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Women With Celiac Disease Present With Fertility Problems No More Often Than Women in the General Population

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CLINICAL AT

This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this CME exercise and reading of the associated paper, successful learners will be able to compare the rates of presentation of fertility problems in women with and without celiac disease.

BACKGROUND & AIMS: Studies have associated infertility with celiac disease. However, these included small numbers of women attending infertility specialist services and subsequently screened for celiac disease, and therefore may not have been representative of the general population. We performed a large population-based study of infertility and celiac disease in women from the United Kingdom. **METHODS:** We identified 2,426,225 women with prospective UK primary care records between 1990 and 2013 during their child-bearing years from The Health Improvement Network database. We estimated age-specific rates of new clinically recorded fertility problems among women with and without diagnosed celiac disease. Rates were stratified by whether celiac disease was diagnosed before the fertility problem or afterward and compared with rates in women without celiac disease using Poisson regression, adjusting for sociodemographics, comorbidities, and calendar time. **RESULTS:** Age-specific rates of new clinically recorded fertility problems in 6506 women with celiac disease were similar to the rates in women without celiac disease (incidence rate ratio, 1.12; 95% confidence interval, 0.88–1.42 among women age 25–29 years). Rates of infertility among women without celiac disease were similar to those of women with celiac disease before and after diagnosis. However, rates were 41% higher among women diagnosed with celiac disease when they were 25–29 years old, compared with women in the same age group without celiac disease (incidence rate ratio, 1.41; 95% confidence interval, 1.03–1.92). **CONCLUSIONS:** Women with celiac disease do not have a greater likelihood of clinically recorded fertility problems than women without celiac disease, either before or after diagnosis, except for higher reports of fertility problems between 25–39 years if diagnosed with CD. These findings should assure most women with celiac disease that they do not have an increased risk for fertility problems.

Keywords: Food Allergy; Gluten; Pregnancy; Risk Factor.

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Celiac disease (CD) affects approximately 1% of the population in North America and Western Europe,[1–3] of whom 0.2% are clinically diagnosed, with women constituting approximately 60%–70% of the clinically diagnosed population.[4] The literature reports several mechanisms through which CD potentially could affect a woman's fertility such as the presence of abnormal villous structure in the intestine and malabsorption of the nutrients leading to nutritional deficiencies (eg, in zinc, iron, folate, and selenium).[5] These nutritional deficiencies are said to affect fertility, however, there is no conclusive evidence on the extent to which this may cause fertility problems in CD.[6] A lower level of ghrelin and leptin in women with CD also has been reported to play a role in fertility problems.[7] In addition, a shortened reproductive period with delayed menarche and early menopause also has been cited as an explanation for the reported increase in fertility problems related to CD.[8] On the contrary, a study based on 99 women being evaluated for infertility in Sardinia found no delay in the age of menarche in women with diagnosed CD (mean age at menarche, 11.8 y).[9]

Based on these explanations, several small studies over the years have assessed the link between CD and fertility problems, with some reporting a higher prevalence of CD in women seeking fertility treatments[10,11] and some showing no increase compared with the general population.[9,12,13] Some of these studies found that although the prevalence of CD was not higher in women with infertility, when restricted to only women with unexplained infertility, the prevalence of CD was significantly higher than in the general population,[9,10,14] whereas others did not find any significant association even with unexplained infertility.[12,13] These studies all were conducted on a very small number of women (the largest study included 535 women) primarily attending infertility specialist services, which represents a very selective group of women in the general population. In addition, these studies did not distinguish the burden of fertility problems in women with diagnosed from

Abbreviations used in this paper: BMI, body mass index; CD, celiac disease; CI, confidence interval; IQR, interquartile range; IRR, incidence rate ratio; THIN, The Health Improvement Network.

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undiagnosed CD. Despite these inconsistent findings from small studies, a wide variety of reviews highlight infertility as one of the key nongastrointestinal manifestations in CD.[15–17] We therefore performed a large population-based study to compare the rates of new clinically recorded fertility problems in a group of women with and without celiac disease that are representative of the UK population.

