CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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The Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Hydrolyzed Formulas, and Timing of Introduction of Allergenic Complementary Foods

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This clinical report updates and replaces a 2008 clinical report from the American Academy of Pediatrics, which addressed the roles of maternal and early infant diet on the prevention of atopic disease, including atopic dermatitis, asthma, and food allergy. As with the previous report, the available data still limit the ability to draw firm conclusions about various aspects of atopy prevention through early dietary interventions. Current evidence does not support a role for maternal dietary restrictions during pregnancy or lactation. Although there is evidence that exclusive breastfeeding for 3 to 4 months decreases the incidence of eczema in the first 2 years of life, there are no short- or long-term advantages for exclusive breastfeeding beyond 3 to 4 months for prevention of atopic disease. The evidence now suggests that any duration of breastfeeding ≥3 to 4 months is protective against wheezing in the first 2 years of life, and some evidence suggests that longer duration of any breastfeeding protects against asthma even after 5 years of age. No conclusions can be made about the role of breastfeeding in either preventing or delaying the onset of specific food allergies. There is a lack of evidence that partially or extensively hydrolyzed formula prevents atopic disease. There is no evidence that delaying the introduction of allergenic foods, including peanuts, eggs, and fish, beyond 4 to 6 months prevents atopic disease. There is now evidence that early introduction of peanuts may prevent peanut allergy.

abstract

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Drs Greer, Sicherer, and Burks contributed to identification, incorporation, and interpretation of the literature used to compose the report; assisted in drafting, reviewing, and editing the manuscript; and approved the final manuscript as submitted.

To cite: Greer FR, Sicherer SH, Burks AW, AAP COMMITTEE ON NUTRITION, AAP SECTION ON ALLERGY AND IMMUNOLOGY. The Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Hydrolyzed Formulas, and Timing of Introduction of Allergenic Complementary Foods. *Pediatrics*. 2019;143(4): e20190281

The incidence of pediatric atopic diseases, particularly allergic skin disease and food allergy, have appeared to increase from 1997 to 2011.[1] Although atopic diseases have a clear genetic basis, environmental factors, including early infant nutrition, have an important influence on their development. Thus, for pediatric health care providers, there is great interest in early nutritional strategies that may ameliorate or prevent this disease. This clinical report updates and replaces a 2008 clinical report from the American Academy of Pediatrics (AAP), which addressed the roles of maternal and early infant diet on the prevention of atopic disease, including atopic dermatitis, asthma, and food allergy.[2] The literature reviewed for this revised clinical report has largely been focused on new randomized controlled investigations, systematic reviews and meta-analyses, and recent recommendations from other professional groups. Of special note for this updated clinical report are the recently published investigations in which the relationship between the introduction (timing and amount) of complementary foods containing peanut and egg proteins and the development of food allergy is evaluated. On the other hand, information regarding the role of prebiotics and probiotics, vitamin D, and long-chain polyunsaturated fatty acids in the prevention of atopic disease is limited at this time and will not be discussed. This report is not directed at the treatment of atopic disease once an infant or child has developed specific atopic symptoms.

DEFINITIONS

The following definitions are used throughout this clinical report:

- allergy: a hypersensitivity reaction initiated by immunologic mechanisms[3];
- allergenic foods: 8 major groups of allergenic foods that account for approximately 90% of all food allergies and must be declared on labels for processed foods in the United States. These include cow milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybean.[4] More than 170 foods have been described to cause allergic reactions, and additional foods (eg, sesame) are included in labeling laws in other countries[4];
- atopy: a personal or familial tendency to produce immunoglobulin E (IgE) antibodies in response to low-dose allergens, confirmed by a positive skin-prick test result[3];
- atopic disease: a clinical disease characterized by atopy. Atopic disease typically refers to atopic dermatitis, asthma, allergic rhinitis, and food allergy. This report will be limited to the discussion of conditions for which substantial information is available in the medical literature[3];
- atopic dermatitis (eczema): a pruritic, chronic, inflammatory skin disease that commonly presents during early childhood and is often associated with a personal or family history of other atopic diseases[3];
- asthma: an allergic-mediated response in the bronchial airways that is verified by the variation in lung function (measured by spirometry), either spontaneously or after bronchodilating drugs[3];
- complementary foods: foods and/or beverages (liquids, semisolids, and solids) other than human milk, infant formula, and cow's milk (consumed in the first year of life) provided to an infant or young child to provide micro- and macronutrients, including energy[5];
- food allergy: an immunologically mediated hypersensitivity reaction to any food, including IgE-mediated and/or non–IgE-mediated allergic reactions[2];
- hypoallergenic: reduced allergenicity or reduced ability to stimulate an IgE response and induce IgE-mediated reactions[3]; and
- Infants at high risk for developing allergy: infants with at least 1 first-degree relative (parent or sibling) with documented allergic disease.[3] Some of the studies included in this report used different criteria for labeling infants high risk for developing atopic disease.

