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Allergic reactions in infants using commercial early allergen introduction products

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Allergic Reactions in infants using commercial early allergen introduction products

Clinical implications: Infants using commercial early allergen introduction products for prevention may experience allergic reactions to the product or subsequently, to the natural food. Studies are needed to understand the efficacy and risks related to early allergen introduction.

Consensus recommendations and guidelines have emphasized early introduction-or lack of delaying introduction- of allergens to infants for the possible benefit of reducing the risk of food allergy (FA).¹⁻³ These approaches emphasize a relatively solid evidence base for peanut, with less robust evidence for egg, and extrapolation of evidence for applying these approaches to other foods. Recommending infants ingest foods that are not traditionally offered in early complementary feeding have resulted in parental concerns for choking and allergic reactions and questions regarding safe feeding.⁴ As a result of new recommendations, a growing number of products are now available and marketed to facilitate early allergen introduction, many advertised with implications for FA prevention.⁵ However, the prevention impact of these products has not been studied directly. Only one study evaluated the acceptability and tolerance of a multi-allergen product but did not evaluate efficacy and excluded infants with increased risk of FA (severe eczema or previous FA diagnosis).⁶

We took note of allergic reactions occurring to these products or to natural versions of the foods (*i.e.* cheese, yogurt, well-cooked egg, peanut and tree nut butters or other infant-safe forms) in infants fed these products. Here, we present a series of infants from our pediatric allergy practice at the Jaffe Food Allergy Institute at Mount Sinai in New York who were exposed to commercial early allergen introduction products yet developed FA. Twelve cases were brought to our attention by the 10 allergists in our referral-based practice, where approximately 1200 infants underwent consultation for FA during

this 27-month period. Medical record review and reporting were approved by our Institutional Review Board.

From December 2018 to February 2021, we identified 12 infants fed a commercial early allergen introduction product who either reacted to the product or subsequently developed a FA to one of the foods in the product. **Table e1** in the online repository presents the allergenic ingredients and the protein content of allergens included in the products. **Table 1** describes the product(s) used, age started, reaction trigger and symptoms. **Table e2** in the online repository provides additional data on each patient including relevant skin prick test results, serum food-specific IgE levels, and atopic conditions.

Three infants had a reaction to the first ingestion of the product. Patient #3 was fed 2 different products at different times; the first product was tolerated, but the infant reacted upon first exposure to the second product. The remaining 2 infants reacting on first exposure had mild (patient #1) and severe (patient #11) reactions. None of these 3 families continued the product. Patient #5 had a mild rash from the product but the family did not view this as a reaction until they noted reaction to the natural food. Another 8 patients experienced an allergic reaction to a natural form of food that had been an ingredient in the product. Of those patients, 5 families decided to continue giving the commercial product, however they excluded the natural form of the allergen from the infant diet.

At least two infants developed FA with interruptions in the product feeding schedule (patients 2 and 12), or with no exposure to the product or the natural form of food for an extended period (patient 4), while other patients developed allergy after completion of the products' recommended feeding schedule (patients 3 and 6).

The specific product components or natural foods to which these patients developed allergy varied. The severity of allergic reactions varied from mild localized dermatologic symptoms in 9 patients, and 3 patients experiencing systemic reactions. One of these 3 infants had a severe reaction with urticaria, vomiting, and lethargy and was monitored in an emergency department, but no infant was treated with

epinephrine, nor required hospitalization. Diagnostic tests among the 12 patients confirmed allergic sensitization to egg, milk, peanut, and tree nuts (Table e2).

Of note, 11 infants had a history of eczema (10 mild, 1 moderately severe), and 9 had a first-degree family history of FA in either a sibling or parent. (Table e2). Three patients had FA that developed prior to these products being introduced or developed FA to foods not in the specific products which they were fed; these foods included sesame, fish, shellfish, avocado, mango, banana, milk and egg. While Bamba™ was the form of peanut offered to infants in the Learning Early About Peanut Allergy (LEAP) study,⁷ we note that none of the patients in our series had selected Bamba™ for introducing peanut to their infants. We do not however expect that it would behave differently from peanut butter, as both are made from dry roasted peanut.