Methods

Data Source and Study Population

In the United Kingdom, any first contact or treatment from specialist infertility services requires a referral from a woman's primary care doctor, commonly known as the general practitioner; this is the first clinical contact for assessment of fertility problems. Therefore, we used The Health Improvement Network (THIN), a UK database of anonymized electronic primary care records to derive our study population. THIN has been shown to have a high validity of recorded diagnoses, medical events, and prescriptions.[18] It has been used previously to assess fertility problem reporting at a population level,[19] and the overall and age-specific fertility rates in THIN are broadly comparable with national fertility rates.[20] The version of THIN used for the purpose of this study contained longitudinal records of prospectively collected health information from 570 general practices across the United Kingdom, covering 6% of the total UK population.[21] Our cohort included all women of potential childbearing age (15–49 y) who contributed 1 or more years of active registration time between January 1990 and January 2013 to a general practice providing data to THIN. We selected women aged 15–49 years in accordance with the World Health Organization denominator for calculating the prevalence of infertility in women.[22]

Defining Celiac Disease

We identified each woman as having CD if she had a recorded diagnosis of CD in her general practice record using Read codes (clinically coded thesauraus used by general practitioners in the UK to record medical information) (Read codes: J690.00 for CD, J690.13 for gluten enteropathy, J690.14 for sprue-nontropical, J690100 for acquired CD, and J690z00 for CD NOS) with or without accompanying evidence of either gluten-free dietary prescriptions or dermatitis herpetiformis. Each woman with CD was assigned a date of diagnosis corresponding to the date of her first record of CD or the date of her first prescription of a gluten-free product (if present). Women with CD were classified further as having the diagnosis after the first fertility problem record (undiagnosed CD) or before (diagnosed CD). The method used to define CD has been validated previously in general practice databases with a positive predictive value ranging between 81% and 89%.[23] Lastly, we used longitudinally recorded information on women's disease symptoms and biological measurements (weight loss, diarrhea, or anemia in the year before celiac disease diagnosis) to give a proxy metric for women with more severe symptomatic CD.

Our comparison group consisted of women of childbearing age without any recorded diagnoses of CD or dermatitis herpetiformis in their primary care data. Women who received a gluten-free prescription in the absence of any CD or dermatitis herpetiformis diagnosis at any point during the study period also were excluded.

Defining Fertility Problems

Fertility problems in women were defined using read codes for fertility investigations (eg, 3189.00 for infertility investigation female), interventions (eg, 7M0h.00 for in vitro fertilization), specific (eg, K5B0000 for primary anovulatory infertility) or nonspecific diagnoses (eg, 1AZ2.11 for infertility problem), specialist referrals (eg, 8HTB.00 for referral to fertility clinic), or drug prescriptions used exclusively to treat fertility problems in women (principally clomiphene citrate).[24] We considered the date of the first record of a fertility problem during the study period to be the date of a new clinically recorded fertility problem. A detailed description of how we defined incident records of fertility problems is available elsewhere.[19] This definition of new clinically recorded fertility problems was shown in our previous work to generate age-specific rates with comparable patterns with those reported by the Human Fertilisation and Embryology Authority, which reports population-based, age-specific rates of women receiving specialized fertility treatments in the United Kingdom.[25] Code lists are available from the authors upon request.

Defining Other Variables

Information on women's sociodemographic factors including age, socioeconomic status, as measured by quintiles of the Townsend Deprivation Index, the most recent smoking status record, and body mass index (BMI) before the first fertility problem record was extracted. For women who did not have a recorded fertility problem, a random date was generated (pseudodiagnosis date) as a reference to extract the most recent recording on smoking status and BMI. Women were classified as smokers and nonsmokers (including never smokers and ex-smokers). If the medical code did not clearly indicate whether women were smokers or not, they were included in the missing/unknown category. Information on BMI was categorized as follows: underweight ($<$18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese ($\geq$30 kg/m^2), and missing BMI. Information on other autoimmune disorders including type 1 diabetes, rheumatoid arthritis, and thyroid disorders also was extracted.

Statistical Analysis

We described and compared baseline characteristics among women with and without CD using means, *t* tests, proportions, and chi-square tests. The distribution of all types of fertility problems across the study period was examined in both women with CD and women without CD. We estimated the incident rates of new clinically recorded fertility problems as the number of first recorded fertility problem per 1000 person-years. Female fertility is known to decrease with age[26,27]; therefore, we stratified the rates of clinically recorded fertility problems by 5-year age groups. We used lexis expansion[28] to construct an age-cohort model in which women could contribute person time to more than one age group. Given that the prevalence of CD has increased over time[29] we used an additional lexis expansion to split the study time by calendar year. We calculated age-specific incident rates of clinically recorded fertility problems in women with CD compared with women without CD. We then used Poisson regression to calculate the incidence rate ratios (IRRs) and corresponding 95% confidence intervals (CIs) for these comparisons, adjusting for socioeconomic status (quintiles of Townsend

Deprivation Index), smoking status, BMI, calendar year, and other autoimmune disorders. The age-specific rates of new clinically recorded fertility problems also were assessed in women with undiagnosed and diagnosed CD and in women with symptomatic celiac disease. These rates then were compared with the rates in women without CD, and IRRs (95% CIs) were calculated in a similar fashion as described earlier.

