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CLINICAL REPORT

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

Guidance for the Clinician in Rendering Pediatric Care

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ABSTRACT

This clinical report reviews the nutritional options during pregnancy, lactation, and the first year of life that may affect the development of atopic disease (atopic dermatitis, asthma, food allergy) in early life. It replaces an earlier policy statement from the American Academy of Pediatrics that addressed the use of hypoallergenic infant formulas and included provisional recommendations for dietary management for the prevention of atopic disease. The documented benefits of nutritional intervention that may prevent or delay the onset of atopic disease are largely limited to infants at high risk of developing allergy (ie, infants with at least 1 first-degree relative [parent or sibling] with allergic disease). Current evidence does not support a major role for maternal dietary restrictions during pregnancy or lactation. There is evidence that breastfeeding for at least 4 months, compared with feeding formula made with intact cow milk protein, prevents or delays the occurrence of atopic dermatitis, cow milk allergy, and wheezing in early childhood. In studies of infants at high risk of atopy and who are not exclusively breastfed for 4 to 6 months, there is modest evidence that the onset of atopic disease may be delayed or prevented by the use of hydrolyzed formulas compared with formula made with intact cow milk protein, particularly for atopic dermatitis. Comparative studies of the various hydrolyzed formulas also indicate that not all formulas have the same protective benefit. There is also little evidence that delaying the timing of the introduction of complementary foods beyond 4 to 6 months of age prevents the occurrence of atopic disease. At present, there are insufficient data to document a protective effect of any dietary intervention beyond 4 to 6 months of age for the development of atopic disease.

INTRODUCTION

Over the past several decades, the incidence of atopic diseases such as asthma, atopic dermatitis, and food allergies has increased dramatically. Among children up to 4 years of age, the incidence of asthma has increased 160%, and the incidence of atopic dermatitis has increased twofold to threefold.[1] The incidence of peanut allergy has also doubled in the past decade.[2] Thus, atopic diseases increasingly are a problem for clinicians who provide health care to children.

It has been recognized that early childhood events, including diet, are likely to be important in the development of both childhood and adult diseases. This clinical report will review the nutritional options during pregnancy, lactation, and the first year of life that may or may not affect the development of atopic disease. Although

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Key Words
atopy, food allergies, breastfeeding, complementary foods, hydrolyzed formula, atopic dermatitis, asthma

Abbreviations
AAP—American Academy of Pediatrics
IgE—immunoglobulin E
OR—odds ratio
CI—confidence interval

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atopic diseases have a clear genetic basis, environmental factors, including early infant nutrition, may have an important influence on their development and, thus, present an opportunity to prevent or delay the onset of the disease. This clinical report replaces an earlier policy statement[3] from the American Academy of Pediatrics (AAP) that addressed the use of hypoallergenic infant formulas and included provisional recommendations for dietary management for the prevention of atopic disease. 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 (adapted from work by Muraro et al[4]):

Allergy: A hypersensitivity reaction initiated by immunologic mechanisms.

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.

Atopic disease: Clinical disease characterized by atopy; 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.

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.

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.

Cow milk allergy: An immunologically mediated hypersensitivity reaction to cow milk, including IgE-mediated and/or non—IgE-mediated allergic reactions.

Food allergy: An immunologically mediated hypersensitivity reaction to any food, including IgE-mediated and/or non—IgE-mediated allergic reactions.

Hypoallergenic: Reduced allergenicity or reduced ability to stimulate an IgE response and induce IgE-mediated reactions.

Infants at high risk of developing allergy: Infants with at least 1 first-degree relative (parent or sibling) with documented allergic disease.

The following definitions are from various industry sources:

Partially hydrolyzed (PH) formula: Contains reduced oligopeptides that have a molecular weight of generally less than 5000 d (Table 1).

Extensively hydrolyzed (EH) formula: Contains only peptides that have a molecular weight of less than 3000 d (Table 1).

Free amino acid—based formula: Peptide-free formula that contains mixtures of essential and nonessential amino acids (Table 1).

TABLE 1 Examples of Hydrolyzed Protein and Amino Acid–Based Infant Formulas Available in the United States

Extensively hydrolyzed casein (cow milk protein)
Enfamil Nutramigen Lipil (Mead Johnson Nutritionals, Evansville, IN)
Enfamil Pregestimil (Mead Johnson Nutritionals)
Similac Alimentum Advance (Ross Products, Columbus, OH)
Partially hydrolyzed whey (cow milk protein)[a]
Good Start Supreme (Nestlé USA, Glendale, CA)
Partially hydrolyzed whey/casein (cow milk protein)[a]
Enfamil Gentlease Lipil (Mead Johnson Nutritionals)
Partially Hydrolyzed Soy (Soy Protein)
Good Start Supreme Soy (Nestlé USA)
Free amino acid–based
Neocate (and Neocate 1+ for children >12 mo) (Nutricia North America, Gaithersburg, MD)
EleCare (Ross Pediatrics)

[a] For infants with known cows milk allergy, the residual milk protein peptides in these formulas may cause an allergic reaction.

