



Timing of allergen exposure and the development of food allergy: treating before the horse is out of the barn

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Purpose of review

Until recently, nutritional guidelines did not support early introduction of allergenic foods into the diet of high-risk infants. Following recent studies, this approach is beginning to change, at least for peanuts. This review will examine the change in nutritional guidelines and the scientific data that led to these changes.

Recent finding

In a recent prospective controlled study, regular consumption of peanut protein in infants from 4–11 months of age with atopic dermatitis or egg allergy, was associated with lower prevalence of peanut allergy (1.9%) at 60 months of age compared with peanut avoidance (13.7%). Other studies demonstrated that earlier introduction of cow's milk protein and egg powder were also associated with decreased risk for milk and egg allergy, respectively.

Summary

Recent studies suggest that early rather than late introduction of allergenic foods reduces the risk of food allergy. The preferred timing of food introduction might be sooner than the current recommendation, and might apply not only to high-risk infants.

Keywords

milk, peanut, prenatal, primary prevention, tolerance

INTRODUCTION

The prevalence of food allergy has been steadily increasing over the past 2 decades. This has been shown in studies from the United States [1,2], United Kingdom [3,4], Canada [5], and China [6]. Although many of these studies are based on self-report or evidence of sensitization only, together they provide clear impression of the worldwide increase in food allergy. Given the short time frame, environmental factors, rather than genetic changes are likely to account for this increase. Guidelines for timing of introduction of potentially allergenic foods, changed in parallel to the rise in food allergy. This study will focus on the shift that recently occurred in international guidelines regarding the effect of timing and route of food exposure on the subsequent development of food allergy to the same food as well as other allergies.

ALLERGEN EXPOSURE DURING PREGNANCY AND LACTATION

In 1996, Hourihane *et al.* [7] published that the age of onset of peanut allergy is decreasing, possibly

secondary to increased peanut consumption by mothers during pregnancy and by infants early in life (Table 1) [7–12,13^a,14]. In 1998, the UK Committee on Toxicity issued a precautionary advice that pregnant women from atopic families may wish to avoid peanut products during pregnancy and lactation [15]. The American Academy of Pediatrics (AAP) stated that excluding peanuts during pregnancy may be necessary and advised mothers of high-risk infants to eliminate peanuts and tree nuts and consider eliminating egg, milk, and fish from the diet while nursing [16]. In a study performed following the UK advice, peanut sensitization was examined in 858 children followed for 2 years. Mothers of 10 of the 13 infants (77%) who were

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KEY POINTS

- Early introduction of peanut protein significantly reduces the risk for peanut allergy in high-risk infants.
- A similar protective effect, not limited only to high-risk infants, seems to occur with early cow's milk and egg introduction.
- The use of well defined criteria for IgE-mediated food allergy is essential, before conclusions could be drawn from studies on primary prevention of food allergy.

sensitized to peanut stated that they had followed the advice and avoided peanuts during pregnancy [11]. Subsequent studies provided conflicting results. Sicherer *et al.* [8] found that peanut sensitization (sIgE > 5 kUA/l), in infants with likely milk or egg allergy, was associated with more frequent peanut consumption during pregnancy and lactation. DesRoches *et al.* [9] described that reported consumption of peanuts during pregnancy was

higher in a cohort of peanut allergic compared with nonallergic infants less than 18 months old. In contrast, others showed that peanut and tree nuts consumption during pregnancy, in nonallergic women, were inversely related with the risk of peanut and tree nuts allergy in infants and with the risk of asthma at age 18 months and 7 years [10,12,17]. Lack *et al.* [10], in a retrospective study of 13 971 preschool children, found no evidence of prenatal sensitization from the maternal diet, and peanut-specific IgE was not detectable in the cord blood. Similar findings were found for other foods. Higher maternal peanut, milk, and wheat intake during the first trimester of pregnancy was associated with reduced odds of peanut allergy, asthma and allergic rhinitis, and atopic dermatitis, respectively, in children at a mean age of 7.9 years [13[■]]. A Cochrane review concluded that antigen avoidance during pregnancy, in high-risk woman, is unlikely to reduce, substantially, the child's risk of atopic diseases [18]. In a study [19] focusing on lactation, atopic/allergic manifestations at 9 months of age

