Mucosal Healing in Patients With Celiac Disease and Outcomes of Pregnancy: A Nationwide Population-Based Study

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BACKGROUND & AIMS: **Studies have associated undiagnosed celiac disease with adverse outcomes of pregnancy. We investigated the association between persistent villous atrophy and outcomes of pregnancy in women with celiac disease.**

METHODS: **We collected data on 337 women with celiac disease who gave birth (to 460 infants) within 5 years of a follow-up biopsy, from 28 pathology departments in Sweden. We compared birth outcomes from women whose follow-up biopsy showed persistent villous atrophy (Marsh score, 3; n = 142; 31% of study population) with those of women with mucosal recovery (n = 318; 69%). We used multivariable logistic regression (adjusted for maternal age, parity, country of birth, smoking, infant sex, and calendar year of birth) to evaluate the association between persistent villous atrophy and pregnancy outcomes.**

RESULTS: **Intrauterine growth restriction occurred during 3.5% of pregnancies in women with persistent villous atrophy vs 3.8% of those with mucosal healing (adjusted odds ratio [OR], 0.61; 95% confidence interval [CI], 0.19–1.99). There was no significant association between persistent villous atrophy and low birth weight (OR, 0.98; 95% CI, 0.41–2.39), preterm birth (OR, 1.66; 95% CI, 0.72–3.83), or cesarean section (OR, 0.86; 95% CI, 0.51–1.46).**

CONCLUSIONS: **Although undiagnosed celiac disease has been associated with adverse outcomes of pregnancy, we found no evidence from a nationwide population-based study that persistent villous atrophy, based on analysis of follow-up biopsies, increases risk compared with mucosal healing.**

Keywords: Autoimmunity; Gluten; Childbirth; Inflammation; Epidemiology.

Celiac disease (CD) occurs in approximately 1% of the Western population,[1–3] and is characterized by small intestinal inflammation, villous atrophy, and the development of autoantibodies to tissue transglutaminase.[4] This disease is triggered by gluten exposure in genetically predisposed individuals. CD has been associated with a large number of complications including excess mortality[5] and increased risk of lymphoproliferative malignancy.[6]

Earlier studies investigating birth outcomes in mothers with CD often were based on studies with small sample sizes and with methodologic concerns.[7–13] These studies often found a highly increased risk of adverse pregnancy outcome in undiagnosed CD, but results were contradicting with regards to those who already were diagnosed with CD at the time of childbirth, in whom a gluten-free diet previously had been instituted.

Three large population-based studies have since shed more light on pregnancy outcomes in CD,[14–16] with 2 studies[14,16] focusing on gestational age and birth weight. Both we[14] and Khashan et al,[16] found an increased risk of preterm birth and intrauterine growth restriction (IUGR) in offspring of women with undiagnosed CD (ie, the diagnosis of CD was made after childbirth), but no increased risk in women with diagnosed CD. However, both of these studies[14,16] were based on mothers diagnosed sometimes more than 30 years ago, when malabsorption was a common feature at diagnosis; we have suggested that malabsorption in undiagnosed CD (as shown by the lower placental weight in mothers with undiagnosed CD in our study[14]) was the underlying reason for poor fetal growth.

After the diagnosis of CD and the prescription of a gluten-free diet, healing of atrophic villi usually occurs,

Abbreviations used in this paper: **aOR, adjusted odds ratio; CD, celiac disease; CI, confidence interval; IUGR, intrauterine growth retardation; OR, odds ratio; tTG, tissue transglutaminase.**

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although this process can be gradual.[17] Persistent villous atrophy on follow-up biopsy, which may be owing to imperfect adherence to the gluten-free diet,[17–19] appears to carry important prognostic information. We previously reported that persistent villous atrophy on follow-up biopsy is linked to an increased risk of lymphoproliferative malignancy[20] and hip fracture.[21]

The aim of the current study was to examine the risk of adverse pregnancy outcome in women with persistent villous atrophy vs those with mucosal healing. We hypothesized that persistent villous atrophy would be associated with adverse pregnancy outcomes, particularly measures of fetal growth and preterm birth.

Methods

For details regarding subject identification and the Swedish Birth Register, see the Supplementary Methods.