The following definitions are from various industry sources[2]:

- partially hydrolyzed formula: formula that contains reduced oligopeptides having a molecular weight of generally less than 5000 Da;
- extensively hydrolyzed formula: formula that contains only peptides that have a molecular weight of less than 3000 Da; and
- free amino acid-based formula: peptide-free formula that contains mixtures of essential and nonessential amino acids.

DIETARY RESTRICTIONS FOR PREGNANT AND LACTATING WOMEN

The earliest possible nutritional influence on atopic disease in an infant is the prenatal diet. However, studies have not supported a protective effect of a maternal exclusion diet (including the exclusion of cow's milk, eggs, and peanuts) during pregnancy or during lactation on the development of atopic disease in infants. The 2008 AAP report concluded that there was lack of evidence to support maternal dietary restrictions during pregnancy and lactation to prevent atopic disease.[2] There are no new clinical trials that would change this conclusion for the current report. This conclusion is affirmed in a 2014 a meta-analysis[6] and 2 new systematic reviews.[7,8] In 1 systematic review, the authors noted that

maternal diets rich in fruits and vegetables, fish, and foods containing vitamin D and Mediterranean dietary patterns were among the few consistent associations with lower risk for allergic disease in their children. On the other hand, foods associated with higher risk included vegetable oils and margarine, nuts, and fast food.[8] However, further randomized controlled trials of maternal antigen avoidance with larger sample sizes and longer follow-up are needed.

EXTENT AND DURATION OF BREASTFEEDING ON THE DEVELOPMENT OF ATOPIC DISEASE

Since the 1930s, authors of many studies have examined the impact of breastfeeding on the development of atopic disease. It has been thought that the immunologic components of human milk may modify induction of immune tolerance and decrease the risk of allergic disease. In general, these studies have been nonrandomized, retrospective, or observational in design and have included many cohort studies.

Duration of Exclusive Breastfeeding

The 2008 AAP report concluded that there were no short- or long-term advantages for exclusive breastfeeding beyond 3 to 4 months for prevention of atopic disease.[2] One new meta-analysis looking specifically at the question of duration of exclusive breastfeeding was published in 2012.[9] It included only 3 studies in which exclusive breastfeeding for 3 to 4 months was compared with exclusive breastfeeding for 6 months or longer.[10–12] Of these 3 studies, 1 was a cluster randomized trial with a 6.5 year follow-up.[11] In this meta-analysis, the authors concluded that there was no difference in atopic eczema, asthma, or other atopic outcomes between exclusive breastfeeding for 3 to 4 months versus exclusive breastfeeding for 6 months or longer.[9] Two other new meta-analyses in which exclusive breastfeeding and atopic disease are addressed have also have been published.[13,14] One of these meta-analyses showed that there was no evidence that exclusive breastfeeding (versus any duration of breastfeeding) offered any significant advantage for the prevention of asthma.[13] The second meta-analysis found no significant association between exclusive breastfeeding for ≥3 to 4 months versus breastfeeding for a shorter duration and asthma at 5 to 18 years of age (13 studies).[14] However, this study did find that exclusive breastfeeding for at least 3 to 4 months decreases the cumulative incidence of eczema in the first 2 years of life, with or without any additional breastfeeding.[14] This conclusion is unchanged from the 2008 AAP report.[2]

Breastfeeding and Asthma

Since the 2008 AAP report,[2] there have been at least 64 new studies on the relationship between asthma and breastfeeding. Descriptions of these studies can be found in 3 new systematic reviews of the relationship between asthma and breastfeeding.[13–15] All 3 reviews concluded that there were concerns about combining the results of these studies given the high degree of heterogeneity among the included studies, with Dogaru et al[13] reporting that the index of heterogeneity (I^2) among the studies was high, ranging from 71% to 92%.

