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Perspective Pro Debate: To introduce solids early or not to introduce, this is the question.

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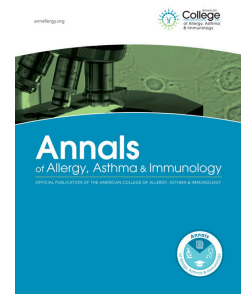
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Title Page

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Perspective Pro Debate: To introduce solids early or not to introduce, this is the question.

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Helen Fisher acts as a consultant for Aimmune therapeutics.

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Peanut allergy; food allergy; allergy prevention; children

Abbreviations:

WHO – World Health Organization

UK – United Kingdom

LEAP – Learning Early About Peanuts

EAT – Enquiring About Tolerance

US – United States

NIH – National Institute of Health

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To introduce solids early or not to introduce, this is the question.

Pro Debate

Early life nutrition has the potential to influence long-term health; what an infant consumes and when they consume it is an important and potentially contentious topic. Breast milk alone will not sustain adequate infant growth beyond 6 months of age, solid food introduction is therefore essential to ensure normal growth through childhood. In the following pro debate, we discuss the evidence for solid food introduction commencing early in an infant's life. The ages we refer to throughout reflect the ages of babies born at full term as prematurity was an exclusion criterion for most studies investigating timings of solid food introduction.

Early for whom?

What constitutes 'early' solid food introduction depends on one's perspective but, for health care professionals, the definition of 'early' is often based upon the World Health Organization (WHO) recommendation that infants should be exclusively breastfed for the first six months of life and given complementary solid foods alongside continued breastfeeding only after this age. Early is thus usually considered to mean commencing solid foods before 6 months of age.

In practice, at least in the Western world, there has been poor adherence to the WHO guidance.

Whilst the age at which infants first receive solid food has increased this century, this change appears to reflect a reduction in the number of children receiving solid food before 3 months of age from approximately 70% in 1990 to 5% in 2010,¹ rather than an increased adherence to the WHO guidance. The United Kingdom (UK) Infant Feeding Survey (2010) found that 75% of infants had been introduced to solid food by 5 months of age and 95% of infants had been given solid food by 6 months of age, a similar figure to the 2005 and 2000 surveys.¹

For the purposes of this debate we thus consider early introduction to be solids given before 6 months of age, however it is important to remember that, in practice, most infants in the Western World are already consuming solid food by this age. This argument thus focuses on whether allergenic foods should be introduced before 6 months of age or whether early weaning should be restricted to low allergen foods such as fruit and vegetables.

Early introduction of solid food can positively influence infant health. In the two last decades there has been a pronounced change in the allergic community's understanding of the mechanisms by which children develop food allergies. Where once prolonged avoidance was considered necessary, this strategy was found to be ineffective, at best delaying the onset of food allergy. Rather, evidence began to develop that introducing allergenic foods early in an infant's life might be the most effective way to prevent food allergy.

The first randomized controlled study to demonstrate this was the LEAP study, which enrolled infants from 4 to <11 months of age and examined whether consumption of peanut protein three times per week was more effective than avoidance in preventing peanut allergy at 60 months of age. The study found an 86% reduction in peanut allergy in children who consumed peanut protein three times per week from study enrolment (4-<11 months of age) when compared to those who avoided peanut until 5 years of age.²

Subsequently the EAT study compared whether the introduction of the six most commonly allergenic foods (cow's milk, egg, peanut, sesame, fish and wheat) to exclusively breastfed infants at 3 months of age was more effective than exclusive breastfeeding to 6 months of age in preventing food allergy at 36 months of age.³ The study had low rates of adherence in the intervention group and did not meet its primary outcome, but per protocol analyses found a reduction in egg and peanut allergy in the early introduction group.³

In 2016 a meta-analysis of all published studies which examined the timing of solid food introduction in the prevention of allergic disease found that, for egg and peanut at least, introduction of the

relevant solid food in early infancy is an effective means of preventing allergy.⁴ Ierodiakonou and colleagues point out that this evidence is consistent with a large body of evidence in animal (predominantly mouse) models, where tolerance can be effectively achieved through early antigen exposure.⁴

Following publication of these studies, many countries and national and international allergy societies have recently updated their allergy prevention guidance.⁵ The amended guidance is country-specific but the overarching message is that solid foods, including allergenic foods such as peanut, should be introduced as soon as the infant is developmentally ready at around 6 months and not before 4 months. The US NIH stratify their guidance according to risk level making a stronger recommendation for children deemed to be at high risk of peanut allergy (those with severe eczema and/or egg allergy). They recommend that peanut protein be introduced from 4 months but by 6 months of age.⁶

When considering egg and peanut, for allergic outcomes at least, early introduction of the relevant food is an effective strategy for preventing the respective food allergy, although the form in which the food is given is relevant to this effectiveness; cooked proteins having both a superior efficacy and, importantly, safety profile.⁵

Few RCTs have investigated the effect of early introduction of other foods on oral tolerance. A meta-analysis found that there is low to very low certainty evidence that early fish introduction reduces the risk of allergic sensitization, and high certainty evidence that age of gluten exposure is not associated with coeliac disease.⁴ The EAT study found a difference in positive skin prick test to wheat at 12 months (1.3% vs 3.2% $p=0.03$) and 36 months of age (1.4% vs 3.2%); children in the early introduction group being less likely to be sensitised than those given allergenic food after 6 months of age.³ There were also non-significant between-group differences in positive skin prick test 12 and 36 months of age to cow's milk, egg, peanut and sesame.³ These findings highlight the potential of early introduction of allergenic foods beyond egg and milk, although further RCTs are required.

