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From menarche to menopause: the fertile life span of celiac women

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Abstract

Objective: We evaluated menopause-associated disorders and fertile life span in women with celiac disease (CD) under untreated conditions and after long-term treatment with a gluten-free diet.

Methods: The participants were 33 women with CD after menopause (untreated CD group), 25 celiac women consuming a gluten-free diet at least 10 years before menopause (treated CD group), and 45 healthy volunteers (control group). The Menopause Rating Scale questionnaire was used to gather information on menopause-associated disorders. The International Physical Activity Questionnaire was used to acquire information on physical activity.

Results: Untreated celiac women had a shorter duration of fertile life span than did the control women because of an older age of menarche and a younger age of menopause ($P < 0.01$). The scores for hot flushes, muscle/joint problems, and irritability were higher in untreated celiac women than in the control women (higher by 49.4%, 121.4%, and 58.6%, respectively; $P < 0.05$). In comparison with untreated CD, long-lasting treatment of CD was not associated with a significant difference in the duration of fertile life span, but was only associated with a significant reduction in muscle/joint problems (a reduction of 47.1%; $P < 0.05$).

Conclusions: Late menarche and early menopause causes a shorter fertile period in untreated celiac women compared with control women. A gluten-free diet that started at least 10 years before menopause prolongs the fertile life span of celiac women. The perception of intensity of hot flushes and irritability is more severe in untreated celiac women than in controls. Low physical exercise and/or poorer quality of life frequently reported by untreated celiac women might be the cause of reduced discomfort tolerance, thus increasing the subjective perception of menopausal symptoms.

Key Words: Menopause – Celiac disease – Fertile life span – Miscarriage – Preterm birth.

Celiac women have a genetic susceptibility to gluten, which turns into disease with the presence of environmental predisposing factors.[1] Women are more frequently affected and/or diagnosed than men (1:2.5).[1] The increased frequency of late menarche, miscarriage, and preterm birth is reported in untreated celiac women.[2-10] The offspring can also be affected by the presence of untreated celiac disease (CD) in mothers because low birth weight for newborns are frequent in women with CD.[11,12] Limited research data regarding the perimenopausal period are available, and, to our best knowledge, there is no study that systematically analyzed menopause in celiac women. Previous studies in the general population showed that, although the menopausal transition is part of the normal aging process, the hormonal changes occurring at this stage of life can have physical and psychological influence in women and can negatively affect quality of life.[13,14] Various tools or instruments have been designed to measure and to assess symptoms during the menopausal transition. Among them is the Menopause Rating Scale, a menopause-specific questionnaire that was developed in the early 1990s as an index of age-/menopause-related complaints.[15,16]

The aim of this study was to investigate the influence of CD on menopause and on the fertile life span. The first set of analyses focused on untreated CD through a comparison between women with CD diagnosis after menopause and healthy postmenopausal women. The second set of analyses focused on the effects of CD treatment with a gluten-free diet (GFD) through a comparison between women with CD diagnosis after menopause and celiac women with menopause after receiving long-lasting treatment.

METHODS

Participants

The study is a cross-sectional analysis of data collected in postmenopausal women defined as women without menses for at least 12 months according to the Stages of Reproductive Aging Workshop.[17] Three groups were studied: the untreated CD group, the treated CD group, and the control group.

The untreated CD group was made up of women in whom the CD diagnosis was made after the menopausal transition.

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These women were enrolled in the study at the time of CD diagnosis. Therefore, they were never treated for CD during the fertile life span. The treated CD group was composed of women in whom menopause occurred after at least 10 years of effective treatment of CD. These chronically treated celiac women were enrolled in the study at the time of menopause, that is, after the completion of a 12-month period without menses. Therefore, these women were regularly treated for CD for at least the last 10 years of the fertile life span. Untreated and treated celiac women were selected among the outpatients of the university clinic. The control group was made up of healthy postmenopausal women. They were either employees of the university staff or friends of the celiac women, and the volunteers were chosen to match the age and level of education of the celiac women.

The diagnosis of CD was made using standardized methods that included small bowel biopsy and search for CD-specific serum antibodies (antiendomysium and antitransglutaminase antibodies).[18,19] The search for the CD-specific serum antibodies was used to exclude the presence of subclinical CD in women in the control group. The compliance and effectiveness of CD treatment through GFD was monitored in the treated CD group through yearly visits that included evaluation of the women's subjective perception of adherence to GFD and the search for serum antitransglutaminase levels.[20-22] The participants were defined as having uncontrolled CD and were excluded from the treated CD group if they had high serum antitransglutaminase due to low compliance to GFD or refractory CD. The exclusion criteria for any group were the lack of written informed consent or the presence of disorders such as hypertension, diabetes mellitus, heart disease, cancer, or drug or alcohol abuse. The protocol was approved by the ethics committee of the Federico II University of Naples, Italy, and informed consent was obtained by all participants.

