

FOOD ALLERGY PREVENTION

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ABSTRACT

Food allergy has significant individual, household and societal costs with the increasing prevalence of allergic disease becoming a public health concern, particularly in westernised, urbanised countries. Consequently there is great interest in the aetiology of food allergy in general, and the primary prevention of food allergy in particular.

The infant's immune system first comes into contact with food allergens as a fetus, continues being exposed after birth via breast milk, and again when solids are introduced into the diet. It is unclear which, if not all, of these exposure time points are important in food allergy development; so food allergy prevention strategies tend to focus on pregnancy and the first year of life.

Recommendations around food allergy prevention strategies have changed greatly in the last decade from some quite detailed prescriptive recommendations to fewer more evidence-focused recommendations and a call for more research into the field.

This paper discusses the current evidence base within a historical perspective and then outlines the recommendations we can currently make to our patients from the available evidence.

BACKGROUND

Food allergy prevention has been of interest to researchers for a number of years, particularly since the prevention of food allergy development may lead to reduced prevalence of asthma and allergic rhinitis because of the concept of the 'allergic march'.^{1,2} That said, food allergy itself has significant individual, household and societal costs.^{3,4} The interest in food allergy prevention strategies has also paralleled the observed increase in food allergy prevalence.⁵

The first allergy prevention measures were developed from epidemiological observations to do with how the infant was fed^{6,7} and serological observations from the fetus, newborn and infant.⁸⁻¹⁰ This led to the situation we now have where allergy prevention strategies focus on pregnancy and the first year of life of the infant.

ALLERGY PREVENTION STRATEGIES

Historical perspective

The first intervention studies looking at allergy prevention used multiple strategies to maximise the likelihood of affecting allergy outcome. Some of these studies showed some promising results in the short term,¹¹⁻¹⁴ but it was not known whether these results were due to all or just some of the interventions. Consequently allergy prevention advice based on these findings recommended all the interventions included in the studies,¹⁵ such as maternal avoidance during pregnancy and lactation and delayed introduction of solids into the infant's diet. Despite the long-term effects of

these interventions being subsequently shown to be disappointing,^{16,17} these recommendations stayed in place for a number of years.

Subsequent research focused on the different time periods thought to be important in allergy prevention; some focused on pregnancy,^{18,19} while others focused on environmental factors^{20,21} and yet others on infant feeding strategies;²² but the picture became no clearer. There was still a question as to whether these strategies were reducing allergy development.

In the first years of the 21st century new immunological and epidemiological considerations were added to the allergy prevention argument. Among these was the concept that acquiring tolerance to foreign (food) proteins was an active rather than a passive process^{23,24} and the epidemiological observations that early introduction to allergenic foods did not necessarily lead to sensitisation or allergic disease.²⁵⁻²⁷

From 2004, a plethora of publications from birth cohort studies added to the evidence base that delaying the introduction of solids into the infants' diet did not reduce the risk of developing allergic disease.²⁸⁻³¹

The current evidence base

Strategies during pregnancy

It has been known for many years that the *in utero* environment affects immunological development and that it is affected by the maternal environmental and nutritional experiences. As has been explained, the concept of avoidance to influence the maternal environment was in the forefront of people's minds, so environmental and dietary avoidance strategies were the norm. However, with the lack of evidence that these strategies were reducing allergy risk, and the advance of knowledge concerning the relationship between the maternal diet and immune function, the emphasis moved from avoidance of certain foods from the diet to the inclusion of certain foods/nutrients into the diet. Maternal dietary factors that have been considered to have an impact on allergic outcome of an infant are polyunsaturated fatty acids, probiotics, vitamins A, C, D and E, selenium, folate, zinc, and a 'healthy diet'.^{32,33} Those with a more robust evidence base of involvement in allergy development are examined in more detail in the following paragraphs.