After identifying female patients with CD who underwent a follow-up biopsy, we merged this data set with the Swedish Medical Birth Register and restricted the analysis to women who underwent childbirth within 5 years of their follow-up biopsy. Births beyond this time period were excluded because persistent villous atrophy gradually may resolve, and effects beyond this time horizon likely would diminish.[17] We included births that occurred before the date of the follow-up biopsy but after the date of the initial CD diagnosis; we did not include births that preceded the mother's CD diagnosis because this investigation did not encompass undiagnosed CD. Births that occurred before the date of the follow-up biopsy (but after the date of the initial CD diagnosis) were classified according to the result of the follow-up biopsy. In an additional sensitivity analysis, we excluded births that occurred within 1 year after the initial diagnosis of maternal CD.

Outcome Measures

Our main outcome measures were IUGR and preterm birth. We used Swedish ultrasound-based reference curves for fetal growth, in which IUGR was defined as a birth weight more than 2 standard deviations less than the sex-specific mean for gestational age.[22] Gestational age was determined using ultrasound, and if there were no ultrasound data, we used the first day of the last menstrual period. Routine ultrasound has been offered in the early second trimester since the 1990s, and approximately 95% of women undergo an ultrasound. We defined preterm birth as fewer than 37 completed gestational weeks and we defined very preterm birth as fewer than 32 completed gestational weeks.

We also examined the following outcomes: low birth weight (<2500 g), very low birth weight (<1500 g), cesarean section, Apgar score of less than 7 at 5 minutes, and neonatal death within 28 days.

Statistical Analysis

Through logistic regression we calculated odds ratios (ORs) for the association between CD and pregnancy outcomes. We compared women with persistent villous atrophy with those with mucosal healing. In our main analyses we adjusted for maternal age at delivery, parity, smoking, country of birth, infant sex, and calendar year of birth.

We subsequently performed a time-stratified analysis, measuring these associations according to the time period after follow-up biopsy. For this analysis, we dichotomized a priori time after follow-up biopsy as births before 2 years after follow-up biopsy and births 2 to 5 years after follow-up biopsy.

We used SAS version 9.3 (Cary, NC) for all analyses. We report the ORs with corresponding 95% confidence intervals (Cis). The chi-square and the Fisher exact tests were used to compare proportions. All *P* values reported are 2-sided.

Power Calculation

At a 2-sided 5% significance level, we had an 80% power to detect a 3.1-fold increased risk of IUGR and a 2.7-fold increased risk of preterm birth in offspring of women with persistent villous atrophy (calculated through the STPlan; The University of Texas M.D. Anderson Cancer Center, Houston, TX).

Ethics

The Ethics Review board of Stockholm, Sweden, approved this study and deemed that no individual informed consent was required because data were strictly register-based. J.F.L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Results

Of the 4832 female patients with CD who underwent a follow-up biopsy between 6 months and 5 years after they were diagnosed with CD, 1517 (31%) had given birth to 2941 infants recorded in the Medical Birth Registry. When restricting this group to those who had given birth within 5 years of follow-up biopsy (but after initial CD diagnosis), we identified 460 births among 337 mothers. Of these 460 births, 357 (78%) occurred after their follow-up biopsy, and 103 births (22%) occurred after their mothers' initial CD diagnosis but before their follow-up biopsy. The median time elapsed between follow-up biopsy and childbirth was 1.9 years after the follow-up biopsy, with childbirth timing ranging from 3.8 years before follow-up biopsy to 4.8 years after follow-up biopsy. The median time between initial CD diagnosis and follow-up biopsy was 1.5 years (range, 0.5–4.99 y)

(Figure 1). Among all 460 births, persistent villous atrophy was present in 142 of the mothers (31%). When including only the first birth for each mother in this data set, among the 337 mothers, persistent villous atrophy was present in 137 (32%).

The mean maternal age was 29.5 years (range, 18–42 y). Forty-eight percent of births were among nulliparous mothers and another 48% were among women who had previously given birth once or twice (Table 1). A slight majority (53%) of the infants born were female, and more than 90% of the mothers were of Nordic nationality. The majority (75%) of the births occurred in the year 2000 or later. Only 4 mothers (0.9%) had diabetes. Nearly 90% of the mothers were nonsmokers. The presence of persistent villous atrophy on follow-up biopsy did not differ significantly according to maternal age, parity, infant sex, country of birth, or smoking status. As was seen in the larger population of CD patients undergoing follow-up biopsy,[23] the prevalence of persistent villous atrophy was more common before the year 2000.

