The Potential of Maternal Dietary Modification for Prevention of Food Allergy

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Abstract

Effective primary prevention strategies aimed at reducing the onset of IgE sensitization are urgently needed as the incidence of childhood food allergy keeps increasing.

Studies eliminating food allergens during pregnancy have failed to show reduction in the prevalence of long-term IgE-mediated food allergy in children, and recent data provides direct evidence supporting early oral exposure as a means of preventing development of allergy. Since effects on early immune programming may be more significant in utero, there has been increasing interest in the potential protective role of maternal dietary modifications on the development of FA in offspring.

In this article, we will review the current knowledge from animal and clinical studies on the role of maternal dietary modification, mainly through supplementation with vitamins, polyunsaturated fatty acids and probiotics, for the prevention of food allergy. Besides, the potential role of some promising FA treatments like Chinese herbal formula FAHF-2 for the primary prevention of FA in offspring will be reviewed.

Keywords: Food allergy; Prevention; Pregnancy; Maternal diet

Introduction

The rates of childhood food allergy (FA) and eczema are continuing to increase as part of what appears to be a “second wave” of the allergy epidemic [1]. In this context, primary prevention strategies aimed at reducing the onset of IgE sensitization are urgently needed.

Because progressively earlier presentations of food allergy implicate early environmental influences, there is intense interest in the prenatal factors inducing tolerogenic immune responses. Studies eliminating food allergens during pregnancy have failed to show reduction in the prevalence of long-term IgE-mediated food allergy in children, and recent data provides direct evidence supporting early oral exposure as a means of preventing development of allergy.

The parallel between the increase in food allergies and changes in dietary components during the last decades has also led researchers to investigate preventive strategies aiming at restoring the dietary and gut microbial balance, mainly through supplementation with vitamins, polyunsaturated fatty acids and probiotics. Other dietary factors currently under investigation in animal studies to prevent food allergy include polyphenols and isoflavones. Furthermore, there are also new data on Chinese herbal formula FAHF-2, proved to be effective in induction of long term tolerance in peanut allergic mice, which was associated with skewing Th2 immune responses to Th1 (and regulatory) response. Because maternal allergies increase the risk of peanut allergy in offspring, restoration of maternal food allergy points to the potential role to FAHF-2 for prevention of offspring food allergy.

In this article we will review current knowledge from previous publications, published abstracts and newly generated data from animal and clinical studies on the role of maternal dietary modification for the prevention of food allergy.

Exposure to Food Allergens

Studies of food allergen avoidance during pregnancy, lactation, and infancy have consistently failed to reduce long-term IgE-mediated food allergy in children [2].

Clinical studies

Approximately 74% of peanut (PN) anaphylatic reactions occur at first known exposure in infants [3,4] suggesting a critical window for early life prevention [5]. The recommendation for mothers to implement a PN restrictive diet during pregnancy/lactation was abandoned in 2008 [6] due to the lack of conclusive evidence of benefit [7], and early evidence that it might even be harmful [8,9]. The theory behind the early life PN restriction diet is mainly based on the conception of “in utero or early life sensitization” based on the findings of allergens/antibodies presented in amniotic fluid and cord blood [10], and placenta [11,12] and peanut antigen in breast milk of lactation women after ingestion of PN [13], although studies providing a direct association of offspring sensitization were lacking. Recently, an alternative hypothesis that early life introduction of PN or other allergenic foods may be beneficial because oral tolerance induction is an active process that requires antigen has been put forward [14,15]. This is based on several observational studies. For example, a recent cross-sectional study of Jewish children in Israel and the UK, found that the prevalence of peanut allergy (PNA) was 10-fold higher in the UK (1.85%) than in Israel (0.17%, p<0.001), and that peanut is introduced earlier and is eaten more frequently and in larger quantities in Israel than in the UK by 8-14 month infants [16,17]. However, the evidence of benefit of early life exposure is no consistent. Recent studies showed that maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants [18,19]. Conflicting findings may...
be due to uncontrolled environmental factors, timing of introduction to PN and different study protocols and populations, as well as undefined co-factors in maternal diet such as microbes [18-20]. In addition, retrospective maternal recall of dietary intake during pregnancy (and or lactation), sometimes months or years later, may contain recall bias. At present, the standard practice for PNA and other food allergies is strict allergen avoidance. There is no clinical study reporting whether or not trigger clinical reactions would prevent offspring peanut or other food allergies.

Maternal allergenic food consumption for preventing food allergy in offspring: Animal studies

In recent years several studies in animal models have provided direct evidence supporting early oral exposure as a means of preventing development of allergy. Melkild et al. [21] showed that intraperitoneal immunization of naive mice with ovalbumin and adjuvant (Al(OH)3) during pregnancy and lactation significantly reduced the specific IgE response and increased the IgG2a response in their offspring. Moreover, the IgE suppression was stronger if maternal allergen exposure was during early pregnancy (3 days into pregnancy) compared to a late pregnancy exposure (17 days into pregnancy). The same group reported that the protective effect of maternal immunization was affected by the type of adjuvant used: while offspring from mothers immunized with OVA and either pertussis toxin (PT) or Al(OH)3, showed reduced levels of OVA-specific IgE and IgG1 and increased levels of OVA-specific IgG2a antibodies, maternal immunization with CpG and OVA did not affect antibody responses in offspring [22]. However, whether this effect is dependent on the specific adjuvant and/or the route of exposure employed has to be further investigated.

Figure 1: Maternal allergenic food consumption for preventing food allergy in offspring. Transmission of maternal specific immunoglobulins by breast milk in two murine models of FA

A: Maternal peanut consumption provides protection in offspring against peanut sensitization [23]. Experimental protocol of mothers' and offsprings' peanut (PN) sensitization. Female C3He/J mice were fed either with peanut and cholera toxin i.g. (PN+CT), peanut i.g. (PN) or cholera toxin alone (CT) for five weeks and, after mating with naïve males, during pregnancy and lactation. An unimmunized group was employed as a control. 5-week old offspring from all the 4 groups were sensitized with PN+CT i.g. weekly for 5 weeks followed by 2 boosting doses. Mothers were sacrificed at weaning and offspring at week 15 for analysis.

B: Transfer of specific immunoglobulin by breast milk leads to antigen-specific offspring protection from food allergy [26]. Left: Experimental protocol. Sensitized mice were exposed to 1% OVA in drinking water for 2 weeks immediately after delivery. Offspring were weaned at 4 weeks and 5-week-old offspring were used for the FA model. Right: OVA-specific IgG1 and IgA levels in mouse milk: peanut-specific IgG2a (ng/mL), peanut-specific IgG1 (ng/mL) and peanut-specific IgA (ng/mL) measured by antigen-specific ELISA. Data are expressed as means ± SEM of duplicates for each group (n=3–4). *P<0.05, **P<0.01 vs Unimmunized.

