

Can We Prevent Food Allergy by Manipulating the Timing of Food Exposure?

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KEYWORDS

- Peanut allergy • Cow's milk allergy • Egg allergy
- Food-specific IgE • Skin-prick test • Food introduction
- Food allergy • Diagnosis

Food allergy is defined as an adverse health effect arising from a specific immune response that is reproducible on exposure to a given food, and thus is an example of a defect in the development or a breakdown in the maintenance of oral tolerance. Little is known regarding which variables are important for the induction or failure of oral tolerance in the neonatal period. Investigations into the underlying mechanisms of neonatal oral tolerance in rodents have demonstrated that antigen administration directly after birth or within 5 to 7 days does not lead to suppression of systemic immunity but primes for subsequent humoral and delayed hypersensitivity responses.^{1,2} Antigen transfer from breast milk induces tolerance in the young, although the antigen dose required for tolerance induction is 2 to 3 log steps lower.³

Clinically, the prevalence of food allergy has increased. Peanut allergy has dramatically increased in children within the last decade, with more than 1% of school children in the United States, United Kingdom, Canada, and Australia affected.^{4–7} The previous advice by the American Academy of Pediatrics (AAP)⁸ in 2000 was for breastfeeding mothers of high-risk infants to strictly avoid peanut and tree nuts and to consider elimination of cow's milk, egg, fish, and possibly other foods during lactation. The AAP went on to recommend that solid foods should not be started until 6 months of age, with dairy products not introduced until age 1 year, eggs until 2 years, and peanut, tree nuts, and fish until 3 years of age. These feeding guidelines were revised

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in 2008 to avoid the strong recommendations on whether foods of high allergenic potential should be ingested during pregnancy, lactation, and infancy (Table 1).⁹ The revision resulted from the controversy in the literature regarding the impact of maternal avoidance diets on food allergy prevention and the lack of information on what is the correct age to introduce foods of high allergenic potential to infants and toddlers.^{10–13} This review provides a careful evaluation of the rationale and existing data on whether the manipulation of the timing of specific food exposures in the diet during pregnancy, lactation, and early childhood affects the development of food allergies in high-risk children.

BIOLOGICAL RATIONALE FOR TOLERANCE DEVELOPMENT ANTENATALLY AND POSTNATALLY

The normal development of immunologic tolerance is poorly understood. Most children become tolerant to common allergens, and a normal response to exposure is

Table 1 Summary of effects of nutritional interventions during pregnancy, lactation, and infancy on the development of atopy	
Intervention	Evidence
Restriction diet during pregnancy	No evidence in prevention of atopic diseases
Restriction diet during lactation	No evidence in prevention of atopic diseases with the possible exception of atopic eczema
Length of exclusive breastfeeding	Exclusive breastfeeding for at least 4 months decreases the cumulative incidence of atopic dermatitis and cow's milk allergy in the first 2 years of life in infants at high risk of developing atopic disease Exclusive breastfeeding for at least 3 months protects against wheezing in early life
Use of hydrolyzed formulas	Modest evidence that atopic dermatitis may be delayed or prevented by the use of hydrolyzed formulas in early childhood in infants at high risk of developing atopic disease. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed formulas in the prevention of atopic disease
Use of soy-based formulas	No evidence in allergy prevention
Timing of introduction of solid foods	No current convincing evidence that delaying introduction of solid food, including highly allergic foods such as fish, eggs, and foods containing peanut protein, beyond 4–6 months has a significant protective effect on the development of atopic disease. In infants after 4–6 months of age, there are insufficient data to support a protective effect of any dietary intervention for the development of atopic disease

Modified from Greer FR, Sicherer SH, Burks AW. American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Allergy and Immunology. 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 2008;121(1):183–91.

production of immunoglobulin G (IgG) as opposed to IgE antibodies, reflecting a T-helper type 1 (Th1)-skewed immune response. Immunologic tolerance can develop during early T-cell development in the thymus during which T cells, which respond to self-antigens, are deleted by “negative selection” (central tolerance) or later in the circulation (peripheral tolerance). Inflammatory signals are required to elicit antigen-presenting cell (APC) activation and expression of costimulatory molecules to activate T cells, but in the absence of APC costimulation, potentially reactive T cells fail to respond and undergo clonal deletion by apoptosis.¹⁴ However, the processes responsible for tolerance to food allergens are still poorly understood.

