Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants

Johanna Bellach,[a] Veronika Schwarz, MD,[a] Birgit Ahrens, MD,[a] Valérie Trendelenburg, MSc,[a] Özlem Aksünger,[a] Birgit Kalb, MD,[a] Bodo Niggemann, MD,[a] Thomas Keil, MD, MPH,[b] and Kirsten Beyer, MD[a,c] *Berlin, Germany, and New York, NY*

Background: Hen's egg is the most common cause of food allergy in early childhood.
Objective: We investigated the efficacy and safety of early hen's egg introduction at age 4 to 6 months to prevent hen's egg allergy in the general population.
Methods: This randomized, placebo-controlled trial included 4- to 6-month-old infants who were not sensitized against hen's egg, as determined based on specific serum antibodies (IgE). These infants were randomized to receive either verum (egg white powder) or placebo (rice powder) added to the first weaning food 3 times a week under a concurrent egg-free diet from age 4 to 6 until 12 months. The primary outcome was sensitization to hen's egg (increased specific serum IgE levels) by age 12 months. Hen's egg allergy (secondary outcome) was confirmed by double-blind, placebo-controlled food challenges.
Results: Among 406 screened infants, 23 (5.7%) had hen's egg–specific IgE before randomization. Seventeen of 23 underwent subsequent double-blind, placebo-controlled food challenges, and 16 were confirmed as allergic, including 11 with anaphylactic reactions. Of the 383 nonsensitized infants (56.7% male), 184 were randomized to verum and 199 to placebo. At 12 months of age, 5.6% of the children in the verum group were hen's egg sensitized versus 2.6% in the placebo group (primary outcome; relative risk, 2.20; 95% CI, 0.68-7.14; $P = .24$), and 2.1% were confirmed to have hen's egg allergy versus 0.6% in the placebo group (relative risk, 3.30; 95% CI, 0.35-31.32; $P = .35$).
Conclusion: We found no evidence that consumption of hen's egg starting at 4 to 6 months of age prevents hen's egg sensitization or allergy. In contrast, it might result in frequent allergic reactions in the community considering that many 4- to 6-month-old infants were already allergic to hen's egg. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Food allergy, hen's egg allergy, allergy prevention, atopic eczema, oral tolerance, randomized controlled trial, complementary feeding*

Although good data are scarce, some studies suggest that in recent decades the prevalence and incidence of food allergy might have increased.[1-3] Hen's egg allergy is the most common food allergy in early childhood.[4] Because there is no causal treatment, prevention strategies are sought keenly. Following international guidelines, there is a lack of evidence justifying the advice to either withhold or encourage the introduction of potentially allergenic foods after 4 months once weaning has commenced irrespective of atopic heredity.[5] The results of the Learning Early About Peanut Allergy trial showed a protective effect of early introduction of peanut regarding the development of peanut allergy in infants with severe atopic dermatitis, hen's egg allergy, or both if peanut was introduced between 4 and 11 months of age in children with a peanut skin prick test response of 4 mm or less.[6] In the wake of this finding, a consensus paper was released by international organizations recommending the early introduction of peanut into the diets of selected high-risk infants in countries with prevalent peanut allergy.[7]

The question remains whether the same preventive effect applies for other allergenic foods. One observational study found that early introduction of hen's egg at 4 to 6 months of age was associated with a lower risk of hen's egg allergy compared with delayed introduction after 10 months of age.[8] In a randomized controlled trial in high-risk infants with eczema, the Australian STAR study aimed to investigate whether early regular egg exposure would reduce IgE-mediated hen's egg allergy.[9] Unfortunately, the trial had to be terminated prematurely because they observed a high number of infants with reactions to the study powder, often on first exposure.[9] The trial showed a slightly lower proportion of infants with the diagnosis of IgE-mediated hen's egg allergy in the hen's egg feeding group compared with the hen's egg avoidance group but without statistical significance.[9]

Here we report the results of the Hen's Egg Allergy Prevention (HEAP) study, the first randomized, placebo-controlled hen's egg intervention study in infants from the general population. The trial was designed to determine whether early introduction of hen's egg could serve as an effective strategy in terms of primary prevention of hen's egg sensitization and allergy in a general population.

METHODS

Trial design

The HEAP study involved a double-blind, randomized, placebo-controlled trial with a 1:1 allocation ratio conducted at a single site, the Department for Pediatric Allergology and Immunology, Charité Berlin, Germany, after recruiting newborns in 8 maternity wards in Berlin (Fig 1). The trial was

From [a]the Department of Paediatric Pneumology and Immunology, Charité-Universitätsmedizin, Berlin; [b]the Institute for Social Medicine, Epidemiology and Health Economics, Charité-Universitätsmedizin-Berlin; and [c]Icahn School of Medicine at Mount Sinai, New York.

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Corresponding author: Kirsten Beyer, MD, Department of Pediatric Pneumology and Immunology, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: kirsten.beyer@charite.de.

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Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
EAT: Enquiring About Tolerance
FPIES: Food protein–induced enterocolitis syndrome
HEAP: Hen's Egg Allergy Prevention
kU_A: Kilounits of antibody
MS: Measuring spoon
RR: Relative risk
STAR: Solids Timing for Allergy Research

approved by the institutional review board of Charité-Universitätsmedizin Berlin (EA 2/00608). Before trial participation, written informed consent was obtained for all participants. The trial was registered by the German Clinical Trials Registry with the registration number DRKS00005668.

