

Does Early Feeding Promote Development of Oral Tolerance?

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Abstract The prevalence of food allergy has continued to rise over the last 10–15 years, with building concern over the underlying causes and the best strategies to reverse this. Although it is still not clear if infant feeding practices play any significant role in either the aetiology of this epidemic or in its prevention, these have nonetheless been core to many previous prevention strategies. Early ‘allergen avoidance’ strategies have not only failed, but have instead been increasingly associated with increased risk of allergic disease. Together with other observations in humans and animals, this suggests that earlier introduction of allergenic foods may be a more logical preventive strategy. Based on this, there are several randomised controlled trials world-wide assessing the merits of early introduction of complementary feeding and/or allergenic foods. Until the results of these studies are available it is difficult to provide definitive recommendations regarding the role of early feeding in the induction of oral tolerance and prevention of food allergy.

Keywords Complementary feeding · Early feeding · Allergy prevention · Infant nutrition · Allergenic foods · Allergen avoidance · Oral tolerance · Birth cohort · Food sensitization

Introduction - The Context

Food allergy has recently emerged as a substantial public health issue. The greatest burden of this new epidemic is in

young children, often developing symptoms in the first months of life.

In some regions preschoolers have experienced a five-fold increase in food anaphylaxis over just ten years [1], with over 20 % of one-year-olds now sensitized to foods and more than 10 % with clinical food allergy [2]. Earlier presentation, more serious presentations [1] and increasing persistence of disease [3] are all adding to this growing impact of food allergy. It has been long recognised that the best strategy to address this disease burden is through early interventions for primary prevention. It is increasingly evident that complex modern environmental changes (including changes in microbial, lifestyle, dietary and pollutant exposures) are increasing the predisposition to allergy, and that interventions to restore more favourable ‘tolerogenic’ conditions during allergen encounter, are likely to be central to future preventive strategies. That said, there is still considerable interest in the role of allergens in both the development of sensitisation and in the primary and secondary induction of tolerance. In this context, considerations and guidelines considering the timing of early feeding and food allergen exposure for primary prevention can be generally divided into three categories:

- 1) the commencement of complementary foods in general,
- 2) avoidance or exposure to specific ‘allergenic’ foods, and
- 3) the use of modified allergens, such as the hydrolysed proteins found in some hypoallergenic formulas.

This review will primarily focus on the first two of these issues, but it should be noted that systematic reviews on the potential benefits of hydrolysed formulas for allergy prevention are currently being revised based on a number of new studies [4, 5]. At the time of writing, most allergy prevention guidelines recommend the use of hydrolysed formulas in infants at high risk of allergy if breastfeeding is not possible, based on the earlier Cochrane meta-analysis [6]. However, a

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preliminary report on the revised meta-analysis from these authors [7] indicates that of the 16 studies now eligible, there is no significant difference in any allergy outcomes (eczema, food allergy, asthma or rhinitis) with the use of hydrolysed formulas, either overall or in subgroup analysis of infants at high risk of allergy. It is important to note that the authors identified substantial methodological concerns in many of the studies and highlighted the need for more well designed studies to address this issue more definitively. Pending a more detailed report, allergy prevention guidelines are likely to be revised on this point and we anticipate that this aspect of early feeding will be discussed in more detail elsewhere in the near future.

The History

The original rationale for 1) delayed complementary feeding and 2) avoidance of allergenic foods was based on concerns that young infants have relatively immature mucosal immunity and increased gut permeability, which may increase the risk of systemic allergic responses [8]. However, there is very little evidence to support this beyond the first 4 months of age. Early cohort studies had indicated that the introduction of 'any solid food' to infants less than 4 months of age is associated with up to 2.5 times increased risk of eczema [9–12] and fivefold increased food allergy [11]. However some studies showed no effect on allergic disease outcomes [13, 14].

The precise role of delayed introduction of 'specific foods' (cow's milk, egg, nuts and fish) has also been difficult to interpret. Most previous intervention studies for allergy prevention have examined infant food avoidance in combination with other strategies such as hydrolysed formulas [15–18], maternal diet restrictions [15, 18–20] and/or other environmental interventions [15, 16, 19, 20]. Furthermore, the duration of specific food avoidance has also varied widely between studies (from 4 to 24 months of age). Although some of the studies reported reductions in allergic disease outcomes, the findings have not been consistent and cannot be solely attributed to the timing of specific food allergen introduction to infant diets.