In addition to the observation on exclusive breastfeeding and asthma as discussed above, the meta-analysis of Dogaru et al[13] found evidence that more breastfeeding (longer duration) as opposed to less breastfeeding (shorter duration) reduced the risk of asthma across all age groups. The greatest protective effect for duration of any breastfeeding, including exclusive breastfeeding (3–6 months), on the risk of asthma was for the first 2 years of life, during which time period wheezing is associated with childhood illness and not considered to be atopic asthma. There is also some evidence the longer duration was protective against childhood asthma until at least 3 to 6 years of age. This finding supports the rationale that wheezing conditions in infants, typically triggered by viral respiratory infections, may be protected by breastfeeding through reduction in the impact of the infections themselves.

The meta-analysis by Brew et al[15] looked at the relationship between any breastfeeding versus no breastfeeding or exclusive breastfeeding for at least 3 to 4 months versus exclusive breastfeeding for a shorter duration and wheezing in children 5 years of age or older. This study found no evidence that any duration of breastfeeding is protective against wheezing illness in children 5 years and older, emphasizing the differences in the asthma "phenotype," or early childhood wheezing versus wheezing beyond 5 years of age. On the other hand, Lodge et al[14] pooled the results of 29 studies that looked at more versus less of any category of breastfeeding (ever versus never [n = 8]; exclusive versus other [n = 13]; more versus less [n = 8]) and found that there was a reduced risk of asthma with longer versus shorter duration of any breastfeeding at 5 to 18 years of age (odds ratio [OR], 0.90; 95% confidence interval [CI], 0.84–0.97; I^2, 63%). Categorizing studies as "more versus less" breastfeeding allowed for inclusion of more studies and might have accounted for the difference in results in the Lodge et al[14] versus Brew et al[15] meta-analysis in older children. The Lodge et al[14] study also found a protective effect of ever breastfeeding versus never breastfeeding on asthma from 5 to 18 years of age when the estimates from 3 cohort studies and 10 cross-

sectional studies were pooled (OR, 0.88; 95% CI, 0.82–0.95, I^2, 44%).

The 2008 AAP report concluded that exclusive breastfeeding for at least 3 months protects against wheezing early in life.[2] In addition, newer evidence now suggests that the protection of breastfeeding in early childhood (wheezing in the first 2 years) occurs because of duration of any breastfeeding, not just exclusive breastfeeding. Unlike in 2008, there is now evidence that longer duration of breastfeeding may protect against asthma after 5 years of age.

Breastfeeding and Eczema

Since publication of the 2008 AAP report, there have been 2 meta-analyses and approximately 7 new studies on the relationship between breastfeeding and childhood eczema (follow-up up to age 7 years). In a meta-analysis by Yang et al,[16] the authors concluded that there was no protective effect of breastfeeding for ≥3 months compared with breastfeeding for a shorter duration or infant formula feeding, even in children with a family history of allergy (OR, 0.78; 95% CI, 0.58–1.05). A second meta-analysis that included 15 cohort studies (7 of which were published since the 2008 AAP report) found no protection of the exposure for more versus less of any duration of breastfeeding and the risk of eczema up to 2 years of age (OR, 0.95; 95% CI, 0.85–1.07).[13] However, another analysis in this same study (pooling only 6 cohort studies in which exclusive breastfeeding for at least 3 to 4 months was compared with a shorter duration of breastfeeding) revealed a significantly reduced risk of eczema below the age of 2 years (OR, 0.74; 95% CI, 0.57–0.97).[13] No association was found between breastfeeding and eczema beyond 2 years of age in this study, again suggesting that protection afforded by breastfeeding may be limited to the infantile eczema phenotype. This study, limiting the analysis to only infants with a family history of atopic disease (7 studies), did not change the results for eczema.[13]

In summary, there is evidence that exclusive breastfeeding for at least 3 to 4 months decreases the cumulative incidence of atopic dermatitis in the first 2 years of life. This is similar to the results found in the Duration of Exclusive Breastfeeding section, noted earlier in this report. There is no evidence that longer duration of any breastfeeding affects the outcome.