Participants and study procedure

Inclusion criteria were a gestational age of 34 weeks or greater and a birth weight of 2.5 kg or greater. Children were excluded from participation if the child's mother was younger than 18 years or if parents had insufficient language skills. Shortly after birth, all participating families received a standardized baseline questionnaire based on the EuroPrevall birth cohort questionnaire.[10] The mothers were advised to follow the German guidelines on allergy prevention.[11]

As soon as the parents planned to begin introducing solid foods, the families were invited to the study center for the screening visit before intervention (Fig 1). During this visit at 4 to 6 months of age, a preinterventional questionnaire based on EuroPrevall[10] was completed, and a physical examination was performed. Blood was drawn to screen for hen's egg white (f1)–specific serum IgE by using the Phadia CAP-System FEIA (Thermo Scientific/Phadia Diagnostics, Uppsala, Sweden). Those children with hen's egg–specific IgE levels of 0.35 kilounits of antibody (kU_A)/L or greater were invited for a double-blind, placebo-controlled food challenge (DBPCFC) and excluded from the intervention. DBPCFCs were performed with pasteurized liquid whole egg manufactured by Wiesenhof Geflügel-Kontor GmbH (Visbek, Germany). Amounts equal to 5.2 mg, 12.9 mg, 51.6 mg, 129 mg, 516 mg, 1.29 g, and 5.16 g of hen's egg protein were administered orally every 30 minutes. Challenges were performed in applesauce as a matrix. Following PRACTALL criteria, food challenge results were scored as positive if objective clinical reactions were noted, such as urticaria, angioedema, vomiting, wheezing, stridor, or decrease in blood pressure.[12,13] In the event of clinical tolerance, the patient received a subsequent cumulative dose of pasteurized whole egg in a total amount of 7 g of hen's egg protein on another day.[14]

Intervention

All children in the trial with hen's egg–specific IgE levels of less than 0.35 kU_A/L were randomly assigned to 2 treatment groups (Fig 1). The verum powder contained pasteurized egg white equal in its allergenicity to raw hen's egg[15,16] and manufactured by Ovobest (Neuenkirchen-Vörden, Germany), whereas the placebo powder contained rice manufactured by Milupa (Friedrichsdorf, Germany). The study powder was administered orally 3 times a week by mixing the allocated study powder with solid baby food using a 10-mL measuring spoon (MS), starting with ½ MS in the first week and 1 MS in the second week and continuing with 1½ MS from the third week of intervention until 12 months of age. In the verum group 1½ MS contained 2.5 g of hen's egg protein, which is equivalent to one third of an egg, and in the placebo group organic white rice was used. Parents in both groups were instructed to follow an egg-free diet for their child, including avoidance of egg-containing products.

Safety

All families were provided with an emergency telephone number in case of reactions to the study powder. Study staff contacted the participating families once a month by telephone to assess adherence to the study protocol and to enquire about allergic symptoms related to the study powder. If the parents reported symptoms, the standard procedure shown in Fig E1 in this article's Online Repository at www.jacionline.org was followed.

Primary and secondary outcome assessment

When the infants reached 12 months of age, all families were invited again to the study center for a final clinical assessment, including physical investigation, blood drawing for measurement of allergen-specific IgE levels, and an interview (Fig 1). Oral food challenges were conducted in all children newly sensitized against hen's egg: as titrated DBPCFCs in the placebo group, as described above, and as open challenges with one dose containing 7.5 g of hen's egg protein in the verum group.

The primary outcome was defined as hen's egg sensitization (specific IgE ≥0.35 kU_A/L in serum) at 12 months of age. The secondary outcome was defined as hen's egg allergy confirmed by clinical reactions to pasteurized hen's egg on oral food challenge tests.

Randomization and blinding

An independent consultant produced a computer-generated randomization schedule, and an independent study nurse allocated the identically packaged dietary intervention powders to the corresponding study number of the child. This study nurse was involved in neither the assessment of the child nor the allocation of the study powder. Participants, care providers, physicians, dieticians, and nurses involved in assessing the outcome were blinded.

Sample size

Three hundred fifty-eight infants were required in each of the 2 groups (considering $\alpha = 0.05$ and $\beta = 0.20$) to be able to determine a 50% reduction of the sensitization to hen's egg by age 12 months (12% in the placebo group vs 6% in the verum group). Allowing for a dropout rate of 10% during the follow-up period up to age 12 months, our original aim was to recruit a total of 788 infants. In February 2014, an interim analysis was performed by an independent statistical consultant, after which it was decided to terminate the trial before reaching the originally planned sample size.

Statistical analysis

Study analysis was performed after all included infants had undergone the final visit at 12 months of age. We performed an analysis of all randomized participants who could be assessed for the primary outcome irrespective of whether some of these patients might have switched or discontinued treatment before the final visit (modified intent-to-treat analysis). A revision of the CONSORT statement suggested acceptance of an analysis of observed data.[17,18] The per-protocol population included participants who could be assessed for the primary outcome and who adhered to the assigned regimen (ie, avoidance of hen's egg–and egg-containing products in the placebo group and regular consumption of hen's egg protein in the verum group, which was defined as the minimal average administration of the study powder twice a week with a maximum interruption of 2 weeks during the intervention phase until 12 months of age). The proportions of infants with hen's egg sensitization (primary outcome) and given a diagnosis of hen's egg allergy at 12 months of age (secondary outcome) were compared between the 2 intervention groups by using a Fisher exact test. Risk ratios were calculated with 95% CIs. Independent-samples t tests, Mann-Whitney U tests, Pearson χ^2 tests, and Fisher exact tests were used to test differences between the sensitized and nonsensitized infants at the screening visit, as well as differences between the 2 study groups at randomization, depending on the variable scaling and distribution.

Statistical significance was assessed at the .05 level. SPSS statistical software (release 22.0; IBM, Armonk, NY) was used for all analyses.