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REVIEW

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The Effect of Maternal Nutrition with a High Antioxidant Diet and Mediterranean Diet During Pregnancy on the Prevention of Allergic Diseases in the Children

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ABSTRACT

The nutrition of the mother during pregnancy is very important on the development of the child's immune system and immune programming. Nutrition with antioxidant-rich fresh vegetables and fruits, dietary fiber consumption, and intake of n-3 unsaturated fatty acids (PUFA) provide important benefits in the development of the child's immune system and intestinal microbiota. Healthy nutritional components such as the Mediterranean diet, which are high in antioxidants, seem to have a direct effect on immune and metabolic processes as a whole and prevent the occurrence of many diseases by reducing chronic inflammation, oxidative damage, and cell destruction. Such a diet during pregnancy is thought to reduce the child's susceptibility to allergic diseases. For this reason, approaches to improving nutrition for the prevention of allergic diseases have been a very important research area in recent years. According to current data, epidemiological studies reveal conflicting results in terms of antioxidant intake and the development of allergic diseases. Many studies and meta-analyses associate low antioxidant intake with wheezing, increased asthma and airway reactivity, and reduced respiratory function. However, it has not been shown that a diet with high maternal antioxidant content has a protective effect on food allergy and other allergic diseases. In this review, the effects of a diet high in antioxidants and a Mediterranean diet during the pregnancy period of the mother on the prevention of food allergy and other allergic diseases in the child will be discussed in detail.

Keywords: Allergy, antioxidant, food allergy, nutrition, diet

The nutrition of the mother during pregnancy has effects on immunological development, microbial diversity, and tolerance in the child's intestine during the intrauterine period and after birth (1). In general, the Mediterranean diet, which is one of the 'healthy eating' methods, is high in antioxidants and protects against asthma, obesity, cardiovascular diseases, autoimmune diseases and allergic diseases. This effect is more effective with feeding with antioxidant-rich fresh foods, fiber consumption in the diet, and n-3 polyunsaturated fatty acids (PUFA) (2). These healthy nutritional components seem to prevent the occurrence of many diseases by reducing chronic inflammation, oxidative damage, and cell destruction from immune and metabolic processes as a whole.

Epidemiological studies provide conflicting results in terms of diet with high antioxidant content and the development of allergic diseases. In some studies, low antioxidant intake has been associated with wheezing, asthma and airway reactivity, and reduced respiratory function (3). However, some studies have reported that there is no relationship between a diet high in antioxidants and allergies (4,5), while others have reported potential adverse effects (6).

In this review, the effect of feeding a diet with high antioxidant content during pregnancy on the child's protection from food allergy and other allergic diseases will be discussed.

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1. Atopy and Allergic Diseases

Allergy is the inappropriate/over-reaction of the immune system to substances that are normally harmless to the body after damage to the 'tolerance mechanisms' in the body. Allergic diseases are diseases that occur with the effect of environmental and genetic factors and as a result of complex multifactorial mechanisms. For this reason, they coexist with varying clinical phenotypes in different age groups, show different prognoses, some may continue throughout life, may transition from one to the other, and sometimes may cause us life-threatening situations.

The immune system is immature at birth and develops with age, and antigen stimulation occurs regularly with age-appropriate nutrition during this development. In addition, microbial colonization develops in the intestine and other organs from the first days of life, and plays an important role in the formation of the immune system and oral tolerance (7). From the immunological point of view, it is thought that atopic diseases are closely related to both the mother's lifestyle and the development in the intrauterine period, starting from the prenatal period. Therefore, maternal nutrition, especially during pregnancy, may be closely related to the child's susceptibility to allergic diseases. Nutrition plays an important role in the development of the immune system, hemostasis, and the functions of immune cells. Omega-3, vitamin D, and zinc contained in nutrients are essential products for the immune response to mature and function properly.

Food allergy, asthma, wheezing, allergic rhinitis, and atopic dermatitis are common allergic diseases in children. The prevalence of food allergy and other allergic diseases has been increasing rapidly in developing countries such as our country as well as in developed countries in recent years (8). Diet has an important role in the prevention of food allergy and asthma and also in the treatment of food allergy. Many studies have been conducted for many years in which factors such as the diet used by the mothers during pregnancy, the weight gained by the mother during pregnancy, the presence of obesity in the mother, the intestinal microbiota of the mother, and breast milk intake have been shown to be effective. A study has reported that introducing the child to foods early (4-6 months) is effective in preventing the development of allergic diseases (9).

