

REVIEW ARTICLE

Infant feeding and the development of food allergies and atopic eczema: An update

Sarah E Gamboni,¹ Katrina J Allen^{2,5} and Rosemary L Nixon¹

¹Occupational Dermatology Research and Education Centre, Skin & Cancer Foundation, ²Department of Allergy, Royal Children's Hospital, Murdoch Children's Research Institute, and ³Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia

ABSTRACT

There is an increasing awareness of food allergies in the community. Dermatologists frequently see patients with atopic eczema, where parents are extremely concerned about the role of food allergy. Advice given to parents regarding the timing of introduction of solid foods has changed markedly over the past decade. Whereas previous advice advocated delaying the introduction of solid foods until the infant's gastrointestinal system had matured, recent studies suggest that the introduction of solids from around 4 to 6 months may actually prevent the development of allergies. Studies on maternal dietary restrictions during pregnancy and lactation have led researchers to believe that antigen avoidance does not play a significant role in the prevention of atopic disease. Breastfeeding exclusively for 4 to 6 months has multiple benefits for mother and child, however, it does not convincingly prevent food allergies or decrease atopic eczema. New evidence suggests that the use of hydrolysed formulas does not delay or prevent atopic eczema or food allergy. This article aims to highlight current evidence and provide an update for dermatologists on the role of food exposure in the development of atopic disease, namely atopic eczema.

Key words: allergy, breastfeeding, eczema, hydrolysed formula, peanut.

INTRODUCTION

Food allergies are increasing in prevalence and may substantially affect quality of life.¹ A food allergy is defined as 'an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food'.² The aetiology of food allergy is likely to be a combination of genetic and environmental factors and hence the timing of introducing foods into an infant's diet has been widely debated. Questions have been raised as to whether the maternal diet can be successfully manipulated or whether the timing and composition of early infant nutrition can be optimised to prevent the subsequent development or delay the onset of food allergies.³ We have summarised recent developments in the literature to help dermatologists approach these issues, with specific relevance for atopic eczema.

EXCLUSIVE BREASTFEEDING AND THE PREVENTION OF ATOPY

The importance of breastfeeding on the development of the child has been widely acknowledged; however, current evidence suggests that it has no conclusive protective effect on the development of food allergy and atopic eczema. Breastfeeding nurtures mother–infant bonding, contains protective immune factors and potentially protects against a variety of health conditions in infancy and childhood. The World Health Organization (WHO) recommends breastfeeding for the first 6 months of life for nutritional reasons and advises that it should be attempted in all infants.⁴

There are many issues when comparing studies on breastfeeding and allergic disease. Randomised controlled trials involving a non-breastfeeding control arm would be unethical, thus level one evidence is not available and guidelines are limited by poorer quality observational studies.⁵ In addition, blinding is obviously impossible.

Abbreviations:

GINI	German infant nutritional intervention
Ig	immunoglobulin
WHO	World Health Organization

Correspondence: Dr Sarah E Gamboni, Occupational Dermatology Research and Education Centre, Skin & Cancer Foundation, Melbourne, Vic. 3055, Australia. Email: sarahgamboni@hotmail.com

Sarah E Gamboni, BMBS, BSc(Hons), Katrina J Allen, FRACP, PhD, Rosemary L Nixon, FACD, FAFOEM.

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Another problem is that there are many ways in which infants can receive nutrition in early life, via a combination of breast milk, infant formulas and supplementation with solids. This choice by the family can lead to potential bias, including 'reverse causation' by which families' feeding practices are influenced by currently published guidelines. Similarly, the WHO criteria for 'exclusive breastfeeding'⁴ which restricts infants to feeding with breast milk and does not allow for the intake of any other liquids or solids (including water) with the exception of vitamins, minerals and medicines is not always adopted by study groups. This makes it extremely difficult to effectively compare studies.

For infants at high risk of developing atopic disease (defined as having one first-degree relative with a diagnosed allergy⁶), it has been suggested that exclusive breastfeeding for at least 4–6 months compared with feeding intact cow's milk protein formula could decrease the cumulative incidence of atopic eczema and cow's milk allergy in the first 2 years of life. An observational study of a birth cohort in Germany examined data from parental questionnaires on 3903 children and concluded that exclusive breastfeeding (52% of children) provided a significant protective effect when compared with feeding with conventional cow's milk formula for the development of atopic eczema.⁷ The European Academy of Allergology and Clinical Immunology reviewed prospective observational studies, and concluded that breastfeeding for at least 4–6 months is associated with a decreased risk of cow's milk protein allergy until 18 months and of atopic eczema up to 3 years of age.⁸ Similarly, a multidisciplinary review of the literature from 1966 to 2001 examined the association of breastfeeding and atopic disease and concluded that exclusive breastfeeding reduces the risk of asthma and protects against the development of atopic eczema.⁹ Nevertheless, observational studies such as those reviewed and mentioned here are significantly limited by widely variable presentations and definitions of atopic eczema, as well as parental bias in completing questionnaires. Interestingly, a more recent systematic review from 2009 found no strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against atopic eczema, even among children with a high risk of atopy.¹⁰ This last study appears to be the best summation of evidence to date.