DIETARY RESTRICTIONS FOR PREGNANT AND LACTATING WOMEN

The earliest possible nutritional influence on atopic disease in an infant is the diet of the pregnant woman. However, studies generally have not supported a protective effect of a maternal exclusion diet (including the exclusion of cow milk and eggs) during pregnancy on the development of atopic disease in infants, as summarized in a 2006 Cochrane review.[5–10] Although previous AAP publications have suggested that pregnant women avoid peanuts,[3,11] a more recent study has reported that there is no association between the maternal consumption of peanuts during pregnancy and childhood peanut allergy.[12] Previous AAP publications have advised lactating mothers with infants at high risk of developing allergy to avoid peanuts and tree nuts and to consider eliminating eggs, cow milk, and fish from their diets while nursing.[3,11] Dietary food allergens can be detected in breast milk, including peanuts, cow milk protein, and egg.[13–15] Two studies found a preventive effect of maternal dietary exclusion of milk, egg, and fish while breastfeeding on the development of atopic dermatitis in the infant.[16,17] Other studies found no association between the development of atopic diseases and a maternal exclusion diet.[8,18,19] A 2003 study found no association between breastfeeding and peanut allergy, and there was no difference in peanut intake during lactation between mothers with and without children with peanut allergy.[12] Dietary food allergens in human milk may interact with the mucosal immune system[20] and induce allergic reactions in infants who are known to be clinically allergic to the antigen. Rare cases of anaphylaxis to cow milk protein present in human milk have been described even in exclusively breastfed infants.[21]

Consideration of a large number of studies on maternal diet, not all of which were randomized or included dietary restriction during lactation, demonstrated no impact on various outcomes among the majority of the studies, particularly when follow-up was beyond 4 years, and led one recent group of reviewers to conclude that there is no convincing evidence for a long-term preventive effect of maternal diet during lactation on

atopic disease in childhood.[22] A 2006 Cochrane review also concluded that there was insufficient evidence that antigen avoidance during lactation was beneficial in preventing atopic disease in the breastfed infant, with the exception of atopic dermatitis.[5] Because the available published trials have had methodologic shortcomings, more data are necessary to conclude that the avoidance of antigens during lactation prevents atopic dermatitis in infants.[5]

ROLE OF HUMAN MILK AND EXCLUSIVE BREASTFEEDING ON THE DEVELOPMENT OF ATOPIC DISEASE

Since the 1930s, many studies have examined the benefits of breastfeeding on the development of atopic disease. In general, these have been nonrandomized, retrospective, or observational in design and, thus, inconclusive.[22,23] Of course, it is not possible to truly randomize breastfeeding, which is always a confounding variable in these studies. Acknowledging this difficulty, Kramer[23] proposed 12 criteria to apply to studies designed to assess the relationship between atopic disease and breastfeeding. These criteria included nonreliance on late maternal recall of breastfeeding, sufficient duration of exclusive breastfeeding, strict diagnostic criteria for atopic outcomes, assessment of effects of children at high risk of atopic outcomes, and adequate statistical power. Unfortunately, no studies to date have completely fulfilled these criteria.

Atopic Dermatitis

A 2001 meta-analysis of 18 prospective studies compared the incidence of atopic dermatitis in infants who were breastfed versus infants who were fed cow milk formula.[24] Overall, there was a protective effect of exclusive breastfeeding for 3 months (odds ratio [OR]: 0.68; 95% confidence interval [CI]: 0.52–0.88), the stronger effect having been shown for infants with a family history of allergy (OR: 0.58; 95% CI: 0.4–0.92). No protective effect of breastfeeding was seen in children who were not at risk of developing allergy (OR: 1.43; 95% CI: 0.72–2.86).[24] A 2005 study published from Sweden[25] found no effect of exclusive breastfeeding for ≤4 months on the incidence of atopic dermatitis in the first year of life with or without a family history of atopic disease. On the other hand, another 2005 study from Sweden[26] found that exclusive breastfeeding for more than 4 months reduced the risk of atopic dermatitis at 4 years of age (OR: 0.78; 95% CI: 0.63–0.96) with or without a family history of allergy. In their review, Kramer and Kakuma[27] also found no benefit of exclusive breastfeeding beyond 3 months of age on the incidence of atopic dermatitis in studies in which parents were not selected for risk of allergy.