Finally, the National Institute for Health and Clinical Excellence recommends that women with fertility problems should be screened for CD.[30] Therefore, women are more likely to be screened for CD if they report a fertility problem. To assess this potential ascertainment of CD in relation to fertility problems we assessed the timing of new clinically recorded fertility problems in women in relation to their CD diagnosis to calculate the time difference between the 2 events.

Sensitivity Analysis

To increase the specificity of our CD definition, we restricted it to include only women who had both a read code for CD and a gluten-free prescription. Age-specific rates of new clinically recorded fertility problems were recalculated in women with CD and in women without CD based on this definition.

Ethical Approval

Ethical approval for this study was obtained from The Health Improvement Network Scientific Research Committee (EPIC Data Company) (reference number 11-027A).

Results

Study Population

Of the total population of 2,426,225 potentially fertile women contributing 15,236,530 years of follow-up time, 6506 (0.3%) women had a diagnosis of CD. The median follow-up time in the women with CD and in the women without CD was 6.5 person-years (interquartile range [IQR], 3.1–11.4) and 4.6 person-years (IQR, 2.4–9.0), respectively. The mean age at the first clinically recorded fertility problem was slightly higher in women with CD compared with women without CD (mean difference, 0.61; 95% CI, -0.13 to 1.34; $P = .107$), however, this difference was not statistically significant (Table 1). Women with CD were more affluent compared with women without CD (25.8% compared with 20.9%, respectively, in quintile 1) and also more likely to be underweight (5.7% in women with CD compared with 3.3% in women without CD). The prevalence of smoking also was slightly lower in women with CD compared with women without CD (12.3% vs 17.0%; $P < .001$). In addition, women with CD also had a higher prevalence of other autoimmune diseases compared with the non-CD group (P for all comorbidities $< .001$).

Of the 6506 women with CD, 290 (4.4%) had clinically recorded fertility problems, and of the 2,419,718 women without CD, 98,366 (4.1%) had clinically recorded fertility problems. When all codes relating to fertility problems appearing in women's primary care records were assessed, there was no statistically significant difference in the

Table 1. Baseline Characteristics of the Study Population

	Celiac disease (N = 6506)		No celiac disease (N = 2,419,718)		*P* value, chi-squared test
	Mean	SD	Mean	SD	
Age at first report of fertility problem (n (%))	33.4 n	6.2 %	32.8 n	6.4 %	.107[a]
Townsend score					
Quintile 1 (least deprived)	1681	25.8	505,211	20.9	
Quintile 2	1356	20.8	439,541	18.2	
Quintile 3	1242	19.1	470,933	19.5	<.001
Quintile 4	1070	16.4	460,980	19.0	
Quintile 5 (most deprived)	711	10.9	341,380	14.1	
Missing	446	6.9	201,673	8.3	
Most recent smoking status at first report of fertility problem[b]					
Nonsmoker	4242	65.2	1,330,425	54.9	<.001
Smoker	802	12.3	412,184	17.0	
Unknown/missing	1462	22.5	677,109	27.9	
Most recent BMI at first report of fertility problem, kg/m^2[b]					
Underweight (<18.5)	372	5.7	79,334	3.3	
Normal (18.5–24.9)	2911	44.7	950,153	39.2	<.001
Overweight (25.0–29.9)	990	15.2	388,762	16.1	
Obese (≥30)	607	9.3	261,830	10.8	
Missing	1626	24.9	739,639	30.6	
Type 1 diabetes	207	3.2	11,345	0.5	<.001
Rheumatoid arthritis	136	2.1	18,737	0.8	<.001
Thyroid disorder	694	10.7	74,947	3.1	<.001

[a] *P* value obtained from *t* test.
[b] A random index date (pseudodiagnosis date) was generated for women without recorded fertility problems.

