

Does early egg introduction prevent egg allergy in children?

SCENARIO

A 4-year-old infant comes into allergy clinic with her parents who say that after eating eggs and egg-containing foods she develops a 'nettle sting' rash around the mouth. This usually happens within an hour of eating. After an oral food challenge, an egg allergy is diagnosed. At a follow-up appointment, the parents ask you whether this could have somehow have been prevented. You look into whether early dietary introduction of egg would have played a role.

STRUCTURED CLINICAL QUESTION

In children (population), does early introduction of egg (intervention) compared with later introduction (comparison) prevent the development of egg allergy (outcome)?

SEARCH

All searches were all performed on 17 February 2021.

SECONDARY SOURCES

Cochrane Library searched: 'egg allergy prevention' and 'early introduction'; 26 results, none relevant. National Institute for Health and Care Excellence evidence searched: 'egg allergy prevention'; 204 results, none relevant.

PRIMARY SOURCES

PubMed searched ("infant*[Title/Abstract] OR "child*[Title/Abstract] OR "paediatric"[Title/Abstract]) AND "introduction"[Title/Abstract] AND ("egg"[Title/Abstract] OR "hen's egg"[Title/Abstract]) AND ("egg allergy"[Title/Abstract]) with 80 results, 6 studies included.

SUMMARY

COMMENTARY

Egg allergy, an adverse immunological reaction to egg proteins, is one of the most common food allergies in infants and young children.¹ With the incidence rates of over 2% in the UK, it has the highest prevalence rate of 8.9% (95% CI 7.8% to 10.0%) in the first year of life.^{2,3} Egg allergy can cause life-threatening anaphylactic reactions that significantly impair the quality of life⁴ and adversely affect morbidity; therefore, the development of effective prevention strategies is key. Early allergen introduction has been associated with reduced food allergy rates with a recent systematic review and meta-analysis by Al-Saud and Sigurdardóttir confirming findings.⁵⁻⁷

The search generated six randomised clinical trials (table 1) with the majority looking into egg allergy and egg sensitisation rates as primary and secondary outcomes. Allergic sensitisation is biochemical evidence of IgE response to an allergen but does not correlate in every case with clinical allergy as evidenced by studies showing significantly higher rates of allergen sensitisation in comparison with true allergy rates.⁸⁻¹⁰

The high heterogeneity from the study participants (healthy infants,^{11,12} infants with hereditary risk^{13,14} or infants with eczema^{15,16}) to varied age ranges at introduction and follow-up times as well as a variation of egg vehicles used (raw egg powders¹²⁻¹⁵ to cooked egg^{11,16}), length of treatment and outcome measures complicates analysis.

Clinical bottom lines

- ▶ Dietary introduction of cooked hen's egg can reduce the risk of egg allergy in infants. (Grade B)
- ▶ The degree to which egg has been processed for early introduction seems to affect clinical outcomes with raw egg powders causing more complications due to increased allergenicity. (Grade C)
- ▶ Pre-testing with either SPT or specific serum markers (e.g., sIgE) in high-risk infants can inform the clinician whether clinical supervision of early egg introduction may be useful. (Grade C)

Perkin *et al* and Natsume *et al* all showed significantly reduced rates of egg allergy with early introduction ($p=0.05$).^{11,16} Tan *et al* and Palmer *et al* showed reduced egg allergy rates that were not statistically significant.^{13,14} Two studies, Bellach *et al* and Palmer *et al*, had to be terminated early due to safety concerns, however, this is thought to be due to the raw egg powder vehicle used and not due to early introduction itself.^{12,15} Conversely, Natsume *et al* used heated egg powder with no allergic reactions and showed a protective effect of early egg introduction between the ages of 6 and 9 months with a significant reduction in the prevalence of egg allergy at 12 months.¹⁶ The change in safety data can be explained by higher allergenicity of raw egg powder in comparison with cooked as children outgrow cooked-egg allergy two times faster than raw-egg allergy.¹⁷