A series of recent reports from the German Infant Nutritional Intervention Program[28–30] also found that breastfeeding reduces the incidence of atopic dermatitis, supporting the results of the meta-analysis.[24] In the interventional arm of this study, 1834 newborn infants identified as being at high risk of developing atopic disease were enrolled in a 3-year longitudinal, prospective study. Breastfeeding infants at risk for atopic disease were enrolled in the study before 14 days of life and, at that time, were exclusively breastfed and had no history of formula supplementation. Infants were randomly assigned at the time of entry to receive supplements of 1 of 3 hydrolyzed formulas (2 extensively hydrolyzed formulas and 1 partially hydrolyzed formula) or a cow milk formula, if formula supplementation had begun. Eight hundred eighty-nine mothers exclusively breastfed for 4 months and did not use any of the formula supplements they were randomly assigned to use. Nine hundred forty-five infants were introduced to the randomly assigned formula before 4 months and, thus, were not exclusively breastfed. Of these, 689 infants were randomly assigned to receive one of the hydrolyzed formulas, and 256 were randomly assigned to receive cow milk formula. The incidence of atopic dermatitis in infants who were exclusively breastfed, breastfed with supplemental hydrolyzed formula, and breastfed with supplemental cow milk formula was 9.5%, 9.8%, and 14.8%, respectively, at the 1-year follow-up.[28–30] Thus, exclusive breastfeeding for 4 months showed a positive effect compared with breastfeeding with supplemental cow milk formula in these infants at high risk of developing allergy. Breastfeeding with supplemental hydrolyzed formula (both partially and extensively hydrolyzed) also showed a positive effect compared with breastfeeding with supplemental cow milk formula; however, breastfeeding with supplements of hydrolyzed formulas showed no advantage compared with exclusive breastfeeding. Both groups showed a one-third decrease in the risk of atopic dermatitis compared with the risk of breastfeeding with supplements of cow milk formula. Thus, exclusive breastfeeding or breastfeeding with hydrolyzed formula is not enough to prevent the majority of cases of atopic dermatitis.

The advantages of breastfeeding are less clear for infants who are not selected for high risk of developing atopic disease, as shown in the noninterventional arm of the German Infant Nutritional Intervention Program.[28] In this arm, mothers unselected for a history of atopy who either formula fed or partially breastfed their infants were free to select cow milk–based or hydrolyzed formulas. No differences in the incidence of atopic dermatitis occurred among the 3 groups of infants (exclusively breastfed for 4 months, cow milk formula fed with or without breastfeeding, and hydrolyzed formula fed with or without breastfeeding). This lack of effect has been attributed to reverse causation; thus, mothers who knew that their infants were at risk of developing allergy were more likely not only to breastfeed but also to breastfeed for a longer period of time. Alternatively, mothers who were not going to breastfeed or were going to supplement with formula were more likely to choose hydrolyzed formula if they believed that their children were at risk of developing atopy. This reverse causation effect may explain why some studies have found an increased incidence of atopic dermatitis in breastfed infants.[31–33]

In summary, for infants at high risk of developing atopy, there is evidence that exclusive breastfeeding for at least 4 months or breastfeeding with supplements of

hydrolyzed infant formulas decreases the risk of atopic dermatitis compared with breastfeeding with supplements of standard cow milk–based formulas. On the basis of currently available evidence, this is less likely to apply to infants who are not at risk of developing atopy, and exclusive breastfeeding beyond 3 to 4 months does not seem to lead to any additional benefit in the incidence of atopic eczema.[27]

Asthma

The evidence for the protective effects of human milk on the development of asthma is more controversial. A 2001 meta-analysis of 12 prospective studies that met preestablished criteria found that exclusive breastfeeding for at least 3 months was protective against the development of asthma between 2 and 5 years of age (OR: 0.70; 95% CI: 0.60–0.81).[34] The effect of breastfeeding was even stronger when the analysis was limited to children from families with a history of atopic disease (OR: 0.52; 95% CI: 0.35–0.79). No benefit was seen in children from families without a history of atopic disease (OR: 0.99; 95% CI: 0.48–2.03).[34] Two more studies[35,36] not included in this meta-analysis supported these results. On the other hand, a 2002 Cochrane review found no benefit of exclusive breastfeeding beyond 3 months on the incidence of asthma in families not preselected for a history of atopic disease.[27]

Two additional reports in the literature with a more accurate definition of asthma[37,38] made a distinction between the wheezy bronchitis associated with viral infections in younger children and that of the allergic disease seen in older children associated with respiratory spirometric changes. In the first of these studies, a cohort of 1246 children in Tucson, Arizona, was followed from birth to 13 years of age.[37] The study found that an association between breastfeeding and asthma at 13 years of age depended on the presence of maternal asthma in children with atopic disease. Infants whose mothers had asthma were at greatest risk of developing asthma by 13 years of age if they had been breastfed exclusively for ≥4 months (OR: 8.7; 95% CI: 3.4–22.2). When infants with atopic disease whose mothers had asthma were exclusively breastfed for any length of time (either greater than or less than 4 months), the risk of developing asthma between 6 and 13 years of age was also increased (OR: 5.7; 95% CI: 2.3–14.1). An increased risk of developing asthma was not found in breastfed children of mothers without asthma. However, in this same study during the first 2 years of life, exclusive breastfeeding was associated with significantly lower rates of recurrent wheezing of infancy (OR: 0.45; 95% CI: 0.2–0.9), similar to results from a recent study performed in Perth, Australia.[35]