Table 2. Rates of New Clinically Recorded Fertility Problems in Women With Celiac Disease, Without Celiac Disease, Undiagnosed and Diagnosed Celiac Disease, and Incidence Rate Ratios

Maternal age, *y*	Incident record of fertility problem	Person-years	Rate per 1000 person-years (95% CI)	IRR (95% CI)[a]
No celiac disease (N = 2,419,718)				
Overall rate	98,366	15,186,536	6.5 (6.4–6.5)	
15–19	1372	1,627,802	0.8 (0.7–0.9)	
20–24	9550	1,961,104	4.8 (4.7–5.0)	
25–29	22,562	2,211,743	10.2 (10.0–10.3)	Reference
30–34	29,473	2,328,794	12.6 (12.5–12.8)	
35–39	21,698	2,390,721	9.0 (8.9–12.8)	
40–44	9905	2,389,596	4.1 (4.0–4.2)	
45–49	3806	2,276,776	1.7 (1.6–1.8)	
Celiac disease (N = 6506)				
Overall rate	290	49,994	5.8 (5.2–6.5)	0.84 (0.75–0.95)
15–19	2	3217	0.6 (0.2–2.4)	0.78 (0.20–3.15)
20–24	20	3968	5.0 (3.2–7.8)	0.98 (0.63–1.52)
25–29	67	5357	12.5 (9.8–15.8)	1.12 (0.88–1.42)
30–34	84	7215	11.6 (9.4–14.4)	0.87 (0.70–1.08)
35–39	70	9068	7.7 (6.1–9.7)	0.83 (0.65–1.04)
40–44	38	10,387	3.6 (2.6–5.0)	0.85 (0.62–1.17)
45–49	9	10,783	0.8 (0.4–1.6)	0.50 (0.26–0.96)
Undiagnosed CD (N = 122)				
Overall rate	122	23,608	5.2 (4.3–6.2)	0.76 (0.64–0.91)
15–19	0	1600	0	-
20–24	11	1828	6.0 (3.3–10.8)	1.11 (0.62–2.01)
25–29	27	2757	9.8 (6.7–14.3)	0.86 (0.59–1.25)
30–34	37	3859	9.6 (6.9–13.2)	0.74 (0.54–1.03)
35–39	30	4472	6.7 (4.7–9.6)	0.78 (0.55–1.12)
40–44	9	4665	1.9 (1.0–3.7)	0.47 (0.24–0.91)
45–49	8	4424	1.8 (0.9–3.6)	1.04 (0.52–2.09)
Diagnosed CD (N = 168)				
Overall rate	168	26,386	6.4 (5.5–7.4)	0.91 (0.79–1.07)
15–19	2	1616	1.2 (0.3–4.9)	1.54 (0.36–6.20)
20–24	9	2139	4.2 (2.2–8.1)	0.86 (0.45–1.65)
25–29	40	2600	15.4 (11.3–20.9)	1.41 (1.03–1.92)
30–34	47	3356	14.0 (10.5–18.6)	1.01 (0.76–1.34)
35–39	40	4596	8.7 (6.4–11.9)	0.86 (0.63–1.17)
40–44	29	5721	5.1 (3.5–7.3)	1.14 (0.79–1.64)
45–49	1	6358	0.2 (0.02–1.1)	0.10 (0.01–0.69)
Symptomatic CD (N = 1143)				
Overall rate	43	10,261	4.2 (3.1–5.6)	0.60 (0.45–0.81)
15-19	0	589	0	-
20–24	3	687	4.4 (1.4–13.5)	0.84 (0.27–2.61)
25–29	6	1000	6.0 (2.7–13.3)	0.53 (0.23–1.17)
30–34	14	1491	9.4 (5.6–15.8)	0.69 (0.41–1.18)
35–39	12	1930	6.2 (3.5–10.9)	0.67 (0.38–1.18)
40–44	7	2250	3.1 (1.5–6.5)	0.71 (0.34–1.50)
45–49	1	2312	0.4 (0.1–3.1)	0.25 (0.04–1.81)

[a]Adjusted for Townsend deprivation index quintiles, smoking status, body mass index, type 1 diabetes, thyroid disorder, rheumatoid arthritis, and calendar year.

distribution of drug treatment, investigations, interventions, referrals, or diagnoses between women with and without CD (Supplementary Table 1).

Age-specific rates in women with CD compared with women without CD. Table 2 shows the rates of new clinically recorded fertility problems in women with and without CD by 5-year age groups. In women with CD, the rate of new clinically recorded fertility problems was highest in the 25–29 year age group (12.5 per 1000 person-years), and in women without CD the rate was highest in the 30–34 year age group (12.6 per 1000 person-years). Across all age groups, however, there were no statistically significant differences between the rates of new clinically recorded fertility problems in women with and without CD (eg, IRR in the 25–29 year age group, 1.12; 95% CI, 0.88–1.42; IRR in the 30–34 year age group, 0.87; 95% CI, 0.70–1.08).

