

Do you recommend early ingestion of egg in infants at high risk? - Pro

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In the 1960, most infants were exposed to solids (complementary feeding) by 4 months of age. However, in the 1970s new guidelines were introduced recommending a delay in the introduction of solids until after 4 months due to an assumption that early introduction of gluten was contributing to a rise in coeliac disease which was observed at the time. The World Health Organisation (WHO) recommended a further delay in the introduction of solid food in the 1990s to 6 months of age, and advised parents to delay the introduction of allergenic solids such as egg and peanut to 10 months and 3 years, respectively. A WHO systematic global review in 2002, which looked at exclusive breastfeeding for 6 months, reported no benefits of introducing complementary foods between 4 and 6 months of age for allergy prevention; despite this, recommendations for exclusive breastfeeding of infants in both developed and developing countries for the first six months of age were made. A similar stance was adopted in the United States with a consensus document recommending that the optimal age for selected foods should be 6 months, specifically dairy products at 12 months, hen's egg at 24 months and at the earliest, peanut, tree nuts, fish and seafood at 36 months of age.

Over the last few decades, despite these measures initiated to prevent allergy by delaying the introduction of allergenic foods, the prevalence of food allergy has continued to rise even in countries where dietary avoidance is practiced. This has led to research looking into the alternate strategy of early introduction of foods for the prevention of food allergy.

The timing of food introduction and oral tolerance has been at the forefront of pediatric food allergy research over the last decade. The concept of oral tolerance is well understood in murine models of which previous work has shown how early and regular oral exposure induces clinical tolerance and immunological change to food allergens. Further research in humans has also shown that early exposure to food allergens can lead to oral tolerance. Nwaru et al. found that in their cohort of 994 Finnish children, having their first introduction of eggs occur when they were 10.5 months or older was associated with sensitization to food

allergens at 5 years of age. Data from the Australian Health Nuts cohort also showed that delayed introduction of egg until 10-12 months or >12 months old was associated with a significantly increased risk of egg allergy compared to those infants who had early introduction at 4-6 months of age. Furthermore, in the early introduction group, first exposure to cooked egg reduced the risk of egg allergy compared to first exposure of egg in baked goods (OR, 0.2, 95% CI 0.06-0.71). Similarly, Leonard et al. found that the initiation of baked egg diet accelerated the development of egg tolerance compared to strict avoidance. Not only may the timing of introduction of egg be important, but the form in which egg is introduced may have an impact on the development of tolerance. More recently, the Enquiring About Tolerance (EAT) study, which is a randomized controlled trial looking at the early introduction of six common food allergens at 3 months of age (early introduction group) alongside breastfeeding compared to exclusively breast-fed infants (standard introduction group), found that the prevalence of egg allergy was significantly lower in the early introduction group (2.4% vs. 7.3%, $p < 0.01$) in the per-protocol analysis. Egg allergy occurred in 3.7% of the early introduction group compared to 5.4% in the standard introduction group (relative reduction 31%, $p < 0.17$). The EAT study concluded that early introduction was safe with no cases of anaphylaxis occurring during the initial introduction regimen as well as no effects on growth or breastfeeding of the infants. Choking related to a study food was not reported for both studies.

The evidence supporting the role of early introduction of potential allergens in the development of oral tolerance to prevent food allergy is mounting. Although there are still questions as to the timing and also which allergens can be introduced safely and with effect, a shift from recommending avoidance of common food allergens to early consumption strategies to prevent the development of food allergy is occurring. Recently, Australasian guidelines (2016) have been updated to include the introduction of allergenic solid foods including peanut butter, cooked egg, dairy and wheat products to all children in the first year of life, including those at high risk of allergy

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Do you recommend early ingestion of egg in infants at high risk?

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I. Introduction

In recent decades, the prevalence and incidence of food allergy have increased.¹⁾ Egg allergy is one of the most common food allergies in early childhood but up to now, avoidance is the only casual treatment. Hence, prevention strategies have been sought constantly. However, the mechanism of food tolerance involves many factors and thus, the complex interactions between the immune system and environmental factors make it difficult to guide a consistent intervention towards prevention of allergic diseases.