In the second of these studies, a long-term longitudinal study from New Zealand,[38] 1037 children from a general population (not selected for risk of allergic disease) were followed from 3 to 26 years of age. Five hundred four infants were breastfed for 4 weeks or more, and 533 infants were formula fed from the time of birth or breastfed for less than 4 weeks. Breastfeeding for more than 4 weeks significantly increased the risk of developing asthma at 9 years (OR: 2.40; 95% CI: 1.36–4.6) and at 21 years (OR: 1.83; 95% CI: 1.35–2.47). This increased risk was not related to the presence of maternal atopic disease, unlike in the Tucson study. The study has been criticized for retrospective determination of breastfeeding and unclear definitions of atopic heredity.[22] There was also no evidence of a "dose-response" effect of breastfeeding on the incidence of atopy or asthma.

In summary, at the present time, it is not possible to conclude that exclusive breastfeeding protects young infants who are at risk of atopic disease from developing asthma in the long term (>6 years of age), and it may even have a detrimental effect.[37,38] On the other hand, breastfeeding seems to decrease the wheezing episodes seen in younger children (<4 years of age) that are often associated with respiratory infections.[35,36]

Food Allergy

Food allergy, similar to atopic dermatitis and asthma, is more likely to occur in infants with a family history of atopic disease. In a prospective study of infants born to families with a history of atopic disease, it was determined that 25% will develop food allergy between birth and 7 years of age.[39] Because both atopic dermatitis and asthma are closely associated with the development of food allergy, it is difficult to sort out the effect of breastfeeding on the development of food allergy. As reviewed above, maternal dietary exposure during pregnancy and lactation is unlikely to contribute significantly to the development of food allergy in the infant, although many food antigens can be found in human milk. In theory, human milk should inhibit food antigen absorption; however, prospective studies have failed to show a protective effect of human milk–specific antibodies to cow milk on infant sensitization.[40] Investigations of the role of breastfeeding on the outcomes of allergies to specific foods have been few, and the results may have been influenced by additional dietary variables such as length and degree of breastfeeding exclusivity. In reviewing the available studies, Muraro et al[22] concluded that exclusively breastfeeding for at least 4 months in infants who are at risk of developing atopic diseases is associated with a lower cumulative incidence of cow milk allergy until 18 months of age. A Cochrane review included only 1 study with a blinded challenge (using the double-blind, placebo-controlled food-challenge technique) and concluded that at least 4 months of exclusive breastfeeding did not protect against food allergy at 1 year of age.[27] Overall, firm conclusions about the role of breastfeeding in either preventing or delaying the onset of specific food allergies are not possible at this time.

ROLE OF HYDROLYZED FORMULA ON THE DEVELOPMENT OF ATOPIC DISEASE

The role of partially hydrolyzed and extensively hydrolyzed formulas for the prevention of atopic disease has been the subject of many studies in both formula-fed and breastfed infants in the last 15 years. Most studies with published results have been of infants at high risk of developing allergy.

Approximately 100 studies in the literature have examined the role of hydrolyzed formulas on the development of atopic disease. However, using the criteria of a 2006 Cochrane review,[41] only 14 randomized or quasi-randomized (eg, using alternation) trials in term infants compared the use of partially or extensively hydrolyzed formula with the use of human milk or an adapted cow milk formula.[42–55] All of these trials have followed up with at least 80% of study participants. It is important to note that none of these studies reported any adverse effects, including any adverse effect on infant growth. No long-term studies have compared partially or extensively hydrolyzed formula to exclusive breastfeeding. Thus, there is no evidence that the use of these formulas is any better than human milk in the prevention of atopic disease.

Three studies of 251 infants examined the effect of partially hydrolyzed formula on reduction of the occurrence of any allergy compared with cow milk formula in infants at high risk of developing allergy.[49,51,52] Two of these studies found no significant effect,[51,52] and a third study found an OR of 0.45 (95% CI: 0.22–0.94) for partially hydrolyzed formula versus cow milk formula.[49] Three more studies[53–55] examined prolonged feeding of extensively hydrolyzed formula compared with partially hydrolyzed formula in 411 infants at high risk of developing allergy. None of these studies found a significant difference in the incidence of atopic dermatitis between the 2 feeding groups. Two of these studies[53,55] of 352 infants also examined other manifestations of atopic disease and did not show a significant difference in the occurrence of food allergy, cow milk allergy, or asthma between the groups of infants who were fed extensively or partially hydrolyzed formula.

