Celiac disease is not a risk factor for infertility in men

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Objective: To examine fertility in men with biopsy-verified celiac disease (CD) in light of research that suggests that men with CD have impaired sperm quality.
Design: Using multinomial logistic regression and Cox regression, we estimated the fertility of the study group compared with that of 31,677 age-matched reference male controls.
Setting: Sweden.
Patient(s): Swedish nationwide population-based cohort of 7,121 men with CD (defined according to duodenal-jejunal biopsy data with [Marsh III] villous atrophy) ages 18–54 years at some point before the end of follow-up.
Main Outcome Measure(s): Number of children according to the Swedish Multi-Generation Register.
Result(s): During follow-up, men with CD had 9,935 children compared with 42,245 among controls. Adjusting for age, calendar period, and parity and stratifying by education, the overall fertility hazard ratio in the men with biopsy-verified CD was 1.02 (95% confidence interval, 0.99–1.04).
Conclusion(s): This study found a normal fertility in men with diagnosed CD. (Fertil Steril® 2011;95:1709–13. ©2011 by American Society for Reproductive Medicine.)

Key Words: Autoimmunity, celiac, cohort, fertility, infertility

About 1% of the Western population has celiac disease (CD) (1). CD is an immune-mediated disorder triggered by exposure to gluten in genetically susceptible individuals of all ages. Although the disease manifestations are mainly confined to the small intestine, with characteristic mucosal changes including villous atrophy (VA) and inflammation, associated extraintestinal symptoms and complications (e.g., malignancies [2], osteoporosis [3], type 1 diabetes [4], and infectious disease [5]) occur frequently. Whereas *women* with active CD have an increased risk of reproductive problems (6), offspring to *men* with CD do not seem to be at increased risk of preterm birth of low birth weight infants (7).

Earlier research suggests that CD is associated with androgen resistance (8, 9) (lower levels of dihyrotestosterone and elevated LH [10]) and lower levels of dehydroepiandrosterone sulphate (11). In their study, Farthing et al. describe two men with CD who had markedly reduced sperm motility (8). Other characteristics of CD include zinc deficiency, low levels of folic acid, and chronic inflammation. All these factors taken individually may have an adverse effect on fertility in males (12–16). Some reports indicate that male reproductive abnormalities reverse on a gluten-free diet (17, 18), but few papers have examined fertility in men with CD (17, 19, 20).

In this study we assessed fertility among 7,121 men before and after a diagnosis of CD. We used biopsy data from all Swedish pathology departments (n = 28) to verify the diagnosis, and through linkage with the Swedish Multi-Generation Register (MGR), we estimated their fertility compared with that among 31,677 age-matched controls.

MATERIALS AND METHODS

The Cohort

We used Swedish regional biopsy data to identify patients with CD (21). Between 2006 and 2008, we collected pathology reports from biopsies of the small intestine that were carried out between 1969 and 2008 at all of the 28 pathology departments in Sweden. For each biopsy, we recorded the arrival date of biopsy, the 10-digit personal identity number (PIN) unique to every Swedish resident, morphology, and topography (duodenum or jejunum). We used SnoMed morphology classification codes equivalent to VA (Marsh III [22]) to define CD (see Supplementary Table 1 in the Appendix). Validation against patient charts has shown that 95% of individuals with VA have CD (21). After the exclusion of duplicates and data irregularities (e.g., recorded date of biopsy before birth or after death), there remained 351,403 biopsy reports in 287,386 unique individuals with data on sex (110,479 males and 176,907 females). This study is restricted to 11,022 men who had duodenal-jejunal VA.

For each man with CD, the government agency Statistics Sweden (Swedish: Statistiska centralbyrån) identified up to five reference individuals matched for age, sex, calendar period, and county of residence (54,663 men). Individuals diagnosed with CD during the follow-up (n = 255) and those who were not alive or were not in Sweden at the time of confirmation of a CD diagnosis of the corresponding case were excluded (3 and 123,

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respectively). The total study cohort consisted of 11,022 men with CD and 54,663 male controls).