Age-specific rates in diagnosed and undiagnosed CD. Of the 290 women who had CD and a recorded fertility problem, 122 (42%) were classified as having undiagnosed CD and 168 (58%) were classified as having diagnosed CD

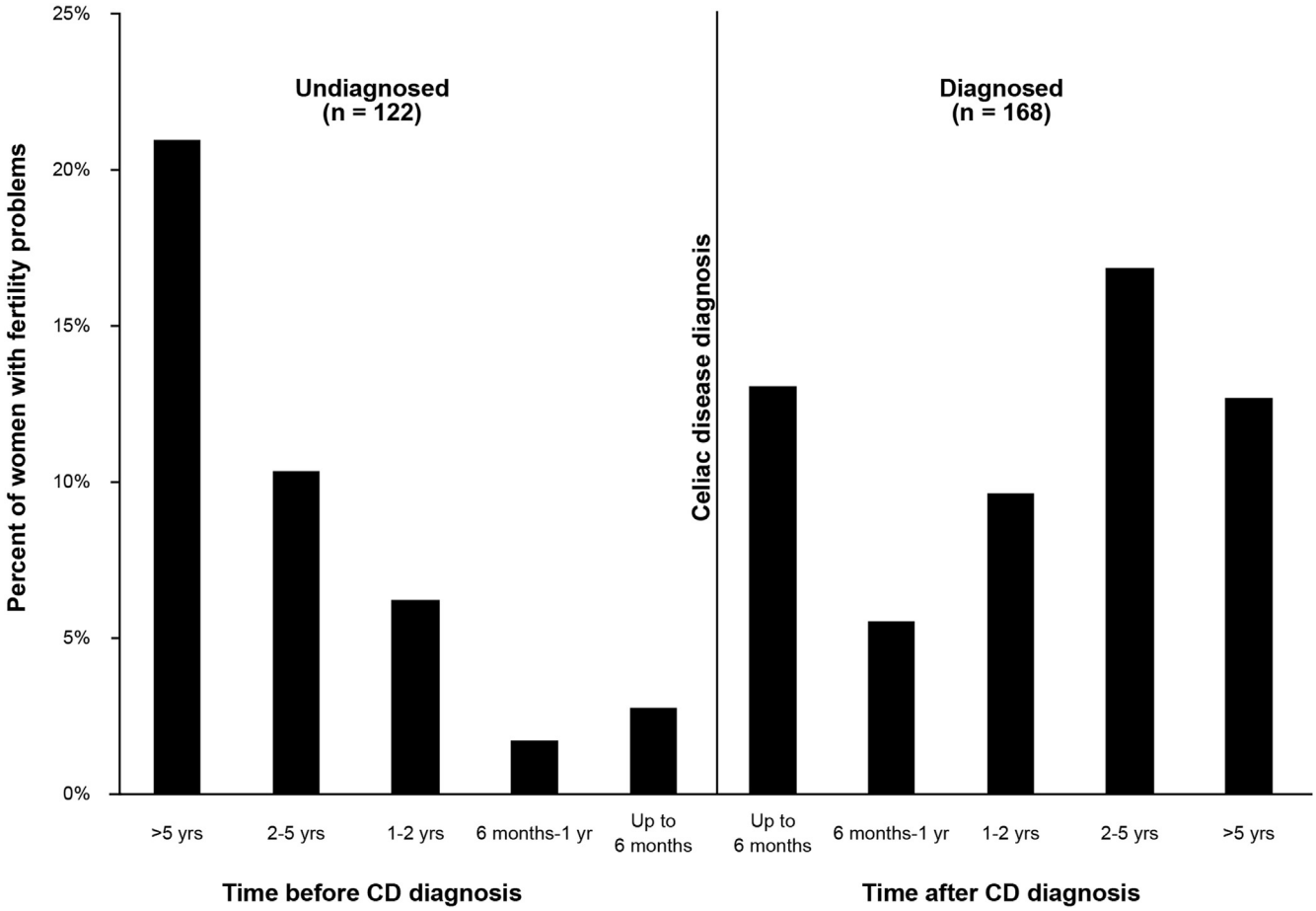

Figure 1. Timing of a new clinically recorded fertility problem in relation to celiac disease diagnosis (N = 290).

in relation to the new clinically recorded fertility problem. The diagnosis of CD happened at a median of 2 months after the fertility problem (IQR, 4 years before, 2.7 years after). Figure 1 shows the time of new clinically recorded fertility problems in relation to the CD diagnosis. Approximately a quarter of the fertility problems were recorded within a year before or after the CD diagnosis, with 5% being recorded within a year before the fertility problem and 19% within a year after the fertility problem.