MATERNAL DIETARY RESTRICTIONS

While breastfeeding, should the mother restrict her diet? Maternal dietary restrictions during pregnancy do not play a significant role in the prevention of atopic disease in infants. Similarly, antigen avoidance during lactation does not generally prevent atopic disease; however, more studies are needed to clarify effects on the risk of developing atopic eczema.

Two relatively recent large reviews have examined the role of diet in the prevention of atopy in children. In 2004 the European Academy of Allergology and Clinical Immunology completed a meta-analysis of the literature surrounding primary prevention of allergic disease and found no convincing evidence for a preventive effect of maternal

diet during pregnancy or lactation.⁸ A Cochrane review reached the same conclusion after the assessment of antigen avoidance diet during pregnancy or lactation, on the prevention of atopic disease in the child.¹¹ The Cochrane team concluded from five trials, involving 952 participants, that maternal dietary antigen avoidance during pregnancy probably does not confer a protective effect on the incidence of atopic eczema during the first 18 months of life.¹¹ Similarly, from another two trials involving 523 participants, a significant protective effect of maternal antigen avoidance during lactation on the incidence of atopic eczema during the first 18 months or on positive skin-prick tests to cow's milk, egg or peanut antigen at 1, 2, or 7 years of age was not observed. Nevertheless, there is clinical evidence that maternal dietary antigen avoidance during lactation may reduce the severity of atopic eczema in already established cases; although this is beyond the scope of this review.^{12,15}

THE EFFECT OF DIFFERENT INFANT FORMULAS ON ATOPY

Effects on cow's milk allergy

There are many options for feeding in infants, including subsidising or replacing breastfeeding with the use of hydrolysed formulas. Problems with early exposure to cow's milk may relate to the immaturity of the infant's gastrointestinal tract, which is permeable to macromolecules.¹⁴ One prospective, blinded randomised controlled trial involving non-breastfed infants at high risk of developing atopic disease concluded that the use of a partial whey hydrolysate decreased the prevalence of cow's milk protein sensitivity during the period when sensitivity is most likely to occur.¹⁵ In all, 58 infants were randomised to either whey hydrolysate formula ($n=28$) or regular cow's milk formula ($n=30$) during their first 6 months of life. At 6 months, the prevalence of cow's milk protein sensitivity was significantly decreased in the whey hydrolysate group (7 versus 43%, $P=0.002$) and these findings were consistent at 60 months' follow up (29 versus 60%, $P=0.016$). The prevalence of eczema was also less frequent in the whey hydrolysate group but only during the first 12 months of life, suggesting a decreased prevalence of cow's milk protein sensitivity during this time. Nevertheless, the study was limited by the small number of patients and by the finding that there was no difference between the study groups if only the new cases of cow's milk protein sensitivity after 6 months of age were considered.

In another prospective study of 6209 healthy full-term infants who were randomly assigned to receive supplementary milk compared with exclusive breastfeeding, it was found that those who received cow's milk formula (1789 infants) had a cumulative incidence of cow's milk allergy of 2.4% compared to 1.7% (OR 0.70, 95% CI 0.44–1.12) in those supplemented with pasteurised human milk (1859 infants) and 1.5% (OR 0.61, 95% CI 0.38–1.00) in those supplemented with whey hydrolysate formula (1737 infants).¹⁶ This compared with a cumulative incidence of 2.1% in the exclusively breastfed group. The findings suggest that feeding with cow's milk formula increases the risk of

developing cow's milk allergy compared with other formulas; however, exclusive breastfeeding is not necessarily protective.

