

The impact of maternal diets during breastfeeding on the prevention of food allergy

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Abbreviations

RAST radioallergosorbent test
SPT skin-prick test

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Introduction

The focus of the articles in this section of *Current Opinion in Allergy and Clinical Immunology* attest to the fact that the expanding spectrum, remarkable severity, and increasing prevalence of food allergy have triggered a race to develop better diagnostic and treatment modalities. A topic that has similarly attracted attention is the prevention of food allergy [1]. Breastfeeding the atopy-prone infant is one key intervention suggested to reduce the risk of food allergy and atopic disease. Two recent meta-analyses [2,3] have indicated a protective effect of breastfeeding on atopic dermatitis [odds ratio (OR) 0.68] and asthma (OR 0.7), with increased protection for those at high familial atopic risk compared with those in the general population. Factors previously shown to be atopy-protective include the delayed introduction of solid foods during infancy, supplementation with hypoallergenic formulas, if needed, and the avoidance of environmental tobacco smoke.

On the basis of the available literature concerning allergy prevention, the Committee on Nutrition of the American Academy of Pediatrics [4] recently published suggestions aimed at 'high-risk' newborns defined by 'a strong (biparental; parent and sibling) family history of allergy'. The risk of atopic disease associated with this general description is 40–60% [5]. The recommendations for prevention are shown in Table 1. I would like to focus on the recommendations for the maternal restriction of peanuts during pregnancy, the maternal restriction of other allergenic foods during breastfeeding, and of the delay in introducing specific foods to the young child, as they pertain to the prevention of atopy and food allergy, in particular.

Maternal dietary restriction during pregnancy

Few studies have evaluated dietary restriction instituted solely during pregnancy. Expectant mothers with at least one atopic family member were enrolled in a randomized, prospective, controlled study, with the diet group instructed to eliminate cows' milk and egg from gestational week 28 to delivery [6]. Patients were followed to the age of 5 years, and eczema, allergic rhinitis, and asthma were equally common in all groups. Interestingly, food intolerance to egg was significantly more common in children of the mothers receiving the exclusion diet: six out of 84 in the dietary exclusion group and none of the 114 controls were affected ($P < 0.05$). However, there was no overall long-term difference in food intolerance. Lilja and colleagues [7] studied 162 women with respiratory allergy, randomly selected to receive a diet of either a very low amount of egg and cows' milk or a daily ingestion of one egg and approximately 1 l of cows' milk during the last 3 months of pregnancy. A total of 163 infants were followed prospectively up to 18 months of age. No significant differences in the distribution of atopic disease were found. The numbers of skin-prick tests (SPTs) positive for ovalbumin, ovomucoid, beta-lactoglobulin and cows' milk were likewise not influenced.

Although the studies did not show a protective effect of maternal dietary avoidance during pregnancy, the severity and longevity of peanut allergy, its apparently increasing prevalence and the ubiquity of peanut consumption has led to a reconsideration of the role of

Table 1. Statement concerning recommendations for allergy prevention

Conclusive studies are not yet available to permit definitive recommendations. However, the following recommendations seem reasonable at this time:

- (1) Breastfeeding mothers should continue breastfeeding for the first year of life or longer. During this time, for infants at risk, hypoallergenic formulas can be used to supplement breastfeeding. Mothers should eliminate peanuts and tree nuts (e.g. almonds, walnuts, etc.) and consider eliminating eggs, cows' milk, fish, and perhaps other foods from their diets while nursing. Solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.
- (2) No maternal dietary restrictions during pregnancy are necessary with the possible exception of excluding peanuts.
- (3) Breastfeeding mothers on a restricted diet should consider the use of supplemental minerals (calcium) and vitamins.

in-utero sensitization to this food in particular. In a study by Frank and colleagues [8], 43 children up to the age of 3 years referred for an evaluation of food allergy were selected for participation on the basis of a positive radioallergosorbent test (RAST) to food. A total of 25 peanut-sensitized subjects and 18 control subjects (children sensitized to milk or egg, but not to peanuts) were found, and further feeding information was obtained by questionnaire. Mothers who reported the consumption of peanuts more than once a week during pregnancy were more likely to have a peanut-sensitized child than mothers who consumed peanuts less commonly [$P=0.063$; OR 3.97, 98% confidence interval (CI) 0.73–24]. Interestingly, there was no significant relationship between peanut consumption during lactation and peanut sensitization ($P=0.47$, OR 2.09, 95% CI 0.39–13.47). Peanuts or peanut butter were introduced into the child's diet from a significantly younger age in the peanut-sensitized subjects ($P<0.03$). Data were not provided to assess confounding variables (for example, earlier feeding of peanuts to children of mothers who consumed them more frequently during pregnancy). The study was based on recall and not evaluated in a blinded fashion. Although suggestive, a prospective study is needed.

