

Role of early egg ingestion in induction of tolerance: An unanswered question

Tamareal Ross, MD^c
Jennifer Swanson, MD^d
Aries Gavino, MD^a

To the Editor:

We read with interest the article “Early regular egg exposure in infants with eczema: A randomized controlled trial” by Palmer et al.¹ The authors attempted a well-designed study to evaluate the role of early exposure to potentially allergenic foods. The primary outcome of reduction in the risk of IgE-mediated egg allergy was not met, and the difference between the 2 groups was not statistically significant (33% in the study group vs 51% in the control group; relative risk, 0.65; 95% CI, 0.38-1.11; $P = .11$). However, the authors conclude that the induction of immune tolerance and reduction in the incidence of egg allergy could be achieved. Unfortunately, because of logistic reasons, the sample size was limited, and the study was not sufficiently powered. Therefore, the conclusion of the study is preemptive and misleading. The increase in the level of food-specific IgG₄ does not provide conclusive evidence of clinical tolerance, nor does a low IgE/IgG₄ ratio.^{2,3}

It is possible that misclassification bias occurred because potential confounding factors, such as maternal egg intake, were not recorded. It is known that dietary allergens can be transmitted via breast milk. Approximately 75% of the women who consume eggs have demonstrable ovalbumin in the breast milk.⁴ A direct dose-response relationship has also been observed between the amount of egg intake and the ovalbumin concentration in breast milk.⁵ Although its clinical significance is not conclusive at this time, unaccounted exposure to egg allergens via breast milk could have potentially altered the study results.

Also, of interest, a high proportion of infants in the study were breast-fed at 4 months (study group 82% and control group 84%). According to the Centers for Disease Control and Prevention, the initiation of breast-feeding occurs in approximately 77% and only 47% are breast-feeding at age 6 months in the United States.⁶ Therefore, one needs to keep this in mind while interpreting the study results in this population.

In addition, the potential for selection bias is unknown, because the process of participant recruitment was not described. It is unclear how many participants were screened, what proportion was enrolled in the study, and the reasons for participation refusal. Another concern is that the intention-to-treat analysis was difficult to interpret because many of the tables and charts had varying numbers of patients in control and experimental groups. For example, 67 of the 86 subjects had baseline immunoglobulins drawn at age 4 months, but in Table III, information is provided regarding only 66 IgE levels (35 in the egg group and 31 in control group) and only 65 IgG₄ levels (35 in the egg group and 30 in the control group).

In summary, this was a very challenging trial because attempting an egg challenge in infancy poses a significant risk. In the study, a high rate of allergic reaction to the study powder and serious adverse effects were observed. However, because of limitations in the study, the question of whether early egg exposure in infancy can prevent the development of egg allergy remains unanswered.

Qurat-Ul-Ain Kamili, MD^a
Rajesh Shah, MD^b

From the Sections of ^aImmunology, Allergy and Rheumatology and ^bGastroenterology, Department of Internal Medicine, and the Departments of ^cNeurology and ^dPediatrics, Baylor College of Medicine, Houston, Tex. E-mail: kamili@bcm.edu.

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Reply

To the Editor:

Kamili et al¹ have raised some important questions that we are pleased to address regarding our recent randomized controlled trial (RCT) on the effects of early regular egg exposure in infants with eczema.² We begin by urging the need for cautious interpretation of our findings, which could have been stated more strongly in our article. As indicated in the article, logistic obstacles prevented us from recruiting the target sample size of 226 infants, and we stressed that the study was not adequately powered to make conclusions about clinical efficacy. That said, the available data did provide some useful and unique insights. First, we determined that a significant proportion (31%) of children with moderate to severe eczema were already sensitized at age 5 months before starting complementary feeding. Second, we observed that many of these children had clinical reactions, including anaphylaxis, at their first taste of egg at age 5 months, highlighting the need for caution when introducing allergenic foods to this group of children. Third, we found that early introduction of egg did *not* significantly reduce the rate of egg allergy at age 12 months. However, given the inadequate sample size, it is not possible to make any definitive conclusions about this finding. Even so, we felt it important to consider the trend for lower incidence of egg allergy in the egg group than in the control group at age 12 months. This is informative and reassuring in several ways. The direction of this trend goes some way to addressing previous concerns that earlier introduction of “allergenic” foods (as being tested in at least 7 other RCTs internationally³) does not appear to *increase* the risk of food allergy. It also lends tentative support for the hypothesis underpinning these studies—that regular allergen exposure may be important in the induction of clinical tolerance.