Polyunsaturated fatty acids

The increased prevalence of allergic disease has been linked causally with the increased consumption of ω -6 long-chain polyunsaturated fatty acids (LCPUFAs),^{34,35} resultant of the health concerns regarding the consumption of saturated fats.³⁶ This possible link is backed up by epidemiological observations³⁷⁻³⁹ and is mechanistically explained by the fact that LCPUFAs are precursors for eicosanoid inflammatory factors including prostaglandins (PG) and leukotrienes (LT). These factors are involved in modulating and controlling the immune response and are generated from LCPUFAs. Eicosanoids derived from ω -6 PUFAs (e.g. sunflower oil) such as PGE₂ and LTB₄ strongly promote inflammatory responses and play a role in allergic sensitisation,⁴⁰ whereas the ω -3 LCPUFAs lead to production of PG and LT which inhibit allergic inflammation, such as PGE₃ and LTB₅.⁴⁰ Consequently there have been studies looking at the

role of LCPUFAs in allergic disease where the mother's diet was supplemented with fish oils.^{41,42} While such studies demonstrated immunological changes in cord blood, they could only hint at an improved clinical outcome.⁴⁰ Further intervention studies are being carried out with details of clinical outcome at 6 months expected in the next year.

Probiotics

Probiotics are live micro-organisms with various, strain-specific immunomodulatory effects which play an important role in the development of the mucosal and systemic immune system,⁴³ specifically the development of oral tolerance. Observational studies show differences in gut microbiota composition between atopic and non-atopic infants. Generally, atopic infants have fewer *bifidobacteria* and more *clostridia* than non-atopic infants. These differences precede the development of atopic disease since they already exist in the first few weeks of life, suggesting a causal relationship.⁴⁴⁻⁴⁶ A number of double-blind randomised placebo-controlled trials have been performed to investigate the ability of probiotics to prevent allergic disease in high-risk infants. These studies have mainly focused on atopic dermatitis (AD) and not on food allergy and have conflicting results. In three studies the incidence of AD was significantly reduced.⁴⁷⁻⁴⁹ However, in the other study no effect on AD incidence was found.⁵⁰ These conflicting results can possibly be explained by differences in study design, the use of different probiotic strains and dosages and/or genetic characteristics of the populations studied. Also, all studies gave the probiotic to the infant after delivery in addition to the mother taking it while pregnant, so any observed effect may be due to direct ingestion by the infant as opposed to via the maternal route. However, a more recent study has shown an effect on allergic disease with maternal supplementation.⁵¹

Vitamin D

The role of vitamin D in allergy development was first proposed in 1999⁵² when its inhibitory effect on the production of the T-helper 1 (Th1) cytokine interleukin (IL)-12 was highlighted. Subsequently, epidemiological observations such as the time course of the prevalence of increase in allergic diseases and vitamin D supplementation, and the clustering of disease in higher socio-economic groups (who are more likely to follow supplementation guidelines) were used to substantiate the argument. Since that date the role of vitamin D has been strongly debated. While the first papers advocated that increased vitamin D supplementation was the cause of rising allergy prevalence^{53,54} because of its effect on IL-12, IL-2 and interferon-gamma (IFN- γ),⁵⁵ others have since argued the protective effect of vitamin D⁵⁶⁻⁵⁸ because of its role in the development of regulatory T (Treg) cells, and the proliferation of tolerising and anti-inflammatory cytokines such as IL-10.⁵⁹ The focus is not always on dietary vitamin D; the role of sunlight exposure (assessed by degrees latitude) has also been investigated. Again there are conflicting results with some papers demonstrating high levels of sunlight (and therefore vitamin D) to be inversely related to allergic disease^{60,61} whereas others have shown the reverse.^{62,63}

As called for by researchers in the field,⁶⁴ intervention studies are currently looking particularly at the role of maternal vitamin D exposure and food allergy in their offspring to try to clarify the role of vitamin D in allergy development.