Maternal dietary restrictions while breastfeeding and infant/child dietary restriction

The fact that food proteins can pass in an immunologically intact form through breastmilk [9], and can elicit reactions in sensitized infants [10], is impetus to study the programs of maternal dietary restriction during breastfeeding. As mentioned previously, breastfeeding has an apparent protective effect against atopic diseases, and studies by Chandra and colleagues [11,12] extended this observation to indicate that maternal avoidance of highly allergenic foods was also protective over breastfeeding without dietary restriction for atopic dermatitis, but the influence on food allergy was not reported.

Maternal dietary avoidance during breastfeeding was studied over a long follow-up period in a group of children in Sweden and included an analysis of food allergy [13–15]. Matched groups of infants with a family history of atopy were treated differently in two locations in Sweden. In the intervention group ($n=65$), the mothers eliminated egg, milk and fish for the first 3 months, whereas the non-intervention group ($n=50$) had no restrictions. The remainder of the diet was equivalent, in that breastfeeding was encouraged for the first 6 months, and extensively hydrolysed casein formula was used for supplementation. Cows' milk products were allowed at 6 months, egg and fish after 9 months. In the first 6 months, there was a significantly lower cumulative incidence of atopic dermatitis in the intervention group,

10.8% versus 28% in controls ($P=0.033$), but the effect waned thereafter. At the age when foods were allowed back into the diet, there was no difference in adverse food reactions between the groups, and equivalent numbers were sensitized to cows' milk and egg [13]. By the age of 4 years, clinical egg allergy was reported in five of the children in the intervention group, but only in one of the group without intervention – the difference was not statistically significant. By 10 years [15] there were no longer significant differences in any atopic disease. Sensitization rates to the foods originally eliminated in terms of the percentage of subjects with positive tests were not significantly different, although the total number of positive tests were higher in the non-intervention group (three times greater). Of seven foods evaluated by prick test and RAST, only two showed a difference in sensitization (positive RAST defined as over 0.35 kU/l and SPT as ≥ 3 mm). Peanut sensitization was greater by SPT but not RAST in the controls, and soy was greater in the controls by RAST but not SPT. An equivalent number of subjects in each group had experienced food-allergic reactions.

The previous studies did not intervene in the aspects of infant feeding apart from infant formula versus breastmilk. A prospective, randomized controlled study of an allergy prevention program, including restrictions on infant solid foods, was conducted with families from the Isle of Wight, UK [16,17]. A cohort of 136 mothers whose infants were at high risk of atopy (two first-degree relatives of the infant with atopy or one relative and a cord blood IgE >0.5 kU/l) were randomly assigned into two groups. Infants in the prophylactic group were fed a soy protein hydrolysate or were breastfed by their mothers excluding milk, egg, fish, and nuts. The infants' diet excluded milk, egg, wheat, soy, orange, fish and nuts. These foods were gradually introduced after 9 months of age. Dustmite control measures were also instituted. At 12 months, 11% of controls and 3% under prophylaxis were determined to have food intolerance; four controls and two prophylaxis subjects had positive SPTs to food. By the age of 4 years, 16 subjects left the study, leaving 58 in the prophylactic group and 62 controls. The infant feeding practices (e.g. length of breastfeeding) were similar in the two groups. The control group showed more definite allergy (OR 5.6, CI 1.8–17.9, $P<0.005$), eczema (OR 3.4, CI 1.2–10.1, $P<0.05$) and positive allergen SPTs (OR 3.7, CI 1.3–10.0, $P<0.02$) at 4 years than the prophylactic group. Asthma was reduced, but the reduction was not statistically significant. Food intolerance was reported in 5% of the intervention group and in 11% of controls ($P=NS$); there were more positive food SPTs (milk, egg, wheat, fish) in the controls (total eight) compared with the intervention group (three, $P=NS$). The relative impact of environmental or dietary intervention could

not be determined. Overall, the influence of maternal and infant diets on food allergy was modest in this small group.