We used the Swedish MGR to identify all children born to men with CD and their reference individuals. The MGR contains information on the parents of all individuals in Sweden born from 1932 onward and who were alive in 1961 (23). Adoption or other nonbiological relations are flagged in the register, with nonbiological and half-siblings excluded from all analyses. Linkage with the MGR was made possible using the PIN, which is assigned to more than 99% of all Swedish residents (24). Migration dates were obtained from the Migration Register, a register that contains data from 1960.

Through linkage with the Education Register, we obtained information on the number of years of formal education completed as of 2005. Men diagnosed before the age of 18 years were assigned the education level of their fathers or the education level of their mothers if paternal education was missing until 2005. From the Total Population Registry, we obtained data on the country of birth of each man.

We restricted the study to men born between 1914 and 1990 whose reproductive history was covered by MGR starting from age 18 years, leaving 8,140 CD patients and 40,387 reference individuals in the study. Men who were not present in Sweden at 18 years of age (365 CD patients and 2,743 reference individuals) or who died before 18 years of age (six CD patients and 16 reference individuals) were excluded. We also excluded all men who gave birth before reaching age 18 (23 CD patients and 102 reference individuals), those born outside the Nordic countries or whose origin was unknown (94 CD patients and 851 reference individuals), and those with no data on educational level (531 CD patients and 2,341 reference individuals). When a CD patient was excluded from the study, we also excluded the corresponding matched controls (2,658 reference individuals). Thus, the main analysis was based on 7,121 men with CD and 31,677 reference men.

This study was approved by the research ethics committee of the Karolinska Institutet, Stockholm, Sweden.

Statistical Analysis

Study participants were followed up from 18 years of age to the age of 54, emigration, death, or January 1, 2008, whichever occurred first. The three CD groups were defined a priori according to the age at the time of diagnosis: before reproductive age (<18 years), during reproductive age (18–54 years), and after reproductive age (≥55 years). In all analyses we maintained the matching design by comparing each CD group to the corresponding matched reference group (25).

Multinomial logistic regression (26) was used to evaluate the association among the three CD groups and the cumulative number of children during the complete fertile period (18–54 years). To remove the effect of potential biases due to delayed pregnancy and catch-up phenomena, this analysis was limited to 3,273 CD men and 14,379 reference men with complete follow-up between 18 and 54 years of age. Odds ratios (ORs) were adjusted for men's year of birth (5-year categories) and education level (four categories, see Table 1).

To compare fertility hazards between CD patients and reference men, we used a Cox regression model for repeated events (27, 28), with age as the temporal axis. Our Cox model was stratified by education level to meet the proportionality assumption (checked by scaled Schoenfeld residuals). Number of children and 5-year calendar periods were included as time-dependent variables in the model.

We included a time-dependent variable for diagnosis of CD in the Cox model to investigate whether a CD diagnosis per se (and its subsequent treatment) might affect the fertility hazard ratio (HR). Specifically, we evaluated different time intervals before (>5 years, between 2 and 5 years, and <2 years) and after (<2 years, between 2 and 5 years, and >5 years) CD diagnosis. This analysis was restricted to men with a CD diagnosis during their reproductive years. Date of conception was estimated by subtracting 40 weeks from the date of birth of the children.

We also assessed unlike-sex twinning rates among offspring of cases and controls as a proxy for fathering of dizygotic twins that is reduced by male subfertility (29). This assessment is a measure of subfertility that is not affected by decisions on family size and is therefore less confounded by socioeconomic class. In the beginning of the 1990s, however, the spread in Sweden of IVF techniques began to influence twinning rates (30), and since then the association between male fertility and dizygotic twinning has reversed, with subfertile couples having a higher (instead of a lower) occurrence of unlike-sex twins among offspring. We therefore carried out analyses

TABLE 1

Characteristics of CD in patients and reference men.

