Clinical practice

Breastfeeding and the prevention of allergy

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Abstract The increase in allergic disease prevalence has led to heightened interest in the factors determining allergy risk, fuelled by the hope that by influencing these factors one could reduce the prevalence of allergic conditions. The most important modifiable risk factors for allergy are maternal smoking behaviour and the type of feeding. A smoke-free environment for the child (to be), exclusive breastfeeding for 4–6 months and the postponement of supplementary feeding (solids) until 4 months of age are the main measures considered effective. There is no place for restricted diets during pregnancy or lactation. Although meta-analyses suggest that hypoallergenic formula after weaning from breastfeeding grants protection against the development of allergic disease, the evidence is limited and weak. Moreover, all current feeding measures aiming at allergy prevention fail to show effects on allergic manifestations later in life, such as asthma. In conclusion, the allergy preventive effect of dietary interventions in infancy is limited. Counselling of future parents on allergy prevention should pay attention to these limitations.

Keywords Allergy prevention · Breastfeeding · Atopy · Hypoallergenic formula

Introduction

In the second half of the twentieth century, the prevalence of immunoglobulin E (IgE)-mediated allergic conditions in the Western World has doubled [5]. The prevalence of allergic disease, in particular wheezing and asthma, varies considerably throughout the world, with the highest risk in Western countries [60]. It is assumed, therefore, that Western lifestyle increases the risk of development of allergic diseases [5, 60]. Although the identification of the factors responsible for this rise in allergy prevalence is important for allergy prevention, it is still largely unclear which environmental aspects are involved [22]. In this article, we briefly summarise the present knowledge on risk factors for allergic disease and provide an overview of the literature on allergy prevention, focusing on breastfeeding. This should serve as a foundation for the advice health care professionals provide to parents of children at increased risk of allergy.

Definitions

According to the 2003 nomenclature revision, allergy is defined as a hypersensitivity reaction initiated by specific immunologic mechanisms, with hypersensitivity being defined as causing objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons [30]. Atopy is defined as a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce...
IgE antibodies in response to ordinary exposure to allergens, usually proteins [30]. In the context of this paper, ‘allergy’ refers to IgE-mediated or type I allergy, which is associated with atopy. For newborns, the risk of becoming atopic increases with the presence of atopy in first-degree family members [2]. Likewise, ‘high-risk infants’ are defined as those children who have one or more first-degree relatives with proven allergic disease, including food allergy, atopic eczema, allergic asthma and rhinoconjunctivitis and, therefore, are at increased risk of developing atopy and allergic disease.

Factors contributing to allergy risk

Genetic factors

IgE-mediated allergy has a strong hereditary component. It is more common in monozygotic than in dizygotic twins [2]. Our current knowledge of the role of genetic factors in allergy development is summarised in Table 1. Allergic diseases are considered complex genetic conditions, with involvement of many genes and environmental factors [7]. The genetic factors involved in different allergic conditions differ considerably. Notably, the genes involved in eczema are more closely linked to those in other skin conditions than to those in other allergic diseases [28, 50].

The practical usefulness of these observations is, however, limited. Presently, the only way to use genetics regarding allergy prevention is by identifying increased allergy risk based on positive family history, in particular for the same condition [2]. Generally, therefore, allergy prevention is aimed at these ‘high-risk infants’ [32].

Hygiene hypothesis

The hygiene hypothesis postulates that the increased prevalence of allergy is caused by reduced exposure to microbial stimuli in early life, resulting in insufficient stimulation of regulatory T cells [7, 53, 64]. The term was coined in 1989 by Strachan, who observed that the more older siblings a child had, the lower the risk of allergic rhinitis [57]. A detailed description of the large body of observational evidence supporting the hygiene hypothesis can be found elsewhere [6].

Although early exposure to microbial stimuli shapes the maturation of the neonatal immune system [25], this concept has not yet yielded effective measures for allergy prevention. BCG immunisation of newborns, for example, does not decrease allergy risk [38, 43]. Although a Finnish study showed up to 50% reduction of eczema risk in infants of mothers using probiotics in late pregnancy and during lactation [31], this has not been confirmed in comparable studies [1, 59], and a recent Cochrane review concluded probiotics to be ineffective in preventing allergic disease [49].