Table 1. Main studies on prenatal food avoidance

Reference	Food	Design	Finding	Allergy definition
Hourihane <i>et al.</i> [7]	Peanut	Cohort, <i>n</i> = 622	Younger age of peanut allergy was associated with more maternal peanuts consumption during pregnancy or breast feeding	Self-reported
Sicherer <i>et al.</i> [8]	Peanut	Cohort, <i>n</i> = 512	Frequent peanut consumption during pregnancy was associated with peanut sensitization in infants with likely allergy to milk and egg	Peanut IgE ≥5 kUA/L
DesRoches <i>et al.</i> [9]	Peanut	Case-control, <i>n</i> = 403	Reported consumption of peanuts during pregnancy was associated with an increased risk of peanut allergy in offspring	A history of clinical reaction to peanuts + peanut-specific sIgE
Lack <i>et al.</i> [10]	Peanut	Cohort, <i>n</i> = 13 971	No significant association between peanut allergy and maternal dietary factors	Clinical reaction, SPT, DBPCFC
Dean <i>et al.</i> [11]	Peanut	Cohort, <i>n</i> = 858	Mothers avoiding peanut during pregnancy were more likely to have peanut allergic infants	Peanut sensitization
Frazier <i>et al.</i> [12]	Peanuts/tree nuts	Cohort, <i>n</i> = 10 907	Higher peripregnancy consumption of peanuts/tree nuts in nonallergic mothers was associated with lower risk of peanut/tree nuts allergy in their offspring	Parental report + medical records + allergy tests
Bunyavanich <i>et al.</i> [13 [■]]	Peanut	Cohort, <i>n</i> = 1277	Higher maternal peanut intake during the first trimester was associated with 47% reduced odds of peanut allergic reaction in mid-childhood	Self-report + sIgE
Järvinen <i>et al.</i> [14]	Milk	Cohort, <i>n</i> = 145	Maternal cow's milk avoidance was associated with lower levels of mucosal-specific IgA levels and the development of CMA in infants	OFC (including delayed reactions)

CMA, cow's milk allergy; DBPCFC, double-blind placebo-controlled food challenge; OFC, Oral Food Challenge; SPT, skin prick test.

were similar between infants and mothers who had an egg, milk, and fish-free diet, during the first 3 months postpartum and those who did not. Another prospective study [14] found that maternal cow's milk avoidance during breastfeeding was associated with lower casein and β -lactoglobulin (BLG)-specific IgA in human milk, and with lower serum casein and BLG-specific IgG(1) and BLG-specific IgG(4) levels in the infants. Lower milk-specific IgG4 and IgA levels were associated with infant cow's milk allergy (CMA). Current guidelines state that no elimination diet is recommended during pregnancy or lactation for the prevention of food allergy [20–22].

