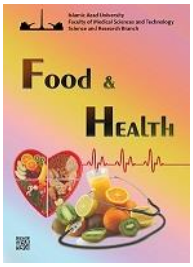

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Food allergy prevention in children: An overview

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ABSTRACT

The increasing prevalence of food allergies in developed and developing countries has raised many questions about that in scientific societies. This prevalence made researchers eager to understand the steps taken to prevent food allergies in children. Children's food allergies are often thought to be the result of exposure to allergens during pregnancy, lactation, and nutrient deficiencies such as vitamin D. in this review, we collected and reviewed new studies about nutritional strategies to prevent food allergies in children. Studies have shown that eliminating food from the mother's diet during pregnancy and lactation is not recommended. Also, despite the many benefits of exclusive breastfeeding for infancy, there is still limited evidence to support food allergy prevention with breastfeeding. Introducing solid foods at 4-6 months of age may reduce the risk of developing allergies in children; therefore, it is not suggested to delay the introduction of food. Also, introducing peanuts and boiled eggs earlier than 12 months of age can reduce the risk of some allergies. There is little evidence to support using a hydrolyzed formula and vitamin D supplement to prevent food allergies. Nutritional interventions to prevent food allergies still have many ambiguous questions; however, it can be said that avoidance of allergenic foods is not suggested, and exposure to foods can induce tolerance.

1. Introduction

The prevalence of food allergies has increased to 6-8% in children over the past thirty years (1, 2). Food allergies are classified into three categories: immunoglobulin E-related food allergies, non-immunoglobulin E-related food allergies, and the combination of immunoglobulin E and non-immunoglobulin E food allergies. Food allergies due to Ig-E Risk-type 1 hypersensitivity reactions usually occur in a few hours after exposure to a food antigen, while non-immunoglobulin E food allergies have a delayed response to immunoglobulin E and symptoms arise after several hours of Food consumption (1, 3). Strong evidence suggests that food allergens have significant effects on the life of infected children and their families. It imposes high financial, emotional, and psychological burdens on them (4, 5). In 1906, it was first discovered that allergies occur during the second encounter with an allergen led to the assumption that exposure to the allergen in the early stages of infancy and during the development of the immune system would play an important role in the onset of allergies (6). With the development of immunological knowledge and the discovery of Ig-E, it became clear that the first exposure could occur in the uterus during pregnancy. Accordingly, the avoidance of allergens was the primary approach for allergy prevention (7). It was then recommended to avoid sensitizing foods during the third trimester of pregnancy, lactation, and delay the onset of solid foods to 6 months of age and allergenic foods to 10-36 months of age (8). However, despite the avoidance and delay of allergenic foods in various countries, the prevalence of food allergies continues to rise, and new studies suggest conflicting results (2). In this article, we review the latest information on allergenic foods during pregnancy, lactation, and food allergy prevention in infants.

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2. Avoid allergenic foods during pregnancy

The traditional approach has been to avoid allergenic foods during pregnancy and early lactation. However, new studies do not support this. A 2012 Cochrane review study looked at the effects of avoiding allergenic foods during pregnancy and lactation on the prevention and treatment of atopic disease, often associated with food allergies in children. In this review, they used the information of 5 trials involving 952 participants. They concluded that avoiding allergenic foods during pregnancy did not have a protective effect on the atopic disease in the first eighteen months of life (risk ratio, 1.01; 95% CI, 0.57-1.79). In this study, the dietary restriction reduced maternal weight gain, a non-significant increased risk of premature birth, and a significant reduction in birth weight (9). A CoFAR study of 503 infants aged 3-15 months with milk or egg allergy risk showed that consumption of peanuts during the pregnancy was strongly associated with high sensitivity to peanuts. In this study, it was revealed that the use of peanuts only during the pregnancy is a strong predictor of subsequent allergies; however, its consumption during lactation, although associated with increased immunoglobulin E, is not significant (10). However, household peanut consumption did not consider in this study. Another study found that peanut ingestion during pregnancy and lactation is not related to immune or clinical reactions to peanut consumption during 4-6 years of age (11). In 2015, Kirsi et al. (12) conducted a study on the effects of peanut consumption during pregnancy and lactation on mice, they found that it had no impact on peanut allergy, and in fact, avoiding peanut ingestion could increase the risk of allergy to it. Based on the latest guideline results, sufficient evidence does not support allergy restriction foods during pregnancy to prevent allergies (13). The latest systematic review and meta-analysis also confirm these results (14).

