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Onset of menarche is not delayed in Slovenian patients with celiac disease

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Abstract

Objective: Celiac disease (CD) is an autoimmune disorder associated with numerous health problems, including reproductive disorders. This study was performed to analyze the association between CD and the menstrual cycle in a group of patients with CD and compare these patients' characteristics with those of healthy women.

Methods: The study included 145 patients with CD (age, 15–51 years) and 162 healthy women (age, 18–55 years). Age at menarche and characteristics of the menstrual cycle were obtained by an anonymous questionnaire developed for the study.

Results: The age at onset of menarche was 12 to 14 years in 72.9% of the patients with CD and 77.3% of the healthy controls. For most patients (74.2%), the length of the menstrual cycle was around 27 to 28 days with 4 to 5 days of bleeding. Furthermore, 8.4% of patients versus 5.9% of controls experienced bleeding between cycles.

Conclusions: Our results suggest that in Slovenia, the age at menarche in patients with CD is 12.7 years, which is comparable with that in healthy women. We conclude that CD (treated or untreated) may not be associated with late menarche.

Keywords

Celiac disease, children and adolescents, menarche age, menstrual disorders, Slovenia, questionnaire

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Introduction

Celiac disease (CD) is a chronic autoimmune disorder that occurs in genetically predisposed individuals and is caused by

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ingestion of gluten and related proteins present in wheat, barley, and rye. CD is one of the most frequent chronic diseases in Europe, with an incidence of approximately 1% in adults and children. The incidence is the same in Slovenia.[1] However, large unexplained differences across different European countries are observed.[2] In the past, CD was considered a gastrointestinal disease of childhood; today, CD is recognized as a systemic disease. It is typically characterized by intestinal mucosal damage and symptoms of diarrhea, flatulence, and malabsorption; however, extraintestinal complications also frequently occur.[3] Most importantly, the latter may often be asymptomatic. Among extradigestive complications associated with CD, delayed menarche, menstrual cycle disorders, impaired fertility, and adverse pregnancy outcomes have been increasingly recognized during the last two decades.[4] Researchers have speculated that these complications could be related to immune-mediated mechanisms or nutrient deficiencies.[5]

Women with reproductive disorders or pregnancy complications frequently have no clear symptoms that appear to be associated with CD.[4] Such reproductive disorders might be the only clinical feature that ultimately leads to the diagnosis of CD. Therefore, it is not surprising that women of childbearing age are a group that is commonly diagnosed with CD.[4] The prevalence of CD among women with unexplained infertility is around 3%, which is higher than that in the healthy population.[6] Several studies have suggested implications of untreated CD on the reproductive health of women, including delayed age at menarche, infertility, endometriosis, recurrent abortions, intrauterine growth restriction, low birth weight (both preterm and/or small-for-gestational-age infants), and early onset of menopause.[5,7–9]

The same studies indicated that the age at menarche among women with CD is delayed when compared with that in healthy women. An increased frequency of secondary amenorrhea has also been documented in women with CD.[7] Likewise, Molteni et al.[10] compared the reproductive health of 54 women with CD with that of 54 healthy women. The results of the study showed that the mean age at menarche was significantly later in women with CD (13.5 vs. 12.1 years). In addition, 38.8% of the women with CD compared with only 9.2% of the healthy women complained of amenorrhea.[8] In a study by Rujner,[11] 59 girls with CD were compared with their mothers regarding age at menarche. The mean age at menarche was significantly higher in untreated girls than in those who were on a gluten-free diet (GFD); consequently, the author speculated that the age at menarche in girls with CD is regulated by treatment with a GFD in addition to genetic and environmental factors. In contrast to previously mentioned studies, a more recent study by Sferlazzas et al.,[12] which included 211 girls with CD from Italy, showed that the age at menarche in girls with CD was not delayed and was comparable with that of their own mothers, those on a GFD, and healthy controls. The authors indicated that the age at menarche might be unrelated to dietary treatment.[12]

The only available treatment of CD is complete elimination of gluten from the diet. A lifelong GFD results in healing of the jejunal mucosa, resolution of malabsorption symptoms, and reversal of the majority of CD symptoms. However, the effect of a GFD on the age at menarche and the prevention of complications in pregnancy remains a subject of debate.[5] Although the connection among CD, the onset of menarche, and fertility is established, it is not yet completely clear. Various reproductive health indicators reportedly differ in patients with chronic

diseases, including untreated CD. To the best of our knowledge, the impact of CD and its consequences on women's reproductive health in Slovenia have not been characterized. For this reason, the aim of the present study was to analyze the association between CD and the menstrual cycle in women with CD who were active members of the Slovenian Celiac Society and compare the characteristics of these women with those of healthy women.