2. High Antioxidant Diet

The imbalance between prooxidants and antioxidants is defined as 'oxidative stress'. Antioxidants are essential for the elimination of oxidative stress. Antioxidants destroy oxidants, neutralize free radicals and prevent them from turning into more toxic molecules, bind to metal ions, and clean damaged molecules. Antioxidants take part in the prevention and repair of the damage caused by free radicals in the epithelium by producing interferon-gamma (10). Thus, they form the body's first line of defense (11).

It is known that antioxidants (vitamins A, C and E), minerals (selenium, zinc, folate and iron), and vitamin D have positive effects on immune and metabolic health. Dysfunction in cell signaling and arachidonic acid metabolism increases systemic inflammation. Oxidative stress may cause the Th1 phenotype to shift towards Th2 and the development of allergic diseases (11-13).

Antioxidants taken from the outside into our body with nutrition are the vitamins C and E, flavonoids, carotenoids, and the oligoelements zinc and selenium. Antioxidants taken with the exogenous diet protect the body from lipid peroxidation (14). The most important sources of antioxidants in foods are vegetables and fruits. These include polyphenols, vitamins (C, E, beta-carotene) and mineral compounds (Se, Zn, Fe, Mn, Cu). The amount of chemicals found in isolated bioactive phytochemical products are much lower than in the content of fruits and vegetables (15).

An antioxidant-high diet and the development of allergic diseases is actually a somewhat complex issue (16,17). Mechanistic studies indicate that antioxidant nutrition may predispose to allergic diseases. Two hypotheses have been proposed in this regard. While the first of these states that allergic diseases may increase if the amount of antioxidants in the diet is low, the second hypothesis is that allergic diseases may develop as a result of antioxidants suppressing helper T cell 1 (Th1)-mediated cytokine release. Anti-inflammatory effects of high-antioxidant diets can cause suppression of the Th1 immune response and increase the Th2 response associated with allergic diseases (10). In an experimental study on this subject, Murr et al. have shown that antioxidant intake may cause a decrease in Th1 differentiation and interferon-gamma release. The authors reported that the decrease in the Th1 response may cause the development of the Th2 phenotype and the development of allergic diseases by cross-regulation (18). According to an opposite hypothesis, nutrients may be effective in oral tolerance by ensuring regulatory T cell (Treg) formation and induction (19). In a retrospective cross-sectional study where the nutrition of the mother during pregnancy was questioned with a questionnaire, it was shown that the mother had consumed significantly less vegetables, fruit, and chocolate-based products in children with atopic dermatitis who developed asthma compared to those who did not (20).

3. Mediterranean Diet

Contrary to the Western diet, it is recommended to consume large amounts of fruit, vegetables, grains and olive oil, moderate white meat, fish and dairy products, and a small amount of sugar and red meat in the Mediterranean diet (21). The Mediterranean diet has a regulatory effect on immune system functions, antioxidant support, and anti-inflammatory properties. It contains intense amounts of micro- and macronutrients, vitamins (A, C, D), minerals (iron, zinc, selenium, folate/folic acid), and fatty acids (mono and polyunsaturated fatty acids and omega 3 fatty acids) (22).

According to the results of studies conducted on this subject, which has been of interest for many years, the Mediterranean diet may protect children from the development of asthma (23-25). The vitamins, fiber, minerals and fatty acids in the Mediterranean diet may have a protective effect on respiratory tract inflammation with their anti-inflammatory effects. The Mediterranean diet also increases endothelial functions and reduces bronchial hyperresponsiveness through proinflammatory markers such as high-sensitivity C-reactive protein, interleukin-6 (IL-6) and adiponectin (23-25). Although many studies conducted to date show that the Mediterranean diet has a protective effect against childhood asthma and allergies (26-28), there are also studies showing that it has no such effect (29-31).

A few recent studies have evaluated maternal nutrition during pregnancy with the measurement of the healthy eating index and have shown that it has no effect on recurrent wheezing that will develop in children up to the age of 3 years (32,33). In a systematic review, three observational studies showing the effect of a Mediterranean diet during pregnancy on the prevention of allergic diseases have reported that the first posed an increased risk for allergic diseases, the second reduced wheezing, and the last one had no effect on the development of allergies (32). In conclusion, although the Mediterranean diet seems to have positive effects on asthma and wheezing attacks, it is thought to have no effect on preventing the development of other allergic diseases (8,33,34). More and larger cohort studies are needed on this subject.

