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Can early introduction of gluten reduce risk of celiac disease?

This UK study revealed the benefits of introducing gluten at age 4 months.

PRACTICE CHANGER

Consider introducing gluten (wheat) in addition to breast milk or infant formula from age 4 months to potentially reduce the risk of celiac disease (CD) at age 3 years.¹

STRENGTH OF RECOMMENDATION

B: Based on a single randomized controlled trial (RCT) with a patient-oriented outcome of CD diagnosis.¹

Logan K, Perkin MR, Marrs T, et al. Early gluten introduction and celiac disease in the EAT Study: a prespecified analysis of the EAT randomized clinical trial. *JAMA Pediatr.* 2020;174:1041-1047.

ILLUSTRATIVE CASE

You are seeing a 2-month-old female infant for a routine well-child visit. The birth history was unremarkable. The infant is meeting appropriate developmental milestones. Growth is appropriate at the 40th percentile. The infant is exclusively breastfed. The parents report that they have heard confusing information about when to introduce solid foods, including bread, to their child's diet. There is no known family history of CD. What anticipatory guidance can you offer regarding gluten introduction and the risk of CD?

CD is an inflammatory disease of the small intestine caused by an immune-based reaction to dietary gluten. The worldwide incidence of CD in children younger than 15 years is 21.3 per 100,000 person-years; this incidence has increased by 7.5% per year over the past several decades.² CD has a range of both gastrointestinal and nongastrointestinal manifestations,

including diarrhea, weight loss, abdominal pain, abnormal liver function test results, and iron deficiency anemia.

Diagnosis of CD in adults is based on a combination of clinical symptoms, elevated levels of immunoglobulin A anti-tissue transglutaminase antibody (tTG-IgA), and biopsy-confirmed villous atrophy of the duodenum on upper endoscopy.³ European pediatric guidelines suggest that use of certain criteria, including very high results of tTG-IgA antibody testing (> 10 times the upper limit of normal), can help to avoid endoscopic biopsies and/or human leukocyte antigens (HLA) testing for diagnosis in children.⁴

The mainstay of CD management is strict adherence to a gluten-free diet.³ Because this can be difficult, and yield an incomplete disease response, emphasis has been placed on primary prevention by modifying introduction of dietary gluten. Multiple prior studies examining the risk of CD have failed to demonstrate a significant association between timing of gluten introduction and development of CD among high-risk infants (eg, those with HLA-DR3 alleles or first-degree relatives with CD or type 1 diabetes).⁵⁻⁷ A 2016 meta-analysis concluded that there was not enough evidence to support early introduction of gluten (at 4-6 months).⁸ RCTs have not previously been conducted to examine the timing of gluten introduction on CD prevalence for infants at average risk, using age-appropriate doses of gluten prior to age 6 months.

Current dietary guidelines in the United States and the United Kingdom recommend

introduction of nutrient-dense foods, including potentially allergenic foods, at about age 6 months to complement human milk or infant formula feedings.^{9,10} These guidelines do not specify the exact timing or quantity of gluten-containing food introduction for infants. A 2016 position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition indicated that gluten could be introduced into the infant's diet any time between 4 and 12 months. They did indicate that the amount of gluten introduced into the diet should be low to start and then increased, and that infants at high risk for CD should wait longer for gluten introduction (4 vs 6 months or 6 vs 12 months).¹¹

STUDY SUMMARY

Gluten introduced at 4 months may be linked to lower occurrence of CD

The Enquiring About Tolerance (EAT) Study was an open-label RCT (N = 1303) with children from the general population in England and Wales. The EAT Study sought to test the prevention of food allergy by introducing allergenic foods to infants at age 4 months compared with exclusively breastfeeding until age 6 months. The median age at enrollment was 3.4 months, but allergenic food was not started until age 4 months.^{1,12} Most patients were White (84.3%-85.4%) and lived in an urban area (77.3%-77.4%). The mean gestational age at delivery was 39.7 to 39.9 weeks.¹²

Infants were exclusively breastfed until age 13 weeks, at which time they were randomized into an early introduction group (EIG) or a standard introduction group (SIG). In addition to breast milk, infants in the EIG consumed 6 allergenic foods (peanut, sesame, hen's egg, cow's milk, cod fish, and wheat [gluten]) in a specified pattern per protocol, starting at age 4 months. Wheat (gluten) was introduced during Week 5 of the EIG protocol (median age, 20.6 weeks).¹² The recommended minimum dose of gluten was 3.2 g/wk from age 16 weeks, or 4 g/wk of wheat protein (given as 2 cereal biscuits or the equivalent). Infants in the SIG avoided allergenic foods, following UK infant feeding recommendations for exclusive breastfeeding until about age 6 months. The EIG had a significantly higher rate of cesarean

births than the SIG, but the study groups were otherwise balanced.¹³

Families completed monthly questionnaires on infant gluten intake and symptoms (eg, gastrointestinal, fatigue) through age 1 year, and then every 3 months through age 3 years. All children were tested for anti-transglutaminase type 2 (anti-TG2) antibodies at age 3 years as a screen for CD. Children with antibody levels > 20 IU/L were referred to independent gastroenterologists for further evaluation, which could include HLA (DQ-2/DQ-8) testing and biopsy in accordance with current European diagnostic guidelines.⁴

In an intention-to-treat analysis for the primary outcome, 595 children in the SIG (91.4%) and 567 in the EIG (87.0%) were included. Between ages 4 and 6 months, the mean (SD) quantity of gluten consumed in the SIG was 0.49 (1.40) g/wk; in the EIG, the mean quantity was 2.66 (1.85) g/wk ($P < .001$). At age 3 years, of a total of 1004 children tested for anti-TG2 antibodies, 9 had anti-TG2 levels requiring referral (7 in the SIG and 2 in the EIG). A diagnosis of CD was confirmed in 7 of 516 children in the SIG (1.4%) vs none of the 488 children in the EIG ($P = .02$). Using bootstrap resampling, the risk difference between the groups was 1.4% (95% CI, 0.6%-2.6%).

WHAT'S NEW

Findings have potential to change nutritional guidance

This study demonstrated that introduction of age-appropriate portions of gluten-containing products at age 4 months, in addition to breast milk, may reduce the risk of CD at 3 years in children at average risk. This finding has the potential to change anticipatory guidance given to parents regarding infant nutrition recommendations.

CAVEATS

More studies needed to confirm prevention vs delay of CD

The homogeneous study population may limit generalizability. Infants in this study were from England and Wales (84.3% were White), born at term, and were exclusively breastfed

➤ Introducing gluten as a complement to breast milk or infant formula from age 4 months may reduce the risk of celiac disease at age 3 years.

until age 13 weeks. Further studies are required to determine whether these findings can be applied to infants who are no longer breastfeeding, are more racially diverse, or are preterm in gestational age at birth. Additionally, the study followed the participants only until age 3 years. Given that the onset of CD after this age is likely, further research is needed to support that CD is truly prevented rather than delayed.

CHALLENGES TO IMPLEMENTATION

Guidance on allergen introduction may be unclear

The EAT Study protocol required parents in

the EIG to sequentially introduce a minimum amount of the 6 allergenic foods specified. Only 42% of the EIG cohort reported adherence to the protocol.¹² It is unclear how important this specific regimen is to the study results and whether introduction of all 6 allergenic foods simultaneously modifies the immune response to gluten. Therefore, there may be challenges to implementation if physicians do not know how to provide anticipatory guidance on the appropriate steps for allergen introduction. **JFP**

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