In addition to rates of clinical allergy, several studies measured the rates of egg sensitisation prior to entering the trials, addressing the question of which infants are sensitised (but are not allergic) to egg but can develop tolerance via regular ingestion, and those who will react on ingestion and become allergic. Four studies (Bellach *et al*, Natsume *et al*, Palmer *et al* and Tan *et al*) measured the level of egg sensitisation prior to ingestion, either as a primary or secondary outcome measure.^{12-14,16} Two of the studies showed an increase in egg sensitisation with early egg introduction with Natsume *et al* showing statistically significant levels ($p=0.001$).¹⁶ Although Palmer *et al* and Tan *et al* showed a general decrease in egg sensitisation in the early introduction groups, Tan *et al* showed statistically significantly higher levels of IgE to egg protein prior to ingestion already present in the serum of infants in the early introduction group ($p=0.001$).^{13,14} These mixed results warrant further investigation to understand the significance of egg sensitisation, especially in high-risk children with atopic conditions or hereditary risk as Palmer *et al* showed that many infants with eczema are already sensitised to egg by the age of 4 months.¹⁵ The current tests for egg sensitisation are not sensitive and specific enough to predict which pre-ingestion sensitised infants will react or be able to induce tolerance with early introduction without confirmatory oral challenges. Therefore, the judicious use of pre-testing in certain high-risk demographic groups may be useful to identify the sensitised patients who might develop clinical reactions with early introduction¹⁸ meaning high-risk infants require specialist input before early egg introduction, but not the general low-risk population.

In conclusion, with the mixed evidence available, an early introduction of egg seems to have a positive effect on egg allergy rates. Future studies will need to consider the egg vehicle used, egg dosage, the length of egg consumption as well as participant comorbidities and demographics (age range, follow-up period and ethnicity among others). There is some evidence that pre-testing for sensitisation may offer useful clinical information;

Table 1

Citation	Study group	Study type	Outcome	Key result	Comments
The Solid Timing for Allergy Research (STAR) Palmer <i>et al</i> (2013) ¹⁵	86 infants with eczema. Participants were divided into two groups receiving either 1 teaspoon of pasteurised raw whole egg powder (n=49) or rice powder (n=37) daily from the age of 4 until 8 months of age	Randomised, double-blinded, placebo-controlled trial	IgE-mediated egg allergy at 12 months	At 12 months, a lower proportion of infants in the egg group (33%) were given a diagnosis of IgE-mediated egg allergy compared with the control group (51%). RR, 0.65; 95% CI 0.38 to 1.11; p=0.11	High proportion of infants receiving the egg powder had an allergic reaction and therefore were not able to continue with the trial, which likely skews the results and limits statistical power
Enquiring About Tolerance (EAT) Perkin <i>et al</i> (2016) ¹¹	1303 exclusively breastfed infants who were 3 months of age. Participants were randomly assigned to either early introduction or standard introduction of 6 allergenic foods (with egg being one of them). Follow-up period until 3 years of age	Single-site randomised controlled trial	Food allergy prevalence to one or more of the six foods between 1 year and 3 years of age Allergy to individual foods and positive results on SPT for individual foods at 12 months	Prevalence of egg allergy Early introduction 1.4% vs standard introduction 5.5% (p=0.009) The consumption of 2 g per week of egg-white protein was associated with a significantly lower prevalence of these respective allergies than was less consumption Reduction of RR by approximately 50% in the early-introduction group with the difference significant in the egg group (p=0.009). 49% lower relative risk (p=0.07) of positive SPT in the early introduction group in the egg group, which was similar to commercial egg extract	The main weakness of the study was the low rate of per-protocol adherence in the early-introduction group as the volume of all six foods and regularity required by the study caused adherence difficulties for infants and parents
Hen's Egg Allergy Prevention (HEAP) Bellach <i>et al</i> (2017) ¹²	383 infants who were not sensitised to egg. Patients were divided into verum (n=184) and placebo (n=199) groups. The verum group received pasteurised raw egg white powder three times a week that increased from ½ of 10 mL measuring spoon (MS) in the first week to 1 MS in the second week to 1.5 MS in the third week until 12 months of age	Randomised, placebo-controlled trial	Sensitisation to hen's egg through the measurement of specific serum IgE levels Rate of hen's egg allergy	4.8% (6/124) in the verum group and 2.6% (4/152) in the placebo group were sensitised to hen's egg by 12 months of age. RR 1.84; 95% CI 0.53 to 6.37; p=0.35 2.1% were confirmed to have hen's egg allergy vs 0.6% in the placebo group at 12 months old. RR, 3.30; 95% CI 0.35 to 31.32; p=0.35	The study was stopped early due to allergic reactions to the egg powder despite in-depth screening for pre-existing egg sensitisation, which was felt to be due to the type of egg powder used
Prevention of Egg Allergy with Tiny Amount Intake (PETIT) Natsume <i>et al</i> (2017) ¹⁶	147 high-risk infants aged between 4 and 6 months with eczema and without previous ingestion of, or reactions to, egg. Participants were divided equally to either the intervention group (n=73) or the placebo group (n=74). Participants in the intervention group consumed 50 mg of cooked egg powder per day from 6 months to 9 months of age and 250 mg per day thereafter until 12 months of age	Two-centre, double-blind, placebo-controlled randomised trial	Proportion of participants with hen's egg allergy confirmed by open OFCs at 12 months of age The effect of egg ingestion on egg-sensitised and non-sensitised individuals through specific IgE measurements	Trial terminated early based on an interim analysis (n=121). Egg group 8% vs placebo group 38% RR, 0.221; 95% CI 0.090 to 0.543; p=0.0001 Egg-sensitised infants (specific IgE≥0.35 kUA/L; p=0.001) Non-sensitised infants (specific IgE<0.35 kUA/L; p=0.31)	Fourteen per cent of infants enrolled did not undergo an oral food challenge at 12 months and thus excluded from the final analysis, therefore an intention-to-treat analysis was not performed, however the per-protocol results were strongly in favour of early introduction in prevention egg allergy but also inducing tolerance in infants already sensitised to egg
Starting Time of Egg Protein (STEP) Palmer <i>et al</i> (2017) ¹³	820 infants with hereditary risk between the ages of 4 and 6 months. Participants were divided into a group that received daily pasteurised raw egg powder (n=407) or a placebo-rice powder (n=413) until 10 months old. Follow-up occurred at 12 months of age	Randomised, double-blinded, placebo-controlled trial	IgE-mediated egg allergy defined by a positive pasteurised raw egg challenge Egg sensitisation rate at age 12 months by a positive SPT result	Egg 7.0% vs control 10.3%. Adjusted relative risk (aRR), 0.75; 95% CI 0.48 to 1.17; p=0.20 Egg 10.8% vs control 15.1%. aRR, 0.77; 95% CI 0.54 to 1.10; p=0.15	The egg dosage (0.4 g egg protein per day) was low compared with other studies and may not have been enough to induce tolerance in all infants