Maternal food consumption

Although there is consensus that pregnant women should not follow elimination diets [34], maternal food consumption may still influence allergy risk in the offspring. For instance, there is some evidence that in children of mothers who were consuming fish at least once a week during pregnancy, the risk of eczema and allergic rhinitis in decreased [68], whereas daily (as opposed to incidental) maternal consumption of nuts or peanuts was associated with increased asthma risk [69]. These results would be consistent with the hypothesis that a disturbed equilibrium between n–3 and n–6 polyunsaturated fatty acid intake may cause an Th1–Th2 imbalance [61, 69].

Cigarette-smoke exposure

The risk of asthma and poor lung function is considerably higher when the mother smokes during pregnancy and when after birth the infant is exposed to cigarette smoke [10, 11, 36, 40, 71]. The association of smoking with other allergic conditions, such as eczema and allergic rhinitis, is less clear. Nevertheless, tobacco-smoke exposure is the most readily available modifiable risk factor for allergic disease in children, and every effort to help pregnant women to stop smoking is worthwhile.

Other environmental factors

Although allergy risk appears to be largely determined in the first few months of life, other environmental factors may play additional roles later in life. Several factors have been implicated, but the evidence is weak and limited. Exposure to antibiotics [39] and paracetamol [42, 70] in the first years of life may increase the risk of asthma. To what extent consumption of certain foods and nutrients by the child could influence the risk of allergic manifestations remains to be determined [61].
Role of breastfeeding

There is no discussion on the fact that breastfeeding is the optimal nutrition for infants [17], preferably exclusive breastfeeding and preferably up to the age of 6 months [17]. Despite the large body of evidence on the role of breastfeeding in the prevention of allergy, however, discussion on its allergy preventive effects continues, mainly because of methodological issues.

Why is it so difficult to obtain evidence?

A principal problem with all studies on the effect of breastfeeding on allergy prevention is that randomised controlled trials (RCTs) are impossible. By consequence, all studies in this field are observational [46, 65] and subject to several confounding factors and biases [46]. Firstly, the multi-factorial nature of allergic diseases implies that the modification of one single cause (breastfeeding) will only have limited effects. Secondly, recall bias plays a role in many studies that record feeding practices retrospectively. Furthermore, the statistical approach itself may unwantedly adjust for secondary factors considered confounders that actually are part of the causal pathway—or the other way around. In addition, genetic background may considerably influence the association between breastfeeding and allergy risk [46].

A major limitation of observational breastfeeding studies is ‘confounding by behaviour’. Since the prevailing opinion is that breastfeeding decreases the allergy risk, the mothers of high-risk infants may be more inclined to breastfeeding than those of low-risk infants. Indeed, an increased incidence of allergic disease in intentionally breastfed children has been found in some studies [8, 29]. The fact, therefore, that systematic reviews nevertheless show an inverse relationship between breastfeeding and allergic disease suggests that the actual protective effect of breastfeeding could even be higher than reported.

Why would breastfeeding reduce allergy risk?

The biological plausibility of the allergy preventive effect of breastfeeding has been studied in a number of ways. Firstly, breast milk contains traces of food proteins consumed by the mother that could promote tolerance to these foods [56]. Other factors in human milk that may modulate mucosal immune processes include IgA, factors that promote gut maturation, oligosaccharides, nucleotides and leukocytes that control the growth of intestinal microbiota and long-chain polyunsaturated fatty acids [46]. For example, n-3 fatty acids have anti-inflammatory and immune modulating properties that could reduce allergy risk [14].

Studies in weaning piglets have provided additional evidence that breast milk may provide protection [51]. Several milk peptides were found to be able to down-regulate neonatal immune activity, suggesting that they may promote neonatal immune competence.

Does breastfeeding have a preventive effect?

Systematic reviews and meta-analyses of observational studies consistently show a protective effect of exclusive breastfeeding up to the age of at least 4 months [19, 45, 63, 65]. For example, one systematic review reported a decrease of asthma in children up to the age of 8 years of 27% in the general population, increasing to 48% in high-risk children [20]. Later, observational studies confirmed the protective effect of exclusive breastfeeding on early life manifestations of allergy, with little or no support, however, to the notion that asthma later in life might be prevented as well [16, 41]. It has been suggested that contrarily, asthma risk at later age might even be increased in breastfed high-risk children. This has recently been refuted, however, by a very large epidemiological survey from the UK [46].

