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

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Q11 **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: Q12 **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],[1] 0.61; 95% confidence interval [CI], 0.19–1.99). There was no significant association between persistent villous atrophy and low birth weight (adjusted 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.

Q13Q14 Q15 Celiac disease (CD) occurs in approximately 1% of the Western population,[2,3] 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] To our knowledge there have been no investigations regarding follow-up histology and birth outcomes among pregnant women with CD.

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 materials.

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, 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.

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