Continued

Table 1 Continued

Citation	Study group	Study type	Outcome	Key result	Comments
Beating Egg Allergy Trial (BEAT) Tan <i>et al</i> (2017) ¹⁴	319 infants with at least one first-degree relative with allergic disease. The participants were divided into egg-receiving group (n=165) or placebo (n=154). The intervention started at 4 months of age and continued until 8 months of age	Randomised, double-blind, single-site, parallel-arm, controlled trial	The proportion of infants in each group sensitised to egg white (EW) on SPTs at 12 months	Egg 10.7% vs placebo 20.5%. OR, 0.46; 95% CI 0.22 to 0.95; FAS: p=0.03 Absolute risk reduction was 9.8% (95% CI 8.2% to 18.9%), with a number needed to treat of 11 (95% CI 6 to 122)	Selection bias may have occurred due to a higher study proportion of higher socioeconomic bracket parents which may not be representative of the general population, and the inclusion of only high-risk infants increases the difficulty in extrapolating to the wider population
			Egg allergy at open OFC at 12 months	No effect; 7/21 had confirmed allergy on the OFC, and 13/21 had a convincing history of allergic reaction to egg	
			IgE (whole egg, ovalbumin, and ovomucoid), IgG4 (EW, ovalbumin, and ovomucoid), and IgG4:IgE ratio at 12 months	Levels of IgG4 to egg proteins and IgG4:IgE ratios were higher in the egg group (p<0.0001 for each)	
			Probable egg allergy at 12 months	No effect; egg 8/130 (6.2%) vs placebo 13/124 (10.5%) (p=0.20)	

aRR, adjusted Relative Risk; EW, Egg White; FAS, Full Analysis Set; IgE, Immunoglobulin E; IgG4, Immunoglobulin G4; kU/L, Kilounits of allergen-specific IgE per liter; MS, Measuring Spoon; OD, Odds Ratio; OFC, Oral Food Challenge; OFC, oral food challenge; RR, Risk Ratio/Relative Risk; SPT, Skin Prick Test.

therefore, further research should consider them in their outcome measures. For real-life applicability of results, there needs to be an approach in which egg would be prepared to simulate true-to-life circumstances.

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