In 2000, the American Academy of Pediatrics Committee on Nutrition [21] made recommendations that included both delayed complementary feeding and delayed exposure to specific foods as part of a combined strategy that also included the use of hydrolysed formulas. Specifically, they recommended that infants at high risk of allergy (based on family history) should have delayed introduction to solid foods until 6 months of age and that the introduction of certain foods be delayed further, including avoidance of cow's milk products until 1 year, eggs until 2 years and nuts and fish until 3 years of age. This delayed introduction to certain foods then became progressively incorporated into infant feeding guidelines over the intervening years.

Importantly, at that stage restrictive feeding recommendations were generally targeting only 'high risk' infants with a family history of allergic disease.

Then, in 2001 the World Health Organisation (WHO) revised its recommendation for exclusive breastfeeding from 4 months of age, to 6 months of age [22]. A natural consequence of extending the period of exclusive breastfeeding was the delayed introduction of complementary foods until 6 months of age, which then applied to *all* infants. It is important to note that this change in recommendation was not directed at allergy prevention, but to reducing the risk of gastrointestinal infectious disease [23] and other morbidities relevant to the more developing regions of the world.

In the years that followed there was a series of reports suggesting that delayed complementary feeding and specific food allergen avoidance (beyond 6 months of age) may actually increase the risk of allergic disease, and that the recommendations for developing-world regions may not be appropriate in the growing world population experiencing progressive industrialisation and escalating risk of immune dysregulation. Specifically, prior to 2008 several cohort studies documented an increased risk of eczema in infants [24–26] and increased asthma, allergic rhinitis and allergic sensitisation [25] with delayed introduction of specific foods (cow's milk, fish and egg). Delayed feeding (>6 months of age) with cereal grains was associated with at least four times the prevalence of wheat allergy [27], although this cohort study only included 16 (1 %) children with parentally reported wheat allergy (and not confirmed by oral challenge).

Based on these emerging findings, in 2008 at least four independent expert groups raised concerns about both the delayed introduction of complementary foods, and prolonged avoidance of specific allergenic foods [28–31]. It was generally concluded that there was insufficient evidence to justify these practices, particularly in developed regions. Nutrition experts [28] concluded that, based on the evidence available, solid foods should not be introduced before 17 weeks (4 months) and not later than 26 weeks (6 months) of age, and that there was no consistent basis for avoiding specific foods. It was also recognised that the level of evidence in this area was generally weak, based largely on observational studies with methodological limitations and that more robust studies and randomised control trials would be needed to address this more conclusively.

As a result, most allergy societies and expert bodies around the globe have subsequently revised their current allergy prevention recommendations to reflect this. However, in many regions this has created discrepancy with the WHO recommendations (that maintains delayed introduction of complementary feeding until 6 months of age), creating difficulties for governments and policy makers generating national consensus guidelines.

Here we examine the more recent studies examining the relationship between early feeding patterns and allergic outcomes, published after the expert opinion papers [28–31] and revised position on allergy prevention in early 2008.

New Reports from Prospective Birth Cohort Studies (2008 Onwards)

There have now been at least eight new reports from cohort studies to examine this issue. These have provided further observational evidence that delayed introduction of complementary foods has either no benefit on allergy prevention [32•, 33, 34], or is associated with increased eczema or atopic dermatitis [35•, 36, 37], increased asthma [38•], increased allergic rhinitis [38•] and increased allergic sensitisation [34, 37, 39•] particularly with delayed introduction of specific foods (oats, wheat, cow's milk, fish and egg) as summarised on Table 1.

In one of the largest population-based prospective birth cohorts, Chuang et al. [32•] found no relationship between the age of introduction of solid foods in 18773 infants in Taiwan and the risk of eczema in the first 18 months of life. Similarly, new follow-up data from the German 'LISA' study ($n=2073$) found no effect of age of introduction of solids on longer term outcomes (asthma or allergic rhinitis) at 6 years of age [34]. This study actually found a higher risk of food sensitisation when solid foods were introduced later than 6 months of age (adjusted OR 2.50, 95 % CI 1.03–6.30) compared with introduction before 4 months. Furthermore, introduction between 4–6 months also increased the risk of sensitisation compared with earlier introduction by 4 months (adjusted OR 3.2, 95 % CI 1.5–6.9). Also consistent with these studies, a smaller United States prospective birth cohort study ($n=594$) found that complementary food by 4 months (reported by 39.7 % of mothers) was not associated with any increase in eczema by 2 years of age [33•]. Rather, these children had a reduced risk of peanut and egg sensitization although this depended on the specific IgE threshold used, and clinical food allergy was not reported.