A very large published study from the German Infant Nutritional Intervention Program[30] raised additional issues. In the interventional arm of this study, 945 newborn infants were identified as being at high risk of developing atopic disease and were enrolled in a longitudinal, prospective study through 12 months of age. Although the majority of infants were breastfed initially, formula was introduced in the first 4 weeks to most infants. The infants were randomly assigned to receive 1 of 3 hydrolyzed formulas ($n = 689$) or cow milk formula ($n = 256$). The 3 hydrolyzed formulas were a partially hydrolyzed whey-based formula, an extensively hydrolyzed whey-based formula, and an extensively hydrolyzed casein-based formula. The incidence of atopic dermatitis was significantly reduced in those using the extensively hydrolyzed casein-based formula (OR: 0.42; 95% CI: 0.22–0.79; $P < .007$) and the partially hydrolyzed whey-based formula (OR: 0.56; 95% CI: 0.32–0.99; $P < .046$) but not the extensively hydrolyzed whey-based formula (OR: 0.81; 95% CI: 0.48–1.4; $P < .44$), compared with the incidence in those in the cow milk formula group. However, the overall results for prevention of allergic disease (atopic dermatitis, urticaria, and food allergy) for the 3 hydrolyzed formulas compared with cow milk formula were less impressive (extensively hydrolyzed whey-based: OR: 0.86; 95% CI: 0.52–1.4; partially hydrolyzed whey-based: OR: 0.65; 95% CI: 0.38–1.1; and extensively hydrolyzed casein-based: OR: 0.51; 95% CI: 0.28–0.92; $P < .025$). Thus, this study indicated that different hydrolysates have different effects on atopic disease, and there may be an advantage for the extensively hydrolyzed casein-based formula. However, as the study demonstrated, it is difficult to show that partially hydrolyzed formulas have a very large effect on the reduction of atopic disease in infants who are fed formula or mixed feedings of human milk and formula, even if they are at high risk of developing allergic disease. If atopic disease associated with cow milk allergy has occurred, partially hydrolyzed formula is not recommended, because it contains potentially allergic cow milk peptides.

More studies are needed to determine if any of the hydrolyzed formulas have any effect on the incidence of atopic disease later in childhood and adolescence and whether the modest effects of the use of extensively or partially hydrolyzed formulas in early childhood can be confirmed and are sustained. Such studies should also include a cost/benefit analysis of the use of the more expensive hydrolyzed formulas. It should be noted that the potential benefit of these formulas has only been documented in infants at risk of developing atopic disease. Additional studies are needed among unselected infants or infants at low risk.

The use of amino acid–based formulas for prevention of atopic disease has not been studied. Soy formulas, on the other hand, have a long history of use for atopic disease in infants. In a recent meta-analysis of 5 randomized or quasi-randomized studies, the authors concluded that feeding with soy formula should not be recommended for the prevention of atopy in infants at high risk of developing allergy.[56]

ROLE OF INTRODUCTION OF COMPLEMENTARY FOODS ON ATOPIC DISEASE

Many studies have examined the duration of breastfeeding and its effect on atopic disease. However, few studies have examined the timing of the introduction of complementary foods as an independent risk factor for atopic disease in breastfed or formula-fed infants. An expert panel from the European Academy of Allergology and Clinical Immunology has recommended delayed introduction of solid foods for 4 to 6 months in breastfed or formula-fed infants.[22] The AAP has also recommended that solid foods be delayed until 4 to 6 months of age and that whole cow milk be delayed until 12 months of age.[11] Before publication of this clinical report, AAP recommendations for infants who are at risk of developing atopic disease were to avoid eggs until 2 years of age and avoid peanuts, tree nuts, and fish until 3 years of age.[3,11] These guidelines for solid food introduction and avoidance of specific allergens were based on the evidence of a few studies with various limitations.[39,57–59] Three newer studies have reported mixed results regarding the timing of the introduction of solid foods and development of childhood atopic disease.[60–62]

In a prospective (nonrandomized) study of infants at risk of developing atopic disease by Kajosaari[57], atopic dermatitis and history of food allergy were reduced at 1

year of age if the introduction of solid foods was delayed until 6 months compared with at 3 months of age. However, in a 5-year follow-up study, no difference was seen in the incidence of atopic dermatitis or symptoms of food allergy.[57] In a second prospective study of a birth cohort of 1210 unselected children between 2 and 4 years of age, there was more atopic dermatitis but not asthma in infants who were fed 4 or more solid foods compared with no solid foods before 4 months of age.[58] This difference was maintained in a 10-year follow-up study in 85% of the original study infants.[59]