Initial immune responses to food allergens are detectable in fetal life, although their significance is still unclear. The ability of the fetus or newborn to respond to antigenic stimuli changes gradually with the maturation of the immune system. IgE production starts at 11 weeks of age,¹⁵ but total IgE is still low (<1 kU/L) at birth¹⁶; cord blood-specific IgE can be detectable, but is also very low.¹⁷ Most infants show early transient lymphoproliferation, and IgG antibody responses to food allergens are typically detected.^{18,19} Also, a transient early IgE response is seen in many nonatopic children, whereas a prolonged, enhanced response is associated with atopy^{20,21} and Th2 cytokine production.²¹ The factors responsible for abrogation in some infants versus enhancement of IgE production in others are still not fully understood.

The current hypothesis is that the Th2-biased milieu of pregnancy²² is typically redirected toward the Th1 (IgG) response postnatally in a normal situation. In those with an atopic predisposition the immune responses remain Th2 dominant (IgE).²³ After birth, maturation of Th1 immune function probably prevents persisting Th2 responses and subsequent allergic disease. Consistent with this, an association between neonatal Th1 immaturity, delayed production of interferon- δ and atopic risk has been reported.^{24–26} Levels of soluble CD14, which may be responsible for downregulation of IgE production by B cells within the lymphoid follicles of the gastrointestinal tract, are lower in amniotic fluid in children who later develop atopic disease.²⁷ Soluble CD14, and therefore reduced soluble CD14, may predispose to a continued Th2 dominant balance. Food-specific cytokine and IgG antibody responses that are present in early infancy tend to persist,²¹ which also speaks for a switch from Th2 (IgE) to Th1 (IgG) dominance.

Immaturity of APC function²⁸ results in low pro-Th1 cytokine (interleukin-12) production and thereby contributes to the Th2-skewed immune response in infants.²⁹ However, neonatal APCs are also less efficient in providing T-cell costimulation, which is more likely to contribute to development of tolerance.^{30,31} Influence by bacteria and bacterial products has been proposed to promote the switch from Th2 responses at birth to balanced Th responses in normal infants. There is evidence in animal models that bacterial colonization is essential for maturation of Th1 function and induction of oral tolerance,³² and that bacterial endotoxin exposure can prevent allergic sensitization.³³

FACTORS AFFECTING TOLERANCE DEVELOPMENT

The factors influencing induction of oral tolerance include external factors such as nature of antigen, dose, duration and time of introduction, and host factors such as genetic background, host immaturity, commensal flora, and antigen uptake.³⁴ However, the proportional and combined effects of individual components on systemic immunity may vary.

In earlier animal studies of cow's milk hypersensitivity, Li and colleagues³⁵ found that whereas 5-week-old mice were susceptible to sensitization with peanut, they were unable to sensitize mice of the same age to cow's milk, even in the presence

of cholera toxin. Oral feeding of milk to younger mice of 2 to 3 weeks of age, however, induced moderate levels of IgE and immediate skin reactions (itching) after oral feeding of sensitized mice. The nature of antigen indeed plays a role in sensitization and likely also affects the ease of tolerance development. When compared with cow's milk, peanut is a special antigen in that it has innate immunity and complement-activating mechanisms^{36,37} in addition to its clinically evident greater allergenicity. For the investigation of neonatal oral tolerance in animal models, hen's egg albumin (ovalbumin [OVA]) and bovine serum albumin have been used the most.

Animal models have suggested that both repeated and single doses of antigen can induce tolerance, but with different conditions and mechanisms. Feeding with repeated doses of a low-dose antigen every other day for 2 weeks is effective for IgG and IgE suppression.^{38,39} Multiple low doses (approximately <0.1 mg/g body weight) are likely to generate antigen-specific regulatory cells.^{40,41} Continuous exposure of antigen in the drinking water may lead to an even more profound tolerance, even for when the administered total antigen dose has been corrected.⁴² A single dose of 1 mg per mouse is suppressive for IgG and cell-mediated responses by direct inactivation of T cells (clonal anergy),^{40,41} whereas a dose ten-fold less was not, and a dose approximately 100-fold less results in priming for systemic and local cell-mediated responses.^{38,39} Furthermore, although priming was observed after a single feed, repeated antigen administrations after a sensitizing feed are capable of suppressing immune responses (delayed-type hyperreactivity more affected than IgG), and multiple feeds with the same total antigen dose as a single feed are more likely to overcome the initial priming effect.^{1,43}