Patients and methods

In the present study, we analyzed the association between CD and the menstrual cycle in a sample of women with CD who were active members of the Slovenian Celiac Society. Most patients originated from northeast Slovenia, whereas approximately 30% of patients came from other Slovenian regions. This retrospective case-control study was conducted from August to December 2017. After obtaining written informed consent, patients with CD were asked to complete an anonymous survey consisting of questions about their history of CD, menstrual history, socioeconomic history, overall health, and other variables. The age at diagnosis of CD was divided in four categories: very early (<2 years of age), early (2–6 years), middle (6–15 years), and late (>15 years). In the study population, CD had been diagnosed based on a small intestinal biopsy according to the Marsh classification. The old European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines were used to establish the diagnosis because the latest ESPGHAN guidelines, which permitted diagnosis of CD without biopsy in certain cases, were published in the year 2012, and all included patients were born significantly before 2012.[13–15] For older patients included in the study, anti-gliadin antibodies (AGA) were used in diagnostic procedures as the only available serological test at that time. Later, however, serum anti-endomysial antibody and/or anti-tissue transglutaminase (TG) antibody positivity was used because of the poor sensitivity and specificity of AGA.

The women in the healthy control group were selected in the general practice office, where every fifth woman was recruited after excluding any women with a gastrointestinal disorder. The healthy controls were comparable with the patients with CD in terms of their socioeconomic status, education, and age. After providing written consent, all controls were administered the same standardized questionnaire used for the patients but without questions about CD. The data were collected from the questionnaires in an electronic database and further analyzed.

The main focus of the questionnaire was the questions regarding overall reproductive health, family history, and particularly the menstrual cycle (disorders). Each question had multiple possible answers. The study was approved by the institutional ethics committee.

For statistical purposes, the collected data were submitted to analysis of variance. Data are expressed as mean ± standard deviation, frequency, and range. The chi-square (χ^2) test was employed to compare the prevalence of menstrual abnormalities between the patients and controls. A P value of <0.05 was considered the cutoff point for statistical significance. Furthermore, Fisher's exact test was performed when an expected variable value was <5. The assessment of significant differences across the means of continuous variables (age at menarche) was based on the t-test for independent samples. Data were analyzed using Predictive Analytics SoftWare (PASW), version 24.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 145 patients with CD (all members of the Slovenian Celiac Society) and 162 healthy controls participated in the study. All participants responded to the questionnaire, for a response rate of 100%. All women with CD were on a GFD. The mean age of women with CD was 27.8 ± 5.8 years (range, 15–51 years), and the mean age of the controls was 26.9 ± 5.7 years (range, 18–55 years). In total, 50.3% of the patients with CD and 60.1% of the controls lived in an urban area, mostly in Maribor (the second largest town in Slovenia) and Ljubljana (the capital of Slovenia) (Table 1). The area of residence and the distribution overlapped between the patients and controls (Table 1). In all cases (100%), CD was diagnosed by a small intestinal biopsy and confirmed by histology. The serum level of anti-TG antibodies was analyzed in 97 (67.4%) patients, the level of anti-endomysial antibodies was assessed in 78 (54.5%) patients, the serum level of AGA was measured in 43 (30.0%) older patients, and human leukocyte antigen genomic typing for DQ2/DQ8 was performed in 75 (52.0%) patients. In addition, 13% of patients with CD also had CD in their immediate family.

Table 1. Description of study participants.