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López-Expósito et al. [23] demonstrated that offspring of peanut allergic mothers exhibited significantly increased susceptibility to PN-induced IgE sensitization, and that low-dose consumption of peanut (beneath the threshold of triggering clinical reactions) with CT during pregnancy and lactation reduced the risk of peanut allergy in murine offspring. Further study by this group also showed that this effect persisted for at least 15 weeks. Importantly, administration of peanut extract alone was markedly less effective than peanut plus the mucosal adjuvant cholera toxin (CT) in the suppression of peanut-specific IgE or Th2 cytokine responses, and CT alone had no effect. Consistently, increased peanut specific-levels of IgG2a and/or IgA in milk were seen when peanut and cholera toxin were administered together, but not PN or CT alone, suggesting that transmission of maternal immunoglobulin may play a role in the observed protection (Figure 1) [24]. The important role of a mucosal adjuvant in providing protection against peanut sensitization was demonstrated in this study and we recently found that offspring protection also occurs when the non toxic to human mucosal adjuvant cholera toxin B is used.

Preventing allergy in offspring by maternal mucosal (intranasal) immunization has also been confirmed in another recent study in which maternal immunization with OVA reduced OVA-specific IgE and IgG1, and increased IgG2a and Th2 cytokine responses in offspring [25].

A recent study by Yamamoto et al. [26], showed that feeding OVA to lactating mice prevented offspring OVA allergy-induced diarrhea and suppressed the increases in plasma OVA-specific IgE levels and Th2 cytokine mRNA expression levels in the proximal colon, as well as the infiltration of mucosal mast cells into the colon. Detection of OVA in breast milk of from OVA-exposed nonallergic mothers during lactation, and increased titers of OVA-specific IgG1 and IgA in breast milk from allergic mothers, suggests that transfer of dietary antigens along with their specific immunoglobulin by breast milk leads to antigen-specific offspring protection from food allergy (Figure 1). How the breast milk antibodies provide protection against FA in the child has not been studied. However, in an asthma model Mosconi et al. [27] demonstrated that milk-borne OVA-IgG complexes were actively transferred from the mothers to the pups through the FcRn. Furthermore, FcRn-mediated transfer of OVA-IgG complexes resulted in the induction of Foxp3 regulatory T cells in mesenteric lymph nodes, and that FcRn-deficient mice breastfed by OVA-exposed sensitized mice were not protected against allergic airway inflammation.

Taken together, the results of these animal studies suggest that induction of oral tolerance by maternal ingestion of food antigens during lactation may be a strategy for prevention of FA in infants.

**Maternal Dietary Supplement Interventions**

In recent years, there is an active research focused on assessing whether the manipulation of nutritional factors, like vitamin D or polyunsaturated fatty acids (PUFA), in maternal diets may prevent the development of food allergy in their offspring.

**Vitamin D**

Vitamin D controls effector immune functions, promotes regulatory immune response and induces innate immune defenses [28,29]; all of which could be relevant to allergic disease.

Some studies have pointed towards an early induction of tolerogenic immune responses by maternal vitamin D intake. Chi et al. [30], have shown that higher vitamin D levels at birth may be associated with a lower number of T regulatory cells, and a relation between vitamin D supplementation during pregnancy and increased cord blood mRNA levels of the leucocyte receptors ILT3 and ILT4, both critical for the generation of T suppressor cells and induction of immunological tolerance, has been recently reported [31].

**Clinical studies:** Clinical studies on the effect of vitamin D in allergic diseases are mainly observational and have yielded very heterogeneous results, suggesting that either excessive or, conversely, vitamin D deficiency result in increased allergies (reviewed in [28]).

On one hand, allergies increased coinciding with vitamin D supplementation intervention programs to prevent rickets in childhood [32], and increased risk for asthma and food allergies has been reported among children receiving early vitamin supplementation [33]. In a recent German cohort study, it has been described that higher maternal 25(OH)D3 results in a higher risk of food allergy sensitization at 2 years of age [34]. On the other hand, the vitamin D deficiency (VDD) hypothesis argues that inadequate vitamin D is responsible for the increase in allergic diseases. Infantile vitamin D has been associated with higher rates of atopic disease at the age of 6 and 14 years [35] and enhanced eczema severity in children aged between 8 months and 12 years [36]. Several studies have reported higher rates of food allergy/anaphylaxis or proxy measures at higher absolute latitudes and in infants born in fall/winter compared with sunnier months in Europe, the United States, and Australia [37], and higher rates of food sensitization have been described in infants born to mothers with low vitamin D intake during pregnancy [38].

However, vitamin D insufficiency itself cannot be related to the increase of a topic diseases since allergy was nearly absent during rickets epidemics that occurred in the last centuries. It can also be argued that in northern developed countries like USA, where the use of dietary supplements is highly extended, VDD may be very unlikely and thus could not explain the increase of atopic disease in these countries. Nevertheless, an 8% of the US population is at risk of vitamin D deficiency [39] and a recent study on infants and their mothers in New England found that more than half of the infants and approximately one third of the mothers who gave birth were vitamin D deficient at the time of delivery even when prenatal vitamin D were taken regularly [40].

Significant genetic variability of the response to dietary supplementation and metabolism of vitamin D, have been recently described [41] and could account for VDD even in people at low risk.

The apparent paradox of both vitamin D insufficiency and vitamin D supplementation having been linked to allergy and asthma may be explained by epigenetic programming in pregnancy by low vitamin D levels. Recent studies provide evidence for gene-vitamin D interaction effects on food sensitization. In a study on 649 children, vitamin D deficiency (VDD) increased the risk of food sensitization only among individuals with certain IL4 and MS4A2 (MS4A2 (Fc epsilon receptor 1 beta-chain) genotypes [42]. Later, Vimaalewaran et al. confirmed the association of VDD with higher total IgE levels in adults with IL4 and MS4A2 SNPs [43]. These data highlight the need to consider possible ethnic differences in the allergy-related responsiveness to VDD.