The genetic background of the host plays a role in tolerance development. Infants at high risk for allergy and a target for prevention include those with at least one first-degree relative (parent or sibling) with a documented allergic condition.^{9,44} The problem with this approach is that such populations include children with varying levels of risk for developing food allergy, including from those with a sibling with food allergy and those with a parent with allergic rhinitis, in whom the impact of these interventions may differ. These populations have been investigated for development of allergic diseases in studies of primary allergy prevention, but unselected populations have been less studied.

Maternal rather than paternal atopic status has a greater effect on the atopic outcome of the progeny.^{45,46} Eczema or perennial rhinitis in the mother is associated with elevated cord blood IgE.⁴⁷ In mice offspring, breastfeeding has been shown to have a crucial role in tolerance induction using adoptive nursing models.^{48–50} This finding raises the question of whether maternal factors such as immunologic constituents of breast milk and dietary exposure in utero and during lactation play a role in tolerance induction.

The remainder of this article focuses on the effect of age on the introduction of food antigens in tolerance development.

EFFECT OF TIMING OF FOOD EXPOSURE: PREGNANCY AND LACTATION

Experimental Models

Maternal exposure to dietary antigen during pregnancy and lactation has generally shown to be protective against specific IgE sensitization in offspring.^{3,51–55} It has been proposed that the protective effect during pregnancy and lactation is dependent on the age at which the offspring are sensitized.⁵²

Although more numerous animal studies have assessed perinatal exposure to an inhaled antigen, few studies have assessed the effect of oral antigen exposure during

pregnancy and lactation, and those studies have used mothers who are either naïve or sensitized to the food in question. Some of these studies have been performed in asthma models assessing the effect of inhaled (or oral in one study) OVA exposure during lactation on the development of OVA sensitization and asthma in the offspring. Using naïve mothers, Polte and Hansen⁴⁹ showed that high-dose exposure during pregnancy was protective against sensitization to OVA. Fusaro and colleagues⁵² proposed that the effect of feeding is dependent on the dose and timing, with only low-dose exposure being protective in pregnancy, and showed in utero allergen priming to occur. In their model, exposure during lactation to a higher amount of OVA in naïve mothers was protective only when pups were sensitized during the first 3 days of life. This finding is in disagreement with that of another similar study, which showed protection via a small dose exposure during lactation.⁵¹ However, humans are rarely naïve to a food antigen, and production of food-specific IgA and IgG is a normal physiologic phenomenon following ingestion of food proteins such as peanut and OVA,⁵⁶ which may be an important additional vehicle for transfer of vertical tolerance in food allergy.

Studies addressing the effect of maternal perinatal antigen exposure in immunized (nonallergic) mothers are fewer and have used doses of inhaled OVA antigen,⁵⁴ but have likewise demonstrated tolerance induction in the offspring by feeding during pregnancy or lactation. These studies may be particularly relevant to humans because food-specific immunoglobulins, including IgG and IgA, are commonly found in healthy, nonallergic subjects. One study assessed the effect of OVA exposure in OVA-sensitized mothers on the development of OVA sensitization in the progeny.⁵³ Using food-antigen exposure in mothers who are sensitized to the antigen in question also poses a problem for translation of the results into a human situation whereby patients with food allergy strictly avoid the allergen. Most of these studies assessed maternal exposure via inhalation and systemic sensitization via the intraperitoneal route in the offspring, although the oral route is the major route of exposure in food allergy. A further limitation is that although some studies have measured IgE sensitization as an outcome, it is known that it is a poor measure of true clinical food allergy. Only one model thus far has assessed anaphylactic allergy to peanut. It was shown that maternal perinatal exposure to peanut resulted in protection against peanut anaphylaxis in the offspring.⁵⁵ The mothers were fed peanut together with cholera toxin, a mucosal adjuvant, which may have effects different from feeding antigen alone.