In a study of 257 preterm infants (34.4 weeks' gestational age; birth weight: 2.3–2.4 kg), the introduction of 4 or more, compared with fewer than 4, solid foods before 17 weeks after term was associated with a higher risk of atopic dermatitis (unconfirmed by skin-prick testing) at 12 months after term (OR: 3.49; 95% CI: 1.51–8.05).[60] Also in this study, the introduction of solid foods before 10 weeks of age or atopic disease in either parent increased the risk of atopic dermatitis in infants (OR: 2.94; 95% CI: 1.57–5.52). In a more recent prospective, longitudinal cohort study in which atopic dermatitis was confirmed by skin testing, 642 infants were followed until 5.5 years of age.[61] The history of the introduction of solid foods was carefully recorded during the first year of life. Most children had at least 1 parent with a positive skin-prick test result. Rice cereal was introduced at a median age of 3 months, milk was introduced at a median age of 6 months, and egg was introduced at a median age of 8 months. However, the later introduction of solids had no effect on the prevalence of asthma or atopic dermatitis (confirmed by skin-prick testing), although there was an increased risk of atopic dermatitis in relation to the late (6–8 months) rather than the earlier introduction of eggs (OR: 1.6; 95% CI: 1.1–2.4) or milk (OR: 1.7; 95% CI: 1.1–2.5).[61]

Finally, an ongoing prospective, cohort study[62] of 2612 infants (without a risk of developing atopic disease) found no evidence to support delayed introduction of solid foods beyond 6 months of age for prevention of atopic disease. However, in the same study, the effect of delayed introduction of solid foods for the first 4 months of life was less clear. Another study has even suggested that children exposed to cereal grains before 6 months of age (as opposed to after 6 months of age) are protected from the development of wheat-specific IgE.[63]

In summary, the evidence from these conflicting studies, in balance, does not allow one to conclude that there is a strong relationship between the timing of the introduction of complementary foods and development of atopic disease. This raises serious questions about the benefit of delaying the introduction of solid foods that are thought to be highly allergic (cow milk, fish, eggs, and peanut-containing foods) beyond 4 to 6 months of age; additional studies are needed.

SUMMARY

It is evident that inadequate study design and/or a paucity of data currently limit the ability to draw firm conclusions about certain aspects of atopy prevention through dietary interventions. In some circumstances in which there are insufficient studies (pregnancy and lactation avoidance diets, timing of introduction of specific complementary foods), the lack of proven efficacy does not indicate that the approach is disproved. Rather, more studies would be needed to clarify whether there is a positive or negative effect on atopy outcomes. The following statements summarize the current evidence within the context of these limitations.

1. At the present time, there is lack of evidence that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants. Similarly, antigen avoidance during lactation does not prevent atopic disease, with the possible exception of atopic eczema, although more data are needed to substantiate this conclusion.
2. For infants at high risk of developing atopic disease, there is evidence that exclusive breastfeeding for at least 4 months compared with feeding intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy in the first 2 years of life.
3. There is evidence that exclusive breastfeeding for at least 3 months protects against wheezing in early life. However, in infants at risk of developing atopic disease, the current evidence that exclusive breastfeeding protects against allergic asthma occurring beyond 6 years of age is not convincing.
4. In studies of infants at high risk of developing atopic disease who are not breastfed exclusively for 4 to 6 months or are formula fed, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk formula, in early childhood. Comparative studies of the various hydrolyzed formulas have also indicated that not all formulas have the same protective benefit. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in the prevention of atopic disease. In addition, more research is needed to determine whether these benefits extend into late childhood and adolescence. The higher cost of the hydrolyzed formulas must be considered in any decision-making process for their use. To date, the use of amino acid–based formulas for atopy prevention has not been studied.
5. There is no convincing evidence for the use of soy-based infant formula for the purpose of allergy prevention.
6. Although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow milk protein formula or human milk. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs, and foods containing peanut protein.

7. For infants after 4 to 6 months of age, there are insufficient data to support a protective effect of any dietary intervention for the development of atopic disease.
8. Additional studies are needed to document the long-term effect of dietary interventions in infancy to prevent atopic disease, especially in children older than 4 years and in adults.
9. This document describes means to prevent or delay atopic diseases through dietary changes. For a child who has developed an atopic disease that may be precipitated or exacerbated by ingested proteins (via human milk, infant formula, or specific complementary foods), treatment may require specific identification and restriction of causal food proteins. This topic was not reviewed in this document.