ALLERGEN EXPOSURE IN INFANCY

Solid foods

The recommended timing of infant exposure to highly allergenic foods has also changed over the years. In a US-based study [23], a decrease in probable food allergy and food sensitization was observed at 12 and 24 months, respectively, in high-risk infants avoiding milk, corn, soy, citrus, and wheat for 12 months, and egg, peanut, and fish for 24 months (Table 2) [16,20,23–27,28²²,29²¹]. Based on that, The AAP recommended in 2000 that 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 [16]. A position statement, issued by the Australian Society of Clinical Immunology and Allergy, stated that avoidance of peanut, nut, and shellfish for the first 2–4 years of life may be recommended in high-risk children [24]. However, a continuation of the US study [25] found no difference in the prevalence of food allergy or any other atopic disease between the avoidance and the consumption groups at 7 years of age. In the Australian population-based 'Health-Nuts' study [26] following 2589 infants, introduction of egg into the diet at 4–6 months was associated with lower risks of egg allergy compared with later introduction. These findings persisted even in children without risk factors. A similar finding was described by Palmer *et al.* [30] for infants aged 4–8 months with moderate–severe eczema. Of note, 36% (24/67) of infants in this study already had egg-specific IgE higher than 0.35 kUA/l and 31% (15/49) of those randomized to receive egg had an allergic reaction to egg powder at 4 months of age, before any known egg ingestion. Other studies [31–33] showed reduced risk of eczema after 1 year of age and of food allergy and asthma at 3–6 years of age with increased diversity of complementary

foods in the first year of life, and reduced risk of peanut sensitization by 2–3 years of age with introduction of complementary foods before 4 months of age in children with a parental history of asthma or allergy. A UK–Israeli study [27] found that the prevalence of peanut allergy in Jewish primary school children in the United Kingdom was nearly 10 times higher (1.85 vs. 0.17%), compared with matched Israeli children, possibly because of the earlier, more frequent, and larger quantities of peanut consumption in Israel than in the United Kingdom. Subsequent guidelines stated that there is no evidence in withholding or encouraging exposure to highly allergenic foods beyond 4–6 months in high-risk infants [20–22]. Recently, a prospective interventional study [28²²], in children aged 4–11 months at risk for peanut allergy, found a prevalence of 13.7% of peanut allergy at 60 months of age in infants avoiding peanut protein compared with 1.9% in those assigned to consume 6 g of peanut protein/week until 60 months of age. Increased levels of peanut-specific IgG4 were found predominantly in the consumption group. Similarly to the study by Palmar *et al.*, 9.1% of patients were already peanut allergic at screening, raising the question whether an even earlier exposure might be necessary. Following this study, a consensus communication was issued, stating that there is now scientific evidence to recommend introduction of peanut-containing products into the diets of high-risk infants between 4 and 11 months of age in countries where peanut allergy is prevalent [29²¹]. It is important to emphasize in that regard that although parental atopy is important for identifying infants at risk for food allergy, the demonstration of IgE-mediated responses to allergens in parents is insufficient to predict which infants are at greatest risk of developing IgE-CMA [34].

Milk

The German Infant Nutritional Intervention Study [35] found that infants fed extensively hydrolyzed casein formula for the first 4 months had reduced rate of atopic dermatitis at 1 year of age compared with infants fed cow's milk formula (CMF) (Table 3) [35–42]. Interestingly, the rate of food-induced urticaria was higher in the extensively hydrolyzed casein formula group (1.4 vs. 0.4% but no *P* value is reported). Feeding with extensively hydrolyzed whey or partially or extensively hydrolyzed casein formula was associated with reduced rate of atopic dermatitis but not of asthma or allergic rhinitis at ages 3, 6, and 10 years compared with CMF [43–45]. A Cochrane review concluded that there is limited evidence that