The hypothesis that avoidance should give a benefit in reducing eczema and cow's milk allergy was based from prospective studies which identified the immaturity of intestinal immune system as the main factors influencing on tolerance. In last 30 years, data sustained and reinforced in many aspects, influencing on the strategies in the way of food introduction for prevention of allergic diseases. (Table 1) Starting 2004, the 'avoidance specific food allergens for prevention' paradigm was challenged by a series of epidemiological studies.⁶⁻¹³⁾ Following noninterventional studies, randomized trials^{14,15)} held in last 2 years have reversed the orientation on the timing of the introduction of foods; from a delayed introduction of allergenic foods to an 'early introduction' according to the hypothesis that the timing window for achieving tolerance is represented by the period between 4 and 6 months of life. (Table 2) The results of these trials are very interesting, but should be interpret together with their limits.

II. Recent interventional studies on early ingestion of hen's egg

1. EAT (Enquiring About Tolerance) study¹⁵⁾

- Randomly assigned. Early introduction group, EIG: 3months vs. Standard introduction group, SIG: 6months

Table 1. Recommendations for complementary food introduction during weaning to prevent food allergy in normal infants and high-risk infants from the most important guidelines in the years 2000-2006

Reference	Scientific Society	All infants	High-risk infants
AAP 2000 ²⁾	American Academy of Pediatrics (AAP)		Solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.
Murano 2004 ³⁾	European Academy of Allergy and Clinical Immunology (EAACI)	“Avoidance of solid foods until preferable 6 months but at least 4 months”... “Thus, there is no evidence of allergy preventing effect of restrictive diets after 6 months of age”.	Prospective interventional studies show evidence of the effect of dietary allergy-preventive measures as regards food allergy, especially cow’s milk protein allergy, and eczema.
Prescott 2005 ⁴⁾	Australasian Society of Clinical Immunology and Allergy (ASCIA)		Complementary foods (including normal cow’s milk formulas) should be delayed for at least 4 - 6 months. There is no evidence that dietary elimination after the age of 4 - 6 months has a preventive effect, though this needs additional investigation. Avoidance of peanut, nut and shellfish for the first 2 - 4 years of life may be recommended in high risk children as this is unlikely to cause harm, however it must be emphasized that there is no evidence to support this.
Fiocchi 2006 ⁵⁾	American College of Allergy, Asthma and Immunology (ACAAI)	Complementary feeding can be introduced from the sixth month, and egg, peanut, tree nuts, fish, and seafood introduction require caution.	The optimal age for the introduction of selected supplemental foods should be 6 months, dairy products 12 months, hen’s egg 24 months, and peanut, tree nuts, fish, and seafood at least 36 months.

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- 1303 exclusively breast-fed infants from general population
- In the per-protocol analysis, the prevalence of egg allergy was significantly lower in the EIG (1.4% vs. 5.5%, p=0.009)
- No efficacy was shown of EIA of egg in intention-to-treat analysis

2. HEAP (Hen’s Egg Allergy Prevention) study²⁰⁾

- Randomized, placebo-controlled trial

Table 2. Recommendations for complementary food introduction during weaning to prevent food allergy in normal infants and high-risk infants from the most important guidelines in the years 2008-2014.

Reference	Scientific Society	All infants	High-risk infants
Greer 2008 ¹⁶⁾		Although solid foods should not be introduced before 4 to 6 months of age, there is no current convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease regardless of whether infants are fed cow milk protein formula or human milk. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs, and foods containing peanut protein.	
Grueger 2013 ¹⁷⁾	Canadian Paediatric Society, Community Paediatrics Committee	Complementary feeding (ie, solid foods and liquids other than breast milk or infant formula and follow-on formula) should not be introduced before 17 weeks and not later than 26 weeks.	There is no convincing scientific evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish and eggs, reduces allergies, either in infants considered at increased risk for the development of allergy or in those not considered to be at increased risk.
Murano 2014 ¹⁸⁾	European Academy of Allergy and Clinical Immunology (EAACI)	Introducing complementary foods from 4 to 6 months of age according to standard local practices and the needs of the infant, irrespective of atopic heredity. The present evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods during infancy (BC). Therefore, for primary prevention, we recommend no withholding or encouraging of exposure to 'highly allergenic' foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced.	
Fleischer 2013 ¹⁹⁾	American Academy of Allergy, Asthma & Immunology (ACAAI)	Complementary foods can be introduced between 4 and 6 months of age. Because no formal recommendations have been previously provided about how and when to introduce the main allergenic foods (cow's milk, egg, soy, wheat, peanut, tree nuts, fish, shellfish), these are now provided, and reasons to consider allergy consultation for development of a personalized plan for food introduction are also presented.	