	Age at biopsy, y					
	<18		18–54		≥55	
Characteristics	CD patients (n = 1,503)	Ref. men (n = 7,089)	CD patients (n = 3,273)	Ref. men (n = 14,379)	CD patients (n = 2,345)	Ref. men (n = 10,209)
	Median (IQR)		Median (IQR)		Median (IQR)	
Year of birth	1986 (83–88)	1986 (83–88)	1957 (48–67)	1957 (48–67)	1934 (28–41)	1934 (28–41)
Age at biopsy/study entry	6 (1–13)	5 (1–13)	39 (30–48)	39 (30–48)	64 (59–70)	64 (59–70)
Age at end of follow-up	22 (20–25)	22 (20–25)	50 (40–59)	50 (40–59)	71 (66–78)	71 (66–78)
Age at first birth	25 (23–29)	27 (23–30)	28 (25–31)	27 (24–31)	27 (24–31)	27 (24–30)
Education level,[a] n (%)						
Low	766 (51.0)	3,558 (50.2)	729 (22.3)	3,243 (22.6)	1,124 (47.9)	4,925 (48.2)
Low middle	101 (6.7)	370 (5.2)	976 (29.8)	4,477 (31.1)	476 (20.3)	2,169 (21.3)
High middle	467 (31.1)	2,282 (32.2)	559 (17.1)	2,544 (17.7)	305 (13.0)	1,407 (13.8)
High	169 (11.2)	879 (12.4)	1,009 (30.8)	4,115 (28.6)	440 (18.8)	1,708 (16.7)
No. of children (%)						
0	1,385 (92.1)	6,484 (91.5)	917 (28.0)	4,111 (28.6)	399 (17.0)	1,748 (17.1)
1	67 (4.5)	334 (4.7)	491 (15.0)	2,250 (15.7)	411 (17.5)	1,706 (16.7)
2	43 (2.9)	210 (2.9)	1,080 (33.0)	5,036 (35.0)	867 (37.0)	3,863 (37.9)
3+	8 (0.5)	61 (0.9)	785 (24.0)	2,982 (20.7)	668 (28.5)	2,892 (28.3)

Note: Ref. = reference.

[a] Low: 9 years or less of primary and secondary school; low middle: 2 years of high school (usually programs for manual, clerical or assistance work); high middle: 3 years of high school (theoretical programmes); and high: college or university studies.

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TABLE 2

Association between CD and total number of children until age 55 years.

Age at biopsy, y	No. of children 0	1	2	3+
18–54				
Reference men (n = 5,395)	Ref.	0.98 (0.79–1.22)	0.95 (0.79–1.14)	1.08 (0.90–1.31)
CD patients (n = 1,203)				
≥55				
Reference men (n = 10,088)	Ref.	1.06 (0.91–1.24)	0.98 (0.86–1.12)	1.01 (0.88–1.17)
CD patients (n = 2,317)				

Note: Ref. = reference. Data are OR (CI 95%). Men with a CD diagnosis between 18 and 54 years of age were 8% more likely to have at least three children until the age of 54 years.

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stratifying by year of birth of offspring, with 1990 as the threshold. ORs and 95% confidence intervals (CIs) for the association between CD and risk of unlike-sex twinning were calculated using a logistic regression, adjusting for parity and age.

All analyses were conducted using Stata release 9.0 (Stata Corp., College Station, TX).

RESULTS

Almost four of five men in the cohort with CD were diagnosed in adulthood (Table 1). Education level and number of children were similar in CD patients and reference men.

There were no differences in the cumulative number of children during fertile years between men with CD and reference men (Table 2). Since no men diagnosed before 18 years of age had a complete follow-up until age 54, men diagnosed before 18 years were excluded from the analysis on the total number of children.

Fertility HRs indicated normal fertility in all three groups of CD patients (Table 3). The HR of having a child for all CD patients combined was 1.02 (95% CI, 0.99–1.04).

Table 4 presents the HRs of supposed conception estimated at set intervals of time around the date of biopsy in men diagnosed with CD during their reproductive years. We found a fertility increase 2–5 years before biopsy. With this exception, HRs were close to unity during all time intervals (Table 4).

We examined the association between CD and having unlike-sex twins during the reproductive years (Supplementary Table 2 and Supplementary Table 3). We stratified our analyses by age at biopsy, calendar year, and temporal relationship to biopsy (prebiopsy vs. postbiopsy). These analyses found no association between CD status and twinning ratio, with the exception of one category: men diagnosed at 18–54 years of age after 1991 postbiopsy (OR = 2.69; 95% CI, 1.08–6.71).