A report from the Dutch KOALA Birth Cohort Study ($n=2558$) [37] also found reduced sensitisation in 2 year olds who had foods (other than cow's milk protein) introduced earlier (at 3 months of age) compared with delayed introduction (>7 months). However, this effect on sensitisation was only for inhalant allergens not food allergen sensitisation. In the same study delayed introduction (>7 months) of solid foods was also associated with a higher risk for eczema.

Since then, four other European prospective, birth cohort studies have reported increased risk of various allergy

outcomes with delayed introduction of particular foods (oats, wheat, fish and eggs) [35•, 36•, 38•, 39•]. Specifically, Nwaru et al. [39•] observed that later introduction of specific foods (including eggs, oats, and wheat), was associated with increased sensitization to food allergens at 5 years of age. Virtanen et al. [38•] found that later introduction of oats and fish increased the risk of persistent asthma and allergic rhinitis (respectively) at 5 years of age. Two recent Swedish prospective, birth cohort studies [35•, 36•] both reported a link between later fish introduction in the diet and increased eczema within the first 18 months of life. It is not clear if a protective effect of earlier fish exposure might relate to higher intake of potentially immunomodulatory fish oils, but it is of note that in the larger study by Alm et al. [35•] 78.6 % consumed lean fish (cod, haddock) and only 18.3 % consumed fatty fish (mainly salmon).

In summary, all of these birth cohort studies provide further evidence that delayed introduction of any or specific complementary foods has either no benefit or even increases the risk of various allergic outcomes. Importantly, none of these shows any evidence that earlier exposure to any foods increases the risk of allergic disease.

Other New Large Scale Unselected Population Studies

The Australian Healthnuts study [40•] has also made a major contribution to this area. This unique large population study has recruited 5000 infants at 12 months of age to make detailed studies of food allergy prevalence. While this is not a birth cohort (and infant feeding data was therefore collected retrospectively), the major strengths of this study include the accurate food allergy outcomes (defined by inpatient oral egg food challenges as well as sensitisation), the large sample size, relatively unselected population, high recruitment rate, and the ability to control for a wide range of potential confounders (parent-reported child reactions to foods, eczema, and family history of allergy). A preliminary report from the first 2589 children assessed [40•] indicated that delayed introduction of egg at 10–12 months (adjusted OR, 1.6, 95 % CI, 1.0–2.6) or after 12 months (adjusted OR 3.4, 95 % CI, 1.8–6.5) was associated with significantly higher risk of egg allergy compared with introduction at 4 to 6 months. There were rigorous attempts to adjust for reverse causation and the findings persisted after adjusting for family history of allergy and infant allergy symptoms. Interestingly after stratifying by first type of egg (baked or cooked) introduced, at age 4 to 6 months, first exposure as cooked egg reduced the risk of egg allergy compared with first exposure as egg in baked goods (OR, 0.2 [95 % CI, 0.06–0.71]). There was no evidence of an association between duration of breast-feeding or age at introduction of any solids and egg allergy.

Table 1 recent observational cohort studies (listed in order of age of children at assessment)