It is natural to question whether the regimen provided by these commercial products may prevent allergy. The best evidence regarding allergy prevention by early introduction regards peanut.^{1-3,7} Seven of our cases involved peanut. Recommendations about dosing with 2 grams 3 times per week are aimed at those with severe eczema² and mirror the approach taken in the LEAP trial by Du Toit et al that showed high efficacy.^{7,8} Based on the study by Perkin et al, dosing of peanut and egg with gram quantities are needed to achieve a prevention effect.⁹ There are no additional published studies of other amounts and frequencies of allergen ingestion, but some of the commercial products used by those in this report have amounts of peanut or egg far below the amounts shown effective in the aforementioned studies.^{7,9} The products with mixed tree nut allergens also generally have quantities well below those suggesting efficacy if extrapolated from peanut and egg studies.

There are intrinsic limitations to conclusions that can be drawn from case series. Although caution is needed, it is interesting to note that several patients continued the commercial product after reacting to the natural form, suggesting a threshold of allergy above the amount in the commercial product. We cannot make comments about general safety or efficacy of these products. The families using these products perceived risk factors for developing allergy in their children, but this report should not be

used to suggest early introduction (with these commercial products or with natural forms of foods) is a risk nor that following current guidance is futile or particularly dangerous. There are however, no efficacy studies using commercial early introduction products for FA prevention. We also do not have evidenced-based recommendations regarding the ideal timing of introduction, frequency of feeding, or duration of regular exposures that are needed for preventing FA. There is a critical need for additional studies about allergen prevention through early introduction.

The convenience of commercial early introduction products is alluring. Still, several factors should be considered when selecting a commercial product, or selecting such products over a conventional food form, including expense, nutritional composition, and whether the dose and processing of food allergens are comparable to the food forms that will be naturally eaten, or are recommended by international guidelines as recently reviewed by Schroer et al.⁵ The reports here underscore the many factors to be considered, that allergic reactions and failure of prevention can occur and should be acknowledged in shared decision-making with families.

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Pt	Product contents	Age of Introduction of product (months)	Reaction at first introduction of product	Description of reaction (to product or natural food)	Continued Feeding of Product?	Allergies Diagnosed
1	Peanut, Egg, TN, Soy, Wheat, Sesame, Shrimp, Codfish (Inspired Start)	6	YES	Reaction to product at 6 months – perioral urticaria, urticaria on arm Reaction to 1 tsp peanut butter (OFC) at 6 months – perioral and trunk urticaria	No	Peanut
2	Peanut (Hello, Peanut!)	7	NO	No reaction to product given at 7 months Reaction to peanut butter at 8 months – trunk urticaria	Yes	Peanut
3	Peanut, Egg, TN, Soy, Wheat, Sesame, Shrimp, Codfish (Inspired Start) Peanut, Egg, Milk (Ready, Set Food!)	4 5	NO (Inspired Start) YES (Ready, Set Food!)	Reaction to Inspired Start at 5 months – perioral erythema, resolved with continuation of product Reaction to Ready, Set, Food! at 5 1/2 months – facial angioedema, facial flushing and facial urticaria Reaction to ½ tsp peanut butter (OFC) at 6 months - urticaria on hands, unilateral conjunctival injection, periocular rash, pruritus	Yes (Inspired Start)) No (Ready, Set, Food!)	Peanut
4	Peanut, Egg, TN, Soy, Wheat, Sesame, Shrimp, Codfish (Inspired Start)	5	NO	No reaction to product Discontinued product at 7 months, introduced natural forms of all foods except walnut + cashew Reaction to cashew butter at 18 months – urticaria (face and extremities), facial erythema	Yes	Cashew, Pistachio
5	Peanut, egg,	7	NO (not	Reaction to product at 7	No	Tree nuts