Strobel³ analyzed the effects of antigen dose during different time points on induction of neonatal tolerance by maternal antigen transfer from breast milk. Suckling mothers were fed for 3 days with a high dose of OVA at several time points between delivery and 18 days of lactation (before weaning). In offspring immunized at 4 weeks of age, feeding mothers during the first 3 days of life demonstrated a lack of tolerance induction. Whereas gavaged animals received 1 mg/g body weight, suckling animals received a smaller dose of antigen that was in a range typically associated with sensitization/priming.³⁹ The timing of immune responses observed after administration of antigen from breast milk were comparable with those after direct antigen administration.

Human Studies

The US Dietary Prevention Program^{10,11} was a randomized, prospective study including 288 subjects with one parent with atopy and sensitization. Subjects were randomized to either prophylaxis or no prophylaxis. Prophylaxis included the following: avoidance of milk, egg, and peanut during the third trimester of pregnancy and lactation; supplementation with casein hydrolyzate; and introduction of solid food at 6 months, with introduction of cow's milk, wheat, and soy at 12 months, egg at

24 months, and peanut and fish at 36 months. Subjects were followed to the age of 7 years. There was a decrease in food allergy in the prophylaxis group; however, milk allergy was responsible for the difference seen. By age 7 years, however, food allergy occurred at similar rates in both groups.

Based on various studies, especially the one by Zeiger and colleagues,^{10,11} as well as expert opinion, the AAP Committee on Nutrition⁸ made recommendations in 2000 for prevention aimed at families with a history of atopic disease, although the wording of the recommendations reflected the limitations in the studies ("may consider," and so forth). A more recent meta-analysis and another review of the literature both concluded, however, that maternal avoidance diets during pregnancy were not effective in preventing allergic diseases (eczema, asthma, allergic sensitization) in children.^{57,58} The data on maternal diets during lactation are too few to make conclusions, although they may reduce the risk of atopic dermatitis during the first 1 to 2 years of life, but this effect is lost in childhood. These and other reports led the AAP to change the recommendations in 2008.⁹

There is great controversy in the literature regarding the impact of maternal diets on peanut allergy, however.^{11–13} A case-control study from South Africa¹² included a standardized questionnaire, which assessed maternal peanut consumption more or less than once a week on the infant's peanut-IgE in 25 children younger than 3 years with peanut sensitization (cases) or 25 without peanut sensitization (milk or egg allergic controls). Higher consumption during pregnancy (odds ratio [OR] 3.97, 95% confidence interval [CI] 0.73–24, $P = .063$) but not during lactation (OR 2.19, CI 0.39–13.47, $P = .47$) was found in peanut-sensitized cases, although the population studied was quite small. Another case-control study from the United Kingdom comprised a telephone survey that assessed maternal peanut consumption (yes or no) during pregnancy and lactation on peanut allergy development assessed by double-blind, placebo-controlled food challenge in 23 subjects with peanut allergy (cases), and in 70 atopic and 140 nonatopic controls. During pregnancy 65% of mothers with a child with peanut allergy consumed peanut compared with 71% atopic and 61% nonatopic controls (not significant); during lactation, 17% of mothers with cases consumed peanut compared with 5% of atopic or nonatopic controls ($P = .03$, but not significant after adjustment).

Since these reports, 2 larger observational studies have created even more controversy. Du Toit and colleagues⁵⁹ suggested that more frequent and larger consumption of peanut during breastfeeding and in infancy was associated with a low prevalence of peanut allergy as seen in Jewish Israeli children (0.17%) compared with Jewish children in the United Kingdom (1.85%). On the contrary, observational data from the United States support the concept that exposure to peanut in pregnancy and lactation may not be tolerogenic; this includes a human cohort of 503 high-risk infants with milk or egg sensitization in whom frequent maternal peanut ingestion during pregnancy predisposed infants to peanut sensitization.⁶⁰ As a limitation, all the studies possess potential recall bias and no controlled human clinical trials are available. Furthermore, infant diet, which is typically linked to maternal diet, may be a confounding factor.

EFFECT OF TIMING OF FOOD EXPOSURE: INFANCY

Experimental Models

Strobel and colleagues^{1,2} investigated the immune responses of neonates after a timed and standardized feed of OVA and bovine serum albumin to see whether tolerance development was affected by age of introduction. Neonatal suckling mice within one litter were fed a single feed of either a high dose of antigen or saline by gavage feeds in utero 2 days before birth and at different times until 90 days of age.