Study	Population characteristics	Sample size	Age at assessment	Allergy outcomes investigated	Main findings
Koplin et al. [40•] (2010) Australia	Population cohort of normal allergic disease risk	n=2589	12 months	IgE mediated egg allergy: skin prick testing (SPT) to egg and oral food challenge to raw egg white	Delayed introduction of egg was associated with higher risk of egg allergy, with 4 to 6 months as the reference, adjusted ORs with 95 % CIs: 1.6 (1.0–2.6) at 10–12 months and 3.4 (1.8–6.5) for >12 months of age First exposure as cooked egg reduced the risk of egg allergy compared with first exposure as egg in baked goods (OR, 0.2 [95 % CI, 0.06–0.71]). Early age at introduction of fish (<9 months of age) was associated with a reduced risk of eczema Median age of fish introduction for children who had not developed eczema was 8 months (IQR 6.0–11.0) compared to 11 months (IQR 8.0–13.0) for those children who had developed eczema but sensitization was not associated with the timing of fish introduction. 16 % increased prevalence of eczema was found for every 2 months that the introduction of fish was delayed No significant effect was found for the timing of solid food introduction on the risk of AD, with <4 months as the reference, adjusted ORs with 95 % CIs: 1.11 (0.80–1.53) at age 4–6 months and 1.08 (0.74–1.57) for >6 months of age Early complementary food (<4 months) was not related to AD (OR, 1.1; P=.758) Early complementary food (<4 months) reduced the risk of peanut sensitization (IgE $\geq$ 0.35 IU/mL) among children with a parental history of allergy (adjusted odds ratio, 0.2 [95 % CI, 0.1–0.7]; P=0.007) and reduced the risk of egg sensitization (IgE $\geq$ 0.70 IU/mL) (adjusted odds ratio, 0.5 [95 % CI, 0.3–0.9]; P=0.022). Delayed introduction of solid foods (>7 months) when compared to introduction at 3 months of age was associated with a higher risk for AD (adjusted OR 2.10, 95 % CI 1.17–3.76, P=0.02). Delayed introduction of solid foods (>7 months) when compared to introduction at 3 months of age was associated with increased risk of sensitization at 2 years (adjusted OR 4.31, 95 % CI 1.14–16.22, P=0.01). Delayed introduction of cow's milk products was associated with a higher risk for AD, with 0–3 months as the reference, adjusted ORs with 95 % CIs: 1.55 (1.03–2.33) at age 7–9 months and 2.29 (1.21–4.33) for >9 months of age Early age at introduction of oats ($\leq$ 5.5 months of age) was associated with a reduced risk of persistent asthma
Alm et al. [35•] (2009) Sweden	Prospective, birth cohort of normal allergic disease risk	n=4953	12 months	eczema and food allergy	
Hesselmar et al. [36•] (2010) Sweden	Prospective, birth cohort of mainly increased allergic disease risk (parental history of allergic disease)	n=184	18 months	clinical allergic disease symptoms and allergic sensitisation	
Chuang et al. [32•] (2011) Taiwan	Prospective, birth cohort of normal allergic disease risk	n=18773	18 months	atopic dermatitis (AD)	
Joseph et al. [33•] (2011) USA	Prospective, birth cohort of normal allergic disease risk	n=594	2 years	atopic dermatitis (AD) and allergic sensitisation	
Snijders et al. [37] (2008) Netherlands	Prospective, birth cohort of normal allergic disease risk	n=2558	2 years	atopic dermatitis (AD) and allergic sensitisation	
Virtanen et al. [38•] (2010) Finland	Prospective, birth cohort of normal allergic disease risk	n=1293	5 years	asthma and allergic rhinitis	

Table 1 (continued)

Study	Population characteristics	Sample size	Age at assessment	Allergy outcomes investigated	Main findings
Nwaru et al. [39•] (2010) Finland	Prospective, birth cohort of normal allergic disease risk	<i>n</i> =994	5 years	allergic sensitisation	and early age at introduction of fish (≤ 8.5 months of age) was associated with a decreased risk of allergic rhinitis Later introduction of specific foods, in particular potatoes (> 4 months), oats (> 5 months), rye (≥ 7 months), wheat (> 6 months), meat (> 5.5 months), fish (> 8.2 months), and eggs (> 10.5 months), were associated with increased sensitization to food allergens
Zutavem et al. [34] (2008) Germany	Prospective, birth cohort of normal allergic disease risk	<i>n</i> =2073	6 years	asthma, allergic rhinitis and allergic sensitisation	No effect of age of introduction of solids on asthma or allergic rhinitis Increased risk for food sensitisation as determined when solid foods were introduced, with < 4 months as the reference adjusted ORs with 95 % CIs: 3.2 (1.5-6.9) at age 4–6 months and 2.50, (1.03-6.30) for > 6 months of age

Limitations of Observational Studies

In all of these observational studies it is important to exclude ‘reverse causation’, as families with a history of allergic disease are also more likely to alter feeding practices. While some of the earlier cohort studies did not address this, the majority of the recent cohort studies, reverse causation has been taken into account by adjusting for parental history of allergic disease [25, 33•, 34, 36•, 38•, 39•, 40••] and/or infants with early allergic symptoms [25, 32••, 34, 36•, 37, 38•, 40••]. However the influence of reverse causation can only truly be eliminated with a prospective double-blinded randomised controlled trial (RCT) design. Without blinded randomisations it is also more difficult to allow for other potential confounding factors. As indicated above, many studies had only limited assessment of food allergy outcomes, relying on less accurate measures of sensitisation without food challenges or other clinical data. The data is also more limited by recall bias in studies which relied on dietary information retrospectively collected [40••].