Folate

The human body requires folate to synthesise, repair and methylate DNA.⁶⁵ Consequently it has been a nutri-

ent of interest in the growing field of epigenetics. Recent research has demonstrated that some epigenetic processes can influence the expression of Th1, Th2 and Treg cells⁶⁶ and consequently affect resultant immune function. Since folate supplementation is widely advocated for pregnant women to protect against neural-tube defects, it is possible that this advice may be leading to epigenetic changes in the offspring which may increase the risk of the child developing an allergic disease. To date three studies have looked at the action of folate on the immune system (particularly allergic mechanisms). Two studies (one an animal study⁶⁶ and one using birth cohort data⁶⁷) have shown a positive relationship between increased folate intake and subsequent allergic disease. The third study used serum folate and total IgE levels from the National Health and Nutrition Survey of the USA and demonstrated an inverse association.⁶⁸ As is the case with vitamin D, further research studies have been urgently called for into the relationship between maternal folate intake and allergy development.³²

'Healthy diet'

In addition to the increased intake of LCPUFAs, the observed increase in the prevalence of asthma and allergic disease since the 1970s has also been proposed to be due to the decreased 'healthiness' of dietary intake.^{58,69} Willers *et al.*³⁸ found an association between maternal fish and apple consumption and wheeze at 5 years whereas Chatzi *et al.*⁷⁰ found an association between degree of adherence to a Mediterranean diet and wheeze and atopy at 6.5 years of age. However, Lange *et al.*⁷¹ found no association between any maternal dietary pattern ('healthful' or not) and childhood wheeze.⁷¹ A meta-analysis carried out by Nurmatov³³ concluded that there was a (weak) protective effect of fruit and vegetable intake in the development of asthma and allergy and also a weak protective effect of a Mediterranean diet for asthma outcome, but more research in this field is required.

Breastfeeding and allergy development

Exclusive breastfeeding is recommended for 6 months^{72,73} because of its protective effect on gastroenteritis,⁷⁴ wheeze,⁷⁵ necrotising enterocolitis⁷⁶ and vomiting.⁷⁷ However, the results of research looking at the relationship between breastfeeding and allergy development is contradictory with some reviews reporting beneficial effects⁷⁸⁻⁸⁰ and others reporting no such effect.^{81,82} Theoretically, breast milk would be expected to be protective as a result of it containing a number of immunomodulatory factors, such as maternal immunoglobulins, oligosaccharides, cytokines, glycoproteins, LCPUFAs, lysozyme, nucleotides and complement. Many of these factors are thought to have a role in the modulation of the allergic response, in particular transforming growth factor β (TGF- β) which has a positive association with infant wheeze⁸³ and atopic eczema,⁸⁴ IL-12 which promotes Th1 cytokine milieu⁸⁵ and soluble CD14 (sCD-14), the levels of which in breast milk have been shown to be negatively associated with eczema at 6 months of age.⁸⁶

Additionally, secretory IgA (sIgA) in breast milk is thought to shield the breastfed infant's gut-associated lymphoid tissue (GALT) from dietary allergens, thereby reducing local immunostimulation and contributing to the establishment of oral tolerance.⁸⁷ Findings to support this theory are that breastfeeding has been shown to significantly protect against the development of coeliac disease in children, an effect that is unrelated to the time of solid-food introduction⁸⁸ and that the infants of mothers with relatively low levels of milk IgA anti-

bodies to bovine proteins are more likely to develop cow's milk allergy.^{89,90}

However, other researchers have not found any association between breast milk cytokines and allergy outcome.^{91,92} This has been explained by the fact that levels of these cytokines differ vastly between breast milk samples. When the level of cytokines in the milk is taken into account in the analysis, a relationship is seen between cytokine levels and allergy development.⁹³ Another differing explanation for the apparent conflicting findings of the role of breast milk on allergy development is that the immunomodulatory role of breast milk is only apparent when breast milk is still consumed during exposure of the immune system to new foods.^{88,94}

Role of infant formula in allergy prevention

If a mother is unable to breastfeed, choosing the right formula to minimise allergy risk can be difficult. It is known that early exposure to cow's milk can increase prevalence of cow's milk allergy^{95,96} and that gut maturation and development of gut mucosal barrier is delayed with early cow's milk feeding.²⁶ Consequently it is important that the risk of allergy development associated with infant formula use should be reduced. Historically this has been achieved by using an alternative protein source to cow's milk such as soya or by the modification of the cow's milk protein in the infant formula by hydrolysis to reduce its allergenicity. There has been debate concerning the relationship between soya-based infant formula use and allergy development.⁹⁷⁻⁹⁹ However, a meta-analysis carried out in 2004¹⁰⁰ concluded that soya formula should not be recommended for the prevention of milk allergy in infants and more recently, the American Academy of Pediatrics supported this recommendation.¹⁰¹