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- 383 not sensitized against hen's egg, 4 to 6 months from general population
- Primary outcome was sensitization to hen's egg by age 12 months; secondary outcome was hen's egg

allergy, confirmed by DBPCFC.

- No evidence of consumption of hen's egg starting at 4 to 6 months of age prevents hen's egg sensitization or allergy

3. STAR (Solids Timing for Allergy Research) trial²¹⁾

- A double-blind randomized controlled trial
- Infants with moderate to severe eczema, 4 to 8 months of age, n=86
- The primary outcome was diagnosis of IgE-mediated hen's egg allergy at 12 months of age
- Results were not conclusive, no statistical significance

4. HealthNuts study²²⁾

- A population-based, cross-sectional study
- 231 infants aged 12 months old were classified as hen's egg allergic
- Lowest risk of hen's egg allergy among infants with first exposure to egg at 4 to 6 months of age in form of cooked egg

III. Against early introduction of egg for the purpose of allergy prevention

1. How early is early?

According to the concept of a window period, there might be a specific time period during which oral exposure to potentially allergenic foods leads to acquire oral tolerance.⁴⁾ However, the timing for introducing complementary food is probably not limited to period from 4 to 6 months of life. HEAP study indicated that the majority of infants with egg allergy were already sensitized and allergic to it before the introduction of solid foods at 4 to 6 months age, and therefore a prevention strategy at this age is too late.¹⁶⁾ An Israeli observational study suggested a protective effect of oral exposure to cow's milk during the first 14 days of life; the highest incidence of cow's milk allergy was found in children introduced to cow's milk at 4 to 6 months of age.²³⁾ In the LEAP study, the authors use the term early, even if in the median age of subjects of the study was 7.8 months (7.8±1.7 months). The significant preventive effect of early introduction observed in infants ranged from 4 to 11 months allows assuming that the time window to achieve immune tolerance could be larger than expected in peanut. The window period seems to differ in its duration and termination depending on each specific food and might vary depending on the infant's environmental exposure to food allergens. Data are not sufficient to conclude a best timing for egg introduction for preventing allergy.

2. Is it safe and practical enough to adopt to the 'high risk' infants?

In the HEAP study, of 406 underwent screening at 4 to 6 months of age to confirm hen's egg sensitization,

5.7% already showed increased hen's egg sIgE levels (specific IgE ≥ 0.35 kUA/L in serum). Six participants declined to undergo DBPCFCs and 17 of the 23 hen's egg-sensitized children underwent DBPCFCs, during which 16 were found to be clinically allergic. Two thirds (10/16) of the children with hen's egg allergy had an anaphylactic reaction. During the trial 14 families reported that their children reacted to the study hen's egg powder. The trial was stopped early because of the allergic reactions at first exposure to the study powder frequently observed in EIG despite screening test. In addition, in the LEAP study, among the 47 infants with skin prick test positive at baseline who were randomly assigned to the consumption group, 6 patients had a positive response. Subjects with a diagnosis of persistent asthma were excluded in LEAP study so those at very high risk of food induced anaphylaxis were excluded. Food protein induced enterocolitis syndrome (FPIES) was also problematic in both studies with hen's egg and peanut. There were 7 cases of reported FPIES-like reactions to peanut in the EIG and 6 cases to hen's egg in the EIG.

First, the definition regarding high risk is not universally adopted throughout studies so it is not yet clear to be applicable. Second, both trials are translated in a real life scenario; we need to perform to all infants, at 3 months of age, skin prick tests with an open food challenge or blood sampling for screening test to avoid serious events. Even worse, results of HEAP study indicate that screening test is not sufficient to exclude the possibility of a large number of allergic reactions observed in the community. Thus, clinicians would be faced with unsustainable condition.

IV. Conclusion

Further studies are needed to continue to investigate whether introduction of certain highly allergenic food at an earlier age, longer length of exposure, in a less allergenic form, at lower amounts or all together might be needed to be more successful at preventing allergic diseases. Also, the risks and benefits of early introduction to allergenic foods on the one hand and those of avoidance of allergenic foods on the other have to be carefully balanced.

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