Immunization was performed at 4 weeks of age. The investigators demonstrated that there is a transition from priming to tolerance induction at around 7 to 10 days of age, affecting antibody and cell-mediated responses.

At weaning there is a rapid change of intestinal morphologic parameters. In mice, feeding antigen close to the day of weaning (around 21 days) leads to a temporary reduction in the ease of tolerance induction in the young adult mouse.¹ It seems that this inability to induce tolerance is not merely a result of the immaturity of the digestive system or antigen-handling capacity of the neonatal gut, but that this regulatory imbalance can be partially restored with adult spleen cells.⁶¹

Human Studies

Length of breastfeeding

There are a few studies that have examined the effects of breastfeeding on the development of food allergies. The results are likely affected by variables including the length and exclusivity of breastfeeding and presence of other atopic disorders. One review of 132 studies with 56 deemed "conclusive" determined that breastfeeding is protective of atopic diseases (asthma, recurrent wheezing, atopic dermatitis), but not of food allergy.⁶² A more recent review, however, found that exclusive breastfeeding for at least 4 months was associated with a lower cumulative incidence of cow's milk allergy until 18 months of age.⁵⁷ Since these meta-analyses and reviews, several additional studies, all of which suffer from certain biases, support or refute these conclusions.^{63–65}

Cow's milk protein

Human milk is the optimal source of nutrition for term infants during the first 6 months of life. Cow's milk allergy (CMA) is typically the first manifestation of an atopic constitution, due to the fact that cow's milk protein, in the form of cow's milk-based infant formulas, often provides the first exposure to a foreign protein in large quantities via the gastrointestinal route.

The risk of developing CMA in infants exposed to cow's milk protein early in life has been assessed. A total of 6209 unselected healthy, full-term infants, of whom 5385 (87%) required supplementary milk while in the hospital, were randomly assigned to receive cow's milk formula (1789 infants), pasteurized human milk (1859 infants), or whey hydrolyzate formula (1737 infants).⁶⁶ The comparison group (824 infants) was composed of infants who were exclusively breastfed. The infants were followed for 18 to 34 months for symptoms suggestive of CMA. As a result, the cumulative incidence of CMA in the infants fed cow's milk formula was 2.4% compared with 1.7% in the pasteurized human milk group (OR 0.70, 95% CI 0.44-1.12) and 1.5% in the whey hydrolyzate group (OR 0.61, 95% CI 0.38-1.00). In the comparison group, CMA developed in 2.1% of the infants. These data indicate that feeding of cow's milk at maternity hospitals increases the risk of CMA when compared with feeding of other supplements, but exclusive breastfeeding does not eliminate the risk.

On the contrary, another more recent study showed that early exposure in infancy (<14 days of age) to cow's milk protein via formula as a supplement to breastfeeding might protect against IgE-mediated CMA.⁶⁷ This large prospective study of 13,019 infants in Israel investigated, by telephone interview, the association of age of introduction of cow's milk formula and the development of CMA. All mothers were encouraged to breastfeed. It was noticed that introduction between 4 and 6 months of age was associated with the highest risk for CMA and before 15 days of life with least risk (OR 19.3, 95% CI 6-62.1). In the study, feeding formula on a daily basis was qualified as introduction of formula. Sporadic exposures, such as in a nursery, were not

counted toward formula introduction, which may be a confounding factor. Symptoms after the start of formula were questioned but symptoms before initiation of formula feeding were not, which may have influenced feeding decisions, raising issues of potential reverse causality. Also, the amount needed to prevent allergy was not determined from the study. Furthermore, the incidence of CMA in this Israeli cohort was surprisingly low in comparison with other studies from Westernized countries, suggesting differences in patient population, potentially based on different genetic backgrounds.

Studies have also been performed to assess the effects of hydrolyzed formulas for the prevention of CMA when compared with breast milk.^{66,68} These studies only examined early and short-term exposure to hydrolyzed formula, which did not seem to have any impact on the development of allergic disease. From a biological standpoint this is logical, as the levels of cow's milk allergens in hydrolyzed formulas are similar to those in breast milk, and therefore the infant's level of exposure is equivalent on both regimens.