	milk, TN, soy, wheat, oat, sesame shrimp, cod, salmon (Spoonful One)		perceived until later)	months – mild rash Reaction to pecan nut pieces at 11-12 months – perioral + upper chest rash Reaction to walnut pieces at 12 months – rash with skin contact		(Walnut, Pecan)
6	Peanut, egg, milk (Ready, Set, Food!)	4	NO	No reaction to product Reaction to ¼ scrambled egg at 4 months – vomiting, facial urticaria	Yes	Peanut, egg
7	Egg, milk (Ready, Set, Food!)	6	NO	Reaction to egg in product at 6 months – vomiting (Did not advance to peanut containing packet) Reaction to peanut butter (1/8 tsp) at 11 months during OFC – hand urticaria and pruritus, vomiting, eye irritation Reaction to milk (cooked cheese and yogurt) at 12 months – urticaria, eczema flare	No	Egg, peanut, milk
8	Peanut, egg, milk, TN, soy, wheat, oat, sesame shrimp, cod, salmon (SpoonfulOne)	9	NO	No reaction to product Reaction to scrambled egg at 9 months – generalized hives, vomiting Reaction to baked egg (in meatballs) at 12 months – cough, facial swelling, facial erythroderma	Yes	Egg
9	Peanut, egg, milk (Ready, Set, Food!)	5	NO	Reaction to egg in product at 5 months – perioral erythema and hives	No	Egg
10	Peanut, egg, milk, TN, soy, wheat, oat, sesame shrimp, cod, salmon	6	NO	No reaction to product Reaction to peanut butter (1/3 tsp) at 9 months – perioral hives	No	Peanut

	(SpoonfulOne)					
11	Mixed TN (Lil Mixins)	5	YES	Reaction to product at 5 months – urticaria, vomiting, lethargy	No	Cashew, Pistachio
12	Peanut, egg milk (Ready, Set, Food!)	5	NO	Reaction to peanut in product at 7 months – perioral and neck urticaria	No	Peanut

Table 1. Description of products introduced, allergic symptoms observed and diagnosed FA for each patient in this series. (TN = tree nuts; see Table e1 for specific tree nuts)

Supplemental tables (for online repository)

Brand	Allergen(s)	Protein content per recommended serving*
Inspired Start**	Pack 1: Peanut, egg, walnut, cashew, almond, soy Pack 2: Wheat, sesame, shrimp, cod	1g each food
Hello, Peanut!	Peanut	1g peanut in maintenance packet
Ready, Set, Food!	Peanut, egg, milk	0.43g milk, 0.125g egg, 0.43g peanut
SpoonfulOne	Peanut, egg, milk, walnut, cashew, almond, hazelnut, pecan, pistachio, soy, wheat, oat, sesame, shrimp, cod, salmon	0.03g each food
Lil Mixins	Almond, pistachio, hazelnut, and walnut	2g mixed tree nuts

Table e1. Early allergen products used by patients in case series and allergen components of the products

*Information adapted from (1)

**product no longer commercially available.

Patient	Breast-fed (BF), Formula-fed, or Both	First Degree Family History of FA (Parent, Sibling, Both)	Personal Atopic History	SPT result (wheal diameter in mm)	Relevant IgE levels (kUA/L)
1	Both	Yes (Sibling)	Mild eczema	Peanut: 5	IgE Peanut: 0.17 IgE Ara h2: 0.15
2	Both	Yes (Parent)	Mild eczema, other FA	Peanut: 5	IgE Peanut: 12.9 IgE Ara h2: 0.97
3	Both	Yes (Sibling)	Mild eczema	Peanut: 8	IgE Peanut: 1.37 IgE Ara h2: 0.99
4	BF	No	Mild eczema	Cashew: 8 Pistachio: 8	IgE Cashew: 1.11 IgE Ana O3: 1.23 IgE Pistachio: 0.75
5	BF	No	Mild eczema, other FA	Walnut: 3 Pecan: 3	IgE Walnut: 7.71 IgE Pecan: 1.41
6	BF	Yes (Sibling)	Mild eczema, other FA	Egg White: 0 Peanut: 3	Not done for this patient
7	BF	No	Moderate eczema	Egg White: 11 Peanut: 7 Milk: 11	IgE Egg white: 43.1 IgE Ovomucoid: 27.0 IgE Peanut: 30.7 IgE Ara h2: 18 IgE Milk: 36.1 IgE Casein: 35.2
8	Both	Yes (Sibling)	Mild eczema	Egg White: 15	IgE Egg white: 6.48 IgE Ovomucoid: 4.86
9	Both	Yes (Parent)	None	Egg White: 5	Not done for this patient
10	Both	No	Mild eczema	Peanut: 4	IgE Peanut: 3.95 IgE Ara h2: 1.04
11	Formula	Yes (Parent)	Mild eczema	Cashew: 8	IgE Cashew: 7.64 IgE Ana O3: 5.41 IgE Pistachio: 3.13
12	Both	Yes (Parent)	Mild eczema	Not done for this patient	IgE Peanut: 0.34 IgE Ara h2: 0.49

Table e2. Pertinent medical, diet, and family history of each patient. FA = food allergy