Studies examining the effect of maternal vitamin D status on food allergy on offspring, summarized in table 1, are mainly observational [44-48]. Randomized control trials are ultimately required to determine any potential role of vitamin D supplementation in preventing allergic disease. Until then, no clear recommendation on the use of vitamin D in pregnancy for the prevention of allergies can be formulated.
Polyunsaturated Fatty Acids (PUFA)

Lower consumption of n–3 PUFA is a key characteristic of modern ‘western’ diets, which are typically rich in more pro-inflammatory n–6 PUFA. This has raised interest in the use of fish oil as a preventative strategy to ‘restore the balance’ of n–3/n–6 PUFA, supported by the recognized anti-inflammatory effects of n–3 PUFA and evidence that metabolic products of n–6 PUFA are more inflammatory.

Animal studies: The dietary ratio of n-6/n-3 fatty acids during gestation and throughout lactation has been found to influence the induction of immunological tolerance to OVA in neonatal rats [49]. Moreover, dietary supplementation with n-3 PUFA (fish oil source) of OVA-sensitized mice reduces serum specific OVA-antiIgE and IgG1, small intestine edema and eosinophil infiltration, mucus production, and Paneth cell degranulation [50]. These results are consistent with the findings of Watanabe et al. [51] that the IgE antibody response to egg albumin was significantly lower in mice fed with safflower seed oil. On the other hand, Johansson et al. [52] found, in a murine model of airway hypersensitization (Th2), that mice fed fish oil produced higher levels of OVA-specific IgE and exhibited greater lung eosinophil infiltration. As far, there has been no report in animal model how maternal PUFA intake influences offspring food allergy outcomes.

Clinical studies: There is interest in the potential protective role of maternal n–3 PUFA supplementation during pregnancy, particularly as effects on early immune programming may be more significant in utero.

A systematic review conducted in 2009 [53] concluded that “supplementation with omega3 and omega6 oils is unlikely to play a role in the strategy for the primary prevention of sensitization or allergic disease”. The few studies specifically addressing the preventive effect of n-3 PUFA supplementation of pregnant women on children at risk of food allergies, summarized in table 2, have not yet confirmed their beneficial role as a strategy for the primary prevention of food allergy [54-58].

Antioxidants

The available epidemiological, animal, molecular and immunological data suggest potentially beneficial associations between maternal intake of some antioxidants during pregnancy and childhood asthma and to a much lesser extent, atopic dermatitis and allergic rhinitis (reviewed in [59]). To date, no such data are available for food allergy.

Fruit polyphenols and soybean isoflavones effect on FA in animal models

Dietary polyphenols are a class of bioactive compounds found in abundance in plant (tea, cocoa, coffee, etc.) and fruit (apple, grapes, pomegranate, etc.) sources. Their effects on allergic disorders are just beginning to be unraveled and future research is required to substantiate their role as anti-allergy agents. Certain classes of polyphenols can influence the development of allergic immune responses at two critical stages, during allergic sensitization and following re-exposure to the allergen. Polyphenols can form insoluble complexes with allergenic proteins and render them hypoallergenic, which leads to inefficient antigen presentation by specialized cells such as dendritic cells (DC) [60].

Of particular importance to food allergy, polyphenols bind irreversibly to peanut allergens and reduce the allergenicity of peanut extracts [61]. Zuercher et al. [62] in an in vivo food allergy murine model showed that consumption of polyphenol enriched apple extract by OVA-sensitized mice attenuated clinical symptoms upon challenge, accompanied by reduced levels of intestinal mast cell protease, diminished cytokine secretion by lymph node (MLN) cells and reduced intestinal mRNA expression of various T-helper type-2 associated and pro-inflammatory genes. These data are in agreement with a previous study by Akiyama et al. [63], in which feeding of complex apple polyphenols reduced systemic anaphylaxis after allergen challenge in OVA-sensitized mice.

A word of caution to this approach must be mentioned, particularly in relation to allergen detection systems; the high polyphenol content within the food matrix can mask the detectable levels of allergen. Further research is needed in order to validate these findings and to generate hypoallergenic foods, by forming insoluble complexes with allergenic proteins, via polyphenol treatment.

Table 1: Clinical studies on the role of vitamin D during pregnancy in food allergy [28].

| Publication | Study design | Outcome |
|-------------|--------------|---------|
| Mullins et al. (2012) [47] | Neonatal serum 25(OH)D3 levels were compared between children with IgE-mediated peanut allergy and matched population births. | Nonlinear relationship between neonatal 25(OH)D level and childhood peanut allergy: slightly higher levels were associated with lower risk than those in the reference group. |
| Jones et al. (2012) [48] | Prospective birth cohort study. Food intake questionnaire last trimester pregnancy. Cord blood 25 (OH)D3 levels at delivery | No association between vitD status and allergen sensitization or presence of IgE-mediated food allergy. Lower cord blood vitamin D status risk factor for the development of eczema in the 1st y. |
| Weisse et al. (2013) [34] | LINA cohort study Maternal and cord blood 25 (OH)D3 levels during pregnancy & at birth. Total IgE, sIgE for infants and food allergens at birth 1 & 2 years. Atopic outcomes (AD, FA) recorded as parental report of a doctor diagnosis | Higher maternal 25 (OH)D3 levels associated with a higher risk of sensitization to food allergens at 2y. Cord blood 25 (OH)D3 levels were negatively associated with regulatory T cell numbers. |

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Resveratrol, a polyphenolic compound abundant in grapes and red wine, has a wide range of biological and pharmacological activities, including anti-inflammatory, anti-oxidative, and anticarcinogenic effects via multiple molecular mechanisms documented mainly in animal disease models (reviewed in [64]). In a recent study, Okada et al. [65] examined the effects of dietary resveratrol in a mouse model of food allergy induced by oral administration of OVA with the mucosal adjuvant cholera toxin (CT). The study demonstrated that ingestion of resveratrol prevented CT-driven mucosal sensitization to OVA in mice, and decreased OVA plus CT-induced spleenocytes and bone marrow derived dendritic cell costimulatory molecule expression levels by as yet undetermined mechanism.

Soybeans are the most common source of isoflavones in the human diet, and some epidemiologic studies have linked soy intake with beneficial effects in patients with allergic diseases [66]. Masilamani et al. [67], showed that the dietary isoflavones genistatin and daidzein suppressed allergic reactions to peanut in mice and regulated CT-activated human monocyte-derived DCs function in vitro. Recently, they extended this study by determining the effects of isoflavones on murine Th1 immune responses in vitro and in vivo [68], and found that they suppressed the expression of LPS-induced DC maturation markers, B7 costimulatory molecules and MHC molecules and selectively suppressed cytokine secretion (TNFα, IL-10, IL-6, IL-12) from LPS-activated DCs. Taken together, these data demonstrate immunoregulatory properties of isoflavones, which could have implications for future allergy prevention strategies. Since vegetables and fruits are the major sources of flavonoids, although there is no direct evidence that maternal consumption of flavonoids influences offspring food allergy outcomes, studies have shown that maternal consumption of vegetables and fruits are negatively associated with asthma risk in offspring [69]. Research into evaluation of the effect of maternal consumption of flavonoid on food allergy outcomes in offspring should be encouraged.

