	8 (28.6)	
Type of father's allergy				
No allergy	45 (75.0)	25 (78.1)	20 (71.4)	
Eczema	2 (3.3)	1 (3.1)	1 (3.6)	
Rhinitis	7 (11.7)	3 (9.4)	4 (14.3)	0.80[b]
Asthma	5 (8.3)	2 (6.3)	3 (10.7)	
Food allergy	1 (1.7)	1 (3.1)	0 (0.0)	
Family relationship between parents				
No relation	37 (61.7)	22 (73.3)	15 (55.6)	0.16 [b]
relative	20 (33.3)	8 (26.7)	12 (44.4)	

Table 1. Continued				
Sibling's allergy				
No	37 (61.7)	25 (78.1)	12 (42.9)	0.005 *[b]
Yes	23 (38.3)	7 (21.9)	16 (57.1)	
Type of sibling allergy				
No allergy	37 (61.7)	25 (78.1)	12 (42.9)	
Eczema	3 (5.0)	1 (3.1)	2 (7.1)	
Rhinitis	6 (10.0)	1 (3.1)	5 (17.9)	
Asthma	6 (10.0)	2 (6.3)	4 (14.3)	0.08 [b]
Food allergy	2 (3.3)	0 (0.0)	2 (7.1)	
Dermatitis	5 (8.3)	3 (9.4)	2 (7.1)	
Urticaria and dermatitis	1 (1.7)	0 (0.0)	1 (3.6)	
PUFA (gr/day) ¶	2.35 (2.98)	2.24 (3.16)	2.48 (2.81)	0.76
IFN-γ (Pg/ml)¶	0.95 (1.01)	0.81 (0.86)	1.11 (1.15)	0.28

NVD: normal vaginal delivery; C/S: caesarean section; PUFA: poly unsaturated fatty acid; LA: linolenic fatty acid; IFN-γ: interferon-Gamma; Mean value (SD).
*Significant at level of 5%. Numbers in bold are those statistically significant.
[a]Using independent samples t-test.
[b] Using Pearson chi-square test.

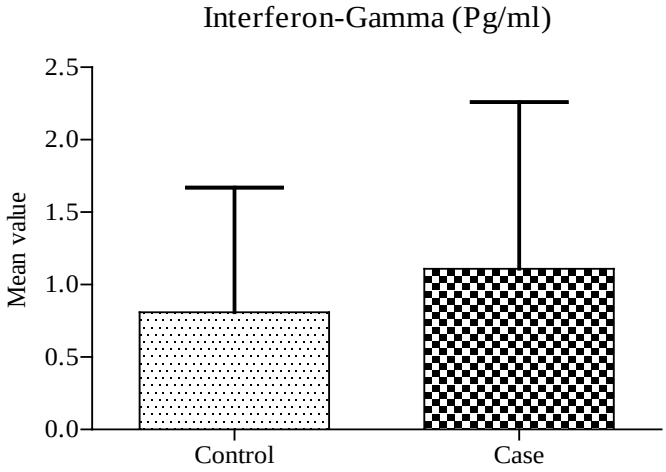

Figure 2. Mean (SD) values of interferon-Gamma in the milk of mothers in the case and control groups

demographic characteristics and prevalence of allergy in the parents and family. The mean age of the mothers was 30.18±5.11 years. In 75.0% of the cases, the delivery type was caesarean section. Almost half of all mothers had high school diploma. Furthermore, 36.7%, 28.3%, and 35% of the mothers had their first, second, and third or more pregnancy, respectively.

Type of allergy in mothers had no significant difference between the two groups (P=0.13). In addition, 46.7% of the mothers used antihistamine medications, with a significantly higher frequency in the case group than in the control group (64.28% vs. 31.25%, P=0.03). Overall, 61.7% of the parents did not have consanguineous marriage. The prevalence rates of allergy in the fathers and siblings were 25.0% and 38.3%, respectively. The prevalence of sibling allergy in the case group was significantly higher than that in the control group (57.1% vs. 21.9%, P=0.005).