TABLE 3

Fertility rates in CD patients and reference men.

	No. of children	HR	95% CI
Reference men	42,245	1.00	Ref
All CD patients	9,935	1.02	0.99–1.04
<18	179	0.93	0.78–1.09
18–54 pre-biopsy	4,404	1.05	1.02–1.09
18–54 post-biopsy	894	1.01	0.94–1.08
≥55	4,458	0.99	0.96–1.02

Note: Ref. = reference.

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DISCUSSION

This study is thus far the largest one on fertility in men with CD. We found that men with biopsy-verified CD had normal fertility, both before and after diagnostic biopsy.

The nationwide population-based design of this study minimizes selection bias. Our data set was constructed through linkages of biopsy reports from all 28 Swedish pathology departments. The use of register-based information for follow-up also minimizes the risk of differential information collection between exposed and unexposed individuals in the cohort.

Our data included more than 7,000 men with CD, which allows for important subanalyses with high statistical precision. In addition, using biopsy records allowed us to establish an exact date of CD diagnosis, information that enabled us to examine fertility in different time intervals around CD diagnosis. This type of information is important since a gluten-free diet is usually introduced after diagnostic biopsy. Except for a 27% increase in fertility between 2 and 5 years *before* biopsy (undiagnosed CD), fertility HRs were approximately 1.

TABLE 4

Effect of diagnosis on fertility rates for CD in patients diagnosed between 18 and 54 years of age.[a]

Time interval, y	No. of children	HR	95% CI
Before biopsy			
≥5	3,596	1.03	0.99–1.06
2–5	504	1.27	1.17–1.38
0–2	304	1.10	0.99–1.23
After biopsy			
0–2	243	1.03	0.92–1.16
2–5	254	0.92	0.81–1.04
≥5	397	1.07	0.96–1.20

[a] Compared with the corresponding group of men without CD.

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Comparison with Previous Literature

Although there are experimental data suggesting that male CD could be a risk factor for subfertility (8–11), few studies have examined actual fertility in men with CD (17, 19, 20), and these were of small size (<100 patients) (17, 19, 20). One of the studies (Meloni et al.) (20) found a CD prevalence of 1% among males in couples suffering from infertility. This finding is comparable to the prevalence in the general population (1). The other two studies (17, 19) reported that 19%–29% of men with CD had no offspring. Given that none of the studies (17, 19) involved any comparison group, it is unclear if this constitutes a true increase in subfertility.

In contrast, the current study involved 7,121 men with CD. About 35% (n = 2,701) had no offspring before the end of follow-up, a proportion that was similar to that in reference men. We used a control group of more than 30,000 men matched for age and calendar year. In addition, we were able to adjust for education as a proxy for socioeconomic status.

Interpretation of Findings

Based on our findings, we suggest that men with biopsy-verified CD are not at an increased risk of infertility before or after biopsy. The 27% increase in fertility 2–5 years before biopsy may be largely due to detection bias. If a child is diagnosed with CD (often at the age of 1–2 years), some physicians may choose to investigate the parents of the child and thus detect CD in the father that would otherwise have remained undiagnosed.

We have previously observed decreased fertility at roughly the time of diagnosis among women with CD (31). The decrease may be due to inflammation or malnutrition inhibiting conception but could also be due to the women postponing a pregnancy because of medical investigation or nutritional concerns (e.g., if they will start or have just started a gluten-free diet). In men we found no evidence of a decrease in fertility around diagnosis, despite evidence that CD is associated with low levels of zinc and folic acid (32, 33).

Our finding of no association with unlike-sex twinning before 1991 is consistent with the null finding on fertility rates. After 1991, twinning rates are likely to reflect IVF rates rather than male fertility. Our finding of increased unlike-sex twins after diagnosis after 1991 could be explained by chance variation, but it could also be explained by a rebound increase in IVF treatments after diagnostic work-up for fertility problems, including screening for CD.