Possible mechanisms of dietary modification on offspring allergy outcomes

Although changes in dietary components during the last decades may have played a role in the increasing incidence of food allergy [1], they cannot explain the allergy epidemic all over the world. On the other hand, the rapid increase of allergic diseases in a short period of time makes it unlikely to be the result of genetic changes alone. It seems more likely that exposure to a combination of environmental factors may be producing, through epigenetic modifications, heritable change in gene expression that increase the risk of allergic disease.

DNA methylation is probably the best characterized inheritable epigenetic modification influenced by environmental factors [70]. DNA methylation status is heritable, but it is also plastic, thereby providing a potential opportunity to convert a Th2 predisposition to a tolerogenic Tregs status by manipulation of the maternal environment. A maternal gestational diet high in folic acid, a methyl donor in methylation reactions, has been shown to enhance the severity of offspring allergic airway disease [71] in mice. Exposing mothers to a farm environment and raw farm milk during pregnancy increased numbers of CD4+CD25+ T cells in cord blood, which was associated with significant DNA demethylation within the foxp3 locus [72]. However, this has not yet been shown to have an effect on their offspring.

Our group recently found that maternal consumption of low doses of peanut plus the adjuvant cholera toxin subunit B in mice reduced peanut allergy risk in offspring that was accompanied by a significant reduction in DNA methylation at the foxp3 promoter CpG site and increased IL-4, IL-5, and IL-13 levels found that oral administration of a mixture of probiotics significantly reduced generation of proinflammatory cytokines characteristic of increased intestinal permeability and unbalanced gut microbiota, the effects of probiotics have been attributed to restoration to normal microflora through probiotic supplements during pregnancy and/or infancy [73]. The Food and Agricultural Organization of the United Nations and the World Health Organization [74], defines probiotics as ‘living microorganisms, which when administered in adequate amounts confer health benefits on the host. The major sources of probiotics are dairy products that contain Lactobacillus and Bifidobacterium species. The effects of probiotics have been attributed to restoration to normal of increased intestinal permeability and unbalanced gut microbiota, improvement of the intestine’s immunologic barrier functions, and reduced generation of proinflammatory cytokines characteristic of local and systemic allergic inflammation [75].

Animal models

Schiavi et al. [76], in a murine model of shrimp-induced anaphylaxis, found that oral administration of a mixture of probiotics significantly reduced symptom scores and fecal histamine levels after challenge as well as serum shrimp-specific IgE levels. IL-4, IL-5, and IL-13 levels in the jejunum were significantly reduced, whereas FOXP3 and IL27 mRNA expression and IL-10, TGF-β, and IFN-β tissue content were increased. However, animal studies on the effect of maternal exposure to probiotics in the offspring are lacking, so further investigation is needed in this field.
Clinical studies

A recent meta-analysis on the impact of probiotics intake during pregnancy on development of eczema in children [77] concluded that administration of lactobacilli, but not a mixture of various bacterial strains, during pregnancy prevents atopic eczema in children aged 2 to 7 years. So far, studies on the preventive effect of probiotic intake during pregnancy/lactation on allergic diseases have not been designed to specifically assess their effect on FA. However, some of them have looked at surrogate markers of FA as secondary outcomes, and their results are summarized in table 3.

In 2009 Niers et al. [78], conducted a double-blind, randomized, placebo-controlled (RDBPC) trial aimed to study the primary prevention of allergic disease in high-risk children by pre- and postnatal supplementation with probiotics. A mixture of three probiotic bacteria (Bifidobacterium bifidum, B. lactis, and Lactococcus lactis) was administered to pregnant mothers during the last 6 weeks of pregnancy and postnatally for 12 months to their offspring. No difference in food allergen sensitization (measured by serum specific IgE (sIgE)) was observed between active and placebo group at 1 and 2 years of age. This lack of effect on FA prevention was also observed by Kim et al. [79] in a RDBPC trial using a combination of three probiotics (Bifidobacterium bifidum, B. lactis and Lactobacillus acidophilus) starting at 4–8 weeks before delivery and continuing for 6 months. The same results were also reported with a probiotic mixture of three strains (Lactobacillus rhamnosus GG, L. acidophilus and Bifidobacterium animalis) given to a nonselected maternal population [80].

When administering only one strain of Lactobacillus (Lactobacillus GG) to pregnant women carrying infants at high risk of atopy, from 36 weeks of gestation until delivery, Boyle et al. [81] found no difference in sensitization to egg or peanut (assessed by positive SPT) in children at 1 year between active and placebo groups. Consistently, a recent RDBPC trial using the same Lactobacillus GG single strain starting at the second trimester of pregnancy did not find differences in the incidence of sensitization to food allergens (sIgE) in the offspring of actively treated mothers compared to the placebo group [82].

In a randomized trial of 1223 high-risk families, pregnant mothers ingested a probiotic mixture of 4 strains (LGG, L. rhamnosus, Bifidobacterium breve and Propionibacterium freudenreichii) from 36 weeks of gestation and their infants received the same probiotics for 6 months [83]. The children were followed until age 5 years and no difference in the cumulative incidence of food allergy sensitization was observed between active and placebo groups. Moreover, there were no differences on serum food-specific IgA, IgG1 or IgG4 concentrations among placebo and active groups at 2 years of age [84,85].

It is important to note that while studies on the potential effect of maternal dietary supplement interventions with either vitamin D or PUFA are mainly observational, the studies on the effect of maternal supplementation with probiotics are randomized controlled trials. Although data point towards a lack of effect of probiotic maternal supplementation on childhood FA, when interpreting these studies, it has to be considered that the microorganisms used, doses, and durations of therapy are different. A recent study also showed that time of probiotic exposure is critical to reducing eczema, and that although eczema incidence was decreased sensitization to food allergens was not [86]. This finding appeared to be contradictory to Lack et al. [5], indicating that eczema in children is highly associated with food allergy. The discrepancy might be due to the current study did not evaluate the food induced clinical reactions by double blind placebo controlled challenges, since sensitization to food allergens as determined by skin testing or IgE is not necessarily diagnostic for true food allergy. More studies specifically aimed at determining a potential preventive role of probiotics on FA sensitization as well as clinical reactions are needed.