As noted earlier, all observational studies on the allergy preventive effect of breastfeeding are subject to bias. Obviously, the same applies to systematic reviews and meta-analyses of such studies. To our knowledge the only study that approaches an RCT design is from Belarus [35]. In this cluster-randomised trial, maternity hospitals were randomised to implementation of the ‘Baby Friendly Initiative’ campaign of the WHO. Although breastfeeding in the first 3 months of life was seven times more common in the intervention group, there was no difference between intervention and control groups with regard to the prevalence of allergic disease and of positive skin prick tests up to the age of 6 years [35]. Although these results may not be considered representative of the Western situation, the study confirms that at the least, breastfeeding does not increase the prevalence of allergic disease in high-risk children.

Other preventive measures

Complementary bottle feeding in the neonatal period

A large Dutch randomised trial in an unselected population of breastfed infants showed that exposure to standard formula in the first days of life did not increase the prevalence of allergic disease [13]. There is no reason, therefore, to provide hypoallergenic formula to breastfed low-risk infants who need complementary formula. This also holds for high-risk infants, although it seems be counter-intuitive to give standard formula in this situation.
Table 2 Methodological problems in the studies with regard to the effects of hydrolysed formula on allergy in high-risk children [9]

| Methodological Problems                  |
|-----------------------------------------|
| Blinding — differences in taste and smell prevent adequate blinding of the parents, [21] which may compromise the appreciation of subjective symptoms and even lead to ‘deblinding’ of the researchers |
| Heterogeneity — studies differ strongly with respect to criteria for allergic disease and hypoallergenicity of formula [45] |
| Confounders — insufficient control for confounding variables |
| Compliance — bad smell and taste of hypoallergenic formula may result in low compliance |
| Severity of disease — prevention may be particularly effective for (very) mild cases |
| Postponement or cancellation — the effects of nutritional measures shrink with longer follow-up and may even reverse |
| Mechanism — pathophysiological mechanism is unclear |

Hypoallergenic formula

Sooner or later, most breastfeeding mothers switch to formula feeding. In contrast to breastfeeding, it is perfectly possible to design RCTs for the comparison of the allergy prevention effects of standard formula with those of hypoallergenic (hydrolysed) formula. Systematic reviews of RCTs conclude that both partially and extensively hydrolysed formulas have a protective effect, in particular on atopic eczema in the first years of life [23, 45]. Based on this, several national and international organisations have issued the advice that high-risk children who are not breastfed should be given hypoallergenic formula in the first 3 to 6 months of life [26, 32, 45].

There seems to be a change of wind, however. Because the author of some of the most convincing studies has been accused of scientific fraud [54], the weight of the evidence has become a matter of discussion. As a result, the conclusions of the original 2003 Cochrane analysis were modified to conclude that: “In high risk infants who are unable to completely breast fed, 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 CMA”, the word ‘limited’ being added [47]. An international expert group, however, opposed to this weakened conclusion, reinforcing their original statement [45] that high-risk infants should use hypoallergenic formula once breastfeeding was not available [27].

How should we judge this discrepancy? It has been pointed out that the quality of the evidence is weak. Table 2 summarises the most important methodological drawbacks of the studies on hypoallergenic formula [9]. Clearly, the pathophysiological model that prompted the use of hypoallergenic formula is no longer valid. The notion that exposure to allergens results in sensitisation and that subsequent repeated exposure causes disease is outdated. Neither for airborne allergens nor for food allergens has a clear relationship been proven between allergen exposure and allergic disease development [13, 37]. Sensitisation to foods has been found in children who never consumed the actual food. Even the first documented contact with food allergens may result in allergic reactions [44]. The avoidance of exposure to airborne allergens such as house dust mite does not prevent house dust mite allergy and asthma [12]. Finally, it is unclear whether and how hypoallergenic formula could influence regulatory T-cell function [9].