Table 2. Main studies and guidelines on postnatal food avoidance

Reference	Food	Design	Finding	Allergy definition
Zeiger <i>et al.</i> [23]	Milk, fish, peanuts, nuts	Randomized controlled, <i>n</i> = 287	Prolonged avoidance of solid foods was associated with decreased food allergy at 12 months and decreased food sensitization at 24 months	slgE + AD/urticaria/vomiting/diarrhea
Committee				
AAP [16]		Resulting recommendations 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		
ASCIA [24]		Avoidance of peanut, nut and shellfish for the first 2–3 years of life may be recommended in high-risk children		
Reference	Food	Design	Finding	Allergy definition
Zeiger and Heller [25]	Milk, peanut, fish, nuts	Randomized controlled, <i>n</i> = 287	Prolonged avoidance of solid foods was associated with decreased food allergy at 12 months and decreased food sensitization at 24 months but not later in life	slgE + AD/urticaria/vomiting/diarrhea
Koplin <i>et al.</i> [26]	Egg	Population-based cross-sectional, <i>n</i> = 2589,	Introduction into the diet at age >6 months was associated with higher risks of egg allergy	Clinical reaction + SPT + OFC
Du Toit <i>et al.</i> [27]	Peanut	Food allergy questionnaire in school aged children, <i>n</i> = 5171 (UK) and 5615 (Israel)	Peanut allergy prevalence was 1.85% in the UK compared to 0.17% in Israel. The median monthly consumption of peanut protein in infants is 7.1 g in Israel compared to 0 g in the UK	History of clinical reaction within 2 hours of eating the food
Committee				
EAACI [20]		Resulting recommendations For primary prevention, we recommend no withholding or encouraging of exposure to 'highly allergenic' foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced.		
AAP [22]		Introduction of solid foods, including potentially allergenic foods, should not be delayed beyond 4 to 6 months of age		
Reference	Food	Design	Finding	Allergy definition
Du Toit <i>et al.</i> [28**]	Peanut	Randomized prospective infants with severe eczema, egg allergy, or both, <i>n</i> = 640	Regular consumption of peanut protein from age 4 to 11 months was associated with lower prevalence of peanut allergy (1.9%) at 60 months of age compared to peanut avoidance (13.7%)	OFC
Committee				
WAO [29*]		Resulting recommendations There is now scientific evidence that health care providers should recommend introducing peanut-containing products into the diets of high-risk infants between 4 and 11 months of age in countries where peanut allergy is prevalent		

AD, atopic dermatitis; OFC, Oral Food Challenge; SPT, skin prick test.

Table 3. Main studies on postnatal cow's milk avoidance

Reference	Design	Finding
von Berg <i>et al.</i> [35]	Partially hydrolyzed whey formula, extensively hydrolyzed whey formula, extensively hydrolyzed casein formula, or standard cow's milk formula for 4 months	Reduced AD at 1, 3, 6, and 10 years. No effect on asthma or AR
Osborn and Sinn [36]	Cochrane review of formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants	In high-risk infants, there is limited evidence that prolonged feeding with a hydrolyzed formula compared with a cow's milk formula reduces infant and childhood allergy and infant CMA
Szajewska and Horvath [37]	The Cochrane Library, MEDLINE, EMBASE, and CINAHL databases were searched for randomized and quasi-randomized controlled trials to determine the efficacy of a partially hydrolyzed whey formula in reducing the risk of allergy in healthy infants at high risk for allergy	The difference between the partially hydrolyzed whey formula and cow's milk formula groups was statistically significant at 4 to 6 months and at 12 months but not at 24 months, and at 30 to 36 months
Chung <i>et al.</i> [38]	Food and Drug Administration review of human intervention studies that evaluated the role of partially hydrolyzed whey formula in reducing the risk of AD	There is little to very little evidence, respectively, to support the relationship between intake of partially hydrolyzed whey formula and a reduced risk of AD throughout the first year after birth and up to 3 years of age
Lowe <i>et al.</i> [39]	620 infants with a family history of allergic disease were randomized to receive cow's milk formula, partially hydrolyzed whey formula, or a soy formula at cessation of breastfeeding. Eczema and food reactions were measured 18 times in the first 2 years of life	There was no evidence that infants allocated to the partially hydrolyzed whey formula or soy formula were at a lower risk of allergic manifestations in infancy compared with cow's milk formula
Vandenplas <i>et al.</i> [40]	Infants at risk fed with adapted formula or whey hydrolysate and followed during the first year of life	Increased rate of CMA (42.8 vs. 15.6%) in infants fed with adapted formula. The diagnosis of CMA was based, in most cases, on delayed symptoms such as AD and most patients had negative skin tests for milk
Saarinén and Kajosaari [41]	A prospective cohort study comparing three groups of infants: no or short (<1 month), intermediate (1–6 months), and prolonged breastfeeding (>6 months) followed until age 17 years	Prevalence of food allergy was highest in the first group at age 1–3 years. The definition of food allergy did not include evidence of IgE sensitization or an OFC
Katz <i>et al.</i> [42]	Prospective, population-based study following infants ($n = 13\,019$) from birth. The prevalence of CMA and risk factors for its development were determined	Earlier introduction of cow's milk protein was associated with decreased risk for milk allergy