Despite the above findings, a new randomised controlled study, the most robust of its kind, has found that partially hydrolysed formulas do not confer a protective benefit for atopic eczema or other allergic disease including cow's milk allergy at either 2 or 6 years of age.¹⁷ When compared to a conventional cow's milk formula, partially hydrolysed formula (OR 1.26, 95% CI 0.84–1.88) and soy formula (OR 1.26, 95% CI 0.84–1.88) did not confer any benefit in the prevention of the development of allergic manifestations or atopic eczema when given after weaning off breast milk.¹⁷

Interestingly, a recent large prospective study has suggested that very early exposure to cow's milk protein may actually be protective against the development of immunoglobulin (Ig) E-mediated cow's milk protein allergy.¹⁸ The feeding history of 13 019 infants was obtained by telephone interview or questionnaire and it was found that the OR was 19.3 (95% CI, 6.0–62.1) for the development of IgE-mediated cow's milk allergy among infants with exposure to cow's milk protein at the age of 15 days or more ($P < 0.001$) compared to infants exposed on days 1–14. Despite these results, this finding is highly controversial and has not been validated in other studies.

Effects on atopic eczema

What about the effects of hydrolysed formulas on atopic eczema? Previous thinking regarding partially hydrolysed formulas has been based on older studies. The large German infant nutritional intervention (GINI) study followed individuals until 6 years of age and evaluated the allergy-preventive effect of three hydrolysed infant formulas compared with cow's milk formula in a randomised, double-blind trial involving 2252 newborn babies with atopic heredity.¹⁹ The study evaluated the relative risk of a physician's diagnosis of allergic manifestation and atopic eczema at 6 years of age and found in the intention to treat analysis that the relative risk for atopic eczema was 0.79 (95% CI, 0.64–0.97) with partially hydrolysed whey formula, 0.92 (95% CI, 0.76–1.11) with extensively hydrolysed whey formula and 0.71 (95% CI, 0.58–0.88) for extensively hydrolysed casein formula compared to cow's milk formula. The authors acknowledge that in the per-protocol analysis all effects were stronger; however, it is recognised that in a randomised controlled trial conclusions should be based on an intention to treat analysis, as per-protocol analysis can be affected by bias.^{17,20}

Current guidelines

Despite the limitations of the older studies, such as GINI,¹⁹ partially hydrolysed formulas (usually labelled 'HA' or hypoallergenic) are recommended for allergy prevention in current feeding guidelines in Australia and New Zealand.²¹ Extensively hydrolysed formulas are only available on prescription for treatment of cow's milk allergic children, and brands available in Australia include Pepti-Junior (Nutricia

Australia Pty Ltd, North Ryde, NSW, Australia) and Alfare (Nestle Healthcare Nutrition, Rhodes, NSW, Australia). In addition, amino acid based formulas such as Neocate (Nutricia Australia Pty Ltd, North Ryde, NSW, Australia) and Elecare (Abbott Australasia, Botany, NSW, Australia) are sometimes needed in cases of allergy. These feeding guidelines were possibly based on the results of a Cochrane review from 2006, despite the authors' caution that further studies were required and that there was a risk of publication bias.²² Support for the use of partially hydrolysed formulas is likely to change once the results of the Cochrane review²² are updated with the recent data from Lowe and colleagues.¹⁷ As mentioned earlier, this is the second largest randomised controlled trial of hydrolysed formulas to date showing no effect of these formulas on allergy prevention, including cow's milk allergy and eczema at any time point up to the age of 6 years.¹⁷

SOLID FOOD INTRODUCTION: THE EFFECT OF TIMING AND COMPONENTS ON ATOPY DEVELOPMENT

Early introduction of solid food

What about the introduction of solid foods? The WHO, the American Academy of Pediatrics and the European Academy of Allergology and Clinical Immunology have all recommend delaying the introduction of solid foods until at least 4 months of age.^{8,25,24} A recent review of literature in the English language identified 2719 article citations and critically evaluated 13 studies to ascertain whether early solid feeding (before the age of 4 months) increases the risk of allergic disease.²⁵ The authors concluded that the literature is inconsistent and conflicting and that there is insufficient evidence to suggest that the early introduction of solids to infants is associated with an increased risk of food allergy. On the other hand, they found that there is a consistent association between the persistence of eczema and the introduction of solid foods before the age of 4 months that is supported by long-term follow-up studies; however, they acknowledged that many of the studies lacked a rigorous design and so were susceptible to multiple biases.

