Perinatal Risk Factors for Development of Celiac Disease in Children, Based on the Prospective Norwegian Mother and Child Cohort Study

Louise Emilsson,[*,‡] Maria Christine Magnus,[§] and Ketil Størdal[§,‖]

*Primary Care Research Unit, Vårdcentralen Värmlands Nysäter, County Council of Värmland, Sweden; ‡Department of Health Management and Health Economy, Institute of Health and Society, University of Oslo, Oslo, Norway; §Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway; and ‖Paediatric Department, Ostfold Hospital Trust, Fredrikstad, Norway

BACKGROUND & AIMS: **There have been inconsistent reports of prenatal and perinatal factors that affect risk for development of celiac disease. We assessed the association of fetal growth, birth weight, and mode of delivery with development of celiac disease within the Norwegian Mother and Child (MoBa) Cohort Study.**

METHODS: **The MoBa cohort contains pregnancy information on 95,200 women and data on their 114,500 children, which were collected in Norway from 1999 through 2008; it is linked to the Medical Birth Registry. Women and children with celiac disease were identified from the National Patient Registry and from women's responses to MoBa questionnaires. We calculated odds ratios (ORs) for celiac disease by using a multivariable logistic regression model, adjusting for maternal celiac disease, sex of children, and children's age (model 1); in a second model, we adjusted for age of gluten introduction and duration of breastfeeding (model 2).**

RESULTS: **We identified 650 children with celiac disease and 107,828 controls in the MoBa database. We found no association between birth weight or height with celiac disease (born small for gestational age was not associated). Celiac disease was not associated with mode of delivery (cesarean section, model 1: OR, 0.84; 95% confidence interval [CI], 0.65–1.09, and model 2: OR, 0.83; 95% CI, 0.63–1.09). Maternal celiac disease, adjusted for age and sex of the children (OR, 12.45; 95% CI, 8.29–18.71) and type 1 diabetes (model 1: OR, 2.58; 95% CI, 1.19–5.53, and model 2: OR, 2.61; 95% CI, 1.14–5.98) were associated with development of celiac disease in children, whereas maternal type 2 diabetes and gestational diabetes were not.**

CONCLUSIONS: **On the basis of analysis of the Norwegian MoBa cohort, development of celiac disease in children is significantly associated with sex of the child, maternal celiac disease, and type 1 diabetes but not with intrauterine growth.**

Keywords: Celiac; Pregnancy Outcome; Prematurity; Perinatal Factors.

Celiac disease (CD) is an immune-mediated disease triggered by the ingestion of gluten. CD affects about 1% of the Western population[1] and is diagnosed in 0.4% of Norwegian children aged 0–12 years.[2] The genetic impact of CD is well-known, but it is still unclear which additional environmental factors (outside gluten ingestion) affect the development of the disease.[3] Earlier studies have suggested that cesarean section, particularly elective, is associated with an increased risk of CD,[4,5] although other studies have suggested that cesarean section is not associated with CD or might even be protective.[6] Being small for gestational age (SGA) has been associated with future CD.[4,7] Also maternal smoking and parity have been reported to increase the risk of CD in offspring[6] as well as low birth weight.[7]

Because previous studies have indicated that reduced birth weight is a risk factor, we tested this hypothesis as well as pregnancy factors known to impair fetal growth such as maternal smoking, preeclampsia, or hypertension. Also impact of maternal diabetes, which on the contrary is likely to increase birth weight of the child, was assessed. Furthermore, we analyzed whether maternal education and parity had an impact on future

Abbreviations used in this paper: **CD, celiac disease; CI, confidence interval; MBRN, Medical Birth Registry of Norway; MoBa, Norwegian Mother and Child Cohort Study; NPR, Norwegian Patient Registry; OR, odds ratio; SGA, small for gestational age.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.10.012

CD because earlier studies have suggested that children of mothers with higher social class and parity are at an increased risk of future CD.[6] In the current study we also examined the impact of cesarean section on future development of CD in the Norwegian Mother and Child (MoBa) cohort.