IUGR was seen in 3.7% of the births (Table 2). There was no difference between those with persistent villous atrophy and mucosal healing with regard to this outcome (adjusted OR [aOR], 0.61; 95% CI, 0.19–1.99). Low birth weight was present in 5.4% among those with mucosal healing and in 6.3% among those whose mothers had persistent villous atrophy. There was no significant association between persistent villous atrophy and low birth weight on multivariate analysis (aOR, 0.98; 95% CI, 0.41–2.39). Analysis of very low birth weight as an outcome similarly was null (Table 2).

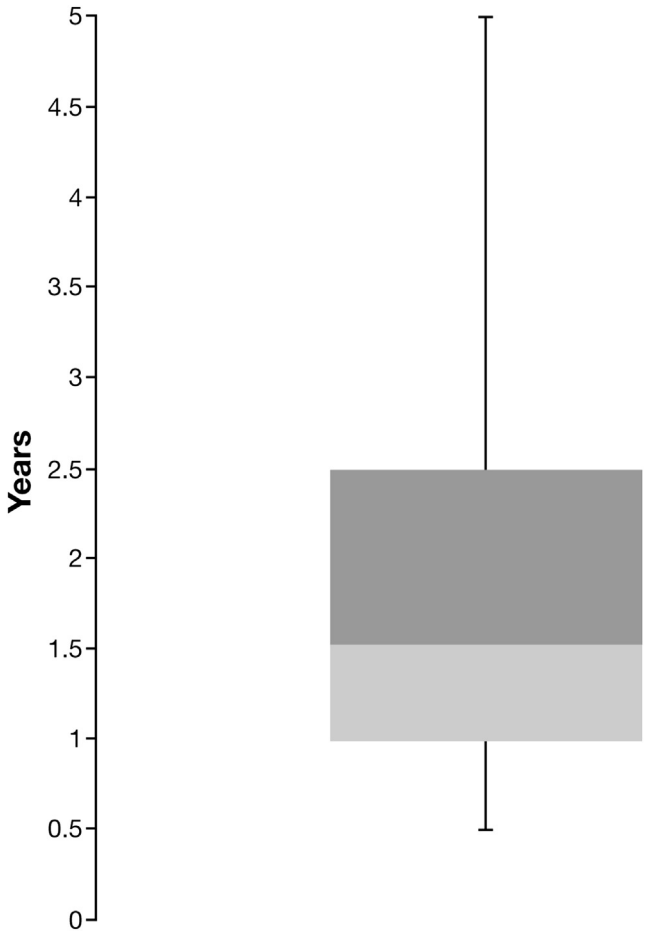

Figure 1. Time elapsed between initial celiac disease diagnosis and follow-up biopsy (*box plot* shows the minimum, 25th percentile, median, 75th percentile, and maximum). *Light gray shading* spans 25th percentile to the median; *dark gray shading* spans the median to the 75th percentile.

Table 1. Characteristics of 460 Pregnancies Involving Mothers With Celiac Disease (n = 337) Who Underwent a Follow-Up Biopsy Within 5 Years of Childbirth

Characteristic	Total (%)	Mucosal healing (%)	Persistent villous atrophy (%)	*P* value[a]
Maternal age, *y*				.061
15–24	70 (15)	52 (74)	18 (26)	
25–29	157 (34)	106 (68)	51 (32)	
30–34	166 (36)	122 (73)	44 (27)	
≥35	67 (15)	38 (57)	29 (43)	
Parity				.38
0	221 (48)	154 (70)	67 (30)	
1–2	219 (48)	153 (70)	66 (30)	
≥3	20 (4)	11 (55)	9 (45)	
Country of birth				.63
Nordic	419 (91)	291 (69)	128 (31)	
Other countries	41 (9)	27 (66)	14 (34)	
Smoking status				.83
Nonsmoker	411 (89)	286 (70)	125 (30)	
1–9 cigarettes/day	16 (3)	10 (63)	6 (37)	
≥10 cigarettes/day	8 (2)	6 (75)	2 (25)	
Unknown	25 (5)	16 (64)	9 (36)	
Maternal diabetes				.32
Yes	4 (0.9)	4 (100)	0 (0)	
No	456 (99.1)	314 (69)	142 (31)	
Infant sex				.74
Male	215 (47)	147 (68)	68 (32)	
Female	245 (53)	171 (70)	74 (30)	
Calendar year of birth				<.0001
≤1989	17 (4)	8 (47)	9 (53)	
1990–1999	99 (21)	50 (51)	49 (49)	
≥2000	344 (75)	260 (76)	84 (24)	

[a]*P* value for comparison between mucosal healing and persistent villous atrophy groups.