Current Randomised Controlled Trials

Despite the now large number of cohort studies supporting the notion that delayed feeding is both unnecessary and potentially harmful in the context of allergy prevention, the level of evidence conferred by these studies is still limited by the observational approach. This has lead to a series of new randomised controlled trials (RCT) in both Europe and Australasia that test the hypothesis that early regular exposure to food allergens will induce oral tolerance, and reduce the risk of allergic disease, as summarised on Table 2.

While most of these trials are targeting the effects of early feeding with one specific food, the EAT Study in the United Kingdom is unique in investigating the intervention of exclusive breastfeeding until 3 months of age then sequential introduction of cow’s milk, egg, fish, wheat, sesame and peanut from 3 months of age compared to exclusive breastfeeding until around 6 months of age. Using a robust RCT design this will attempt to confirm the findings of recent observational cohort studies [33•, 34, 37] that early introduction of complementary food (< 4 months of age) was associated with reduced risk of allergic sensitization. The results of this trial are awaited with great interest.

Other current studies all investigate of the timing of specific ‘allergenic’ foods (namely egg and peanut) on food sensitization and food allergy outcomes (Table 2). This includes our own study of healthy infants ($n=1512$) at ‘high risk’ of allergic disease (the STEP study), randomized to receive egg powder (or a placebo) daily from when they *first* introduce ‘solid’ complementary foods between 4–6 months

Table 2 Current randomised controlled trials

Study	Study type and sample size	Trial registration details	Population characteristics	Intervention	Comparison	Primary outcome
STAR Adelaide & Perth, (Australia)	Blinded, randomised placebo controlled trial ($n=226$)	ACTRN 12609000415202 Date of trial registration 5/06/2009	High risk—infants with moderate to severe eczema	Daily consumption of egg powder from 4 months until 8 months of age. Cooked egg introduced from 8 months of age.	Daily consumption of placebo, rice powder from 4 months until 8 months of age. Cooked egg introduced from 8 months of age.	IgE mediated egg allergy at 12 months of age based on positive SPT and egg challenge
STEP Adelaide & Perth (Australia)	Blinded, randomised placebo controlled trial ($n=1512$)	ACTRN 12610000388011 Date of trial registration 13/05/2010	Intermediate risk—maternal history of allergy + positive maternal SPT - no allergic disease in infant	Daily consumption of egg powder from 4–6 months until 10 months of age. Egg introduced from 10 months of age.	Daily consumption of placebo, image-matched rice powder from 4–6 months until 10 months of age. Egg introduced from 10 months of age.	IgE mediated egg allergy at 12 months of age based on positive SPT and egg challenge
BEAT Sydney (Australia)	Blinded, randomised placebo controlled trial ($n=600$)	ACTRN 12611000535976 Date of trial registration 24/05/2011	Intermediate risk—first degree relative with atopy - no infant IgE sensitisation to egg at 4 months of age	Daily consumption of egg protein from 4–6 months until 8 months of age, with egg free diet until 12 months then introduction of 'normal unrestricted diet' from 8 months of age.	Daily consumption of placebo rice powder from 4–6 months until 12 months of age, with egg free diet until 8 months then introduction of 'normal unrestricted diet' from 8 months of age.	IgE sensitisation to egg measured by SPT at 8 and 12 months of age.
EAT London (United Kingdom)	Randomised controlled trial ($n=2500$)	ISRCTN 14254740 Date of trial registration 31/03/2009	Normal risk—general population	Exclusive breastfeeding until 3 months of age then sequential introduction of cow's milk, egg, wheat, sesame, fish and peanut from 3 months of age.	Exclusive breastfeeding until around 6 months of age and no early introduction of allergenic foods before 6 months of age.	Prevalence of IgE mediated food allergy to any of the 6 foods between 1 and 3 years of age, as defined by food challenge.
LEAP London (United Kingdom)	Randomised controlled trial ($n=640$)	NCT00329784 Date of trial registration 23/05/2006	High risk—infant with eczema and/or egg allergy	Peanut consumption in the form of an age appropriate peanut snack commencing from 4–10 months of age.	Peanut avoidance	Prevalence of clinically-defined peanut allergy at 5 years of age.
HEAP Berlin (Germany)	Randomised placebo controlled trial ($n=800$)	Personal communication	Normal risk—general population	Hen's egg powder 3 times a week from 4–6 months of age.	Placebo powder 3 times a week from 4–6 months of age.	IgE mediated egg allergy at 12 months of age based on egg-specific serum IgE and DBPCFC.
PEAAD Berlin (Germany)	Non-randomized self-allocated controlled trial ($n=460$)	Personal communication	High risk—eczema without peanut sensitization	Peanut snack 3 times a week from 5–30 months	Peanut avoidance	IgE-mediated peanut allergy after one year of consumption or avoidance