AD, atopic dermatitis; AR, allergic rhinitis; CMA, cow's milk allergy; OFC, Oral Food Challenge.

prolonged feeding with a hydrolyzed formula reduces infant and childhood allergy and infant CMA compared with CMF in high-risk infants [36]. A meta-analysis, examining the utility of partially hydrolyzed whey formula (W-pHF) in the prevention of allergy, found that infant-fed W-pHF had reduced atopic dermatitis at 4–6 and 12 months but not at 24 months, and 30–36 months [37]. The Food and Drug Administration concluded that there is little evidence to support the relationship between intake of W-pHF and reduced risk of atopic dermatitis up to 3 years of age [38]. Since then, an additional study by Lowe

et al. [39] revealed that infants fed W-pHF were not at lower risk of eczema and food reactions in the first 2 years after birth compared with CMF. Based on these data, the European Academy of Allergology and Clinical Immunology, the AAP, and the Australian guidelines recommended exclusive breastfeeding or, in the absence of breast milk, formulas with documented reduced allergenicity combined with avoidance of cow's milk for the first 4 months [46–47].

Most aforementioned studies used atopic dermatitis as an outcome. In contrast, there are very limited data on the effect of CMP introduction

on the development of CMA. Vandenplas *et al.* [40] found increased rate of CMA (42.8 vs. 15.6%) in infants at risk fed with adapted formula or whey hydrolysate, respectively. However, the diagnosis of CMA was based, in most cases, on delayed symptoms such as atopic dermatitis and most patients had negative skin tests for milk. Saarinen and Kajosaari [41], comparing three groups of infants with no or short (<1 month), intermediate (1–6 months), and prolonged breastfeeding (>6 months) reported that food allergy was more frequent in the first group. However, their definition of food allergy did not include evidence of IgE sensitization or an Oral Food Challenge. Høst *et al.* [48] described 9 infants who developed CMA while exclusively breast-fed. They speculated that sensitization occurred while the infants were fed CMP in the nursery. The diagnosis was based on a variety of symptoms, including colic, diarrhea, and eczema, and not all patients were sensitized to milk, making the diagnosis of IgE-CMA unlikely. In contrast, in a large single-center prospective study [42] from Israel, the prevalence of CMA was examined in 13 019 infants followed for 2 years. CMP was introduced to healthy infants at a mean age of 61.6 ± 92.5 days compared with 116.1 ± 64.9 days in infants with IgE-mediated CMA. The odds ratio for developing CMA was 19.3 (95% confidence interval, 6.0–62.1) among infants exposed to CMP after more than 15 days compared with those exposed in the first 14 days of life. These findings suggest that early exposure to CMP may be protective against the development of CMA. Similar findings arise indirectly from other studies. Although in many countries, including the United States, 50% of infants are already exposed to CMP during the first days of life, CMA does not typically develop in these infants. CMA usually does develop only in infants aged 2–4 months shortly after they are exposed to CMP [49].