As presented in Table 1, the mothers' age, gravidity, history of medication use for allergy were significantly different between the two groups. Generally, the mean value of PUFA in mothers' diet during the last month of pregnancy was 2.35±2.98 g/day. There were no statistically significant differences between the two groups regarding PUFAs. The mean values of IFN-γ in breast milk were 0.81±0.86 and 1.11±1.15 Pg/ml in the control and case groups, respectively, without any statistically significant differences between the two groups. The results for IFN-γ are depicted in Figure 2.

As seen in Table 2, no statistically significant difference existed in the mean values of

Table 2. Anthropometric measurements and prevalence of allergy in the case and control groups

	Total (n=60)	Control (n=32)	Case (n=28)	P-value
Gestational age (days)	271.72 (10.91)	272.28 (11.59)	271.07 (10.24)	0.672 [a]
Age (at the time of milk sampling) (days)	129.97 (9.45)	131.53 (10.62)	128.18 (8.25)	0.172 [a]
Gender§				
Female	34 (56.7)	20 (62.5)	14 (50.0)	0.330 [b]
Male	26 (43.3)	12 (37.5)	14 (50.0)	
Infant's allergy §				
No	49 (81.7)	25 (78.1)	24 (85.7)	0.338 [c]
Yes	11 (18.3)	7 (21.9)	4 (14.3)	
Incidence of allergic disease §				
No allergy	49 (81.7)	25 (78.1)	24 (85.7)	
Atopic dermatitis	6 (10.0)	4 (12.5)	2 (7.1)	
Food allergy	2 (3.3)	1 (3.1)	1 (3.6)	0.840 [b]
Eczema	1 (1.7)	1 (3.1)	0 (0.0)	
Prolong cough	2 (3.3)	1 (3.1)	1 (3.6)	
Weight at birth (kg)	3.07 (0.39)	3.11 (0.37)	3.02 (0.42)	0.357 [a]
Height at birth (cm)	49.99 (2.41)	50.36 (2.76)	49.57 (1.89)	0.209 [a]
Head circumference at birth (cm)	34.75 (1.20)	34.78 (1.09)	34.71 (1.33)	0.823 [a]
Weight after 2 months (kg)	5.20 (0.62)	5.13 (0.60)	5.29 (0.65)	0.335 [a]
Height after 2 months (cm)	57.08 (2.43)	57.45 (2.19)	56.64 (2.66)	0.200 [a]
Head circumference after 2 months (cm)	38.48 (1.29)	38.41 (1.31)	38.57 (1.28)	0.624 [a]
Weight after 4 months (kg)	6.63 (0.71)	6.58 (0.67)	6.69 (0.77)	0.543 [a]
Height after 4 months (cm)	62.98 (2.57)	62.97 (2.39)	62.98 (2.80)	0.984 [a]
Head circumference after 4 months (cm)	41.13 (1.22)	41.03 (1.18)	41.23 (1.27)	0.529 [a]
Weight gain after 2 months (kg)	2.13 (0.51)	2.02 (0.51)	2.27 (0.48)	0.057 [a]
Weight gain after 4 months (kg)	3.56 (0.66)	3.47 (0.62)	3.67 (0.69)	0.224 [a]
Height increase after 2 months (cm)	7.08 (2.59)	7.09 (2.44)	7.07 (2.80)	0.974 [a]
Height increase after 4 months (cm)	12.98 (2.40)	12.61 (2.19)	13.41 (2.60)	0.200 [a]
Head circumference increase after 2 months (cm)	3.73 (0.90)	3.62 (0.90)	3.86 (0.90)	0.317 [a]
Head circumference increase after 4 months (cm)	6.37 (1.11)	6.25 (1.15)	6.52 (1.05)	0.345 [a]

§ N (%)
[a] Using independent samples t-test.
[b] Using Pearson Chi-square test.
[c] Using Fisher's exact test.

gestational age, infants' age at the time of milk sampling, and infants' gender (P=0.672, P=0.172, and P=0.330, respectively). Out of 60 infants, 11 (18.3%) cases showed the symptoms of allergic diseases. In this regard, 6 (10.0%), 2 (3.3%), 1 (1.7%), and 2 (3.3%) infants respectively had a history or physical examination compatible with atopic dermatitis, food allergy, eczema, and prolonged cough. There was no significant difference between the two groups regarding allergic diseases.