Several arguments are often levied against the early introduction of solid food. These include the potential effect on breastfeeding, consequences for infant health outside of allergic disease and the practicalities of solid food introduction. In the final section we briefly debunk these arguments.

Early solid food introduction has a negative impact on breastfeeding

For most infants and mothers, the benefits of breastfeeding are undisputed. One concern that is often raised regarding introduction of solid foods before 6 months of age is the cessation of breastfeeding. Evidence from LEAP and EAT can allay these fears. In the EAT study no between-group difference were found in the number of infants who were still breastfed at either 6 or 12 months of age.⁷ This suggests that, for infants who had been exclusively breastfed for at least 3 months (i.e. where breastfeeding was well established), introduction of solid foods had no adverse consequences for continuation of breastfeeding after complementary weaning commenced.

Early solid food introduction may prevent allergies but what about other health conditions? The scientific merit of universal application of the WHO recommendation that infants are not given solid foods until after 6 months of age has been questioned. Fewtrell highlights the limitations of this guidance, particularly in developed world, including the observational nature of many of the studies included in the Cochrane Review upon which the WHO recommendations were based, and the risk of iron deficiency anaemia in infants who are exclusively breastfed for 6 months.⁸ She also points out that, whilst exclusive breastfeeding has been shown to be protective against infection, it is the introduction of infant formula which increases the risk of infection, rather than the introduction of solid food.

The long term and wider health implications of introducing solid foods before 6 months of age are an important consideration. In 2009 the European Food Safety Authority conducted a review of prospective studies of breastfed infants, examining a variety of health outcomes and considering whether there were any links with the age at which complementary weaning was commenced. They

found that, in developed countries, food may safely be introduced between 4 and 6 months of age with no deleterious outcomes for infections, weight gain, allergy or obesity.⁹

Analysis of LEAP and EAT study data find similarly reassuring results. Despite the high protein and caloric content of allergenic foods such as peanut, the LEAP study found no differences in anthropometrics or energy intake between the groups at any time point (12mo, 36 m, 60m and 72m).¹⁰ The EAT study similarly found no differences in anthropometrics between the early introduction and standard introduction groups at any study time point.³ Follow up of these two cohorts now the children are 12 (LEAP) and 9 (EAT) years of age is ongoing and will encompass both allergic and more broad child health outcomes. These data will provide essential information regarding the long-term effect of the introduction of allergenic solid food in early infancy on both allergic and general child health.

Early solid food introduction is not achievable in practice
Whether early solid food introduction is achievable will depend upon a variety of factors.⁵ In practice families have already demonstrated the practicability of this because only 5% of UK parents have not weaned their infants 'early'.¹ Despite this, the low rates of adherence to the intervention reported by the EAT study have been cited as evidence that early solid food introduction is not practicable: 31.9% of infants who were enrolled to the early introduction arm of the EAT study adhered to the protocol with rates of adherence to specific foods ranging from 85.2% for cow's milk to 43.1% for egg.

Whilst EAT study parents were asked to feed their infants 4g of each of the six study foods weekly evidence from other studies suggests that 2g of peanut or egg protein per week is sufficient to prevent peanut and egg allergy.⁵ This quantity is likely to be achievable for most infants but studies which establish the relative merits of daily versus weekly consumption of the 2g dose of protein are also required. Furthermore, whilst there is good evidence that regular consumption (without long periods of avoidance) is necessary for tolerance to be established, trials which explore both the

maximum interval for which the food may be avoided and the minimum time frame for which 'regular' consumption is required to develop long lasting tolerance are needed. Until these data are available, it is reassuring that children who did not meet the EAT study protocol definition of adherence were at no greater risk of food allergy than children in the standard introduction group. This indicates that consuming a small portion of allergenic food will not increase the risk of food allergy above that of a child who is exclusively breastfed until 6 months of age.

Conclusion

The notion of early weaning is somewhat moot. In the Western World the vast majority of infants have commenced complementary weaning onto solid foods before six months of age. Although allergenic foods are not commonly introduced by parents before six months of age, there is now good evidence that, after 4 months of age, once a parent chooses to wean their child, avoidance of allergenic foods is unnecessary. Furthermore, for egg and peanut at least and particularly in children at risk of developing food allergy, consumption of allergenic foods early in the weaning process offers protection against food allergy with no evidence of deleterious effects on established breastfeeding, wider childhood health, or nutrition.

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