In another systematic review published this year, where compliance with the Mediterranean diet and the development of asthma and other allergic diseases in children was investigated, a total of 12 studies, 3 from our country, were evaluated (35). Only one of these studies is a cohort study, one is a longitudinal study, and the others are cross-sectional studies. In all studies, the relationship of the Mediterranean diet with asthma and/or wheezing, and eczema in only two were investigated, while none of them evaluated the relationship with food allergy. In many of the studies included in the analysis, adherence to the Mediterranean diet was associated with reduced asthma frequency, airway inflammation, and symptom frequency, and higher respiratory function and asthma-related interleukin levels. However, no relationship was found between adherence to the Mediterranean diet and the presence of allergic rhinitis, eczema, rhinoconjunctivitis, or atopic condition. Among the studies included in this systematic review, the heterogeneity between study design, number of patients, Mediterranean diet adherence scales, and assessment criteria may have influenced the results of the analysis (35).

A systematic review (36) and several meta-analyses (37-40) published in previous years also investigated the effect of the Mediterranean diet on asthma. These analyses showed that the presence of asthma (34,36,39), and the presence of wheezing (34,37-39) and severe wheezing (37) were decreased in children who followed the Mediterranean diet. However, its relation with lung functions and bronchial hypersensitivity could not be determined (41).

4. Nutritional Diversity

Microbiota is a very important component for maintaining the integrity of the intestinal wall and the balance of the immune system. Dietary diversity is highly influential on the diversity of the microbiome. Compounds produced by the breakdown of nutrients along with their natural microbial load are necessary for the development and differentiation of the intestinal microbiota. Thus, the development and maturation of the immune system in the whole body system, starting from the intestine, can be regulated. Food diversity can therefore be protective on the development of allergic diseases as well as many diseases such as cancer. Many studies have shown that food diversity can reduce the development of allergic diseases (42-45). Introducing children to different food groups at an early age, especially during infancy, has an effect on the differentiation and development of the intestinal microbiota repertoire, and also induces the development of tolerance to foods.

To date, case-control studies have been published showing that fermented food diversity is effective on the development of atopic dermatitis, allergic proctocolitis, and cow's milk allergy (46-48). Another important issue is that home-style nutrition can reduce the development of food allergy from allergic diseases. In a study, the frequency of food allergy was found to be lower at the age of two years in home-fed children (42). The authors stated that the microbial load, which is found at a higher rate in homemade foods than ready-made commercial products, may be protective regarding the development of the disease (49).

In conclusion, according to our current knowledge, maternal use of antioxidant supplements during pregnancy does not reduce the risk of developing allergic diseases in their children. The most correct approach should be to support mothers to continue their diet with high antioxidant content during pregnancy.

5. Vitamin A and Beta-Carotene

Beta-carotene is a red-orange pigment that can convert to vitamin A and is commonly found in vegetables and fruits. After beta-carotene is taken into the body, it accumulates in the nine membranes, fights with the superoxide anion, and interacts with peroxyl free radicals. It is most commonly found in carrots, cabbage, mangoes, and peaches (50).

Vitamin A is an antioxidant as well as a protectant against infections. It helps in monocyte, macrophage, and lymphocyte differentiation (51,52). It helps to maintain the integrity of mucous membranes, provides hematopoiesis, increases antibody production, and induces the production of transforming growth factor (TGF-beta). It also regulates T and B cell functions and provides gene transcription. In vitamin A deficiency, the number of CD4+ T lymphocytes decreases, and the CD4+/CD8+ ratio decreases (51). An experimental study conducted in previous years showed that consumption of vitamin A and its components may elicit Th2 responses (52).

In a birth cohort study conducted in Finland, a 1.12-fold increase in the risk of developing cow's milk allergy in children at the age of 3 was found if the mother consumed foods containing beta-carotene or beta-carotene as nutritional support during pregnancy. In this study, it is seen that the socioeconomic status and education level of mothers who are fed a diet with high antioxidant content were higher. This diet have also enabled mothers to adopt a healthier lifestyle and to care about their children's allergic conditions (53). When looking at other allergic diseases, the beta-carotene levels in Vitamin A content were found to be lower in many children with asthma and wheezing compared to healthy control groups (54-56).

6. Vitamin C

Vitamin C (ascorbic acid) is the most abundant antioxidant in the body. It scavenges oxygen free radicals and suppresses superoxide anions secreted from macrophages. It is most commonly found in cherries, citrus fruits, broccoli and cabbage. It has a reducing effect on oxidative damage, infections and inflammation in tissues.