Breastfeeding and Food Allergy

Data are insufficient regarding a direct relationship of breastfeeding on food allergy outcomes. It has been suggested that the early introduction of allergenic foods while breastfeeding might be protective against development of food allergy. However, there are no published trials directly comparing timing of introduction of allergenic foods in exclusively formula-fed versus exclusively breastfed infants on the development of food allergy. In the recent Enquiring About Tolerance (EAT) trial in infants who were breastfed, discussed in more detail elsewhere in this report, the goal was to determine if the early introduction of common allergenic foods at 3 months of age in infants who were exclusively breastfed in the general population would prevent food allergies, but the control group was both breastfed and formula fed.[17] Similarly, in the Learning Early About Peanut Allergy (LEAP) trial (described in more detail later), in which infants were randomly assigned to ingest or avoid peanuts, the subjects were mainly infants who were breastfed (92%), without sufficient controls to evaluate the effect of breastfeeding itself on peanut allergy outcomes.[18]

In summary, as in the 2008 report,[2] no conclusions can be made about the role of breastfeeding in either preventing or delaying the onset of specific food allergies.

THE ROLE OF HYDROLYZED FORMULAS ON THE DEVELOPMENT OF ATOPIC DISEASE

The role of partially hydrolyzed and extensively hydrolyzed formulas in the prevention of atopic disease has been the subject of many studies, and it has been suggested that if high-risk infants cannot be exclusively breastfed, use of such formulas will prevent atopic disease. Since the AAP report was published in 2008, 1 randomized trial of partially hydrolyzed formula and 1 meta-analysis of the effects of hydrolyzed formula on allergic disease were published.[19,20] There is also a new trial in which a partially hydrolyzed formula is compared with added prebiotics to a standard formula for the prevention of atopic disease.[21] In addition, for a study initially cited in the AAP 2008 report (the German Infant Nutritional Intervention study), there is now a 10-year follow-up of the effects of partially and extensively hydrolyzed infant formulas on atopic disease.[22] The overall results of these new studies have weakened previous conclusions that there was modest evidence that the use of either partially or extensively hydrolyzed formula prevents atopic dermatitis in high-risk infants who are formula fed or initially breastfed after birth.

In a study published in 2011 by Lowe et al,[19] 620 infants with a family history of allergic disease were randomly assigned to receive standard cow's milk formula, partially hydrolyzed formula, or soy formula after cessation of breastfeeding. Fifty percent of the infants were receiving their allotted formula by 4 months of age. The primary outcome was development of allergic manifestations (eczema and food reactions) measured 18 times in the first 2 years of life, with follow-up until 6 or 7 years of age. There was no

evidence that infants allocated to partially hydrolyzed formula were at a lower risk for allergic manifestations in infancy compared with infants allocated to conventional formula (OR, 1.21; 95% CI, 0.81–1.80). Similarly, in the new trial of the combination of partially hydrolyzed protein and prebiotics in an infant formula, there was no impact on eczema at 12 months of age, compared with a standard formula in high-risk infants (OR, 0.99; 95% CI, 0.71–1.37).[21]

In the 10-year follow-up to the 2003 German Infant Nutritional Intervention study (cited in the 2008 report), the relative risk (RR) for the cumulative incidence of any allergic disease through 10 years of age in the intention-to-treat analysis (n = 2252) was 0.87 (95% CI, 0.77–0.99) for the partially hydrolyzed whey-based formula, 0.94 (95% CI, 0.83–1.07) for the extensively hydrolyzed whey-based formula, and 0.83 (95% CI, 0.72–0.95) for the extensively hydrolyzed casein-based formula, compared with standard cow's milk formula. The corresponding figures for atopic eczema and/or dermatitis were 0.82 (95% CI, 0.68–1.00) for partially hydrolyzed whey-based formula, 0.91 (95% CI, 0.76–1.10) for extensively hydrolyzed whey-based formula, and 0.72 (95% CI, 0.58–0.88) for extensively hydrolyzed casein-based formula, compared with standard cow's milk formula.[22] Although the prevalence of atopic dermatitis at 7 to 10 years of age was significantly reduced with extensively hydrolyzed casein-based formula, there was no preventive effect on asthma or allergic rhinitis. The study was weakened by the 37% drop-out rate at 10 years; thus, the authors concluded that there was insufficient evidence of ongoing preventive activity of hydrolyzed formulas between 7 and 10 years of age for prevention of atopic disease.