There are more unsolved problems posed by intervention studies with hypoallergenic formula. Objective endpoints, such as serum concentrations of specific IgE against common allergens, have never been shown to differ between intervention and control groups [9]. It is likely that any protection from allergy primarily involves mild cases. With longer follow-up, the effect size of protection appears to decrease, suggesting that allergic manifestations are delayed rather than truly prevented [9]. The risks of prolonged use of hypoallergenic formula have been poorly studied [62]. A recent large observational ‘real life’ study from the Netherlands showed that the delayed introduction of cow’s milk in the diet of high-risk infants was associated with increased atopy risk at the age of 2 years [55]. Long-term allergen avoidance in itself may induce the ‘activation’ of allergy in sensitised children [18]. As a result, the risk–benefit ratio of hypoallergenic formula use is unknown [9].

Considering all of the above, we tend to counsel parents of high-risk infants as follows: we encourage exclusive

| Prevention recommendations                  |
|--------------------------------------------|
| All infants                                |
| Exclusive breastfeeding for at least the first 4 months of life |
| Continuation of breastfeeding up to 6 months of life |
| Complete avoidance of exposure to cigarette smoke, before as well as after birth |
| Introduction of supplementary feeding starting between 4 and 6 months of life |
| High-risk infants (positive family history) |
| Children who are not breastfed (anymore) should be given hydrolysed formula until 4 months of life |
| Partially hydrolysed formula is preferable above extensively hydrolysed formula |
| The parents should appreciate the limited effects of these measures |
breastfeeding for at least 4 months; after weaning of breastfeeding, hypoallergenic formula may postpone manifestations of atopic eczema during the first 2 years of life and there is no reason to prefer extensively hydrolysed above partially hydrolysed formula [32, 47].

Introduction of complementary feeding

Until recently, it was common use to postpone the introduction of complementary feeding (solids) as part of allergy prevention measures until the age of 6 months [32]. This is in line with the WHO advice, aiming at exclusive breastfeeding for the first half year of life. There is no proof, however, that any further decrease of allergy risk is obtained by postponing the introduction of solids until after 4 months of life [55, 58, 72]. Likewise, there is no scientific basis for the avoidance of strongly allergenic foods, such as peanuts and chicken egg, beyond this age [27, 58]. On the contrary, there are reasons to believe that postponement of the introduction of, for instance, peanuts until the third year of life increases the prevalence of peanut allergy [67]. Current evidence suggests that the optimal window for the introduction of solids in non-high-risk as well as in high-risk children is between 4 and 6 months of age [52]—preferably while maintaining breastfeeding until 6 months of age [17, 52].

Breast milk mimicry

Given the apparent protective effects of breastfeeding, interventions have been tested that aimed at mimicking certain properties attributed to breast milk. These include the supplementation of formula with fish oil, probiotics and prebiotics. Recent meta-analyses, however, found insufficient evidence for a protective role of either fish oil supplements [4], probiotics [49] or prebiotics [48]. Probiotics might even have an adverse effect on wheezing [33].

Prevention of food allergy

Some words have to be said on the prevention of food allergy irrespective of other manifestations of allergy. Obviously, it can be anticipated that manipulation of the feeding of newborn infants specifically would influence the development of food allergy. Studies concentrating on food allergy prevention have, however, not produced more convincing results than other preventive studies [24, 66].

Apparently, exposure to (traces of) foods during the ‘window’ period of 4–6 months of age may serve as a means of inducing tolerance [29]. Early introduction of peanut into the infants’ diet in Israel is associated with a 10 times lower prevalence of peanut allergy [24] than in Great Britain, where peanut introduction is postponed [67]. The effect of postponement of solids may be even more outspoken in high-risk children [15]. The strict avoidance of allergens, therefore, might have a contrary effect [3, 67].

Recommendations

It should be concluded that there are only limited possibilities for allergy prevention. Table 3 gives an overview of the advice that present scientific evidence allows us to give to parents. Exclusive breastfeeding, avoidance of cigarette smoke and introduction of complementary foods between 4 and 6 months of life are measures that are applicable to all children, irrespective of their risk assessment. When exclusive breastfeeding is impossible, hydrolysed formula feeding might postpone mild manifestations of eczema in high-risk children. There is no reason to prefer extensively hydrolysed formula above partial hydrolysates.

Conflict of interest The authors declare that they do have do conflict of interest and no financial relationships that might have influenced the present work.

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