The role of hydrolysed formula in allergy prevention has been examined in a number of intervention studies on high-risk infants. They compared both partially and extensively hydrolysed cow's milk formulas to formulas based on intact cow's milk in respect of the development of cow's milk allergy. Two studies showed a protective effect of extensively and partially hydrolysed infant formulas^{102,103} while in another three studies, no difference was seen.¹⁰⁴⁻¹⁰⁶ Another study which followed up to age 7, showed no differences.¹⁶ To try to finally clarify the situation the GINI study looked at three different hydrolysed infant formulas and standard infant formula, comparing different allergy outcomes between the groups. They found the extensively hydrolysed casein formula and partially hydrolysed whey formula were shown to have a preventative effect on both physician diagnosis of allergic manifestation and AD, but this was not seen for the extensively hydrolysed whey formula.¹⁰⁷ It is because of these somewhat contradictory findings that current recommendations specify that for allergy prevention a formula should be used but that it should be of 'proven reduced allergenicity'.¹⁰⁸ Despite the fact that all these studies have often been conducted as randomised, controlled trials, they have frequently been characterised by a number of methodological shortcomings, including problems with blinding, inadequate outcome assessments, and inability to distinguish true prevention from delaying symptoms.¹⁰⁹ A Cochrane review on this topic conducted in 2006¹¹⁰ concluded that 'there is no evidence to support feeding with a hydrolysed formula for the prevention of allergy compared to exclusive breastfeeding. In high risk infants who are unable to be exclusively breastfed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's milk allergy.'

EAACI have recently stated that for high-risk infants who are not breastfed a formula with documented reduced allergenicity should be used.¹⁰⁸ This advice applies only to infants born into high-risk families, i.e. mother, father or sibling suffers from documented allergic disease.⁷⁹

In an endeavour of infant formula companies to further reduce the allergenicity of their infant formulas and make their composition more comparable to breast milk, they have started to include pre- and/or probiotics into their infant formulas. A number of double-blind randomised placebo-controlled trials have been performed to investigate the ability of probiotics and prebiotics to prevent allergic disease in high-risk infants but they have conflicting results.¹¹¹ Meta-analyses into the role of pre- and probiotics in allergy have been carried out. In both cases the conclusion was that there was currently insufficient evidence to determine their role in allergy prevention and further trials have been called for.^{112,113}

Role of infant feeding and allergy development

The age at which solids should be introduced into the infant diet for allergy prevention is also an area of controversy. The first studies in the field were observational and carried out in the 1980s. First to publish were Fergusson *et al.*⁶ who looked at both the timing and rate of introduction of solids into an infant diet with the later development of eczema. They found that solid food introduced before 4 months of age and the number of foods introduced was associated with an increased incidence of physician-reported eczema.⁶ This association persisted to 10 years of age.⁹⁵ Secondly, Kajosaari compared the early introduction of allergenic foods (3 months of age) with that after 6 months of age and showed no differences in the prevalence of food allergy, either in the first year of life⁷ or at age 5.¹¹⁴ A number of similar studies followed and a systematic review looking at complementary feeding and allergy development could find few data linking the introduction of solids into the diet before 4 months of age and allergic conditions, other than an association with early solid introduction and persistent eczema.¹¹⁵

As a result of the new epidemiological and immunological findings suggesting that early exposure of the immune system to allergens may help establish immunological tolerance, researchers used existing data from birth cohort studies to further investigate the relationship between solid introduction and the later development of allergy. No study found any benefit on allergic outcome by delaying the introduction of solids and three found an association between the delayed introduction of milk³¹ and egg^{30,116} and increased incidence of eczema and atopic sensitisation. More recently it has been 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 IgE²⁹ and researchers in Sweden have shown an association between the delayed introduction of fish and subsequent allergy.^{117,118} All these studies collected feeding data retrospectively which makes the findings vulnerable to both recall bias and reverse causality. Nevertheless these findings have raised the possibility that delaying the introduction of foods into an infant's diet (particularly delaying the introduction of allergenic foods) is not beneficial and may actually increase the risk of the child developing allergic diseases.^{25,27,29-31,116} However, before we recommend the introduction of allergenic foods before 6 months these study findings need to be replicated in additional studies.