Although preterm birth (occurring before 37 weeks' gestation) was more common among infants whose mothers had persistent villous atrophy (8.5%) than among those whose mothers had mucosal healing (4.7%). This did not meet statistical significance (aOR, 1.66; 95% CI, 0.72–3.83). The outcome of very preterm birth (occurring before 32 weeks' gestation) occurred in only 5 of the 460 births (1.1%), and a low Apgar score likewise occurred in only 5 of the births (1.1%).

Cesarean section occurred in 21% of all births; there was no significant association between persistent villous atrophy and cesarean section (aOR, 0.86; 95% CI,

Table 2. Fetal Outcomes According to Maternal Follow-Up Villous Histology

Outcome	Proportion meeting outcome	Unadjusted OR (95% CI)	*P* value	Adjusted OR[a]	*P* value
IUGR					
Overall	17/460 (3.7)				
Mucosal healing	12/318 (3.8)	1.00		1.00	
Persistent VA	5/142 (3.5)	0.93 (0.32–2.69)	.89	0.61 (0.19–1.99)	.41
Low birth weight					
Overall	26/460 (5.7)				
Mucosal healing	17/318 (5.4)	1.00		1.00	
Persistent VA	9/142 (6.3)	1.20 (0.52–2.76)	.67	0.98 (0.41–2.39)	.97
Very low birth weight					
Overall	6/460 (1.3)				
Mucosal healing	4/318 (1.3)	1.00		1.00	
Persistent VA	2/142 (1.4)	1.12 (0.20–6.19)	.89	0.80 (0.13–4.86)	.81
Preterm birth					
Overall	27/460 (5.9)				
Mucosal healing	15/318 (4.7)	1.00		1.00	
Persistent VA	12/142 (8.5)	1.86 (0.85–4.09)	.12	1.66 (0.72–3.83)	.23
Very preterm birth					
Overall	5/460 (1.1)				
Mucosal healing	3/318 (0.9)				
Persistent VA	2/142 (1.4)	1.50 (0.25–9.01)	.65	1.40 (0.16–12.64)	.95
Low Apgar score					
Overall	5/453 (1.1)				
Mucosal healing	2/315 (0.6)				
Persistent VA	3/138 (2.2)	3.48 (0.57–21.1)	.17	4.22 (0.58–30.5)	.15
Cesarean section					
Overall	97/460 (21)				
Mucosal healing	68/318 (21)	1.00		1.00	
Persistent VA	29/142 (20)	0.94 (0.58–1.54)	.8154	0.86 (0.51–1.46)	.58
Neonatal death					
Overall	1/460 (0.2)				
Mucosal healing	0/318 (0)				
Persistent VA	1/142 (0.7)	NC	NC	NC	NC

NC, not calculated because of the low number of events; VA, villous atrophy.
[a]Adjusted for maternal age at delivery, infant sex, parity, nationality, calendar year of birth, and maternal smoking.

0.51–1.46). The outcome of neonatal death only occurred in 1 patient (whose mother had persistent villous atrophy on follow-up biopsy).

We performed a sensitivity analysis, restricting the period of follow-up biopsy to 1 to 5 years after the initial CD diagnosis. Of 330 pregnancies associated with a follow-up biopsy in this narrower time period, villous atrophy was present on the follow-up biopsy in 100 (30%), similar to the prevalence of villous atrophy in the main analysis (31%). As was the case in the main analysis, there was no significant association between persistent villous atrophy and neonatal outcomes with one exception: mothers with persistent villous atrophy had a higher prevalence of preterm birth than those with mucosal healing (adjusted OR, 3.95; 95% CI, 1.37–11.38). On additional sensitivity analysis, now excluding all births that occurred within 1 year of maternal CD diagnosis, there was no significant association between persistent villous atrophy and any neonatal outcome (data not shown).