Methods

Data for this study were extracted from the prospectively collected Norwegian MoBa cohort[8] conducted by the Norwegian Institute of Public Health. Pregnant women were recruited around 18 gestational weeks from all over Norway from 1999 to 2008. The participation rate was 40.6%. Mothers could participate with more than 1 pregnancy. In total, approximately 95,200 mothers and 114,500 children were included in the cohort. Written informed consent was obtained from all participants. The current study used version VII of the quality assured data files, which included all follow-up information available around June 2013 and included 114,285 children. The questionnaires used for this study were filled out around weeks 18 and 30 of pregnancy and at ages 6 and 18 months as well as 7 and 8 years of age. (All of the questionnaires are available at www.fhi.no/moba.)

The cohort database is also linked to the Medical Birth Registry of Norway (MBRN) and the National Patient Registry (NPR) by using unique personal identification numbers. The Norwegian Data Inspectorate has approved the ongoing data collection in MoBa. The Regional Committee for Medical Research Ethics in Southeastern Norway approved the current study.

The National Patient Registry

The NPR contains information on all diagnoses according to the International Classification of Diseases, 10th revision codes, set in all government-owned Norwegian hospitals and outpatient clinics. The information is mandatory and virtually complete. Information in this registry has been available on an individual level since 2008, when the Norwegian 11-digit personal identification number was included. The International Classification of Diseases, 10th revision code used to classify CD was K90.0.

Selection of Patients

CD was defined as being reported in the questionnaires at 7 or 8 years of age (n = 159) or at least 2 different registrations of CD diagnosis in NPR (in absence of being reported in the questionnaires, n = 491, many participants have not reached the age of 7). All other participants were defined as controls/non-CD. We demanded 2 registrations in the NPR because the diagnosis sometimes is set only once as a working diagnosis before knowing the result of biopsies. No further restrictions were made. Children participating in MoBa without data from MBRN available (n = 5689) or uncertain diagnosis of CD (eg, recorded only once in the NPR, n = 118) were excluded. A comprehensive flow chart of study participants in our different models is found in Figure 1. In a validation sample, participants identified with CD through questionnaires or NPR completed a separate questionnaire to provide details about the diagnostic process. Of 468 respondents, 94.2% (277 of 294) of those identified with 2 or more entries in the NPR confirmed the diagnosis, and only 4% and 1.8% had a false-positive or uncertain diagnosis, respectively. Of those who had reported the CD diagnosis in a previous questionnaire, 92.4% confirmed the diagnosis in the validation study. Diagnosis confirmed by biopsy was reported in 83.0%, 15.7% had been diagnosed through positive antibody tests, and only 1.3% was reported without serology or biopsy.

Data Collection

Exposures. Data on birth weights and lengths, maternal diabetes and pregnancy factors, maternal age at delivery, gestational age, gestational hypertension, and preeclampsia were gathered from the MBRN. Data on mode of delivery and indication for cesarean section, parental smoking, maternal education, maternal CD, and parity were collected from the MoBa follow-up questionnaires. Concerning maternal and paternal smoking, the data came from the questionnaire filled out at 18 weeks of pregnancy (current smoking) and at 6 months after birth where the mothers answered if they themselves or their partner were smoking (partly or daily) in different time frames: last 3 months pre partum, 0–3 months post partum, and 4–6 months post partum. Being SGA was defined as having a birth weight below the 10th percentile at a given gestational week of certain reference points that were based on data derived from a reference population,[9]

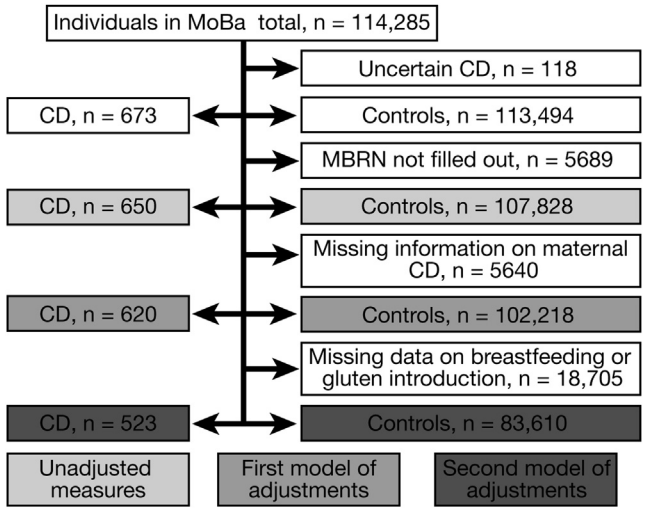

Figure 1. Flow chart of participants.