Zeiger and colleagues [18–20] also studied a comprehensive dietary intervention program, but without environmental allergen intervention, in a randomized, prospective study of 288 subjects with follow-up until the age of 7 years. Families were included in the study if at least one parent had an atopic disease and evidence of specific IgE antibody. For the prophylactic group ($n=103$), the avoidance of milk, eggs, peanuts, concentrated soy foods, and reduced servings of wheat was begun in the third trimester of pregnancy and followed through lactation, while extensively hydrolysed casein formula was used for supplementation. In addition, solids were introduced after 6 months in a specific order but cows' milk, wheat and soy were delayed until 12 months, eggs until 24 months and peanuts and fish to 36 months. The control group ($n=185$) was encouraged to breastfeed and allowed to introduce solids at 4 months, egg yolk at 6 months, egg white and whole cows' milk at 12 months. The cumulative prevalence of atopy was lower at 12 months in the prophylactic-treated (16.2%) compared with the control (27.1%) group ($P=0.039$), resulting from reduced atopic dermatitis, urticaria or gastrointestinal disease by 12 months (5.1 versus 16.4%; $P=0.007$), and any positive food SPT by 24 months (16.5 versus 29.4%; $P=0.019$), caused primarily by fewer positive milk SPTs (1 versus 12.4%; $P=0.001$). There was no significant difference in the number with positive SPTs to peanuts (five in the treatment versus seven in the control group). The prevalence of allergic rhinitis, asthma, and inhalant SPTs was unaffected. By 2 years of age, the period prevalence was not significantly different for any atopic disorder. Serum IgE levels in the prophylactic-treated group were marginally lower only at 4 months. By 7 years, there were no differences between the groups in period prevalence for food allergy or food sensitization or any other parameters (only one subject remained milk-sensitized). Overall, the study showed that maternal dietary interventions can reduce atopic disease, but do not have a significant long-term impact.

The elimination of peanuts during breastfeeding for the prevention of peanut allergy is of particular interest and was partly evaluated in several of the studies reviewed above, with disparate results in terms of sensitization. Hourihane and colleagues [21] evaluated a number of parameters among families of 622 individuals with peanut allergy. Peanut allergy was reported by 0.1% (3/2409) of grandparents, 0.6% (7/1213) of aunts and uncles, 1.6% (19/1218) of parents, and 6.9% (42/610) of siblings, thus reflecting an increase over generations and a hereditary component. All forms of atopy were

significantly more common in successive generations. Although the study did not control for recall bias, mothers of younger probands (5 years old) were significantly more likely than mothers of older probands ($P<0.005$) to have eaten peanuts regularly when pregnant or breastfeeding. An additional observation was that the age of onset correlated inversely with the year of birth ($r=-0.6$, $P<0.001$). Putting these latter two observations together may imply that the increasing ingestion of peanuts by pregnant/breastfeeding mothers and earlier ingestion by children is partly responsible for the apparently increased prevalence of the allergy, but the impact of the confounding variables (increased general atopic disease through the generations) is not known.

Our group, in collaboration with the Food Allergy and Anaphylaxis Network, reviewed the data in the US Peanut and Tree Nut Allergy Registry, a voluntary registry of 5149 individuals with peanut or tree nut allergy [22]. The registry was established through the use of a structured questionnaire distributed to all members of the Food Allergy and Anaphylaxis Network and to patients by allergists. Briefly, peanut allergy was reported in 94% of infants whose mothers specifically recalled eating peanuts during lactation, in 88% who specifically avoided it, and in 90% who were not breastfed. The modest differences were statistically significant ($P<0.05$) for the first group compared with the latter two. The study is limited in several ways, including that it is not population-based, is potentially recall-biased, and did not control for the age of introduction of foods (it is likely that those avoiding the food during lactation would also delay/avoid introducing the solid form). Overall, the effect of avoidance during breastfeeding appeared to be modest. Additional prospective, randomized studies are warranted.

The immunomodulatory components of breastmilk (cytokines, fatty acids, immunoglobulin, leukocytes, etc.) may vary, and can influence the outcome of food allergy in breastfed infants. Wright and colleagues [23] showed that among 664 children classified as never breast-fed, breast-fed less than 4 months, or breast-fed 4 months or longer, in whom maternal and child IgE were determined, the effect of breastfeeding depended upon maternal IgE. Among children whose mothers were in the two lower tertiles of IgE, breastfeeding was associated with lower total serum IgE at the age of 6 years (24.2 versus 44.3 IU/ml for never breastfed children; $P<0.02$). In contrast, for children whose mothers were in the highest tertile of IgE, breastfeeding for 4 months or longer was associated with higher IgE levels in the child compared with those never breastfed or breastfed less than 4 months (97.0 versus 38.9 IU/ml;

$P < 0.005$). These results reflect potential confounding variables not considered in the aforementioned dietary intervention studies.

Conclusion

A number of recommendations have been proposed regarding allergy prevention through infant dietary manipulation, with the best evidence being for a general recommendation to breastfeed and delay the introduction of solid foods. So far, it does not appear that maternal dietary exclusion diets have a convincing long-term impact on atopic disease, including food allergy, but may influence disease over the short term. This observation begs the question: is it better to advise dietary interventions before the onset of disease in high-risk patients or to wait and address disease with dietary treatment? Certainly, the availability of more exact methods to predict atopic disease would influence the decision. Clinically, the practitioner and family may elect to follow the less studied, less proved dietary manipulations for families with the strongest history of atopic disease where the risks would be expected to be highest. Such diets have potential emotional and nutritional risks associated with them, and these drawbacks must be considered. It is clear that further studies are needed to validate these recommendations and assess their impact. Unfortunately, it is no easy task to carry out the studies necessary to evaluate these issues.

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