The 2016 meta-analysis by Boyle et al,[20] which included 37 studies, found no consistent evidence to support a protective role of partially or extensively hydrolyzed formula for reducing risk of allergic disease, even in high-risk infants. This review included studies of any hydrolyzed formula of cow's milk origin as the intervention of interest, compared with any nonhydrolyzed cow's milk formula or human milk. Also included were studies in which hydrolyzed formula was given as part of a multifaceted intervention. ORs for eczema at age 0 to 4 years, compared with standard cow milk formula, were 0.84 (95% CI, 0.67–1.07) for partially hydrolyzed formula, 0.55 (95% CI, 0.28–1.09) for extensively hydrolyzed casein-based formula, and 1.12 (95% CI, 0.88–1.42) for extensively hydrolyzed whey-based formula.

In summary, there is lack of evidence that partially or extensively hydrolyzed formula prevents atopic disease in infants and children, even in those at high risk for allergic disease. This point is a change from the 2008 AAP clinical report, which concluded that there was modest evidence that the use of either partially or exclusively hydrolyzed formula prevents atopic dermatitis in high-risk infants who are formula fed or initially breastfed after birth.

TIMING OF INTRODUCTION OF ALLERGENIC COMPLEMENTARY FOODS AND FOOD ALLERGY

Since the 2008 AAP report, there has been considerable new information published relative to the timing of introduction of allergenic complementary foods and the subsequent development of food allergy. There have been 7 new randomized controlled trials[17,23–28] and 1 new meta-analysis that includes these studies.[29] Egg allergy was evaluated in 6 trials,[17,24–28] and peanut allergy was evaluated in 2 trials.[17,23]

In the EAT study on the timing of introduction of allergenic complementary foods in infants who were breastfed, all infants in the early introduction group (n = 567) were exclusively breastfeeding at 3 months of age and still breastfeeding at 5 months.[17] Six different allergenic foods were introduced between 3 and 5 months of age (median age, 3.4 months): peanut (peanut butter), cooked egg (1 small hardboiled egg), cow's milk, sesame, whitefish, and wheat. In the standard introduction group (n = 595), the allergenic foods were not introduced before 5 months, at which time all infants were still breastfeeding but consuming up to 300 mL of formula per day. In the intention-to-treat analysis, food allergy developed in 5.6% of the subjects in the early introduction group (mostly breastfeeding) and in 7.1% of the subjects in the standard introduction group (mixed feeding), a difference that was not significant. However, only 43% of participants in the early introduction group could follow the protocol, presumably because many of the infants were not developmentally ready to accept complementary foods at 3 months of age or because parents observed avoidance behaviors, leading to their cessation (reverse causality). However, in the per-protocol analysis, the prevalence of any food allergy was lower in the early introduction group than in the standard introduction group (2.4% vs 7.3%; P = .01). For the prevalence of specific food allergies in the per-protocol analysis, there was a significant protective effect of early consumption of both peanuts (0% vs 2.5%; P = .003) and eggs (1.4% vs 5.5%; P = .009). This was not observed for any of the other allergenic foods introduced.[17] The data were analyzed according to allergy outcomes and mean weekly dose ingested; consumption of 2 g/week of peanut or egg-white protein was associated with a significantly

lower prevalence of these allergies, respectively, compared with less consumption. This subgroup analysis suggests that in infants who are breastfed, prevention of peanut and egg allergy (see discussion below) may depend on the amount and duration of early exposure.

In the LEAP trial of the early introduction of peanut products, 640 infants who were severely atopic (severe eczema and/or egg allergy) 4 to 11 months of age were randomly assigned to consume 6 g of peanut protein per week (Bamba or cooked peanut product) or to avoid peanut protein until age 60 months.[23] Infants were given skin-prick tests for peanuts, and all infants randomly assigned to the early consumption group underwent an open-label food challenge to ensure tolerance before incorporating peanuts into the diet. The mean age at randomization was 7.8 ± 1.7 months, but only 18% (116 infants) of the total cohort was younger than 6 months at the time of the first peanut introduction. Ninety percent of the subjects had received formula at the time of randomization; 42% of the subjects were still breastfeeding at the time of randomization, and in these 268 infants, breastfeeding continued for an average of 4.8 ± 4.9 months after randomization. There were no differences between the intervention and control groups in breastfeeding characteristics. Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months (blinded food-challenge test) was 13.7% in the avoidance group and 1.9% in the early peanut consumption group, an 11.8 percentage point reduction (95% CI, 3.4–20.3; $P < .001$). This represents an 86% reduction in peanut allergy. Among infants who had an initial positive result on the skin-prick test ($n = 98$) who still participated in the protocol and underwent random assignment, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the early consumption group ($P = .004$; 70% RR reduction). A follow-up study revealed that this approach was long-lasting, demonstrating induction of tolerance rather than transient desensitization.[30]