As depicted in Figure 3, the mean anthropometric measurements for the infants were plotted to monitor their growth over time (at birth, after 2 months, and after 4 months). In general, there was no statistically significant difference between the two groups studied in terms of weight, height, and head circumference.

Discussion

In our study, the mean level of IFN-γ in breast milk was higher in the case group, compared with that in the control group; however, this difference was not statistically significant. Furthermore, the incidence of allergic disease was lower in the infants of omega-3 group in comparison with that in the placebo group, but this difference was not statistically significant. These results were consistent with those of some other similar studies.

The prevalence of allergic diseases is increasing all over the world (1). Allergic diseases are likely to increase the proliferation of Th2 cells and secretion of the related cytokines and decrease Th1 response. These cytokines (e.g., IFN-γ and IFN-γ) are the major Th1 cytokines and have a central role in Th1 differentiation. In addition,

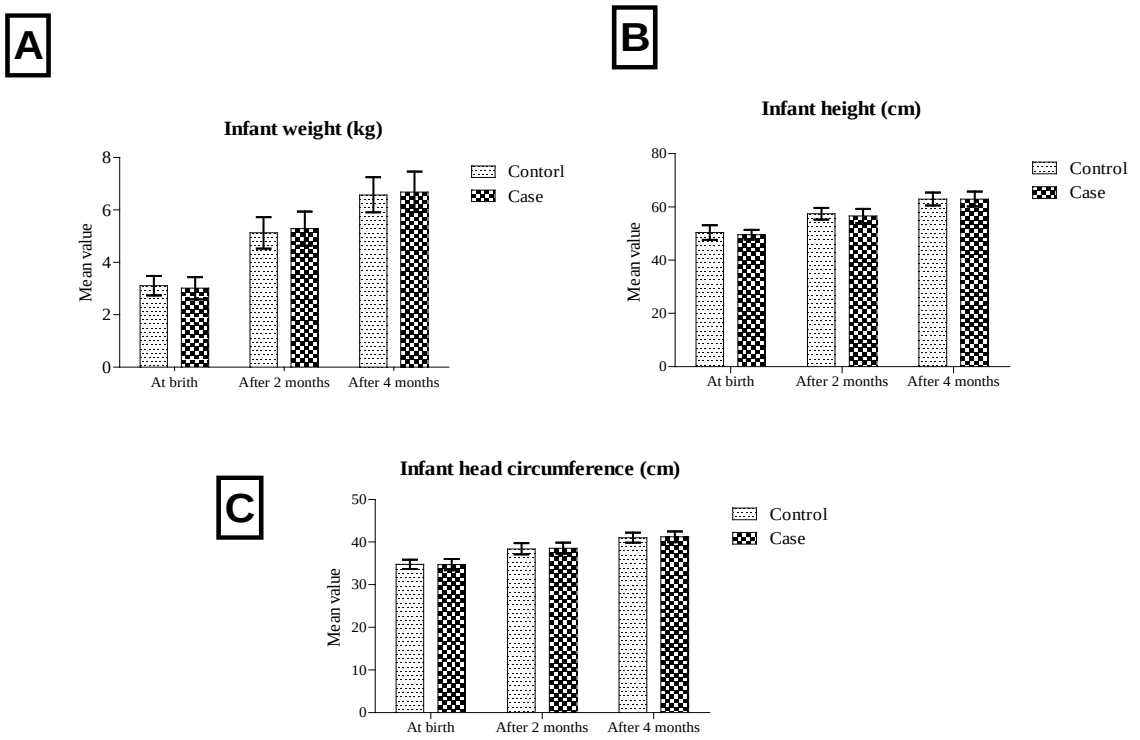

Figure 3. Mean values of longitudinal follow-up anthropometric measurements (A: weight, B: length, and C: head circumference) in the control and case groups in three times of measurement (at birth, after 2 months, and after 4 months)

the inhibitory effect of IFN-γ on the differentiation of Th2 cells, secretion of their cytokines, suppression of IgE isotype switching, and promotion of T-cell and eosinophils apoptosis can explain the anti-inflammatory mechanism of IFN-γ (24). Though much has been documented on the suppressive effect of IFN-γ on allergic inflammation, our knowledge about this role is limited and contradictory.