ROUTE OF ALLERGEN EXPOSURE

Initial reactions to certain foods, and most initial reactions in the case of peanuts, develop on first known exposure, suggesting that sensitization to that particular food has already occurred. As previously discussed, sensitization *in utero* or during lactation is unlikely. Also, the initial conception that consumption during infancy might increase the risk of food sensitization and allergy is gradually replaced by the theory that early consumption is in fact protective, at least for high-risk patients. Increased household peanut consumption (weekly median of 18.8 g) was found in the homes of 133 peanut allergic patients compared with

150 nonallergic controls (6.9 g) and 160 high-risk controls (1.9 g) [50]. In another study [51], increased household peanut consumption was associated with increased peanut levels in house dust in the eating area and/or in bed. Also, a positive correlation was reported between peanut protein levels in the infant's bed, crib rail, and play area and between household peanut consumption over 1 and 6 months [52]. Not only is peanut protein present in house dust but it was also shown to be biologically active and capable of activating mast cells and basophils [48]. Together, these data suggest another route for sensitization. Epidemiological data are linking potential skin exposure to the development of food allergy. Food allergy and food sensitization are significantly more prevalent in patients with atopic dermatitis and approximately 40% of infants and young children with moderate to severe atopic dermatitis were reported to have food allergy [53]. In addition, peanut allergy in preschool children was independently associated with rash over joints and skin creases, with oozing, and with crusted rash, and was significantly and independently related with the use of skin preparations containing peanut oil [10]. Filaggrin loss-of-function mutations, which lead to an impaired skin barrier and are associated with atopic dermatitis, were independently associated with peanut sensitization and peanut allergy in children aged 8–11 years [54]. Further, In peanut allergic patients, peanut-specific T-cell proliferation was found predominantly in the skin-homing [cutaneous lymphocyte antigen (CLA)+] subset of memory T cells, whereas peanut-tolerant groups had a mixed CLA+ and a4b7+ (gastrointestinal homing marker) response. These differences were allergen specific. Moreover, cytokine responses showed trends toward Th1 skewing in the gastrointestinal homing a4b7+ cells of peanut-tolerant groups and Th2 skewing in the skin-homing CLA+ cells of peanut allergic patients [55]. In a recent study, reduction of food sensitization via eczematous skin lesions was attempted by applying emulsion-type moisturizer daily during the first 32 weeks of life to neonates at high risk for atopic dermatitis. A significant reduction in atopic dermatitis/eczema by week 32 was observed in the treatment group, and infants with atopic dermatitis/eczema were more likely to be sensitized to egg, but no significant effect of emollient on allergic sensitization was found [56].

Animal models have provided additional evidence to the potential of the skin to be the site of sensitization. BALB/c mice, which were epicutaneously sensitized to ovalbumin (OVA) by repeated application of OVA to tape-stripped skin over 7 weeks, exhibited expansion of thymic stromal

lymphopoietin-elicited basophils in the skin, IgE-dependent expansion of connective tissue mast cells in the jejunum, increased serum IL-4 levels, and systemic anaphylaxis following oral challenge with OVA [57,58]. Mice which were orally immunized with OVA + cholera toxin failed to increase serum IL-4 levels, expand their intestinal mast cells, or develop anaphylaxis following oral challenge, despite OVA-specific IgE levels, suggesting that the presence of specific IgE is necessary but not sufficient to induce an allergic reaction. In another study, mice exposed to repeated topical peanut protein extract, Ara h 1 or Ara h 2, this time on undamaged areas of skin, were sensitized and responded with anaphylaxis upon rechallenge. Moreover, a topically applied milk allergen α -lactalbumin induced sensitization only in the presence of peanut extract and Ara h 2, suggesting that both serve as adjuvants for bystander sensitization [59].

Taken together, these data are consistent with the hypothesis that allergic sensitization occurs through the skin and that allergen exposure through the gastrointestinal tract induces tolerance.

CONCLUSION

Guidelines for infant feeding with respect to the development of allergy and primarily food allergy have changed dramatically in recent years. The current concept is that sensitization in infancy occurs primarily through the skin and that early oral introduction of allergenic foods might prevent the development of food allergy. Current data suggest that this approach might be beneficial for low-risk infants as well, and that the optimal age for introduction of allergenic foods might be earlier than what is currently recommended.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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