	Patients %	Controls %
Place of residence		
Urban	50.3	60.1
Rural	49.7	39.9
Age at confirmation of celiac disease		
≤2 y	7.0	–
2–6 y	4.8	–
6–15 y	16.5	–
≥15 y	71.7	–
Age at menarche		
≤11 y	3.0	5.0
12–14 y	89	90
≥15 y	8.0	5.0
Bleeding between two menstruations		
Yes	8.4	5.9
No	91.6	94.1
Painful menstruation		
Yes	61.7	68.9
No	38.3	31.1

Only 7% of the study participants had CD confirmed during the first 2 years of life: 4.8% at 2 to 6 years of age, 16.5% at 6 to 15 years of age, and, unexpectedly, 71.7% at >15 years of age (Figure 1). Only 28.3% of women with CD had the diagnosis of CD confirmed before the onset of menarche. Accordingly, 71.7% of participants in the study started a GFD

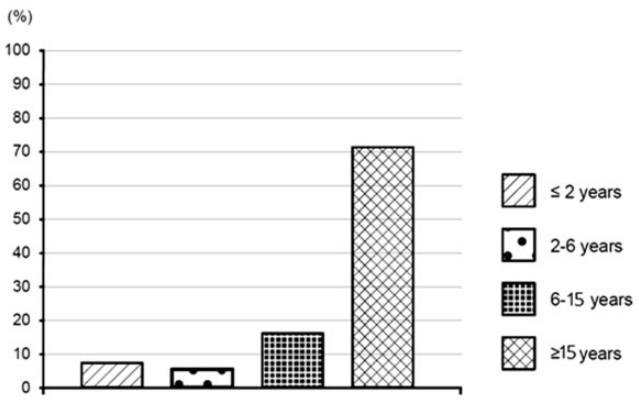

Figure 1. Age at which celiac disease was confirmed.

after 15 years of age and were not on a GFD at the onset of their menstrual cycle. Considering that most patients with CD were diagnosed late, it is not surprising that at the time of diagnosis, only 16.5% had typical symptoms of CD such as diarrhea, abdominal cramps, unexplained anemia, bloated stomach, and weight loss. Furthermore, 71.7% of patients had no clear symptoms or signs of CD at the time of diagnosis, and for that reason, CD was diagnosed later in life.

A total of 89% of the patients with CD reported onset of menarche at 11 to 15 years of age, 8% after 15 years of age, and 3% before 11 years of age. The mean age at menarche was 12.7 ± 1.3 years for the patients and 12.5 ± 1.2 years for the controls, with no significant difference. For most patients (74.2%), the length of the menstrual cycle was around 27 to 28 days with 4 to 5 days of bleeding. Furthermore, 91.6% of patients with CD did not experience bleeding between the cycles, which was comparable with 94.1% of healthy controls. A total of 61.7% of patients with CD reported having painful periods, and 24% of them regularly took medication for that reason. Furthermore, 68.9% of healthy women reported having painful periods, although the difference was not statistically significant. A total of 42.7% of patients with CD reported a negative impact of menstruation on their everyday life, which was comparable with 47.5% of the healthy controls. In addition, only 3.5% of patients with CD were treated for amenorrhea, which was comparable with 5.0% of healthy controls.

Discussion

When CD is undiagnosed and untreated, patients are exposed to the risk of long-term complications such as cancer, osteoporosis, and reproductive disorders.[16–20] In older children and adults, the symptoms of CD tend to be less severe and more atypical, and the disease is diagnosed later in life. Accordingly, many studies have shown the connection between CD and disorders of fertility in women, such as late menarche, early menopause, amenorrhea, infertility, and pregnancy complications.[10,19–21] For this reason, these researchers recommended routine screening for CD in women with otherwise unexplained infertility. However, results of different studies are conflicting. A cohort study by Tata et al. included 1521 women with a recorded diagnosis of CD in the United Kingdom from 1987 to 2002.[22] The results showed that women with CD have fertility similar to that of healthy women but become pregnant at an older age. The slightly higher risk of cesarean sections and miscarriage in this study population compared with healthy women was subsequently attributed to the age of women with CD and not the disease itself.[22]

Another common problem among women with CD is dysfunctional uterine bleeding, which is defined as abnormal uterine bleeding in the absence of organic disease, complications of pregnancy, or systemic disease.[23] In a study by Ehsani-Ardakani et al.,[23] women with untreated CD were at higher risk of dysfunctional uterine bleeding than healthy women. The authors also found that introduction of a GFD might have a beneficial effect on lowering the risk of dysfunctional uterine bleeding in women with CD.