3. Exclusive breastfeeding

Breastfeeding is considered to be the first choice of infant food, despite this widespread acceptance, information about the breastfeeding rate and duration is often unclear in most countries. Due to human milk contains specific antiallergenic factors, it is thought that long-term use of breast milk can reduce allergies. However, studies in this area are not very consistent (15). A 2015 systematic review study examined the link between breastfeeding and allergies. Eighty-nine articles were included in this review. Exclusive breastfeeding for 3-4 months decreased the risk of eczema at the age of younger than two years; however, the studies were cross-sectional and had poor methodological quality. Despite this observation, no protective evidence was observed for food allergies (16). The results of another review study were also contradictory in this regard (17). Based on the latest guideline results, there is no conclusive evidence that exclusive breastfeeding can prevent or delay food allergy (13). To investigate the association of exclusive breastfeeding with a food allergy, we will need clinical trial studies with better methodological quality. However, because breastfeeding is of great benefit to both the mother and the infant, exclusive breastfeeding for up to six months is recommended to prevent allergies (17, 18).

4. Peanut allergy

A randomized controlled cohort study called LEAP was conducted in 2015 to assess food intolerance to peanuts in high-risk children between the ages of 11-14 months in the UK. Infants were randomly divided into two groups: the first group included peanut consumers that ingest at least three times a week (an average of 6 grams of peanut protein per week) and the control group who avoided any peanut products ingestion up to 60 months of age. The results showed that in children at high risk of atopic disease, primary and regular consumption of peanuts led to a significant reduction (81% relative decrease) in the number of children with allergies at five years of age in comparison with children who avoided peanuts. In this study, 17.2% of children at five years of age were positive for peanut allergy in the group that avoided eating peanuts compared to 3.2% in the group that consuming peanuts (19). The LEAP-ON study, which was a continuation of the LEAP study, looked at the resistance to peanut allergy after 12 months of non-consumption. 556 infants were enrolled in the trial; 90.4% of participants adherent to the trial. At 72nd months, peanut allergy was significantly higher in the peanut avoidance participants (18.6% compared to 4.8%, $p<0.001$). Three new infants with allergy appeared in both groups; however, after 1 year of avoidance prevalence of allergy in the intervention group was 3.6% at 60 months and 4.8% at 72 months, which showed no significant difference to the control group. Thus, the LEAP study showed that early consumption of peanuts to 60 months reduces peanut allergy, and this effect remained after a 12-month delay in peanut consumption (20). A systematic review and meta-analysis study showed that early introduction of eggs at 4 to 6 months of age and peanuts at 4 to 11 months reduced egg and peanut allergy risk (21). The results of a 2018 review study were consistent with these findings (22). The results of the most guidelines in 2019 show evidence that the early introduction of peanuts prevents allergies to peanuts (13).

5. Egg allergy

In 2013, Palmar et al. examined the relationship between egg consumption and allergies. In this randomized trial study, the moderate to severe eczema infants were divided into two groups: the intervention group who consumed pasteurized raw egg powder from 4 months of age and the control group who did not consume eggs. A high proportion (31%) of infants in the intervention group was allergic to egg powder and did not continue to use it. After 12-month, the results were not significant, although they showed a small ratio to the egg allergy in the intervention group compare control group (51-53%, relative risk 0.65, CI 0.38-1.11, $p=0.11$). IgG4 levels were significantly higher in the egg group at both 8 and 12 months of age (23). In a cross-sectional study based on Health

Nuts cohort data (2,589 participants (73% response)), Koplin et al. (24) showed that delayed egg consumption until the age of 10-12 months or more significantly increased the risk of egg allergy to infants who began to consume eggs at the age of 6 months. Also, in the group with earlier egg consumption, exposure to boiled eggs for the first time reduces the risk of egg allergy compared to the group that consumed fried eggs (OR, 0.2, 95% CI, 0.06-0.71). In a randomized controlled trial study, infants with exclusive breastfeeding ingest six allergenic foods (milk (first), peanuts, eggs, sesame, fish, and wheat (last) at 3 or 6 months, and the group control consumed exclusively breastfeeding. This study showed that earlier food consumption reduced, albeit not significantly, the risk of allergies compared to the standard introduction of food allergens. This decrease for the egg was 3.7% in the early-introduction group and 5.4% in the delayed egg consumption group (relative reduction 31%, p=0.17); also, the prevalence of egg allergy significantly decreased in the group with earlier egg consumption (2.4% compared to 7.3%, p=0.01). Egg ingestion was less likely related to the texture and smell of boiled egg than milk and ground eggplant (25). Also, the results of a systematic review and meta-analysis study in 2020 showed that although early-onset with cooked eggs and peanuts reduces the risk of allergies, more studies will need in different populations and countries (14).