The contributing role of omega-3 FAs in the maturation of the immune system in allergy treatment and its prevention are well discussed (3). However, the results of previous studies have been inconclusive in this regard. In the studies examining the effect of omega-3 supplementation on the prevention of allergic diseases, omega-3 has been prescribed for pregnant or lactating mothers, or infants themselves.

Some studies demonstrated that n-3 FAs are effective to decline the prevalence or severity of allergic diseased, but others reported contrary results. In a study, Dunstan et al. investigated 98 atopic pregnant women (who received fish oil or placebo from 20 weeks of gestation until delivery) and showed a potential reduction in subsequent infant's allergy after maternal PUFA supplementation. However, the result was not statistically significant. In the mentioned study, although there was no difference in the frequency of atopic dermatitis at 1 year of age, the infants in the fish oil group had significantly less severe diseases (25).

In another study by Furuhjelm et al. on 145 mothers, the incidence of food allergy and IgE-associated eczema during the first year of life in the infants with a family history of allergic diseases was decreased by maternal omega-3 supplementation (26), but this effect was removed until 2 years of age (27). On the other hand, Palmer et al. showed that there was no difference in the percentage of the allergic offspring of the pregnant women who received 900 mg n-3 long-chain polyunsaturated fatty acids (LCPUFA) or placebo (13, 14).

Altogether, the consequence of the results of the studies in this field develops the idea that a longer consumption of higher doses of omega-3 by mother may decrease allergy in their offspring. However, in a systematic review in 2015, only limited evidence supported the impact of maternal n-3 LCPUFA supplementation during pregnancy and/or lactation on reducing allergic diseases in children (15).

These contradictory results were also seen in

studies investigating the effect of n-3 FAs on IFN-gamma level. In a study conducted by Lauritzen et al. in Denmark in 2005, 122 lactating mothers randomly received 4.5 g/d fish oil or olive oil in first 4 months of lactation. In the mentioned study, the median level of IFN-gamma in the fish oil group was four folds higher than that in the olive oil group (16). In another study, Damsgaard et al. investigated the infants receiving cow's milk or infant formula alone or with fish oil within 9-12 months of age. The infants of the case group had higher IFN-γ concentrations in whole-blood cultures (4). On the other hand, Dunstan et al. found that children with atopic dermatitis had a significantly lower level of IFN-gamma, compared with their unaffected counterparts (17).

The second objective of the research was investigating the effect of omega-3 on infants' growth. In our study, the growth measures of infants (i.e., height, weight, and head circumference) were not significantly different between the case and control groups at birth and 2 and 4 months after delivery. However, the mean values of these three measures were lower in omega-3 group at birth, but were increased after 2 and 4 months.

The results of a study by Tinoco et al. showed that premature infants' growth is directly associated with the n-3 PUFA composition of mothers' breast milk (28). Lauritzen et al. showed no difference between the fish oil and olive oil groups in terms of growth measures (i.e., weight, height, and head circumference) at the age of 9 months. But at the age of 2.5 years, the fish oil group had significantly higher waist circumference, body mass index, and head circumference, compared with the olive oil group (29).

In a systematic review conducted by Delgado-Noguera et al. in 2015, final conclusions showed that supplementing a mother's diet with LCPUFA (i.e., arachidonic acid and/or DHA supplementation) during the pregnancy and the first four months after birth did not improve the child's growth measures (i.e., height, weight, and head circumference) (30).

Our study had some limitations; in this regard, the sample size was small and the follow-up was short (4 months). Moreover, compared to the similar studies, the amounts of DHA and EPA in omega-3 supplements were lower in our study because the other types of omega-3 supplements were not available in the markets. Future studies can be conducted with more amounts of omega-3 supplements, larger sample size, and longer duration of follow-up. Due to financial constraints, we only measured IFN-γ level in breast milk after the intervention, while measuring cytokines before and after the intervention can provide more accurate results.

Conclusion

Overall, fish oil consumption by lactating mothers did not have a significant effect on IFN-γ level in their breast milk and the incidence of allergic disease in their infants. Longitudinal studies with longer follow-ups are needed to evaluate the role of this supplement in allergic diseases.

Acknowledgments

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Conflicts of interests

None to declare.

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