A meta-analysis of the LEAP and the EAT studies revealed that, for peanut allergy, early peanut introduction at 4 to 11 months of age was associated with a reduced risk of peanut allergy (RR, 0.29; 95% CI, 0.11–0.74; $I^2 = 66\%$; $P = .009$).[29] Largely on the basis of the results of the LEAP trial, an expert panel recently advised peanut introduction as early as 4 to 6 months of age in infants at high risk (presence of severe eczema and/or egg allergy).[31] Given that the pathophysiology of protection is likely to be similar for infants at a lower risk and on the basis of additional studies in an unselected population, the guidelines based the timing of early peanut introduction on the degree of risk (see below).[31]

Egg allergy is a common early food allergy. Six new studies have been published since the 2008 AAP report regarding the early introduction of eggs for the prevention of egg allergy.[17,24–28] There are significant differences among all of these studies, including the risk characteristics of the population exposed, differences in dosing of eggs, and the formulation of the egg introduced.

Two recent studies using heated forms of egg showed a benefit of early egg introduction for prevention of egg allergy. In the first of these 2 studies, the EAT trial (discussed previously), authors concluded that, in a subgroup analysis of the 43% of the subjects who completed the protocol, the introduction of whole boiled eggs between 3 and 5 months of age significantly reduced the prevalence of egg allergy.[17] The poorest compliance rate for individual foods introduced was for eggs (43%), which may reflect the poor acceptance of the texture of hardboiled eggs by the infants or subtle infant avoidance behavior observed by parents. Only 3 infants in the early introduction group demonstrated egg allergy at baseline (oral food-challenge test) and were not exposed to additional egg protein.

In a second randomized controlled trial, Natsume et al[24] introduced infants to increasing amounts of heated whole-egg powder in a stepwise approach, beginning with 50 mg at 6 months of age and increasing to 250 mg at 9 months of age. The final outcome was an open oral food-challenge test at 12 months, assessed blindly by standardized methods by using the same product given for the intervention. In the primary analysis population, 5 (8%) of 60 participants had an egg allergy in the egg group, compared with 23 (38%) of 61 in the placebo group. This difference was highly significant ($P < .0002$; RR, 0.221; 95% CI, 0.09–0.543; $P = .001$). The 90% compliance rate was much higher than that in the EAT study.[17] Of note, the study was terminated early after an interim analysis of the first 100 patients revealed a significant difference between groups. In this study, the authors concluded that heated whole-egg powder introduced in a stepwise manner prevents egg allergy in high-risk infants.

In 2 studies, pasteurized, uncooked egg-white powder was used, with differing results.[25,26] In the Hen's Egg Allergy Prevention trial, a randomized placebo-controlled trial of early egg introduction in 383 infants between 4 and 6 months, the primary outcome was sensitization to hen eggs (increased serum IgE levels) by age 12 months. The secondary outcome was confirmation of hen egg allergy by clinical reaction to pasteurized hen eggs on an oral food-challenge test. The study was terminated early because of the

increased sensitization rate in the early egg introduction (4–6 months) group at 12 months of age. The authors of the study concluded that there was no evidence that consumption of hen eggs in the amount of 1 egg per week in its most allergic form, starting at 4 to 6 months age, prevents hen egg sensitization in a general population.[25] However, the authors acknowledged that additional data were needed to determine if eggs introduced even earlier than 4 months or in a less allergic form may prevent egg food allergy. In a second randomized trial of egg-white power introduced between 4 and 6 months of age in 319 infants, the primary outcome was a positive result on the skin-prick test at 12 months of age.[26] Egg sensitization (skin prick) was significantly reduced at 12 months in the egg group (10.7%) compared with placebo group (20.5%), with an OR of 0.46 (95% CI, 0.22–0.95; $P = .03$).[26]