6. Use of a hydrolyzed formula

In a meta-analysis review, Boyle examined the consumption of hydrolyzed protein to reduce food allergies. Thirty-seven trial studies involving 19,000 participants in this meta-analysis were included. The study found that hydrolyzed formulas did not mitigate the allergies risk in infants at risk for allergies. At 0-4 months of age the odds ratios for eczema, compared to standard cow's milk formula, for partially-hydrolyzed formulas were 0.84 (95% CI, 0.67-1.07), and for the extensively-hydrolyzed formula based on casein was 0.55 (0.28-1.09; I2=74%), and for the extensively-hydrolyzed formula based on whey was 1.12 (0.88-1.42; I2=0%). This analysis did not support the Food and Drug Administration's claim that cow's milk-hydrolysis formula reduced the risk of allergy to cow's milk (26). A cohort study of 1,172 infants in France showed that the use of a partially-hydrolyzed formula increased the risk of food allergy at the age of two years compared to the non-hydrolyzed formula age two months (27). The latest guideline in 2019 showed that there is still insufficient evidence that partial or extensively-hydrolyzed formulas reduce the risk of allergies in infants (13). These results were also observed in the latest systematic review and meta-analysis (14).

7. Vitamin D and allergies

A cohort study found that deficiency of vitamin D (≤50 nM/L) at age 12 months was associated with food allergies, especially among infants with the GG polymorphism (CI, 0.9-38.9). Vitamin D supplementation during pregnancy and lactation was associated with lower food allergies, especially in the GT/TT polymorphism (OR, 0.10; 95% CI, 0.03-0.41). Inadequate vitamin D intake increases the risk of food allergies, especially in infants with GG genotype (OR, 12.6; 95% CI, 1.5-106.6) (28). Allen et al. in 2013 (29), based on epidemiological data with 5276 one-year-old Australian children, found that infants born with vitamin D deficiency (≤50 nM/L) were more likely to be allergic to peanuts (adjusted odds ratio [aOR], 11.51; 95% CI, 2.01-65.79; p=0.006), and eggs (aOR, 3.79; 95% CI, 1.19-12.08; p=0.025) compare to the group with sufficient vitamin D. These children were more likely to be allergic to several foods (≥2) than to one food allergy (aOR, 10.48; 95% CI, 1.60-68.61 / aOR, 1.82; 95% CI, 0.38-8.77). A cohort study in Germany called LINE (with 378 participants) showed that high vitamin D levels in pregnant women's serum increased the risk of food allergies in the children at first two years of life (30). A randomized two-blind study of 164 mothers with facial eczema showed that food allergy at age 2 was higher in the vitamin D supplement group (10/39, 25.7%) than in the placebo group (3/40, 7.5%). Besides, at least one secondary outcome was significantly higher in the vitamin D supplement group than in the control group (31). The results of a long-term cohort study of 14 children with food allergies and 130 children without food allergies in 2019 showed that children with food allergies had lower levels of vitamin D. Supplementation at age six was more likely to cause a decrease in food allergies in the children (OR=0.2, 95% CI=0.1-0.98) (32). A systematic review and meta-analysis study in 2017 showed no association between vitamin D deficiency (the level below 20 ng/ml) and allergies in the children. Still, when the level below 30 ng/ml was considered as a deficiency, this relationship was significant (33). A systematic review conducted on clinical trials showed that vitamin D supplements did not prevent primary allergy (34). On the other hand, the results of the latest review study in 2019 showed that vitamin D deficiency is strongly associated with food allergies (35). The current information does not show the benefits or harms of allergies. We need further research to elucidate the association of vitamin D with allergy risk.

8. Conclusion

Contrary to traditional attitudes about eliminating allergenic foods during pregnancy, lactation, and the first years of infant life to reduce allergies, new studies support the potential role of allergens consumption in preventing food allergies by causing tolerance. However, many questions exist in this regard, and more extensive and high-quality studies will be needed to examine the type of food, as well as the order in which it is introduced. However, changing attitudes from eliminating suspicious foods to introducing suspicious foods seems to be a useful way to prevent food allergies. More research will need exclusive breastfeeding, vitamin D, and hydrolyzed formulas to decrease food allergies.

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