Chinese Herbs

Food allergy herbal formula-2

The Chinese herbal medicine FAHF-2 has attracted attention as an allergen non-specific therapy for food allergy [87]. FAHF-2, a tablet form of a 9-herb extract (Prunus mume, Zanthoxylum schinifolium, Angelica sinensis, Zingiber officinalis, Cinnamomum cassiae, Phellodendron chinense, Coptis chinensis, Panax ginseng and Ganoderma Lucidum) has been shown to completely eliminate PN-induced anaphylaxis in murine food allergy models and has an excellent safety profile in humans [88,89]. Protection persists for up to 6 months following therapy in mice (half of the murine life span) and is associated with sustained reduction of serum PN-IgE levels. It also reduces the numbers of peripheral blood basophils and peritoneal mast cells and FceRI, FceRI γ mRna subunit expression by mast cells and basophils, and T-cell proliferation as well as histamine release following food allergy challenge in a murine model of food allergies [90]. FAHF-2 treatment protection is also associated with immunomodulatory effect on T and B cells [91]. To increase the potency and ease of clinical use, (assessed by either a positive SPT or serum sIgE) could be found between active and placebo groups. Moreover, there were no differences on serum food-specific IgA, IgG1 or IgG4 concentrations among placebo and active groups at 2 years of age [84,85].

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| Publication | Target | Probiotic Intake (from/until) | Study | Findings and Summary |
|-------------|--------|-----------------------------|-------|----------------------|
| Kim et al. [79] | pregnant women with family history of allergic disease | Mixture of 2 strains 32 w.gestation/3m postnatally | RDBPC | No difference in food sensitization or probable food allergy in treatment versus placebo groups after 1 year |
| Niers et al. [78] | pregnant women with family history of allergic disease | Mixture of 3 strains 34 w.gestation/12m postnatally | RDBPC | No difference in food sensitization in treatment versus placebo after 1 & 2y. |
| Boyle et al. [81] | pregnant women with family history of allergic disease | Lactobacillus GG 36 w.gestation/until delivery | RDBPC | No difference in food sensitization in treatment versus placebo after 1 year |
| Dotterud et al. [80] | Nonselected maternal population | Mixture of 3 strains 36th w.gestation/3m postnatally | RDPCC | Reduced cumulative incidence of atopic dermatitis, but no effect on atopic sensitization |
| Kultunen et al. (2009) [83] | pregnant women with family history of allergic disease | Mixture of 4 strains 36 w.gestation/6m postnatally | RDPCC | No difference in cumulative incidence of allergic diseases and IgE sensitization versus placebo at 5 y. |
| Kukkonen et al. (2011) [84] | pregnant women with family history of allergic disease | Increased IL-10 and decreased casein IgA Abs in breast milk from mothers treated with probiotic vs placebo. |
| Kultunen et al. (2012) [85] | pregnant women with personal history of allergic disease | Lactobacillus GG 24 w.gestation/until delivery | RDPCC | Reduced severity of maternal allergic disease but not the incidence of childhood allergic disease. |

Table 3: Clinical studies assessing the preventive effect of probiotic intake during pregnancy/lactation in children’s food allergy [95].
we recently developed a more concentrated version of FAHF-2 by butanol purification, named B-FAHF-2, which reduced daily doses by 80% [92]. Given that concomitant egg and peanut sensitization is high (>70%) in infants [16] and we previously found in murine model that maternal peanut allergy significantly increased offspring susceptibility to PN sensitization [23], we asked whether maternal peanut allergy also increased susceptibility to egg sensitization and whether B-FAHF-2 can reduce this risk. To this end, female C3H/HeJ mice were sensitized with peanut and then treated with FAHF-2 or PBS (Sham). They were then mated with naive male mice. 5-week-old offspring were sensitized with egg white plus CT epicutaneously 3 times at weekly intervals. It was shown that offspring of PN allergic mothers receiving preconception sham treatment showed significantly higher egg specific IgE levels than in offspring of naive mothers (p<0.05; Figure 2). Interestingly, offspring of B-FAHF-2 treated mothers showed marked and significant suppression of egg-specific IgE (p<0.05) than offspring of Sham treated mothers, and were essentially the same as in naive offspring (Figure 2). These data suggested that in addition to the potential of B-FAHF-2 as a therapeutic botanical drug, it may also have a potential approach by preconception treatment to prevent maternal allergy mediated food allergy risk in offspring. More research is required to develop maternal preconception biological B-FAHF-2 treatment as safe and effective interventions to prevent offspring food allergy high risk.

That such an approach is worth pursuing is shown by the finding in a murine model of asthma that treatment of asthmatic mothers with ASHMI (Anti-Asthma Herbal Medicine Intervention) prevent early onset of allergic airway inflammation and mucus cell development in offspring [93].

Clinical studies

Our recent phase-1 safety trial in 19 food-allergic subjects (12-45 years old) demonstrated the safety and tolerability of FAHF-2, also showed that FAHF-2 increased IFN-γ and IL-10 and reduces IL-5 and IL-13 production by peripheral blood mononuclear cells from adults and children with food allergy in vitro [91]. In an extended phase 1 study, 6 months of FAHF-2 was safe, well tolerated and associated with a significant reduction in basophil CD63 expression upon ex vivo stimulation and a trend for reduced numbers of basophils.

A multicenter double-blind placebo controlled phase II trial on
safety and efficacy of the treatment with FAHF-2 in patients (age 12-45 y) allergic to peanut, tree nuts, sesame, fish, and/or shellfish, is currently ongoing (clinicaltrials.gov identifier: NCT00602160). As yet no clinical study of FAHF-2 or B-FAHF-2 as preventive approach for high-risk children has been conducted, and such studies should be encouraged given its high safety profile and immunomodulatory effects.

Methodological Limitations

Before concluding, the reader has to bear in mind that the results of the studies reviewed in the present article should be interpreted with caution due to their inherent limitations.

On one hand, animal models results cannot be directly extrapolated to humans but they are important to establish the mechanistic basis of interventions and to generate hypothesis that have to be validated in human clinical studies. On the other hand, designs of clinical studies on pregnant women are constraint by logical ethical limitations. Another major limitation of these studies is the phenotypic description of food allergy, most commonly diagnosed through a surrogate marker (such as skin prick test or serum sIgE) rather than using the gold standard food challenge method. In addition, dietary intake is usually determined by food frequency questionnaires that are subject to recall bias. Other limitations of these studies include selection bias and reverse causality [94]. For this reason, potential strategies to prevent food allergy in infants need to be tested in randomized controlled intervention studies.