It has been shown that feeding the mother with foods high in vitamin C and copper protects her child from food allergy, but this result it is not associated with consumption of zinc, vitamin E and beta-carotene (39). In the literature, there are many studies with conflicting results showing that there is a direct and inverse relationship between vitamin C consumption and the frequency of wheezing. In a meta-analysis including 22 (cohort, cross-sectional, and case-control) studies examining the relationship between fruit intake with high vitamin C content and asthma and asthma-like symptoms, a negative correlation was shown between vitamin C intake and the development of asthma (57). With a more limited dataset, a meta-analysis of two published birth cohort studies found no association between maternal vitamin C intake in pregnancy and wheezing at the age of 2 years (57). Intervention studies with vitamin C in pregnancy for the prevention of allergic diseases are insufficient.

7. Vitamin E

Vitamin E is one of the first antioxidants and is the common name of 8 different vitamin E components in its content. Alpha- and gamma-tocopherol are the most common vitamin E components. Alpha-tocopherol has an anti-inflammatory effect, while gamma-tocopherol has an inflammatory effect (57). Alpha-tocopherol is the most important fat-soluble antioxidant. It prevents cell membrane damage due to oxidation in humans, and stops chain reactions related to lipid peroxidation. Alpha-tocopherol is abundant in green leafy vegetables, seed oils, olive oil, and sunflower oil. Canula and soybean oil contain gamma-tocopherol and inhibit the beneficial effects of alpha-tocopherol (58).

Vitamin E prevents long chain-PUFA and protein oxidation. In addition, it helps to reduce Th2 responses while supporting the formation of Th1 responses in T cell differentiation (59). It also causes an increase in lymphocyte proliferation, NK cell activation, antibody production, and phagocytic activity of macrophages. Vitamin E levels of the mother during pregnancy are very important for fetal growth, lung development, and maturation (60).

Finally, it was shown in a recently published meta-analysis that maternal nutrition during pregnancy, especially vitamin E consumption, is protective against wheezing in children, but has no effect on other allergic diseases (61). However, a cohort study conducted in Finland found that consumption of foods and vitamin E caused the development of cow's milk allergy, while selenium consumption was protective (62).

These results are also supported by many studies (63-65). The results are inconsistent for other high antioxidant diets. In conclusion, although the high consumption of antioxidants in the mother's diet during pregnancy protects her children from asthma or wheezing, there is not enough evidence for food allergy as yet. However, it has not been shown that taking vitamin E supplements in addition to the diet prevents the development of allergic diseases.

8. Selenium

Selenium is a mineral that acts as a coenzyme of glutathione peroxidase. It is most commonly found in seafood, meat, nuts, and wheat. Selenium content in food is related to its amount in the soil. It participates in the structure of glutathione peroxidase and protects cells from the oxidative damage of lipid peroxidation. Vitamins C and E increase selenium absorption (59).

If the amount of selenium in the serum of the mother is high during pregnancy, the frequency of wheezing was found to be lower in the children (66). In another study, it was shown that high levels of selenium in the mother's blood during pregnancy and in the cord blood during delivery were associated with lower wheezing in the first two years (67), while it had no effect at the age of five (68). In other studies, an inverse relationship between the amount of selenium in the serum and the prevalence of asthma and respiratory symptoms and a direct correlation with lung functions were found (16,65,69).

9. Zinc

Zinc is an element that interacts with superoxide dismutase (SOD) and vitamin E metabolism. Continuous exposure to antigenic molecules in the intestines causes chronic inflammatory changes and increased reactive oxygen radicals (ROS) (70). Excessive amounts of ROS are neutralized by antioxidant barrier compounds. In the absence of an adequate defense barrier, oxidation resulting from enzymatic and non-enzymatic reactions can damage lipid compounds in the cell membrane (70).

Zinc is an essential trace element involved in many cellular enzymatic reactions. It acts as a cofactor of many enzymes, especially SOD, which are involved in maintaining the oxidant-oxidant balance. To date, there is no study investigating the role of zinc in preventing the development of food allergy. Only one study has found low concentrations of zinc in serum samples of children aged 1-36 months with food allergies. The authors stated that zinc deficiency weakens the antioxidant barrier. Finally, a recently published meta-analysis has shown that the mother's consumption of zinc during pregnancy was protective against wheezing in her children, but had no effect on other allergic diseases (61).

10. Essential Fatty Acids

Essential fatty acids (EFAs) are important immune regulators. Fatty acids are divided into saturated and unsaturated fatty acids. It contains PUFA in unsaturated fatty acids. Among PUFAs, linoleic acid includes alpha-linolenic acid, while long chain polyunsaturated fatty acids (LC-PUFAs) include omega-3 and omega-6 fatty acids.