Consequently the advice should remain that if it is necessary to introduce solids into an infant's diet before the age of 6 months then that food should be of low

allergenicity.¹¹⁹ However, from 6 months there is no reason to further delay the introduction of allergenic foods (e.g. wheat, egg, peanut, cow's milk products, fish) into the diet since delaying the introduction of solids into the diet to prevent the development of allergic disease has not been shown to be beneficial.^{101,108,120} However, from a practical standpoint it seems prudent to introduce allergenic foods one at a time into the diet of high-risk infants.¹²⁰

Other (non-food) strategies

An important allergy prevention measure is to avoid smoking during pregnancy and to ensure the baby is not exposed to tobacco smoke, since passive smoke exposure has been associated with development of asthma and allergic disease in the infant.^{121,122}

House-dust mite reduction measures have been shown to reduce sensitisation to house-dust mite at 1 year in high-risk infants¹²³ and research is currently being undertaken to establish if they lead to reduced allergic disease. In the meantime anti-dust mite procedures such as covering the mattress, ventilation of the infant's room, regular vacuuming and cleaning with a damp cloth seem prudent for high-risk infants.

The intake of paracetamol (acetaminophen) and anti-reflux medication during pregnancy has been linked to the development of allergic disease in the child¹²⁴⁻¹²⁶ as has non-steroidal anti-inflammatory drug (NSAID) intake during lactation,^{127,128} and paracetamol and antibiotic use in infancy.¹²⁹⁻¹³² However further work is needed in all these areas to substantiate any possible associations.

RECOMMENDATIONS

Although more research needs to be carried out for us to be able to offer definitive allergy prevention advice, a number of recommendations can be made from the evidence base at this time.^{101,108,120}

All infants

- Mothers should eat a healthy, balanced diet during pregnancy and lactation, including all major allergens.
- Ideally, breastfeeding should be the sole source of nutrition until around the age of 6 months.
- Milks other than standard cow's milk formula, including soy, goat milk formulas, or non-formula off-the-shelf cow, goat, sheep, soy or rice milk, must not be given as they are unproven in allergy prevention.
- Weaning should never commence before the age of 17 weeks and any solids introduced between 4 and 6 months should be low-allergenic foods.
- Weaning foods should ideally be introduced while an infant is still being breastfed.
- By the age of 12 months all the major allergenic foods, which would normally be suitable for a child of this age, should have been introduced into the diet.
- Delaying weaning beyond 6 months could adversely affect the normal dietary and developmental milestones essential to establishing a good varied diet and may increase the risk of allergy development.
- Avoid exposure to cigarette smoke during pregnancy as well as to the infant after birth.
- During pregnancy and lactation, keep the use of anti-reflux medication, paracetamol and NSAIDs to a minimum.

For high-risk infants

- Standard cow's milk formula should not be given for the first 4-6 months unless the child has other forms of cow's milk in his/her diet.

- Recommended alternatives to breast milk are partially or extensively hydrolysed formula milks. Infants at highest risk should be given extensively hydrolysed casein formula milk. These hydrolysed formulas should be used for 4-6 months or until the time that cow's milk in any form has been introduced into the infant's diet.
- When allergenic foods such as wheat, egg and milk, are commenced, introduce each allergenic food category singly, starting with a small amount, e.g. half a teaspoon. No more than one new allergenic food group should be introduced at a time.
- Avoid exposure to high levels of house-dust mite.

Declaration of conflict of interest

The author declares no conflict of interest.

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