Conclusion

The prevalence of food allergy has increased over the past 10-15 years and there is no indication that this trend will decrease. It is important to develop primary preventive approaches for prevention. The suggestion that there is a critical window for early life prevention has raised interest in the potential of dietary interventions for mothers of infants at high risk of atopy as an early food allergy prevention strategy. Several studies have provided evidence supporting early oral exposure as means of preventing development of food allergy, but the data are not consistent. There are limited intervention- based clinical studies of the relationship between maternal diet and offspring food allergy. Continued effort is required to overcome the many methodological challenges of maternal preventive studies and to make safe and effective dietary interventions an early preventive strategy for FA. Epigenetic alterations appear to cause, and may possibly prevent food allergy. Future strategies should focus on the creation of favorable epigenetic modifications in offspring of atopic and non-atopic mothers by dietary modification. Animal models that mimic IgE mediated food allergies are required to establish the mechanistic basis of interventions and to generate hypothesis that have to be validated in human clinical studies.

References

1. Prescott S, Allen KJ (2011) Food allergy: riding the second wave of the allergy epidemic. Pediatr Allergy Immunol 22: 155-160.
2. Kramer MS, Kakuma R (2012) Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev 9: CD001133.
3. Hourihane JO, Kilburn SA, Dean P, Warner JO (1997) Clinical characteristics of peanut allergy. Clin Exp Allergy 27: 634-639.
4. Sicherer SH, Furlong TJ, Muñoz-Furlong A, Burks AW, Sampson HA (2001) A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. J Allergy Clin Immunol 108: 128-132.
5. Lack G, Fox D, Northstone K, Golding J; Avon Longitudinal Study of Parents and Children Study Team (2003) Factors associated with the development of peanut allergy in childhood. N Engl J Med 348: 977-985.
6. Sicherer SH, Leung DY (2008) Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2007. J Allergy Clin Immunol 121: 1351-1358.
7. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology (2008) Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 121: 183-191.
8. Burks AW (2008) Peanut allergy. Lancet 371: 1538-1546.
9. Hourihane JO, Aken R, Briggs R, Gudgeon LA, Grimshaw KE, et al. (2007) The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. J Allergy Clin Immunol 119: 1197-1202.
10. Holloway JA, Warner JO, Vance GH, Diaper ND, Warner JA, et al. (2000) Detection of house-dust-mite allergen in amniotic fluid and umbilical-cord blood. Lancet 356: 1900-1902.
11. Szépfalusi Z, Loibichler C, Piclier J, Reisenenger K, Ebner C, et al. (2000) Direct evidence for transplacental allergen transfer. Pediatr Res 48: 404-407.
12. Szépfalusi Z, Loibichler C, Hanel-Dekan S, Dehlink E, Gerstmayr M, et al. (2006) Most of diaplacentally transferred allergen is retained in the placenta. Clin Exp Allergy 36: 1130-1137.
13. Schmitt DA, Cheng H, Maleki SJ, Burks AW (2004) Competitive inhibition ELISA for quantification of Ara h 1 and Ara h 2, the major allergens of peanuts. J AOAC Int 87: 1492-1497.
14. Du Toit G, Katz Y, Sasiemi P, Mesher D, Maleki SJ, et al. (2008) Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 122: 984-991.
15. Kull I, Bergström A, Lilja G, Pershagen G, Wickman M (2006) Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy 61: 1098-1105.
16. Sicherer SH, Wood RA, Stabilein D, Lindblad R, Burks AW, et al. (2010) Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants. J Allergy Clin Immunol 126: 1191-1197.
17. DesRoches A, Infante-Rivard C, Paradis L, Paradis J, Haddad E (2010) Peanut allergy: is maternal transmission of antigens during pregnancy and breastfeeding a risk factor? J Investig Allergol Clin Immunol 20: 289-294.
18. Palmer DJ, Meltzaffe J, Prescott SL (2012) Preventing disease in the 21st century: the importance of maternal and early infant diet and nutrition. J Allergy Clin Immunol 130: 733-734.
19. Järvinen KM, Fleischer DM (2012) Can we prevent food allergy by manipulating the timing of food exposure? Immunol Allergy Clin North Am 32: 51-65.
20. Lack G (2012) Update on risk factors for food allergy. J Allergy Clin Immunol 129: 1187-1197.
21. Mekkild I, Groeng EC, Leikvold RB, Granum B, Lavik M (2002) Maternal allergen immunization during pregnancy in a mouse model reduces adult allergy-related antibody responses in the offspring. Clin Exp Allergy 32: 1370-1376.
22. Ellertsen UK, Nyaagaard UC, Mekkild I, Lavik M (2010) Maternal allergen immunisation to prevent sensitisation in offspring: Th2-polarising adjuvants are more efficient than a Th1-polarising adjuvant in mice. BMC Immunol 11: 8.
23. López-Expósito I, Song Y, Järvinen KM, Srivastava K, Li XM (2009) Maternal peanut exposure during pregnancy and lactation reduces peanut allergy risk in offspring. J Allergy Clin Immunol 124: 1039-1046.
24. López-Expósito I, Järvinen KM, Castillo A, Seppe AO, Song Y, et al. (2011) Maternal peanut consumption provides protection in offspring against peanut sensitization that is further enhanced when co-administered with bacterial mucosal adjuvant. Food Res Int 44: 1649-1656.
25. Hansen JS, Nyaagaard UC, Lyle R, Lovik M (2012) Early life interventions to prevent allergy in the offspring: the role of maternal immunization and postnatal mucosal allergy exposure. Int Arch Allergy Immunol 158: 261-275.
26. Yamamoto T, Tsubota Y, Kodama T, Kageyama-Yahara N, Kadowaki M (2012) Oral tolerance induced by transfer of food antigens via breast milk of allergic
mothers prevents offspring from developing allergic symptoms in a mouse food allergy model. Clin Dev Immunol 2012: 72:1085.

27. Mosconi E, Rekima A, Seitz-Polaki B, Kanda A, Fleury S, et al. (2010) Breast milk immune complexes are potent inducers of oral tolerance in neonates and prevent asthma development. Mucoosal Immunol 3: 461-474.