Time-Stratified Analysis

When we measured outcomes according to time after maternal follow-up biopsy, the results similarly were null. When considering the outcome of preterm birth, restricted to births 2 to 5 years after follow-up biopsy, there appeared to be an association between maternal villous atrophy and preterm birth, however, this did not meet statistical significance (aOR, 3.08; 95% CI, 0.79–11.99; $P = .11$). In none of the other outcomes was there an association between persistent villous atrophy birth outcomes (Supplementary Table 1).

Discussion

This nationwide population-based study was designed to expand on earlier findings of an increased risk of preterm birth and IUGR in associated with CD. We found that, among patients with CD who underwent a follow-up biopsy in close temporal proximity to pregnancy, adverse childbirth outcomes were similar regardless of whether the mother had persistent villous atrophy or mucosal healing.

Both Swedish[14] and Danish[11,16] studies have shown an increased risk of IUGR or low birth weight in undiagnosed CD. In contrast, a recent study from The Netherlands found no increased risk of low birth weight in women with

positive tissue transglutaminase (tTG) antibody levels.[24] The failure to detect an increased prevalence of low birth weight in the study from The Netherlands probably was owing to insufficient statistical power, and when grouping mothers with positive and intermediate tTG levels the OR for low birth weight offspring was 1.59 (95% CI, 1.04–2.42).[24] The present study did not include a non-CD control population, and it did not include patients with undiagnosed CD. Although this limited our ability to compare the present results directly with previous studies, our results suggest that follow-up histology after CD diagnosis does not provide further risk stratification regarding these outcomes.

Although malabsorption used to be a frequent feature of CD,[25] classic symptoms[26] have become less prominent in adult CD,[27] and when Kiefte-de Jong et al[24] recently examined tTG levels in pregnant women they found that women with positive and intermediate tTG had lower birth weights (average, 3300 and 3307 g, respectively) than tTG-negative women (3418 g), however, no difference was seen in markers of malabsorption between the 3 groups. Maternal malabsorptive states other than CD may predispose to low birth weight, as has been reported in women who have undergone bariatric surgery.[28] An increased risk of adverse fetal outcomes has been shown in mothers with inflammatory bowel disease, but the mechanism more likely is related to chronic inflammation as opposed to malabsorption.[29]

In the current study we saw no increased risk of IUGR or low birth weight among mothers with persistent villous atrophy compared with those with mucosal healing. In this population of patients with diagnosed CD, the prevalence of IUGR (3.5%) was similar to the prevalence of this outcome in a previous Swedish study of patients with diagnosed CD (3.4%),[14] which was, in turn, lower than the risk among undiagnosed CD (5.5%). In our study, the prevalence of low birth weight (5.7%) was between that of patients with diagnosed CD (4.1%) and undiagnosed CD (7.0%) that previously was reported.[14] Because our previous study in 2005 found that these outcomes were increased significantly only among those with undiagnosed CD (and not increased among those with diagnosed CD),[14] the null results of the current study may be interpreted as being caused by the fact that all of these patients had diagnosed CD; villous atrophy in and of itself, or as a marker of disease activity, does not confer the increased risk of obstetric outcomes that was found in undiagnosed individuals.

There are several additional explanations for our negative results. Villous atrophy on a first follow-up biopsy represents only a one-time status of the duodenal mucosa, and some patients with villous atrophy on a first follow-up biopsy have normal villi on a subsequent biopsy[17]; in our data set we only had access to the results of the first follow-up biopsy. Our small sample size (460 births) and relative rarity of our primary outcomes of IUGR and low birth weight (occurring in fewer than 30 births) limited our power to detect small effects. As noted previously, we had an 80% power to detect a 3.1-fold increased risk of IUGR and a 2.7-fold increased risk of preterm birth in offspring to women with persistent villous atrophy. Third, patients who were found to have villous atrophy on follow-up biopsy (particularly those who were contemplating pregnancy) may then have been spurred to improve their adherence to the gluten-free diet, thus obscuring differences in outcomes according to follow-up histology.[30] Therefore, those with persistent villous atrophy may have improved risk profile compared to those with undiagnosed (and therefore untreated) CD.