The pathogenesis behind delayed menarche and reproductive disorders as a consequence of CD is still subject of research and has not yet been clarified. The pathogenetic mechanism most probably involves malabsorption due to atrophy of villous structures in the small intestine, leading to anemia and deficiencies of nutrients such as zinc, selenium, and folic acid.[20] CD can also cause selective malabsorption of micronutrients (e.g., iron or folic acid) that are

essential for the metabolism of carrier or receptor proteins for sex hormones.[4,5,24] Furthermore, deficiencies of different trace elements can lead to ovarian dysfunction.[4,5,24] Encouragingly, improvement of CD after the introduction of a GFD will result in restoration of the small bowel mucosa and consequently may lower miscarriage rates and improve fetal nutritional support and overall perinatal outcomes.[4,5,21] Another hypothesis behind the increased incidence of gynecological disorders in patients with CD includes immune-mediated mechanisms based on increased levels of serum autoantibodies, especially anti-TG antibodies.[20]

The onset of menarche is an important milestone in the female reproductive cycle.[14] Since the 19th century, the age at menarche in Europe has decreased at a rate of 2 to 3 months per decade; however, it has now stabilized at an age of 12.5 years.[25,26] The onset of menarche has been established as both a footprint for chronic disease risk and a compass for healthy development. An earlier age at menarche is linked to a higher risk of breast cancer, depression, cardiovascular disease, and metabolic syndrome, and a later age at menarche is associated with depression, fractures, and lower bone mineral density.[27] Risk factors for age at menarche include growth patterns, body composition, diet, energy expenditure, and the presence of chronic disease.[28,29]

Fergusson et al.[29] conducted one of the first studies to investigate reproductive health in women with CD. They assessed 54 patients on a normal diet and 20 patients on a GFD and found that the onset of menarche was significantly delayed in untreated patients with CD.[29] Furthermore, menopause occurred earlier in such patients.[30] Similarly, in the study by Rujner,[11] the onset of menarche among 59 girls with CD was significantly later in untreated girls than in those on a GFD. A study by Hassan et al.[30] also showed a later onset of menarche in women with CD, often after 16 years of age (64.1%).

In 2004, a study by Kotze[31] showed that the degree of malnutrition is an important factor that variably impacts menstrual dysfunction in patients with CD. Accordingly, later onset of menarche occurred in women with moderate malnutrition than in those without malnutrition or with only mild malnutrition. The author also found that delayed menarche frequently occurred in patients with untreated CD and not in patients with CD who were on a GFD.[31]

Interestingly, most (71.7%) of our patients with CD were untreated during the years when menarche normally occurs, which is 11 to 15 years according to data reported by the National Health Survey in Slovenia and other European countries.[22,31] The present study showed that the average age at menarche among women with CD was 12.7 years, which was comparable with that among healthy women (12.5 years). Based on our results, we can assume that the age at menarche is not frequently delayed in patients with untreated CD. This is in accordance with the study by Sferlazzas et al.,[12] although other studies have shown that the probability of menarchal retardation is higher. We cannot conclude that there is a direct protective effect of a GFD but can speculate that the nutrition of adolescents in Slovenia is well balanced and that malnutrition does not occur, at least not in a serious form that could result in delayed onset of menarche.

In conclusion, considering that age at menarche is often reported to be delayed in patients with chronic diseases, our findings are encouraging in that they suggest that the age at menarche in patients with CD in Slovenia is not delayed and is comparable with that in healthy women. Similar results (i.e., no difference in the onset of menarche between patients with CD and healthy controls) were found in the study

by Sferlazzas et al.,[12] who concluded that the age at menarche is not associated with the age at diagnosis of CD and/or dietary management. Additionally, in our study population, nutrition did not have a significant impact on the onset of the menstrual cycle as indicated by the fact that healthy women and patients with CD had comparable ages at menarche. Of course, the influence of genetics cannot be overlooked in autoimmune disorders such as CD.

List of abbreviations

CD, celiac disease; GFD, gluten-free diet; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; AGA, anti-gliadin antibodies; TG, transglutaminase.

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Author's note

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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