28. Reinholz M, Ruzicka T, Schaubter J (2012) Vitamin D and its role in allergic disease. Clin Exp Allergy 42: 817-826.

29. Jones AP, Tulic MK, Rueter K, Prescott SL (2012) Vitamin D and allergic disease: sunlight at the end of the tunnel? Nutrients 4: 13-28.

30. Chi A, Wildfire J, Mccoughlin R, Wood RA, Bloomberg GR, et al. (2011) Umbilical cord plasma 25-hydroxyvitamin D concentration and immune function at birth: the Urban Environment and Childhood Asthma study. Clin Exp Allergy 41: 542-550.

31. Rochat MK, Ege MJ, Plabsl D, Steine J, Bitter S, et al. (2010) Maternal vitamin D intake during pregnancy increases gene expression of IL3 and ILT4 in cord blood. Clin Exp Allergy 40: 786-794.

32. Wist M (2009) Introduction of oral vitamin D supplementation and the rise of the allergy pandemic. Allergy Clin Immunol 5: 8.

33. Milner JD, Stein DM, McCarter R, Moon RY (2004) Early infant multivitamin supplementation is associated with increased risk for food allergy and asthma. Pediatrics 114: 27-32.

34. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, et al. (2013) Maternal and newborn vitamin D status and its impact on food allergy development in the German LINa cohort study. Allergy 68: 220-228.

35. Hollams EM, Hart PH, Holt BJ, Serralha M, Parsons F, et al. (2011) Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. Eur Respir J 38: 1320-1327.

36. Peroni DG, Piacentini GL, Cametti E, Cinelliato I, Boner AL (2011) Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. Br J Dermatol 164: 1078-1082.

37. Mullins RJ, Camargo CA (2012) Latitude, sunlight, vitamin D, and childhood food allergy/anaphylaxis. Curr Allergy Asthma Rep 12: 64-71.

38. Nwaru BI, Ahonen S, Kaila M, Erikkola M, Haapala AM, et al. (2010) Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. Pediatr Allergy Immunol 21: 29-37.

39. Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, et al. (2011) Vitamin D status: United States, 2001-2006. NCHS Data Brief 1-8.

40. Merewood A, Mehta SD, Grossman X, Chen TC, Mathieu JS, et al. (2010) Widespread vitamin D deficiency in urban Massachusetts newborns and their mothers. Pediatrics 125: 640-647.

41. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, et al. (2010) Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 376: 180-188.

42. Liu X, Wang G, Hong X, Wang D, Tsai HJ, et al. (2011) Gene-vitamin D interactions on food sensitization: a prospective birth cohort study. Allergy 66: 1442-1448.

43. Vimalasearan KS, Cavadino A, Hyppönen E (2012) Evidence for a genetic interaction in allergy-related responsiveness to vitamin D deficiency. Allergy 67: 1033-1040.

44. Vassallo MF, Banerji A, Rudders SA, Clark S, Mullins RJ, et al. (2010) Season of birth and food allergy in children. Ann Allergy Asthma Immunol 104: 307-313.

45. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, et al. (2011) Season of birth and childhood food allergy in Australia. Pediatr Allergy Immunol 22: 583-589.

46. Keet CA, Matsui EC, Savage JH, Neuman-Sunshine DL, Skripak J, et al. (2012) Potential mechanisms for the association between fall birth and food allergy. Allergy 67: 775-782.

47. Mullins RJ, Clark S, Wiley V, Eyles D, Camargo CA Jr (2012) Neonatal vitamin D status and childhood peanut allergy: a pilot study. Ann Allergy Asthma Immunol 109: 324-328.

48. Jones AP, Palmer D, Zhang G, Prescott SL (2012) Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. Pediatrics 130: e1128-1135.

49. Korotkova M, Telenko E, Yamashiro Y, Hanson LA, Strandvik B (2004) The ratio of n-6 to n-3 fatty acids in maternal diet influences the induction of neonatal immunological tolerance to ovalbumin. Clin Exp Immunol 137: 237-244.

50. de Matos GO, Amaral SS, Pereira da Silva PE, Perez DA, Alvarezena DM, et al. (2012) Dietary supplementation with omega-3-PUFA-rich fish oil reduces signs of food allergy in ovalbumin-sensitized mice. Clin Dev Immunol 2012: 236564.

51. Watanabe S, Sakai N, Yasui Y, Kimura Y, Kobayashi T, et al. (1994) A high alpha-linoleinate diet suppresses antigen-induced immunoglobulin E response and anaphylactic shock in mice. J Nutr 124: 1566-1573.

52. Johansson S, Lonnqvist A, Ostman S, Sandberg AS, Wold AE (2010) Long-chain polyunsaturated fatty acids are consumed during allergic inflammation and affect T helper type 1 (Th1) and Th2-mediated hypersensitivity differently. Clin Exp Immunol 160: 411-419.

53. Anandan C, Nurmatov U, Sheikh A (2009) Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. Allergy 64: 840-848.

54. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, et al. (2003) 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 112: 1176-1184.

55. Lauritzen L, Kjær TM, Fruekilde MB, Michaelensen KB, Fratklaer H (2005) Fish oil supplementation of lactating mothers affects cytokine production in 2 1/2-year-old children. Lipids 40: 669-676.

56. Furuhjelm C, Warstedt K, Larsson J. Fredriksson M, Böttcher MF, et al. (2009) Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. Acta Paediatr 98: 1461-1467.

57. Furuhjelm C, Warstedt K, Fagerás M, Fälth-Magnusson K, Larsson J, et al. (2011) Allergic disease in infants up to 2 years of age in relation to plasma omega-3 fatty acids and maternal fish oil supplementation in pregnancy and lactation. Pediatr Allergy Immunol 22: 505-514.

58. Palmer DJ, Sullivan T, Gold MS, Prescott SL, Heddie R, et al. (2012) Effect of n-3 long chain polyunsaturated fatty acid supplementation in pregnancy on infants’ allergies in first year of life: randomised controlled trial. BMJ 344: e184.

59. Allan K, Kelly FJ, Devereux G (2010) Antioxidants and allergic disease: a case of too little or too much? Clin Exp Allergy 40: 370-380.

60. Singh A, Holvoet S, Mercenier A (2011) Dietary polyphenols in the prevention and treatment of allergic diseases. Clin Exp Allergy 41: 1346-1359.

61. Chung SY, Elaine T (2009) Reducing the allergenic capacity of peanut extracts and liquid peanut butter by phenolic compounds. Food Chem 115: 1345-1349.

62. Zuercher AW, Holvoet S, Weiss M, Mercenier A (2010) Polyphenol-enriched apple extract attenuates food allergy in mice. Clin Exp Allergy 40: 942-950.