Secondary outcomes in this analysis included cesarean section, low Apgar score, and neonatal mortality. Although the prevalence of preterm birth (5.9%) was similar to the prevalence among those with diagnosed CD in our previous analysis (6.3%[14]), as was the outcome of low Apgar score (1.1% vs 1.0%), the outcome of cesarean section was much more common (21% vs 3%). The difference in this latter outcome is large and likely is owing to higher rates of cesarean section in recent years in Sweden.[31]

We found that the lack of association between follow-up histology and birth outcomes remained stable over time after biopsy. The one exception was the outcome of preterm birth, which showed a trend in the long term that did not meet statistical significance (aOR, 3.08; 95% CI, 0.79–11.99; $P = .11$). This same outcome met statistical significance on sensitivity analysis when restricting the follow-up biopsy period to 1 to 5 years after initial CD diagnosis (OR, 3.95; 95% CI, 1.37–11.38; $P = .01$). Although this finding may be owing to chance, we cannot rule out the possibility that persistent villous atrophy, and its attendant inflammation and malabsorption, may have an impact on this birth outcome. Another mechanism behind a detrimental effect on birth outcome is high levels of CD-associated antibodies.[32,33] With a gluten-free diet and decreasing antibody levels, it is possible that birth outcome improves independently of histopathology.

Strengths and Limitations

A strength of this study was its population-based setting: we used biopsy record data to identify individuals so that we could ascertain patients with CD with high confidence. In our earlier study on pregnancy outcome we used relevant International Classification of Diseases codes for CD,[14] but this was limited to inpatients, an occurrence that is rare in the modern-day management of CD. Identification of patients via villous atrophy also has a higher positive predictive value (95%)[34] for CD than the relevant International Classification of Diseases code (86%),[35] and other causes of villous atrophy are rare. When 2 examiners manually scrutinized more than 1500 biopsy reports (with villous atrophy and inflammation), only 0.3% of individuals with villous atrophy had inflammatory bowel disease (which was the most common comorbidity according to duodenal/jejunal biopsy reports).[34]

A significant limitation of this study was our lack of data on dietary compliance. According to patient chart data available for a subset of patients, some 17% of individuals with CD in this population were deemed to have poor compliance.[34] Given the fact that validated measures of adherence have been shown to correlate with healing in other studies[17,36] and that the relationship between educational attainment and mucosal recovery has been shown previously in this population,[23] it is highly likely that dietary noncompliance was a prominent driver of persistent villous atrophy. Nevertheless, the lack of adherence data for individual patients was a limitation. As noted earlier, we did not have access to serial biopsy results, and thus were unable to distinguish those whose persistent villous atrophy was long-lasting from those who eventually would heal. We also did not review pathology specifically for this article, although earlier data have suggested that Swedish pathologists correctly identify 90% of specimens with villous atrophy.[34]

The lack of data regarding levels of antibodies to tTG and gliadin was another significant limitation. As noted earlier, a prior study showed an inverse relationship between circulating maternal tTG antibodies and birthweight,[24] and these antibodies have been shown to bind to placental trophoblasts, interfering with normal trophoblast function.[33] In a previous analysis of this database that included initial and follow-up serology data that were available for a subset (<10%) of patients, we found that persistent seropositivity of antibodies to tTG or gliadin was present in 41% of individuals. Persistent villous atrophy was more common in those with persistent seropositivity (62%) than in those with conversion to a negative CD serology (21%).[37] Therefore, although serologic status correlates with histology, there is a possibility that serologic status may affect birth outcomes whereas histologic status does not.

In conclusion, this study found that, although the prevalence of IUGR and low birth weight was similar to previous studies of patients with diagnosed CD, there was no significant difference between women with persistent villous atrophy on follow-up biopsy compared with women with mucosal healing. Although persistent villous atrophy has adverse health effects regarding lymphoproliferative malignancy[20] and fracture risk,[21] adverse birth outcomes do not appear to be affected.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2014.11.018.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Methods

Subject Identification

Maternal CD was defined as having villous atrophy (histopathology stage Marsh 3) noted in a small intestinal biopsy report at one of Sweden's 28 Swedish pathology departments).[1] Data on CD were retrieved in 2006 to 2008 whereas biopsies had been performed from 1969 through 2008. Data included personal identity number,[2] biopsy date, morphology (using a list of relevant morphology codes according to the Swedish Systematized Nomenclature of Medicine [SnoMed] system[3]), and topography (duodenum or jejunum). In an earlier validation study, we examined the charts of 114 randomly selected individuals with villous atrophy and found that 108 (95%) had CD.[3] Biopsy reports were, on average, based on 3 tissue specimens,[4] and this should rule in approximately 95% of all CD cases.[5] Although we did not require a positive CD serology for diagnosis, among those validated through patient charts approximately 88% had positive CD serology (85% were positive for tTG) at the time of CD diagnosis (defined as the date of first biopsy with villous atrophy).[3]