The protective effects of partially hydrolyzed formulas (pHFs) in comparison with cow's milk-based formulas in preventing CMA have been studied as well. Comparing a partial whey hydrolyzate with cow's milk-based formula in 2 relatively small studies, Vandenplas and colleagues^{69,70} found significantly lower prevalence of cow's milk sensitivity at 6 months based on skin-prick test in pHF-fed infants. In the 5-year prospective study, however, there was no new statistical difference between the 2 groups after 6 months unless new cases of cow's milk sensitivity were considered, suggesting the primary effect of the pHF had occurred during the first 6 months of life. In both studies there was an overall high prevalence of cow's milk sensitivity, likely due to less strict diagnostic criteria and selection bias.

The feeding of high-risk infants with a pHF as opposed to an extensively hydrolyzed formula (eHF) to prevent food allergy has been compared.^{71,72} The combined analysis of 2 of these studies, with a total of 352 infants, found no significant difference in the incidence of infant food allergy. However, other studies have identified some differences between feeding with pHFs and eHFs.

The German Infant Nutritional Study followed 945 high-risk newborn infants in a randomized trial investigating the effects of breastfeeding supplemented with partially hydrolyzed whey formula (pHF-W), extensively hydrolyzed whey formula (eHF-W), or extensively hydrolyzed casein formula (eHF-C) in the first 4 months of life.^{73,74} Mothers were encouraged to breastfeed exclusively for 4 months; however, about two-thirds in each formula group introduced study formula during the first month. Clinician diagnosis of any allergic disease (atopic dermatitis, food allergy, allergic urticaria, asthma, and allergic rhinitis) was significantly lower in the eHF-C and pHF-W groups at 3 and 6 years of age (eHF-C: OR 0.76, 95% confidence interval [CI] 0.63–0.93 and OR 0.80, 95% CI 0.69–0.93, respectively; pHF-W: OR 0.78, 95% CI 0.64–0.95 and OR 0.82, 95% CI 0.70–0.96, respectively). However, rates of urticaria, food allergy, and asthma were not affected at 3 years of age for any of the formulas.^{74,75}

Solid food introduction

Several recent studies, most of which are population-based, prospective birth cohorts, do not support delaying the introduction of solid foods beyond 4 to 6 months for the prevention of allergic disease.^{59,76–78} In one of these cohorts, 642 children were followed to the age of 5.5 years.^{76–78} Data on the introduction of solids were collected during the first year of life. Results were corrected for parental asthma and atopy. Sixty-two percent of the children were ever breastfed, with 3 months as the median duration of breastfeeding. Rice was the first solid food introduced at a median age

of 3 months, and milk and egg were introduced at 6 and 8 months, respectively. A follow-up at age 6 years⁷⁶ showed that the introduction of solid foods after 4 to 6 months was not associated with a decreased OR for asthma, allergic rhinitis, or sensitization against food or inhalant allergens at 6 years of age. In fact, food sensitization was more frequent in children who began solids later.

Joseph and colleagues⁷⁹ recently explored the relationship between introduction of complementary food at younger than 4 months (by interviews) and sensitization to egg, milk, and peanut allergen at 2 years in 594 maternal-infant pairs. In multivariable analysis, early feeding reduced the risk of peanut sensitization (serum specific IgE >0.35 IU/mL) among children with a parental history (adjusted OR 0.2, 95% CI 0.1–0.7; $P = .007$), but only for children with a parental history of asthma or allergy. The relationship also became significant for egg when a cutoff for IgE of greater than 0.70 IU/mL was used (adjusted OR 0.5, 95% CI 0.3–0.9; $P = .022$). A major limitation is that only food sensitization was assessed with low specific IgE cutoffs.

A study of 1612 children followed to the mean age of 4.7 years examined the association between cereal grain exposures (wheat, barley, rye, oats) in the infant diet and the development of wheat allergy.⁸⁰ The data demonstrated that delaying the introduction of cereal until after 6 months did not protect against the development of parent-reported wheat allergy (4 cases with wheat-specific IgE), but may actually increase the child's risk, even after controlling for family history of allergy, breastfeeding duration, any food allergy, and introduction of rice cereal. Limitations to the study were a low number of subjects with wheat allergy (1%) and that the study was performed in a population with HLA predisposition to diabetes and celiac disease.