In 2 additional randomized studies from the same Australian investigators, pasteurized, raw whole-egg powder was used versus rice powder as the control.[27,28] In the smaller of these 2 studies, 86 infants at high risk with moderate to severe eczema were randomly assigned at 4 months of age and continued on daily egg or rice powder until 8 months of age. At 8 months of age, cooked egg was introduced to both groups.[27] The primary outcome was IgE-mediated egg allergy at 12 months of age on the basis of results of an observed pasteurized raw-egg challenge and skin-prick testing. At 12 months of age, a lower proportion of infants in the egg group (33%) were given a diagnosis of IgE-mediated egg allergy compared with controls (51%), but the results were not significant (RR, 0.65; 95% CI, 0.38–1.11; $P = .11$). Of note, this study was not sufficiently powered to rule out a significant difference, as acknowledged by the authors. In the second, much larger, study, more than 800 infants (without a diagnosis of eczema) were randomly assigned at 4 to 6 months of age to consume pasteurized, raw whole-egg powder (0.4 g) or rice powder daily until 10 months of age.[28] Cooked whole egg was then introduced to both groups. Again, the primary outcome was IgE-mediated egg allergy by a positive result on a pasteurized raw-egg challenge and egg sensitization at 12 months of age. However, the study revealed no evidence that raw-egg intake from 4 to 6 months of age significantly altered the risk of egg allergy by age 1 year (7.0% in the egg group versus 10.3% in the control group; RR, 0.75; 95% CI, 0.48–1.17; $P = .20$). The authors did note that 90% of infants who had a reaction to the pasteurized raw-egg challenge were tolerating cooked eggs in their diet at 12 months of age, which raises the question of how many infants would have had egg allergy diagnosed if whole cooked egg rather than raw egg was used for the oral food-challenge test.

In a 2016 meta-analysis that included $5^{17,24–27}$ of these 6 studies, the authors concluded that there was moderate certainty of evidence from the 5 trials (1915 participants) that early egg introduction at 4 to 6 months of age was associated with reduced egg allergy risks (RR, 0.56; 95% CI, 0.36–0.87; $I^2 = 36\%$; $P = .009$).[29] In a number of these studies, it was reported that many of the infants tested positive for the presence of an egg allergy (range, 5% to 31%) before random assignment at 4 to 6 months of age, suggesting that 4 months may be too late for the introduction of eggs to prevent egg allergy.[25–27] In addition, it is not clear from these studies that early introduction of cooked eggs, as opposed to more reactive raw eggs, may decrease the prevalence of egg allergy. These are questions that must be addressed in future studies. For egg introduction, thousands of additional trial participants would be needed to confirm with reasonable certainty that early egg introduction has an effect size of a 30% reduction.[32]

Since the publication of the LEAP and EAT trials, there have been revised recommendations from a number of groups regarding the early nutritional interventions for the prevention of atopic disease, specifically regarding food allergies.[31,33–36] In general, these groups have acknowledged that there is no need to delay the introduction of allergenic foods beyond 6 months of age and that they should not be introduced before 4 months of age. An expert panel from the National Institute of Allergy and Infectious Diseases has recommended a 3-pronged approach,[31] specifically for the introduction of infant-safe forms of peanuts to infants, on the basis of the level of risk for peanut allergy and the results of the LEAP trial.[23] The AAP has endorsed these guidelines.[37] These guidelines are detailed and resource intense, and evaluation of their implementation requires more study. The details of the guidelines are not reiterated here, but briefly, infants with severe eczema, egg allergy, or both (highest risk) should have peanuts introduced as early as between 4 and 6 months of age (peanut allergy testing before introduction is recommended). This highest-risk group is the only one for which testing for peanut allergy is recommended. For infants with mild to moderate eczema (less risk), peanuts should be introduced as early as 6 months of age. For infants with no history of eczema or food allergy (lowest risk), peanuts should be introduced when age appropriate and in accordance with family preferences and cultural practices (ie, 6 months and later for infants who are exclusively breastfed). The level of evidence for the recommendations for infants other than those in the highest-risk category is not based on

randomized controlled trials, especially for those in the lowest risk group. It is hoped that the screening process for the infants at highest risk (specific IgE measurement, skin-prick test, and oral food-challenge test) will not be a deterrent or generate "screening creep" for infants not in the high-risk category. Furthermore, these guidelines may be difficult to follow in communities where there is no access to the medical care needed for their implementation. Information on how these guidelines are being adopted in clinical settings is needed. It is hoped that further research will provide more information on how to introduce peanuts to populations not at risk for peanut allergy.

In the 2008 clinical report, the AAP concluded that there was no convincing evidence of benefit for delaying the introduction allergenic foods beyond 4 to 6 months for the prevention of atopic disease, including peanuts, eggs, and fish.[2] This conclusion has not changed. However, there is now strong evidence from a randomized trial that purposeful early introduction of peanuts may prevent peanut allergies in high-risk infants, resulting in the recommendation to introduce peanut protein as early as between 4 and 6 months. As reviewed previously, the data supporting a beneficial effect of early introduction of eggs is less clear.