Omega-3 fatty acids have anti-inflammatory properties, while omega-6 fatty acids have pro-inflammatory properties (71).

PUFAs generally regulate dendritic cell and Treg functions. At the same time, they form the building blocks of resolvin and protectorins, which are anti-inflammatory molecules. They inhibit the release of free radicals and increase the expression of MHC I and II (71).

Among the essential fatty acids, linoleic acid and n-6 PUFA are converted to arachidonic acid (AA), eicosanoid degradeted by elongase and desaturase enzymes and plays an important role in the development of allergy. On the other hand, alpha-lineloic acid (ALA), which is n-3 PUFA, is converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into anti-inflammatory and/or prosoluble lipid molecules (for example, resolvin and protectorin). EPA also biologically converts to less potent prostaglandin and leukotriene precursors than n-6 compounds. Since n-3 and n-6 compounds are in competition for the same metabolic pathway, the increase in n-3 PUFA intake will theoretically result in EPA and DHA intake instead of AA, together with a decrease in n-6 PUFA intake, and will result in a decrease in many immunological responses such as allergy (72).

Eicosapentaenoic acid is taken as part of the normal diet from birth through breast milk, infant formula, and foods (72). Eicosapentaenoic acid is involved in the formation of the protective hydrolipidic film layer of the skin and intestinal mucosa (73). Although it is considered to be a strong possibility that EFA has a role in the prevention and treatment of allergic diseases, it was shown that it has no effect on the prevalence and incidence of food allergy in childhood in a systematic review evaluating the previous studies (73). However, the limited number of studies and the high heterogeneity among them (3 studies; 915 children; RR (risk ratio) 0.81, 95% CI 0.56-1.19%, I^2 (fraction of variance due to heterogeneity) = 63%; RD (risk difference) 0.02, 95% CI: 0.06-0.02% , I^2=74%) may have affected the results. Longitudinal studies with large series are needed on this subject.

In a recently published meta-analysis, it was shown, contrary to expectations, that the mother's intake of n-3 essential fatty acids (omega 3 fatty acids) during pregnancy is associated with atopic diseases that will develop in the child (74). The results were inconsistent as the effect on fewer patients was investigated in interventional studies. There is a need for new studies with a homogeneous structure that will reveal that the mother should use the right nutritional strategies and omega-3 support during pregnancy. In observational studies investigating the effect of PUFA consumption during pregnancy on allergic diseases, consuming omega-3 rich foods during pregnancy and lactation reduced the risk of developing allergic diseases (75,76).

In a Cochrane meta-analysis, 8 randomized controlled trials were analyzed, five of which evaluated the risk of developing allergic disease in the offspring of mothers who took omega-3 supplements during pregnancy, two during lactation, and one during pregnancy and lactation. When the children were evaluated at 12-36 months, the frequency of all allergic diseases decreased with no effect detected at 36 months. The reduction in a single food allergy is seen at the 12th month evaluation although this effect disappeared between 12-36 months. As a result, it can be said that there is limited evidence yet in terms of protecting the children from food allergy by providing omega-3 supplementation to the mother during pregnancy (77).

11. Vitamin D

Vitamin D is required for calcium metabolism and bone health, as well as for natural and adaptive immune system responses (78). The active component of Vitamin D, 1,25(OH)2D (calcitriol), has positive effects on epithelial cells, T and B cells, dendritic cells, and other immune system cells. It has been shown that there are receptors for vitamin D on all cells that make up the adaptive immune system. Vitamin D is involved in the production of cathelicidin, one of the antimicrobial proteins. Thus, the formation of mucosal integrity is ensured. In addition, Vitamin D affects the development of tolerance by inducing regulatory T cells (Treg) and tolerogenic dendritic cells by many mechanisms. Vitamin D plays an important role in the prevention of food allergies (79). In clinical studies to date, the administration of vitamin D supplementation has been found to be ineffective in preventing the development of food allergy. In a systematic review, it was shown that vitamin D supplementation does not have a protective effect on the development of allergic diseases, but the low level of evidence available at present should be considered (80).

As a result, studies to date have shown that the mother's high antioxidant diet and Mediterranean diet have an effect on the prevention of allergic diseases such as asthma and wheezing, but not the development of food allergy and eczema. The limited number of studies with large series on this subject and the differences in the designs of the studies are an obstacle for us to make a definitive approach. It is quite necessary to focus on studies on the regulation of nutrition and to develop new anti-allergy approaches. In this regard, it is very important that allergists and dietitians work in cooperation.

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Authorship Contributions

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