Overall, the age-specific rates of new clinically recorded fertility problems were higher in women with diagnosed CD compared with women with undiagnosed CD (15.4 per 1000 person-years in diagnosed CD compared with 9.8 per 1000 person-years in undiagnosed CD in the 25–29 year age group) (Table 2). There was no statistically significant difference between the rates of new clinically recorded fertility problems in women with both undiagnosed and diagnosed CD compared with women without CD, except for the 25–29 year age group, in which women with diagnosed CD were 41% more likely to have new clinically recorded fertility problems compared with women without CD (IRR, 1.41; 95% CI, 1.03–1.92). However, the absolute excess risk was only 0.5% (5.2 per 1000 person-years).

Age-specific rates in women with symptomatic CD. Of the 6506 women with celiac disease, 1143 (17.6%) were recorded as symptomatic (with weight loss, diarrhea, or anemia) in the year before diagnosis. The age-specific rates of new clinically recorded fertility problems in this subset of women with symptomatic celiac disease were not statistically significantly different compared with women without celiac disease. The overall rate was found to be 40% lower, however, the absolute risk difference was only 2.3% (Table 2).

Sensitivity Analysis

Of 6506 women with CD, 4649 (71.4%) had received a gluten-free prescription. Of these women, 211(4.5%) had clinically recorded fertility problems, which was almost exactly the same as in the overall population. The age-specific rates of new clinically recorded fertility problems were very similar to the main results, with no statistically significant increase in the rates of new clinically recorded fertility problems in women with CD based on the more specific criteria compared with women without CD (Supplementary Table 2).

Discussion

Principal Findings

In this large population-based contemporary cohort study from the United Kingdom, we analyzed more than 2 million women of childbearing age, of whom 0.3% were diagnosed with CD.

We have shown that the presentation of fertility problems in primary care in women with and without CD is very similar. In addition, the rates of new clinically recorded fertility problems in women with diagnosed and undiagnosed CD were similar and comparable with the rates in women without CD except for the 25–29 year age group in women with diagnosed CD, who had a 40% relative increase in fertility problems compared with women without CD, which corresponded to an absolute excess risk of 0.5%.

Strengths and Limitations

We assessed the association between celiac disease and fertility problems with data on over 2 million women over a period of 20 years. Given the natural decrease in fertility with age, an overall prevalence would mask the effects of increasing association between CD and fertility problems. Therefore, we have presented age-specific rates of new clinically recorded fertility problems in women, which are more meaningful in planning interventions. To account for the increasing prevalence of CD[29] and reporting of fertility problems[19] over time, we also adjusted for calendar year and also for other potential confounders such as smoking, socioeconomic status, BMI, and other autoimmune diseases known to be common in women with CD and associated with fertility problems.[31]

Previous studies have identified women with CD from specialist infertility clinics[9,10,14,32] or obstetrics and gynecology units in the hospital.[11–13] This may be only a selective group of women because not all women who experience difficulties in conceiving seek medical help. The proportion of women seeking medical help for their fertility problem in the United Kingdom ranges from 70% to 85%.[33,34] Studies from the United Kingdom report that between 30% and 49% of women reporting fertility problems are given referrals or undergo fertility treatments.[33,35] Therefore, women selected from specialist fertility clinics may be significantly different from the majority of women experiencing fertility problems, especially in terms of sociodemographics, making the previous studies highly prone to selection bias. By contrast, we identified women from routinely collected primary care data in which the women initially will consult for fertility problems before going for specialized treatments or investigations. Primary care data therefore provide a more complete picture of the extent and distribution of clinically recorded fertility problems at a population level while minimizing the potential for selection bias. It could be argued, however, that women with CD in our population are more likely to have fertility problems that require specialist medical treatment than women without CD. When we compared the available information on coding of fertility problems, this was not supported; we noted no important differences in types of infertility, treatments, and referrals between women with and without CD.