In this study, we identified all female patients with CD who subsequently had a follow-up biopsy. As has been performed in our prior analyses of follow-up histology,[6–9] we excluded patients whose first follow-up biopsy was performed less than 6 months or more than 5 years after the initial CD diagnosis. Those patients whose follow-up biopsy showed Marsh 3 histology were classified as having persistent villous atrophy, whereas those whose follow-up histology showed less advanced Marsh lesions (including intraepithelial lymphocytosis with normal villous architecture) were classified as healed.[10] In a sensitivity analysis, we redefined the follow-up biopsy window period, restricting it to 1 through 5 years after initial CD diagnosis.

Swedish Medical Birth Register

The Swedish Medical Birth Register started in 1973 and contains data on more than 98% of all births in Sweden. It collects prospective information throughout pregnancy, using standardized records for maternal and infant health.[11]

From the Medical Birth Register we collected data on age, parity, maternal country of birth, early pregnancy smoking status (data available since 1982), any diabetes, and delivery year. We divided country of birth into Nordic (Sweden, Denmark, Norway, Finland, and Iceland) vs non-Nordic countries. Smoking status (at the first antenatal visit) was based on self-reported cigarette consumption (nonsmoker, 1–9 cigarettes per day, or $\geq$10 cigarettes per day). Any diabetes was recorded in the Medical Birth Registry and included both type 1, 2, and gestational diabetes.

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Supplementary Table 1. Time-Stratified Analysis, Comparing Infants Whose Mothers Had Persistent Villous Atrophy With Those Whose Mothers Had Mucosal Healing

Outcome	Births less than 2 years after follow-up biopsy	*P* value	Births 2–5 years after follow-up biopsy	*P* value
IUGR				
Mucosal healing	7/158 (4.4)		5/160 (3.1)	
Persistent VA	3/82 (3.7)		2/60 (3.3)	
Adjusted OR[a] (95% CI)	0.67 (0.15–3.11)	.61	0.19 (0.01–2.51)	.21
Low birth weight				
Mucosal healing	9/158 (5.7)		8/160 (5.0)	
Persistent VA	5/82 (6.1)		6/60 (6.7)	
Adjusted OR[a] (95% CI)	0.92 (0.27–3.13)	.89	1.18 (0.29–4.83)	.82
Very low birth weight				
Mucosal healing	2/158 (1.3)		2/160 (1.3)	
Persistent VA	2/82 (2.4)		0/160 (0)	
Adjusted OR[a] (95% CI)	1.24 (0.13–11.45)	.85	NC	NC
Preterm birth				
Mucosal healing	9/158 (5.7)		6/160 (3.8)	
Persistent VA	7/82 (8.5)		5/60 (8.3)	
Adjusted OR[a] (95% CI)	1.36 (0.45–4.10)	.58	3.08 (0.79–11.99)	.11
Very preterm birth				
Mucosal healing	1/158 (0.6)		2/160 (1.3)	
Persistent VA	2/82 (2.4)		0/60 (0)	
Adjusted OR[a] (95% CI)	4.79 (0.2–100.3)	.31	NC	NC
Low Apgar score				
Mucosal healing	2/156 (1.3)		0/159 (0)	
Persistent VA	2/79 (2.5)		1/59 (1.7)	
Adjusted OR[a] (95% CI)	2.89 (0.32–26.3)	.35	NC	NC
Cesarean section				
Mucosal healing	34/158 (21.5)		34/160 (21.3)	
Persistent VA	19/82 (23.2)		10/60 (16.7)	
Adjusted OR[a] (95% CI)	1.10 (0.55–2.19)	.79	0.57 (0.23–1.39)	.22

NC, not calculated owing to low numbers of events; VA, villous atrophy.
[a]Adjusted for maternal age at delivery, infant sex, parity, nationality, calendar period of birth, and maternal smoking.