Strengths and Limitations

Two main strengths of this paper are the high sensitivity and specificity of biopsy reports with VA for diagnosed CD. More than 96% of all pediatricians and gastroenterologists in Sweden perform a biopsy before CD diagnosis (21). In a blinded examination, Swedish pathologists correctly classified 90% of biopsies with CD, and a validation of a subset of patients with VA from our data set found that 95% (108/114) had CD (21). VA is also highly specific for CD. Less than 1% of biopsy records with VA had other disease than CD listed in the biopsy report (21) (0.3% suggested that the VA might be due to irritable bowel disease and 0.2% to *Helicobacter pylori*). We did not require a positive CD serology for this diagnosis. Still, an earlier validation in a subset of patients showed that 88% of individuals with VA had positive CD serology at time of biopsy (21).

The relative ethnic/genetic homogeneity of our study population can be seen both as a strength and as a weakness. It is likely to have reduced the need to add multiple variables to our statistical model, variables that in a more heterogeneous population could have affected fertility rates. Meanwhile the exclusion of men born outside Sweden and those not present in Sweden at age 18 years reduces the generalizability of our findings. And we cannot rule out that in genetically different CD populations fertility rates may be different.

A weakness of the paper is our lack of data on smoking. The effect of smoking on *male* reproduction is still under debate (34). Several studies have failed to show that male smokers have a reduction in fecundity if the cigarette consumption does not exceed 15 cigarettes per day (34). Still, it seems likely that sperm count and sperm volume and fertility are affected negatively by smoking (35). Most studies have suggested an inverse relationship between smoking and CD (36, 37), but not all (38, 39). If patients with CD are less often smokers, this possibility may have overestimated fertility in men with CD in our study. We also lacked data on body mass index (BMI) in our patients. Men with low BMI are more likely to have a future diagnosis of CD (40), but since a low BMI is not known to be associated with higher semen quality (41), BMI is unlikely to have confounded our estimates. Other weaknesses include our lack of data on conception methods, semen parameters, and genital pathology.

Conclusions

In conclusion, men with CD seem to have normal fertility rates, both before and after diagnosis of the disease.

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SUPPLEMENTARY TABLE 1

A comparison of small intestinal histopathology classifications.

Classification used in this project		VA	
Marsh classification	Type IIIa	Type IIIb	Type IIIc
Marsh description	Flat destructive		
Corazza et al.[a]	Grade B1		Grade B2
SnoMed codes	M58, D6218, M58005	M58, D6218, M58006	M58, D6218, M58007
KVAST/Alexander classification	III Partial VA	IV Subtotal VA	IV Total VA
Characteristics			
VA	+	++	++
IEL#	+	+	+
Crypt hyperplasia	+	++	++

[a] Corazza GR, Villanacci V, Zambelli C, et al. Comparison of the interobserver reproducibility with different histologic criteria used in coeliac disease. Clin Gastroenterol Hepatol 2007;5:838–43.

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SUPPLEMENTARY TABLE 2

Characteristics of study participants in the twinning analyses.

	No. of singletons	No. of like-sex twins	No. of unlike-sex twins
Reference men	42,500 (81.2)	287 (81.5)	126 (78.3)
All CD patients	9,835 (18.8)	65 (18.5)	35 (21.7)
<18 y	176 (0.3)	2 (0.6)	1 (0.6)
18–54 y	5,236 (10.0)	42 (11.9)	20 (12.4)
≥55 y	4,423 (8.5)	21 (6.0)	14 (8.7)
Total	52,335 (100.0)	352 (100.0)	161 (100.0)

Zugna. Fertility in men with celiac disease. Fertil Steril 2011.

SUPPLEMENTARY TABLE 3

Association between CD and unlike-sex twins until 55 years of age compared with the corresponding group of men without CD.

	Unlike-sex twins, OR (95% CI)			
	Pre-1991		Post-1991	
Age at biopsy, y	Prebiopsy	Postbiopsy	Prebiopsy	Postbiopsy
18–54				
Reference men (n = 6,051)	1.22 (0.60–2.46)	No estimate	0.78 (0.22–2.70)	2.69 (1.07–6.71)
CD patients (n = 1,394)				
≥55				
Reference men (n = 12,606)	1.05 (0.59-1.89)	No estimate	No estimate	No estimate
CD patients (n = 2,892)				

Zugna. Fertility in men with celiac disease. Fertil Steril 2011.