SPT: skin prick test

DBPCFC: double-blinded placebo-controlled food challenge

of age. We are also conducting a smaller pilot study using a similar design in children with eczema (the STAR study). Results from one of these trials, the STAR Trial conducted in Australia, are anticipated during 2012.

The rationale for these studies is also based on animal studies which demonstrate that the tolerance is an allergen-driven process, through early regular oral exposure to food proteins [41]. This is also illustrated in studies using food allergens to induce 'secondary' specific oral tolerance in food allergic children [42].

The default response to oral exposure is normally immune tolerance. In other words, oral antigens are normally processed in a manner that results in a regulated immune response, which does not injure the host and ensures systemic hypo-responsiveness on subsequent oral challenge with the same antigen. Deviation from this process can lead to a range of inflammatory responses, including food allergy. Still poorly understood, oral tolerance induction is thought to occur via a number of possible mechanisms, these include both anergy and active cellular suppression through the recruitment of particular subsets of regulatory T cells, which suppress subsequent immune responses via secreted or membrane-bound cytokines (most notably IL-10 and TGF β) [43] or direct cell contact (CD4+CD25+Foxp3+ Treg). A number of environmental factors are likely to determine the success of tolerance induction, including optimal colonisation, breastfeeding and other immunomodulatory exposures during this period (discussed in [31]). Changes in these factors and their interaction may be key to understanding the allergy epidemic. It is logical to optimise both the patterns of allergen exposure and the environmental context in order to promote tolerance during this early period of immune programming.

Food Sensitisation as an Even Earlier Event

In the course of both of our randomised controlled trials (the STAR and the STEP studies) we have noted a significant proportion of infants who already have clinical reactivity at 4–6 months. This is detected at randomization, to the first 'known' exposure. Specifically, an interim analysis of the eczema study revealed that 22 % had early clinical reactions (19/86 infants entering this pilot study), including one case of anaphylaxis requiring treatment with adrenaline (unpublished interim data). This indicates that sensitization has occurred much earlier than when complementary foods are typically started (4–6 months) and suggests earlier strategies may be needed in some children. Importantly, in all cases there was no previous history of known direct ingestion of the food (egg) by the infant, indicating previous exposure through other routes potentially through the cutaneous barrier, breast milk or even across the placenta.

a) The role of allergens in breast milk:

Food allergens secreted in breast milk are an important early source of oral exposure [44, 45]. However, in a double-blinded RCT of lactating women fed 55 g/day of egg (vs egg-free placebo) for 21 days, we observed individual differences in ovalbumin (egg protein) secretion in breast milk between women [46]. It has also been shown that allergens in breast milk have tolerogenic effects particularly as allergen-IgG complexes which induce antigen-specific Treg cells in newborn animals [47] and now also found in human milk [48]. Breast milk cytokines (such as TGF β [49]) also have tolerogenic properties. It is possible that variations in breast milk composition (including cytokines and allergen-antibody complexes) may influence the risk of sensitisation.

b) The role of transcutaneous sensitisation:

In the absence of oral exposure, there is concern that exposure through 'less tolerogenic' routes, such as the skin is more likely to induce sensitisation, particularly in children with impaired cutaneous barrier function exposure [50]. This may be because children are still exposed to low level potentially sensitising doses in their environment [51]. Food allergens can be readily detected in house dust [52] and household consumption of food allergens increases the risk of allergy [51]. It has been proposed that cutaneous exposure in the absence of infant oral exposure leads to allergic sensitisation, whereas high levels of oral exposure lead to tolerance irrespective of environmental exposure [50].