The changing doctrine of introducing solid food

Advice given to mothers on the timing of introduction of foods into an infant's diet has changed markedly over the past decade. In 2008 the American Academy of Pediatrics replaced their earlier policy from 2000.^{6,26} The original doctrine advocated maternal dietary restrictions during pregnancy or lactation on the basis that if highly allergenic foods were withheld from the infant until the immune and digestive systems were more mature, then allergic sensitisation would be prevented or significantly reduced.²⁶ Nevertheless, recent evidence seems to suggest the opposite. It appears that early exposure to allergens, that is, from around 4–6 months of age (as opposed to very early at less than 4 months) may actually allow the infant immune system to become tolerant and prevent the allergic

sensitisation to food.²⁷ This discussion has been heightened since the publication of a large study that found that there was less prevalence of peanut allergy in Jewish children in Israel than in those in the UK.²⁸ Interestingly, Israeli children are introduced to peanut snacks earlier in life and in larger quantities. Regardless of breastfeeding or cow's milk protein formula feeding, delaying the introduction of solid food beyond 4 to 6 months of age does not significantly protect against the development of atopic disease. This includes potentially highly allergenic foods such as fish, eggs and peanut protein. Similarly, after 4 to 6 months of age, there is no protective effect of any dietary intervention for the development of atopic disease.

The Influences of lifestyle-related factors on the immune system and the development of allergies in childhood study was a prospective birth cohort study, that enrolled 3097 infants at birth.²⁹ By means of chronological questionnaires, the study found no clear protective effect of delaying the introduction of solids beyond 4 or 6 months of age for the prevention of eczema or sensitisation at 2 years of age and no evidence of protective effect on asthma, allergic rhinitis or food or inhalant sensitisation at 6 years of age.^{29,50} Nevertheless, results for eczema were conflicting at 6 years of age and a protective effect of a delayed introduction of solids could not be excluded.

Effects on wheat allergy

In regard to wheat allergy, one study enrolled 1612 children at birth and followed them to the mean age of 4.7 years, examining the association between cereal grain exposures in the infant diet and the development of wheat allergy.⁵¹ Of 16 (1%) children of whom a wheat allergy was reported, those who were first exposed to cereals after 6 months of age had an increased risk than children first exposed before 6 months. Thus, they concluded that delaying initial exposure to cereal grains until after 6 months may actually increase the risk of developing wheat allergy.

Effects on egg allergy

In terms of egg allergy, the large HealthNuts population-based cross-sectional study involved 2589 infants.⁵² They found that, compared with its introduction at 4 to 6 months, introducing egg into the diet later was associated with higher risks of egg allergy (adjusted OR 1.6 [95% CI, 1.0–2.6] and 3.4 [95% CI, 1.8–6.5], irrespective of eczema status). The introduction of cooked egg versus egg in baked goods appeared to be the most protective, with those introducing cooked egg between 4–6 months five times less likely to develop egg allergy at the age of 1 year than if it was introduced after the population-recommended timing for egg introduction at that time: after 10 months of age. The study was able to adjust for a significant number of confounders including family history of allergy and infant history of eczema.

Effects on peanut allergy

In relation to peanut allergy, as mentioned above, a retrospective clinically validated questionnaire study involving

8600 children was undertaken recently.²⁸ The investigators sought to determine the prevalence of peanut allergy among Israeli and UK Jewish children and evaluated the relationship of peanut allergy to infant and maternal peanut consumption. They found that the adjusted risk ratio for peanut allergy between Israel and the UK was 9.8 (95% CI, 3.1–30.5). Interestingly, peanuts are introduced earlier and are eaten in larger quantities in Israel, with the median monthly consumption of peanuts in Israeli infants aged 8–14 months being 7.1 g of peanut protein compared to 0 g in the UK ($P < 0.001$). The results suggest that the early exposure, rather than avoidance, of peanuts during infancy may actually be protective against the development of peanut allergy. Similarly, a 2011 study observed that complementary food introduced to infants < 4 months of age was associated with a reduced risk of peanut (and potentially egg) sensitisation by the age of 2–3 years, but only for children with a parental history of asthma or allergy.⁵³

This area is controversial and is still being studied across the world. In the UK, the Learning early about peanut allergy study is a prospective randomised controlled trial, assessing whether eating peanuts during infancy enables the immune system to become tolerant or sensitive to peanuts.⁵⁴ Research projects are also underway at the Royal Children's Hospital in Melbourne. Nevertheless, there is a substantial amount of conflicting information available, especially on the Internet.⁵⁵ Dermatologists should be aware of these controversies.

CONCLUSION

Food allergies are a considerable area of concern for many parents. Exclusive breastfeeding for 4 to 6 months remains important, but there is no role for maternal dietary restrictions in pregnancy. It is important for dermatologists to be aware that there has been a considerable change in the advice given to new mothers on to the timing of the introduction of solid foods and its effect on food allergy development. It is reasonable to hypothesise that previous advice to delay the introduction of allergenic foods may have contributed to the increased prevalence of food allergy; however, further studies are required.

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