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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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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