Because we did not have detailed information on serologic tests and histology of the small bowel to confirm CD, we used specific medical read codes instead to identify women with CD in the general population. The method used to define CD has been validated previously in general practice databases,[23] therefore we believe the ascertainment of CD in our study is likely to be good. Other recent studies also have made use of read codes in primary care data to identify cases of CD, reiterating that this method to identify a CD population is valid.[36,37] When we further increased the specificity of our CD diagnosis by restricting our analysis only to cases with supporting evidence of a gluten-free prescription, our estimates remained broadly unchanged.

Approximately 30% of the women with CD did not have any record of a gluten-free prescription in our study. Gluten-free prescriptions are considerably costly when prescribed on the UK National Health Service compared with similar products purchased directly.[38] Therefore, women may end up purchasing gluten-free products directly, in which case there will be no primary care data recorded on these purchases. Our study also lacked data on compliance with a gluten-free diet. However, similar to most CD studies, we assumed that all women with diagnosed CD are broadly compliant with a gluten-free diet, which seems reasonable given previous evidence suggesting that complete nonadherence to a gluten-free diet is uncommon among patients with CD.[39]

We must acknowledge that approximately 1% of women in the United Kingdom have serologic evidence of CD[40] and therefore it is likely that there are women with undiagnosed CD among our general population comparison group. It therefore is possible that the presence of these women could have increased the rate of fertility problems in our comparison group if there was truly an increased risk of infertility among women with undiagnosed CD as has been implied previously.[10,11,14,41] However, against that hypothesis, our analysis of the women with undiagnosed CD showed that, if anything, their rates of clinically recorded fertility problems were even lower than in the women with diagnosed CD in almost all of the age groups we studied.

Finally, there were communication delays between secondary and primary care.[42] Although the exact time for this is unknown, there may be inaccuracies in the recording of the exact date of diagnosis of CD, which may have resulted in the misclassification of some diagnosed cases as being undiagnosed. Nevertheless, the rates of fertility problems in both diagnosed and undiagnosed CD were found to be very similar, and also were comparable with the rates in women without CD.

Comparison With Current Literature

Results from the limited studies assessing CD in women with fertility problems have been inconsistent. Some studies have reported a higher prevalence of CD in women undergoing fertility treatments compared with controls,[10,11] and some have shown no statistically significant difference between the prevalence of CD in women undergoing fertility treatment and controls.[9,12,13] The small sample sizes ($<$600 women) and a very selective baseline population in these studies makes sensible comparisons with our study very difficult. Another important consideration when comparing our findings with the previous studies is that these studies captured women at more advanced stages in the management of fertility problems (ie, specialist fertility clinics or where women already had a specific diagnosis; eg,

unexplained infertility), whereas our study also included women who had fertility problems recorded in primary care but may not have gone on to receive specialist fertility services. Furthermore, the age-specific rates calculated in our study are not directly comparable with the prevalence estimates from previous studies.

Some studies, however, have reported fertility rates in women with and without CD, using the number of children as an indicator of fertility. For example, a case-control study that included 68 women with CD and 68 controls from England found that women with CD had a mean number of children = 1.9 (SD, 0.9) children compared with a mean number of children = 2.5 (SD, 1.2) in controls, suggesting that the fertility profile of women with CD was slightly inferior to the general population, and that it improved after the diagnosis and treatment of CD (0.5 children; SD, 0.9) compared with controls (0.7; SD, 1.2).[41] In contrast, a Swedish population-based study including 11,945 CD cases and 51,109 controls found slightly higher cumulative numbers of children in the CD population compared with controls and a fertility hazard ratio of 1.03 (95% CI, 1.01–1.05), with a similar fertility hazard ratio for women younger than age 18, women between ages 18 and 44, and women older than age 45.[43] Similarly, a population-based study using the UK primary care data showed fertility rates in CD and non-CD women to be very similar.[44] Our findings mirror these patterns because they show no statistically significant differences in the age-specific rates of new clinically recorded fertility problems in women with and without CD. Furthermore, no differences were observed in the rates of reporting of fertility problems before and after the diagnosis of CD. Rates of reporting fertility problems were slightly higher in younger women with diagnosed CD between the ages of 25–29 (1.41; 95% CI, 1.03–1.92); however, this effect did not hold for women in other age groups. Furthermore, approximately 50% of the fertility problems reported in women with diagnosed CD in the 25–29 year age group were within 2 years of CD diagnosis, again indicating that the small increase in clinically recorded fertility problems we observed in those ages 25–29 years could well be related to the ascertainment of CD or vice versa rather than depicting a causal relationship. It also is worth noting that although the relative risk was 40% higher in women with diagnosed CD, the absolute excess risk was calculated to be only 0.5%. The overall rate of new clinically recorded fertility problems in women with symptomatic CD was found to be slightly lower than the rates in women without CD. These lower rates may be explained by an increased focus on resolving celiac symptoms before women try to conceive or the lack of more specific metrics of disease severity in our data.