63. Akiyama H, Sato Y, Watanabe T, Nagaoa MK, Yoshioka Y, et al. (2005) Dietary genistein and daidzein, regulate mucosal immune response by suppressing allergic inflammation in ovalbumin-sensitized mice. Clin Dev Immunol 2012: 236564.

64. Chung SY, Elaine T (2009) Reducing the allergenic capacity of peanut extracts and liquid peanut butter by phenolic compounds. Food Chem 115: 1345-1349.

65. Miyake Y, Sasaki S, Ohya Y, Miyamoto S, Matsunaga I, et al. (2005) Soy, isoflavones, and prevalence of allergic rhinitis in Japanese women: the Osaka Maternal and Child Health Study. J Allergy Clin Immunol 115: 1176-1183.

66. Masilamani M, Wei J, Bhatt S, Paul M, Yakir S, et al. (2011) Soybean isoflavones regulate dendritic cell function and suppress allergic sensitization to peanut. J Allergy Clin Immunol 128: 1242-1250.

67. Wei J, Bhatt S, Chang LM, Sampson HA, Masilamani M (2012) Isoflavones, genistein and daidzein, regulate mucosal immune response by suppressing dendritic cell function. PLoS One 7: e44338.

68. Fitzsimon N, Fallon U, O’Mahony D, Loftus BG, Bury G, et al. (2007) Mothers’ dietary patterns during pregnancy and risk of asthma symptoms in children at 3 years. Ir Med J 100: suppl 27-32.

69. Goldberg AD, Allis CD, Bernstein E (2007) Epigenetics: a landscape takes shape. Cell 128: 635-638.
71. Hollingsworth JW, Maruoka S, Boon K, Garantziotis S, Li Z, et al. (2008) In utero supplementation with methyl donors enhances allergic airway disease in mice. J Clin Invest 118: 3462-3469.

72. Schaub B, Liu J, Höppler S, Schleich I, Huen J, et al. (2009) Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol 123: 774-782.

73. Prescott S, Nowak-Wegrzyn A (2011) Strategies to prevent or reduce allergic disease. Ann Nutr Metab 59: 28-42.

74. Report of a Joint FAO/WHO Working Group (2002) Guidelines for the Evaluation of Probiotics in Food.

75. Isolauri E, Rautava S, Salminen S (2012) Probiotics in the development and treatment of allergic disease. Gastroenterol Clin North Am 41: 747-762.

76. Schiavi E, Barletta B, Buttneri C, Corini H, Boirivant M, et al. (2011) Oral therapeutic administration of a probiotic mixture suppresses established Th2 responses and systemic anaphylaxis in a murine model of food allergy. Allergy 66: 499-508.

77. Doerge K, Grajecki D, Zyliax BC, Detinkina E, Zü Eulenburg C, et al. (2012) Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood—a meta-analysis. Br J Nutr 107: 1-6.

78. Niers L, Martin R, Rijkers G, Sengers F, Timmerman H, et al. (2009) The effects of selected probiotic strains on the development of eczema (the PandA study). Allergy 64: 1349-1358.

79. Kim JY, Kwon JH, Ahn SH, Lee SI, Han YS, et al. (2010) Effect of probiotic mix (Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus) in the primary prevention of eczema: a double-blind, randomized, placebo-controlled trial. Pediatr Allergy Immunol 21: e386-393.

80. Dotterud CK, Større O, Johnsen R, Oien T (2010) Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. Br J Dermatol 163: 616-623.

81. Boyce RJ, Ismail IH, Kivivuori S, Licciardi PV, Robins-Browne RM, et al. (2011) Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. Allergy 66: 509-516.

82. Ou CY, Kuo HC, Wang L, Hsu TY, Chuang H, et al. (2012) Prenatal and postnatal probiotics reduces maternal but not childhood allergic diseases: a randomized, double-blind, placebo-controlled trial. Clin Exp Allergy 42: 1386-1396.

83. Kuitunen M, Kukkonen K, Juntunen-Backman K, Korpeila R, Poussa T, et al. (2009) Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. J Allergy Clin Immunol 123: 335-341.

84. Kukkonen AK, Savilahti EM, Haahtela T, Savilahti E, Kuitunen M (2011) Ovalbumin-specific immunoglobulins A and G levels at age 2 years are associated with the occurrence of atopic disorders. Clin Exp Allergy 41: 1414-1421.

85. Kuitunen M, Kukkonen AK, Savilahti E (2012) Impact of maternal allergy and use of probiotics during pregnancy on breast milk cytokines and food antibodies and development of allergy in children until 5 years. Int Arch Allergy Immunol 159: 162-170.

86. Rautava S, Kainonen E, Salminen S, Isolauri E (2012) Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. J Allergy Clin Immunol 130: 1355-1360.

87. Land MH, Burks AW (2012) Future of immunotherapy for food allergy. Immunotherapy 4: 13-15.

88. Ou C, Srivastava K, Ko J, Zhang TF, Sampson HA, et al. (2007) Induction of tolerance after establishment of peanut allergy by the food allergy herbal formula-2 is associated with up-regulation of interferon-gamma. Clin Exp Allergy 37: 846-855.

89. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, et al. (2005) The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. J Allergy Clin Immunol 115: 171-178.

90. Song Y, Ou C, Srivastava K, Yang N, Busse P, et al. (2010) Food allergy herbal formula 2 protection against peanut anaphylactic reaction is via inhibition of mast cells and basophils. J Allergy Clin Immunol 126: 1208-1217.

91. Wang J, Patil SP, Yang N, Ko J, Lee J, et al. (2010) Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study. Ann Allergy Asthma Immunol 105: 75-84.

92. Srivastava K, Yang N, Chen Y, Lopez-Exposito I, Song Y, et al. (2011) Efficacy, safety and immunological actions of butanol-extracted Food Allergy Herbal Formula-2 on peanut anaphylaxis. Clin Exp Allergy 41: 582-591.

93. Lopez-Exposito I, Birmingham N, Castillo A, Li X-M (2010) ASHMI (Anti-Asthma Herbal Medicine Intervention) Prevents Maternal Transmission of Early Onset of Allergic Airway Inflammation and Mucus Cell Development in Offspring. J Allergy Clin Immunol 126: 667-675.

94. Du Toit G, Lack G (2011) Can food allergy be prevented? The current evidence. Pediatr Clin North Am 58: 481-509, xii.

95. Lieberman JA, Wang J (2012) Nonallergen-specific treatments for food allergy. Curr Opin Allergy Clin Immunol 12: 293-301.

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