SUMMARY AND RECOMMENDATIONS

As with the previous 2008 AAP clinical report, the available data still limit the ability to draw firm conclusions about various aspects of atopy prevention through early dietary interventions. The statements below summarize the current evidence within the context of the limitations of the published reports.

1. There is lack of evidence to support maternal dietary restrictions either during pregnancy or during lactation to prevent atopic disease. This conclusion is unchanged from the 2008 report.
2. The evidence regarding the role of breastfeeding in the prevention of atopic disease can be summarized as follows:
   A. There is evidence that exclusive breastfeeding for the first 3 to 4 months decreases the cumulative incidence of eczema in the first 2 years of life. This conclusion is unchanged from the 2008 report;
   B. There are no short- or long-term advantages for exclusive breastfeeding beyond 3 to 4 months for prevention of atopic disease. This conclusion is unchanged from the 2008 report;
   C. The evidence now suggests that any duration of breastfeeding beyond 3 to 4 months is protective against wheezing in the first 2 years of life. This effect is irrespective of duration of exclusivity. This conclusion differs slightly from the 2008 report, which stated that exclusive breastfeeding for at least 3 months protects against wheezing early in life;
   D. unlike the 2008 report, there is now some evidence that longer duration of any breastfeeding, as opposed to less breastfeeding, protects against asthma, even after 5 years of age; and
   E. similar to the 2008 report, no conclusions can be made about the role of any duration of breastfeeding in either preventing or delaying the onset of specific food allergies.
3. There is lack of evidence that partially or extensively hydrolyzed formula prevents atopic disease in infants and children, even in those at high risk for allergic disease. This is a change from the 2008 report, in which the AAP concluded that there was modest evidence that hydrolyzed formulas delayed or prevented atopic dermatitis in infants who were formula fed or not exclusively breastfed for 3 to 4 months.[2]
4. The current evidence for the importance of the timing of introduction of allergenic foods and the prevention of atopic disease can be summarized as follows:
   A. There is no evidence that delaying the introduction of allergenic foods, including peanuts, eggs, and fish, beyond 4 to 6 months prevents atopic disease. This conclusion has not changed from the 2008 report[2];
   B. There is now evidence that the early introduction of infant-safe forms of peanuts reduces the risk for peanut allergies. Data are less clear for timing of introduction of eggs; and
   C. The new recommendations for the prevention of peanut allergy are based largely on the LEAP trial and are endorsed by the AAP.[37] An expert panel has advised peanut introduction as early as 4 to 6 months of age for infants at high risk for peanut allergy (presence of severe eczema and/or egg allergy). The recommendations contain details of implementation for high-risk infants, including appropriate use of testing (specific IgE measurement, skin-prick test, and oral food challenges) and introduction of peanut-containing foods in the health care provider's office versus the home setting, as well as amount and frequency.[31] For infants with mild to moderate eczema, the panel recommended introduction of peanut-containing foods at around 6 months of age, and

for infants at low risk for peanut allergy (no eczema or any food allergy), the panel recommended introduction of peanut-containing food when age appropriate and depending on family preferences and cultural practices (ie, after 6 months of age if exclusively breastfeeding).

5. This report describes means to prevent or delay atopic disease through early dietary intervention. For the child who has developed atopic disease, treatment may require specific identification and restriction of causal food proteins; this topic is not addressed in this report.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
CI: confidence interval
EAT: Enquiring About Tolerance
IgE: immunoglobulin E
LEAP: Learning Early About Peanut Allergy
OR: odds ratio
RR: relative risk

DOI: https://doi.org/10.1542/peds.2019-0281

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Sicherer received royalties from UpToDate and Johns Hopkins University Press; grants to his institution from HAL Allergy Group, Food Allergy Research and Education, the Immune Tolerance Network, and the National Institute of Allergy and Infectious Diseases; and honoraria from the American Academy of Allergy, Asthma, and Immunology (as an associate editor) and is a medical advisor to the Food Allergy Fund and the International Association for Food Protein Enterocolitis. He was a member of the following sponsored expert panel: Guidelines for the Prevention of Peanut Allergy in the United States: Summary of the National Institute of Allergy and Infectious Diseases; and Drs Greer and Burks have indicated they have no potential conflicts of interest to disclose.

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