c) The role of allergen exposure in utero:

The role and significance of allergen exposure in utero has been controversial and unclear, but needs to be revisited in light of increasing evidence of very early sensitization. There is good evidence that environmental allergens can be detected both in placental tissue [53] and in the fetal circulation [54] from where they could foreseeably interact with the developing immune system. In addition to systemic blood, allergens are also detected in amniotic fluid [55]. These and other proteins are hydrolysed through the gastrointestinal tract after fetal swallowing and are also in contact with the fetal skin and lungs. There is clear evidence that the human fetus develops regulatory responses to both self antigens and to exogenous antigens (alloantigens [56], microbial antigens [57•] and allergens [58]) encountered across the placenta. While fetal T cells are responsive to allergens [59] as early as 22 weeks gestation [60] these appear to be 'promiscuously responsive' recent thymic emigrants (RTE) [58] (rather than 'conventional adult' T cell memory) which preferentially give rise to regulatory populations. Fetal Treg 'memory' to other exogenous antigens encountered in utero (alloantigens [56]

and microbial agents [57•]) are long-lived, persisting after birth to influence postnatal responses to these antigens [56, 57•]. There is therefore intense interest in how these early regulatory responses influence early postnatal immune response on postnatal allergen encounter.

Before designing earlier interventions to promote oral tolerance and prevent disease, it is critical to define the underlying immune events, particularly to address the continued uncertainty surrounding questions of allergen ‘dosing’ versus ‘avoidance’ in pregnancy, lactation and the subsequent infant diet. This highlights the need to more fully understand the role and mechanism of early allergen encounter, and how variations in the context of allergen encounter can influence the risk of sensitization. It is likely that allergen exposure is a key part of a series of inter-related events that, when functioning normally, lead to appropriate allergen-specific tolerance.

The Importance of the Background Environment and the Tissue Milieu During Allergen Encounter

Variations in the local and systemic context of initial allergen encounter critically determine the pattern of effector responses and the efficacy of regulatory mechanisms. Rising rates of allergic disease clearly indicate that modern environmental changes are promoting the risk of early sensitisation, beginning before birth and culminating in the early postnatal period. This means that in the ‘modern’ context, allergen exposure is more likely to lead to sensitisation when these background environmental conditions (such as changing microbial exposure, diet and lifestyle patterns and modern pollutants) appear to be promoting less favourable conditions for tolerance. The local tissue micro-environment is also an important determinant of the pattern of immune response [61••], and many of the environmental factors implicated in the rise of allergic disease are recognised to alter tissue milieu [62–65]. It is, therefore, important to understand the effects of both a) allergen exposure (dose, timing and route) and b) local tissue milieu on developing immune responses during this very early period. In this high risk modern setting, strategies to optimise each of these are likely to have a role in allergy prevention.

Conclusions

Primary prevention strategies are of prime importance as rates of food allergies in children continue to increase. Regular exposure to ubiquitous proteins such as foods and other innocuous environmental proteins may be a part of developmental processes that promote subsequent clinical tolerance. This may be why allergen avoidance strategies

(delayed exposure) have not only failed to prevent allergic disease, but may have contributed to an increased allergic risk. The most recent cohort studies provide further evidence that the delayed introduction of any and or specific foods (oats, wheat, cow’s milk, fish and egg) is associated with increased allergic sensitisation and allergic disease. This gives continued support for the current recommendations by expert bodies [29–31] that there is no evidence that delayed introduction of complementary foods beyond 4 months of age is beneficial. The results of current randomised controlled trials investigating the timing of introduction of complementary foods are eagerly awaited. However preliminary evidence from these studies that a significant proportion of infants *already* have established food sensitisation and clinical reactivity (including anaphylaxis) *prior* to the ‘first’ introduction of foods at 4–6 months of age indicates that the processes leading to sensitisation are already strongly established by this age in many infants, and that even earlier preventive interventions will ultimately be required. This underscores the pressing need to better define events around much earlier allergen encounter and it is essential to have a better understanding of the antecedent events that lead to the establishment of food allergy so early in infancy.

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