REFERENCES

1. Eichenfield LF, Hanifin JM, Beck LA, et al. Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics.* 2003;111:608–616
2. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol.* 2003;112:1203–1207
3. American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics.* 2000;106:346–349
4. Muraro A, Dreborg S, Halken S, et al. Dietary prevention of allergic diseases in infants and small children. Part II: evaluation of methods in allergy prevention studies and sensitization markers. Definitions and diagnostic criteria of allergic diseases. *Pediatr Allergy Immunol.* 2004;15:196–205
5. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy and/or lactation for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev.* 2006;(3): CD000133
6. Fälth-Magnusson K, Kjellman NI. Development of atopic disease in babies whose mothers were receiving exclusion diet during pregnancy: a randomized study. *J Allergy Clin Immunol.* 1987;80:868–875
7. Fälth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy: a 5-year follow-up of a randomized study. *J Allergy Clin Immunol.* 1992;89: 709–713
8. Lilja G, Dannaeus A, Fälth-Magnusson K, et al. Immune response of the atopic woman and fetus: effects of high- and low-dose food allergen intake during late pregnancy. *Clin Allergy.* 1988;18:131–142
9. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to 18 months of age: in-vivo results. *Clin Exp Allergy.* 1989; 19:473–479
10. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of IgE and egg- and milk-specific IgE and IgG antibodies in infants. *Clin Exp Allergy.* 1991;21:195–202
11. American Academy of Pediatrics. Food sensitivity. In: Kleinman RE, ed. *Pediatric Nutrition Handbook.* 5th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2004:593–607
12. Lack G, Fox D, Northstone K, Golding J; Avon Longitudinal Study of Parents and Children Study Team. Factors associated with the development of peanut allergy in childhood. *N Engl J Med.* 2003;348:977–985
13. Sorva R, Makinen-Kiljunen S, Juntunen-Backman K. Beta-lactoglobulin secretion in human milk varies widely after cow's milk ingestion in mothers of infants with cow's milk allergy. *J Allergy Clin Immunol.* 1994;93:787–792
14. Vadas P, Wai Y, Burks W, Perelman B. Detection of peanut allergens in breast milk of lactating women. *JAMA.* 2001;285: 1746–1748
15. Cant A, Marsden RA, Kilshaw PJ. Egg and cows' milk hyper-

sensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk. *Br Med J (Clin Res Ed).* 1985;291:932–935
16. Businco L, Marchetti F, Pellegrini G, Cantani A, Perlini R. Prevention of atopic disease in "at-risk newborns" by prolonged breast-feeding. *Ann Allergy.* 1983;51:296–299
17. Lovegrove JA, Hampton SM, Morgan JB. The immunologic and long-term atopic outcome of infants born to women following a milk-free diet during pregnancy and lactation: a pilot study. *Br J Nutr.* 1994;71:223–238
18. Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk, and fish during lactation: effect on allergic manifestations, skin-prick tests, and specific IgE antibodies in children at age 4 years. *Pediatrics.* 1992;89(4 pt 2):735–739
19. Hattevig G, Sigurs N, Kjellman B. Effects of maternal dietary avoidance during lactation on allergy in children at 10 years of age. *Acta Paediatr.* 1999;88:7–12
20. Järvinen KM, Makinen-Kiljunen S, Suomalainen H. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. *J Pediatr.* 1999;135:506–512
21. Lifschitz CH, Hawkins HK, Guerra C, Byrd N. Anaphylactic shock due to cow's milk protein hypersensitivity in a breast-fed infant. *J Pediatr Gastroenterol Nutr.* 1988;7:141–144
22. Muraro A, Dreborg S, Halken S, et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommendations. *Pediatr Allergy Immunol.* 2004;15:291–307
23. Kramer MS. Does breast feeding help protect against atopic disease? Biology, methodology, and golden jubilee of controversy. *J Pediatr.* 1988;112:181–190
24. Gdalevich M, Mimouoni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol.* 2001;45:520–527
25. Ludvigsson JF, Mostrom M, Ludvigsson J, Duchen K. Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. *Pediatr Allergy Immunol.* 2005;16:201–208
26. Kull I, Bohme M, Wahlgren CF, Nordvall L, Pershagen G, Wickman M. Breast-feeding reduces the risk for childhood eczema. *J Allergy Clin Immunol.* 2005;116:657–661
27. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. *Cochrane Database Syst Rev.* 2002;(1):CD003517
28. Laubereau B, Brockow I, Zirngibl A, et al. Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life: results from the GINI-birth cohort study. *J Pediatr.* 2004;144:602–607
29. Schoetzau A, Filipiak-Pittroff B, Koletzko S, et al. Effect of exclusive breastfeeding and early solid food avoidance on the incidence of atopic dermatitis in high-risk infants at 1 year of age. *Pediatr Allergy Immunol.* 2002;13:234–242
30. von Berg A, Koletzko S, Grubl A, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol.* 2003;111:533–540
31. Bergmann RL, Diepgen TL, Kuss O, et al. Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy.* 2002;32:205–209
32. Miyake Y, Yura A, Iki M. Breastfeeding and the prevalence of symptoms of allergic disorders in Japanese adolescents. *Clin Exp Allergy.* 2003;33:312–316
33. Purvis DJ, Thompson JM, Clark PM, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol.* 2005:152;742–749
34. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr.* 2001;139:261–266
35. Oddy WH. Breastfeeding and asthma in children: findings from a West Australian study. *Breastfeed Rev.* 2000;8(1):5–11
36. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol.* 2004;114:755–760
37. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax.* 2001;56:192–197
38. Sears MR, Greene JM, Willan AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet.* 2002;360:901–907
39. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol.* 1995;95:1179–1190
40. Duchen K, Casas R, Fageras-Bottcher M, Yu G, Bjorksen B. Human milk polyunsaturated long-chain fatty acids and secretory immunoglobulin A antibodies and early childhood allergy. *Pediatr Allergy Immunol.* 2000;11:29–39
41. Osborn DA, Sinn J. Formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev.* 2006;(4):CD003664
42. Chirico G, Gasparoni A, Ciardelli L, De Amici M, Colombo A, Rondini G. Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula. *Allergy.* 1997;52:82–88
43. Juvonen P, Mansson M, Andersson C, Jakobsson I. Allergy development and macromolecular absorption in infants with different feeding regimens during the first three days of life: a three-year prospective follow-up. *Acta Paediatr.* 1996;85:1047–1052
44. Mallet E, Henocq A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. *J Pediatr.* 1992;121:S95–S100
45. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. *Acta Paediatr Suppl.* 1996;414:1–21
46. Saarinen KM, Juntunen-Backman K, Järvenpää AL, et al. Breast-feeding and the development of cows' milk protein allergy. *Adv Exp Med Biol.* 2000;478:121–130
47. Szajewska H, Albrecht P, Stoitiska B, Prochowska A, Gawecka A, Laskowska-Klita T. Extensive and partial protein hydrolysate preterm formulas: the effect on growth rate, protein metabolism indices, and plasma amino acid concentrations. *J Pediatr Gastroenterol Nutr.* 2001;32:303–309
48. Tsai YT, Chou CC, Hsieh KH. The effect of hypoallergenic formula on the occurrence of allergic diseases in high-risk infants. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi.* 1991;32:137–144
49. Vandenplas Y, Hauser B, Van den Borre C, Sacre L, Dab I. Effect of a whey hydrolysate prophylaxis of atopic disease. *Ann Allergy.* 1992;68:419–424
50. Vandenplas Y, Hauser B, Blecker U, et al. The nutritional value of a whey hydrolysate formula compared with a whey predominant formula in healthy infants. *J Pediatr Gastroenterol Nutr.* 1993;17:92–96
51. Willems R, Duchateau J, Magrez P, Denis R, Casimir G. Influence of hypoallergenic milk formula on the incidence of early allergic manifestations in infants predisposed to atopic diseases. *Ann Allergy.* 1993;71:147–150
52. de Seta L, Siani P, Cirillo G, Di Gruttola M, Cimaduomo L, Coletta S. The prevention of allergic diseases with a hypoaller-

genic formula: a follow-up at 24 months—the preliminary results [in Italian]. *Pediatr Med Chir.* 1994;16:251–254
53. Halken S, Hansen KS, Jacobsen HP, et al. Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: a prospective, randomized study. *Pediatr Allergy Immunol.* 2000;11: 149–161
54. Nentwich I, Michkova E, Nevoral J, Urbanek R. Szepfalusi Z. Cow's milk-specific cellular and humoral immune responses and atopy skin symptoms in infants from atopic families fed a partially (pHF) or extensively (eFH) hydrolyzed infant formula. *Allergy.* 2001;56:1144–1156
55. Oldaeus G, Anjou K, Bjorksten B, Moran JR, Kjellman NI. Extensively and partially hydrolysed infant formulas for allergy prophylaxis. *Arch Dis Child.* 1997;77:4–10
56. Osborn DA, Sinn J. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev.* 2004; (3):CD003741
57. Kajosaari M. Atopy prophylaxis in high-risk infants: prospective 5-year follow-up study of children with six months exclusive breastfeeding and solid food elimination. *Adv Exp Med Biol.* 1991;310:453–458
58. Fergusson DM, Horwood LJ, Shannon FT. Asthma and infant diet. *Arch Dis Child.* 1983;58:48–51
59. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. *Pediatrics.* 1990;86:541–546
60. Morgan J, Williams P, Norris F, Williams CM, Larkin M, Hampton S. Eczema and early solid feeding in preterm infants. *Arch Dis Child.* 2004;89:309–314
61. Zutavern A, von Mutius E, Harris J, et al. The introduction of solids in relation to asthma and eczema. *Arch Dis Child.* 2004; 89:303–308
62. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics.* 2006;117:401–411
63. Poole JA, Barriga K, Leung DY, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics.* 2006; 117:2175–2182

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