Association Between Maternal Iron Supplementation During Pregnancy and Risk of Celiac Disease in Children

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BACKGROUND & AIMS: **The aim of our study was to determine whether the use of iron supplements during pregnancy affects the risk for celiac disease in children.**

METHODS: **We assessed data from the prospective Norwegian Mother and Child cohort study, in which individuals with celiac disease were identified by answers on questionnaires and linkage to the Norwegian Patient Register. Complete data were available for 78,846 children (mean age 5.9 years, range 2–12 years); 314 children were identified with celiac disease. Questionnaires were given to pregnant women to collect information on use of iron-containing supplements, diet, anemia, and levels of hemoglobin.**

RESULTS: **Celiac disease was diagnosed in 4.65 of 1000 children whose mothers took iron supplements while they were pregnant, compared with 3.15 of 1000 children whose mothers did not. After adjusting for children's age, sex, and age of gluten introduction, and the presence of celiac disease in mothers, iron supplementation during pregnancy remained significantly associated with celiac disease in children (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.05–1.68; $P = .019$). However, celiac disease was not associated with the mothers' intake of iron from foods (adjusted OR, 1.00; 95% CI, 0.97–1.03). Anemia before or during the early stages of pregnancy was not significantly associated with the risk of celiac disease in children (adjusted OR, 1.24; 95% CI, 0.84–2.00; $P = .24$). The use of iron supplements during pregnancy remained significantly associated with celiac disease in children after adjusting for children who were given iron supplements before 18 months of age, which itself was associated with celiac disease.**

CONCLUSIONS: **In a prospective Norwegian Mother and Child cohort study, we found an increased risk of celiac disease in children whose mothers used iron supplements during pregnancy; this association does not appear to arise from maternal anemia.**

Keywords: MoBa Study; Enteropathy; Genetic Factor; Immune Development.

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The interplay between genes and environment is depicted in the current knowledge on the pathophysiology of celiac disease.[1] A strong genetic predisposition through the presence of HLA haplotypes encoding the DQ2.5- or DQ8-molecules[2] and detailed understanding of how the HLA-molecules present modified deamidated gluten to reactive T-cells[3] are the pillars of the current understanding of how celiac disease develops. The 70%–75% disease concordance found in monozygotic twins compared with 10% in dizygotic twins and 30% in HLA-identical siblings illustrates the importance of genetic factors.[4] The >20% frequency of the haplotypes encoding the high-risk HLA-DQ molecules in the general population demonstrates the role of non-HLA genes and environmental factors.[1] Recently, genome-wide association studies have identified single nucleotide polymorphisms with significant but weak effects on celiac disease, which are located mainly in regulatory elements for genes involved in immunity.[5,6]

Changing environmental factors are suggested by a doubled prevalence with a 20-year interval[7] and a 4-fold increase in 50 years[8] using the same screening methods

Abbreviations used in this paper: CI, confidence interval; MoBa, The Norwegian Mother and Child cohort study; NPR, Norwegian Patient Register; OR, odds ratio.

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in population-based samples. In addition to the required presence of gluten in the diet to develop celiac disease, several lines of evidence point to the timing of gluten introduction and the dose of gluten in the weaning diet to impact on disease risk.[9] A lower risk associated with breastfeeding during gluten introduction has been found in case-control studies and summarized in a meta-analysis.[10] The role of infant feeding may, however, be limited to celiac disease with early onset: A protective effect of breastfeeding has been observed only when celiac disease is diagnosed at <2 years of age, suggesting a delay more than actual prevention of the disease.[9]

Infections and interactions between infections at the time of gluten introduction have been associated with the risk of celiac disease in some studies[11,12] but not all.[13] Rotavirus infections in genetically predisposed individuals have been associated with the development of celiac disease–associated autoimmunity.[14]

The recognition of conditions during the fetal period and early life as predictors for later health and disease has led to an immune programming hypothesis underlining the plasticity of the developing immune system modified by maternal nutrition, micronutrients, and gut microbiota.[15–17] Iron is important for the development and function of the immune system[18] and has recently been shown to influence adaptive immune responses and macrophage function.[19]

The aim of this study was to test in a prospective cohort study whether maternal iron supplement intake during pregnancy is associated with the risk of celiac disease in childhood.

Material and Methods

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[20] Participants were recruited from all over Norway from 1999 to 2008, and 91,000 mothers (39% of invited women) participated with one or more pregnancies. Follow-up is conducted by questionnaires at regular intervals and by linkage to national health registries. In the current study, we use information from 7 questionnaires: 3 completed during pregnancy, 2 at the age of 6 years and 18 months, and 2 at the age of 7 and 8 years. Written informed consent was obtained, and the Regional Committee for Medical Research Ethics in Southeastern Norway approved the substudy and linkage to the patient register. The current study is based on version VII of the quality-assured data files released for research in June 2012.

Case Identification

Cases of celiac disease were identified from the Norwegian Patient Register (NPR) and from parental questionnaires. The questionnaires administered when the children were 7 and 8 years old contain a specific question of celiac disease diagnosed in the child. The NPR is an administrative database containing activity data from all Norwegian government-owned hospitals and outpatient clinics. Reporting data to the NPR is mandatory and linked to the governmental reimbursement system for funding of health services. Diagnoses are reported as *International Classification of Diseases, Tenth Revision* codes, and individual patient files or histology reports were not available. The 11-digit personal identification number unique to every Norwegian citizen was included in the NPR files from 2008 onward, making individual-level research data available.

Health care is free of charge for children up to 16 years of age in Norway. All hospitals for children and most child outpatient clinics are owned by the government. In addition, there are currently 29 pediatricians with private practices. Private practices receiving government reimbursements are obliged to report their data to the NPR similar to the government-owned institutions. However, the reporting of personal identification numbers from private practices is not yet complete, and private practice data were not included in the data file used for this study.

The European Society of Paediatric Gastroenterology, Hepatology, and Nutrition's diagnostic criteria from 1991, which were in use during this period, require a small-bowel biopsy for diagnosis of celiac disease.[21] Because biopsies are performed in government-owned hospitals only, all children with biopsy-proven celiac disease have been diagnosed at facilities reporting to the NPR. However, because the registration started January 1, 2008, cases diagnosed before this date, and not seen regularly as recommended in the outpatient clinic, would not be registered in the NPR. For this study, the NPR provided data from 2008 through 2011.

Because blood samples are not collected from the children in MoBa after birth, we could not test for antibodies to screen for undiagnosed celiac disease as part of the study.

Case Definition

Children subjected to intestinal biopsy on suspicion of celiac disease may be registered in the NPR on discharge before a final histologic report and a confirmed diagnosis. To reduce the possibility of including false-positive cases without the final diagnosis based on biopsy results, we restricted the case definition in NPR to individuals registered at a minimum of 2 occasions in the NPR (n = 326).

The children identified with celiac disease from parental questionnaires without NPR registrations (n = 67) were added to the ones identified twice in the registry, giving a total of 393 cases of celiac disease (245 females, 62%) among 106,917 live births. After exclusion of participants with missing information on iron supplement use or gluten introduction, the final analysis included 78,846 subjects with complete data, of which 314 were identified with a celiac disease diagnosis (Figure 1).