

# Can Feeding Practices during Infancy Change the Risk for Celiac Disease?

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Celiac disease is an immune-mediated disorder that occurs in genetically susceptible individuals and manifests as gastrointestinal and systemic symptoms that are induced by gluten and related prolamines (found in wheat, rye and barley) [1]. In recent years it became apparent that celiac disease is much more common than previously thought, affecting 0.5%–1% of the population [2]. In addition to symptoms that range from minor complaints to severe symptomatic presentation [3], celiac disease carries an increased morbidity burden (iron deficiency anemia, osteopenia, increased prevalence of autoimmune disorders, infertility) and increased mortality [4,5]. Since celiac disease requires the life-long elimination of prolamines from the diet, a gluten-free diet is currently the only treatment available for the disease [3]. In addition, the economic burden of celiac disease on society is high; our group recently showed that in certain situations the early identification of celiac disease can be cost-effective [6,7]. However, the best strategy that will decrease the burden of this disorder is to prevent its occurrence.

The aim of this review is to provide readers with current evidence on the effects of feeding practices during infancy on the risk of celiac disease developing.

## THEORETICAL CONSIDERATIONS

Breast milk is the natural food for infants and the optimal exclusive food for infants until the age of 6 months [8]; all infants should therefore be breastfed. However, in the context of celiac disease, the question is whether breastfeeding protects the infant from developing the disease. Theoretically, breast milk could induce tolerance to gliadin due to several factors: the presence of gliadin in human milk, the reduction in prevalence of acute gastroenteritis in breastfed infants, differences in gut

microbiota, and the reduced intestinal permeability observed in breastfed infants.

More than 20 years ago, Troncone and colleagues [9] showed that after the ingestion of 20 g of gluten by breastfeeding mothers (n=53), gliadin was detected in 54 of 80 human milk samples (41/53 in the first week, 8/17 at 6 weeks, 3/6 at 3 months and 2/4 at 5 months of age). In that study, maximum levels were found 2–4 hours after the ingestion of gliadin and the concentration of gliadin ranged between 5 and 95 ng/ml. In that study [9] no gliadin was detected in maternal serum. In another study, Chirido et al. [10] found gliadin in all 49 milk samples and the concentration ranged between 5 and 1200 ng/ml. In colostrum (n=14), gliadin levels were much higher (range 28–9000 ng/ml) and gliadin was present in 14/31 serum samples.

Breastfeeding protects against acute gastroenteritis, while repeated episodes of acute gastroenteritis have been linked to increased risk of celiac disease [11,12]. This reduction in the incidence of acute gastroenteritis could be mediated via immunoglobulins and cytokines present in human milk as well as by the reduced intestinal permeability observed in breastfed infants compared to formula-fed infants [13]. In addition, human milk causes alterations in gut microbiota [14] and there are emerging data on the association between changes in gut microbiota and celiac disease [15,16].

## CLINICAL EVIDENCE

A few retrospective studies have demonstrated a negative association between the duration of breastfeeding and the occurrence of celiac disease [17–20]. However, in one of these cohorts, it was noted [17] that there was no change in the overall prevalence of celiac disease in breastfed infants compared to controls, suggesting that breastfeeding may only delay the presentation of the disease but does not prevent it. Furthermore, there are studies where no significant difference in the prevalence of celiac disease was detected between breastfed and non-breastfed subjects [21,22].

Some indications for the role of breastfeeding can be taken from the Swedish epidemic, where recent data suggest a 3%

**Gluten should be introduced to the infant's diet when the infant is still being breastfed and not before 4 months or after 7 months of age**

**The introduction of gluten while the infant is being breastfed may be beneficial in delaying or preventing celiac disease**

prevalence of celiac disease in the cohort born during the epidemic [20,23]. When analyzing the association between feeding practices and celiac disease during the epidemic, Ivarsson et al. [20] found that the risk to develop celiac disease was lower in children under 2 years of age if these children were still being breastfed when dietary gluten was introduced (odds ratio 0.59, 95% confidence interval 0.42–0.83).

A further decrease in the risk to develop celiac disease was observed when breastfeeding was continued after gluten was introduced to the diet (OR 0.36, 95% CI 0.26–0.51) [20].

In a meta-analysis including the Ivarsson cohort, it was shown that the risk to develop celiac disease was significantly reduced in infants who were breastfed at the time of gluten introduction to their diet (pooled OR 0.48, 95% CI 0.40–0.59) compared to infants who were not breastfed at the time of gluten exposure [24]. In a later study, Akobeng and co-researchers [25] estimated that if all babies were breastfed at the time of gluten introduction, 2500 cases in the United Kingdom would be prevented every year.

The best available data on the age of gluten introduction come from a prospective study done in the United States [26]. This study was a prospective observational study that followed 1560 children in Denver between 1994 and 2004. These children were at increased risk for type 1 diabetes mellitus defined as having a first-degree relative with type 1 diabetes, or celiac disease defined as having human leukocyte antigen-DR3 or DR4 alleles. Risk for celiac disease was defined based on positive serology for the disease (tissue transglutaminase antibodies) on two or more consecutive visits or being serology-positive on one visit with a positive small bowel biopsy for celiac disease. This prospective study by Norris et al. [26] showed that children exposed to gluten in the first 3 months of life had a fivefold increased risk of having celiac disease than children exposed to gluten between 4 and 6 months of age. Furthermore, children not exposed to gluten until 7 months of life or later had an almost twofold increased risk compared with those exposed at 4 to 6 months (hazard ratio 1.87, 95% CI 0.97–3.60). When the analysis was limited to biopsy-diagnosed celiac disease, the hazard ratio was 23.97 (95% CI 4.55–115.9) for children exposed to gluten during the first 3 months of life compared to the 4–6 months exposure group, and 3.98 (95% CI 1.18–13.46) in the group exposed at 7 months or later.

Despite all of the above, it is not clear whether breastfeeding and the age of introduction of gliadin prevent celiac disease or merely delay its onset. In order to shed light on the relationship of breastfeeding, age at introduction of gluten and celiac disease, a prospective cohort funded by the European Union (PREVENTCD, FP6) was initiated in 10 European centers [27]. In this PREVENTCD cohort, pregnant women with a family

history of celiac disease were recruited and HLA4 of the newborn was determined at birth. By the end of December 2010, a total of 1345 children were recruited at birth and 986 (73%)

with positive HLA DQ status were enrolled. Mothers were instructed to breastfeed for 6 months if possible. At the age of 4 months, infants were randomized to a study group ingesting 100 mg of gliadin or placebo (no gliadin) every day.

Complete results will be available when all children reach the age of 3 years, and it is hoped that the study will provide us with answers on the effect of breastfeeding and age of gluten introduction on the occurrence of celiac disease.

Meanwhile, based on all available data until 2009, the ESPGHAN Committee on Nutrition recommendations are still valid. These recommendations state that both early (less than 4 months) and late (7 or more months) introduction of gluten should be avoided and that gluten be introduced into the diet when the infant is still being breastfed [8].

**While the infant's age at introduction of gluten and the amount are yet to be established, we should remember that breast milk is the natural food for infants and is the optimal exclusive food for infants until the age of 6 months**

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