Another study compared 2 cohorts of children with similar ethnic backgrounds, 1 in Israel and 1 in the United Kingdom.⁵⁹ The prevalence of peanut allergy in primary

Table 2

Recommended practical advice for feeding infants at high risk for allergy (ie, those with at least one first-degree relative with a documented allergic condition, especially moderate to severe atopic dermatitis, food allergy, or asthma)

Breastfeeding	For the minimum first 4–6 months
Supplementation	With partially ^a or extensively ^b hydrolyzed formula for the first 6 months if unable to exclusively breastfeed
Solid food introduction	At 4–6 months starting with yellow/orange vegetables, fruits, and baby cereals; then advance to meats and different-stage foods as appropriate for feeding skills
Highly allergenic foods	Egg, dairy products other than cow's milk per se, peanut, tree nuts, fish, and shellfish can be gradually introduced to infants who have already tolerated the introduction of less allergenic foods (although cow's milk should be avoided until 1 year of age for reasons unrelated to allergy). If, however, an infant has an allergic reaction to a food, or develops moderate to severe atopic dermatitis, or has a sibling with peanut allergy, then evaluation by an allergist is suggested to determine a personalized plan for food introduction

Examples of hypoallergenic formulas available in the United States:

^a Partially hydrolyzed whey (cow's milk protein): Good Start Supreme (Nestlé USA, Glendale, CA). Partially hydrolyzed whey/casein (cow's milk protein): Enfamil Gentlease Lipil (Mead Johnson Nutritional, Evansville, IN).

^b Extensively hydrolyzed casein (cow's milk protein): Enfamil Nutramigen Lipil (Mead Johnson Nutritional); Enfamil Pregestimil (Mead Johnson Nutritional); Similac Alimentum Advance (Ross Products, Columbus, OH).

school children was assessed by one validated questionnaire (approximately 5000 children in each country). Peanut consumption in infants was assessed by a second validated questionnaire (77 children in the United Kingdom and 99 in Israel). The prevalence of peanut allergy was 1.85% in the United Kingdom and 0.17% in Israel. Peanut was introduced earlier and consumed both more frequently and in larger quantities in Israel than in the United Kingdom. A randomized trial is under way to determine whether early introduction of peanut is protective of peanut allergy (www.leapstudy.co.uk).

The HealthNuts study, which is a population-based, cross-sectional study of 2589 infants in Australia, assessed the effect of age of egg introduction and development of egg allergy.⁸¹ The risk of developing egg allergy increased when egg was introduced after 6 months when compared with before 6 months, and the risk further increased the later egg was introduced (adjusted ORs 1.6, 95% CI 1-2.6, and 3.4, 95% 1.8-6.5, for introduction at 10-12 and after 12 months, respectively). Effects were seen in high-risk and low-risk infants with introduction of cooked egg. The type of egg introduction was also important, as cooked egg as opposed to baked egg appeared to have the greatest effect. Results were adjusted for confounding factors, and egg allergy was confirmed by an oral food challenge.

Taken collectively, these studies do not support delaying the introduction of solid foods beyond 4 to 6 months for the prevention of allergic disease. In fact, this practice may even increase the risk of allergy. Thus, general guidelines for introducing solid foods to an infant's diet are also appropriate for infants at high risk for allergic disease (Table 2).

SUMMARY

Prevention of food allergies by the alteration of maternal and infant feeding practices serves as a simple and cost-effective approach to address the increasing prevalence of food allergy in children. Although antigen exposure during pregnancy and lactation has been shown to be protective in animal models, such studies have mostly been performed in OVA-induced asthma models with inhalation exposure. Few have used models of food allergy, including peanut allergy, and these have used mothers that are either naïve or sensitized to the antigen in question. However, humans are rarely naïve to a food antigen, and production of food-specific IgA and IgG is a normal physiologic phenomenon following ingestion of food proteins, making translation of most data from existing experimental models to humans challenging. In the few clinical trials available, the modification of maternal diets during pregnancy and/or lactation does not seem to influence the risk of food allergy, with the possible exception of peanut allergy. In infant diets, clinical data suggest that the use of certain hydrolyzed formulas rather than cow's milk formula may affect the development of CMA. The most recent and compelling data may be for a critical timeframe for introduction of the highly allergenic solid foods to infants' diet, as emerging studies are showing that earlier introduction may be better in preventing allergy.

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