Conclusions

The current evidence regarding CD in small groups of women with unexplained infertility from a small number of studies has been generalized to raise concern among all women with CD by highlighting women with infertility as one of the associated conditions in CD.[17,45,46] Although undiagnosed CD is likely to be an underlying cause of unexplained infertility for some women, our findings indicate that most women with celiac disease, either undiagnosed or diagnosed, do not have a substantially greater likelihood of clinically recorded fertility problems than women without CD. Therefore, screening when women initially present with fertility problems may not identify a significant number of women with CD, beyond the general population prevalence. This may not always apply to subgroups of women with severe celiac disease. However, in terms of the clinical burden of fertility problems at a population level, these findings should be reassuring for women with CD and all stakeholders involved in their care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.08.025.

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The authors disclose no conflicts.

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Supplementary Table 1. Detailed Description of Fertility Problem Read Code Categories Appearing in the Clinical Records for Cases of Fertility Problems

	Celiac disease (N = 290)[a]	No celiac disease (N = 98,366)[b]	*P* value for overall category
Drug treatment	55 (19.0%)	16,843 (17.1%)	.406
Chorionic gonadotropin	12	2273	
Clomiphene citrate	45	14,495	
Follitropin α and β	7	807	
Human menopausal gonadotropin	2	359	
Urofollitropin	6	1242	
Investigations	41 (14.1%)	14,562 (14.8%)	.750
Ovulation tests	1	261	
Methylene blue tubal test	0	66	
Nonspecific infertility investigations	40	14,290	
Interventions	49 (16.9%)	18,001 (18.3%)	.537
Counseling	22	8803	
Surgical intervention	3	419	
In vitro fertilization	15	4650	
Intrauterine insemination	0	18	
Nonspecific management codes	19	6682	
Referrals	40 (13.8%)	12,758 (13.0%)	.677
Diagnoses	230 (79.3%)	77,270 (78.6%)	.754
Infertility: cervical origin	0	4	
Infertility: ovulatory origin	1	556	
Infertility: pituitary hypothalamic	0	5	
Infertility: tubal origin	0	125	
Infertility: uterine origin	0	6	
Infertility: vaginal origin	0	9	
Infertility: nonspecific	229	76,622	

[a]Percentage of 290.
[b]Percentage of 98,366, total may not be equal to the sum of all columns because each woman may have had more than 1 code.

Supplementary Table 2. Age-Specific Rates (95% CI) of New Clinically Recorded Fertility Problems in Women With and Without Celiac Disease and Incidence Rate Ratios (95% CI) Using a Restricted Definition of CD

	Celiac disease (N = 4649)			No celiac disease (N = 2,419,718)			
Age, *y*	Incident record of fertility problem	Person time	Rate per 1000 person-years (95% CI)	Incident record of fertility problem	Person time	Rate (95% CI)	IRR (95% CI)[a]
Overall	211	37,400	5.6 (4.9–6.4)	98,366	15,186,536	6.5 (6.4–6.5)	0.85 (0.74–0.98)
15–19	2	2331	0.8 (0.2–3.4)	1372	1,627,802	0.8 (0.7–0.9)	1.44 (0.36–5.77)
20–24	12	2699	4.4 (2.5–7.8)	9550	1,961,104	4.8 (4.7–5.0)	0.93 (0.52–1.68)
25–29	50	3690	13.5 (10.3–17.9)	22,562	2,211,743	10.2 (10.0–10.3)	1.08 (0.78–1.47)
30–34	61	5304	11.5 (8.9–14.7)	29,473	2,328,794	12.6 (12.5–12.8)	0.87 (0.67–1.14)
35–39	52	6834	7.6 (5.8–9.9)	21,698	2,390,721	9.0 (8.9–12.8)	0.88 (0.66–1.16)
40–44	28	7968	3.5 (2.4–5.1)	9905	2,389,596	4.1 (4.0–4.2)	0.90 (0.62–1.32)
45–49	6	8572	0.7 (0.3–1.6)	3806	2,276,776	1.7 (1.6–1.8)	0.46 (0.19–1.09)

[a]Adjusted for Townsend deprivation index quintiles, smoking status, body mass index, type 1 diabetes, thyroid disorder, rheumatoid arthritis, and calendar year.