Data collection

Data collection was based mainly on the administration of questionnaires at the time of enrollment into the study. The Menopause Rating Scale (MRS) questionnaire was used for the assessment of menopause-related symptoms.[15,23] The MRS questionnaire is a self-administered instrument and includes a total of 11 items divided into three subscales: somatic, psychological, and urogenital. The somatic subscale includes four items: hot flushes, heart discomfort/palpitation, sleeping problems, and muscle/joint problems. The psychological subscale includes four items: depressive mood, irritability, anxiety, and physical or mental exhaustion. The urogenital subscale includes three items: sexual problems, bladder problems, and dryness of the vagina. Each one of these 11 items can be graded from 0 to 4 (0, absent; 1, mild; 2, moderate; 3, severe; 4, very severe). The subscale score is calculated as the sum of the scores of the items of the specific subscale. The total MRS score is calculated as the sum of the three subscale scores.[24] A short version of the International Physical Activity Questionnaire (IPAQ) was administered for the assessment of habitual physical activity at the time of the menopausal transition.[25] Physical activity is known to influence the perception of physical self and also to report menopause-related symptoms.[26,27] The IPAQ estimates the frequency and the intensity of physical activity, including activities at home, during transportation, at work, and during leisure time. The IPAQ questionnaire was used to define physical activity as low, moderate, or high (with numerical values of 1, 2, and 3, respectively).[28]

Information about the fertile life span was collected using a standardized questionnaire that was administered by a physician. Data collection included the age of menopause and the age of menarche for the calculation of fertile life span, number of pregnancies, number of miscarriages, and number of preterm births. Moreover, with a specific focus on the last 10 years before menopause, the questionnaire also collected information on the use of contraceptive pills; the presence of dysmenorrhea (yes/no) and, if present, its intensity using a visual analog scale (from 0 to 10); the use of analgesics for dysmenorrhea; the habitual rhythm of menses; and the habitual intensity of menses. Alcohol intake and smoking habits affect the perception of dysmenorrhea.[29,30] Therefore, information was also collected on habitual alcohol intake (yes/no) and smoking habits (yes/no and number of cigarettes per day) in the last 10 years before menopause.

Weight and height were measured at the time of the enrollment into the study for the calculation of body mass index (BMI = weight [in kilograms]/height squared [in square meters]). Information on the level of education assessed as school degree was collected.

Statistics

Data are expressed as mean (SD) and prevalence. χ^2 test and analysis of variance (ANOVA) were used to compare categorical and continuous data, respectively. The significance level was set at 0.05. Statistical significance after correction for multiple comparisons was evaluated using the Bonferroni correction (0.05/number of comparisons). The statistical program used was SPSS version 12.0 for Windows.

RESULTS

Descriptive statistics

Table 1 reports the descriptive statistics in the three groups upon enrollment into the study, that is, upon the administration of questionnaires. Women with treated CD had a significant lower age at study enrollment than did the women from other groups. The age of diagnosis in this group was 31.1 (10.1) years, and the duration of CD treatment ranged from 10 to 35 years. The differences among the groups were also statistically significant for BMI, the prevalence of alcohol drinkers, and habitual physical activity, which were lower in the untreated CD and treated CD groups than in the control group. The differences were not significant for education and indices of smoking habits.

CD and menopause

Table 2 shows the data on menopause and associated disorders. In comparison with no CD (control group), untreated

TABLE 1. *Descriptive statistics for age at enrollment in the study (ie, at administration of questionnaires), education, BMI, smoking, alcohol intake, and physical activity*

	Control group	Untreated CD group	Treated CD group	P^a
No. of women	45	33	25	
Age, mean (SD), y	59.04 (8.13)	61.18 (7.46)	49.76 (2.47)	0.001
Women with high school degree, %	40	48.5	48	0.70
BMI, mean (SD), kg/m^2	24.50 (3.30)	21.06 (3.03)	22.52 (3.25)	<0.001
Percentage of smokers	20.5	24.2	40	0.197
No. of cigarettes/day among smokers, mean (SD)	12.9 (11.6)	13.3 (8.01)	11.30 (6.68)	0.87
Percentage of alcohol drinkers	27.3	15.2	4.0	0.046
Physical activity (IPAQ score), mean (SD)	1.49 (0.66)	1.1 6 (0.37)	1.20 (0.41)	0.013

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; CD, celiac disease; ANOVA, analysis of variance.
[a] P values were computed using ANOVA or χ^2 among the three groups.

CD was associated with a significant elevation only in the scores for hot flushes (an elevation of 49.4%), muscle/joint problems (121.4%), and irritability (58.6%) but not in other items. The difference in the muscle/joint problem score was also significant with the Bonferroni correction ($P < 0.05/11$). In ANOVA with control for physical activity, the differences between women with untreated CD and controls were confirmed significant in the scores for hot flushes (adjusted means in women with untreated CD and controls, 2.48 and 1.54, respectively; $P = 0.001$), muscle/joint problems (1.56 and 0.70, respectively; $P = 0.024$), and irritability (1.71 and 1.07, respectively; $P = 0.017$). The selective elevation in only 3 of 11 items resulted in a weak, borderline significant elevation in the score of two subscales (somatic and psychological) and in the total score (Table 2).

Regarding the effects of CD treatment, data on the comparison between the untreated CD and treated CD groups indicated that long-term treatment of CD was associated with a significant reduction in muscle/joint problems (reduction of 47.1%) but not in other subscale and scale scores (Table 2). This finding was significant after correction for physical activity (adjusted means in untreated CD and treated CD groups, 1.54 and 0.81, respectively; $P = 0.024$).

CD and fertile lifespan

Table 3 shows data on the fertile life span. In comparison with no CD (control group), untreated CD was associated with a significant reduction in the duration of fertile life span (because of the combination of low age of menopause with high age of menarche). With control for alcohol intake and smoking habit, the difference was confirmed significant for age of menopause (adjusted means in women with untreated CD and controls, 47.7 and 50.4 y, respectively; $P = 0.005$) and for the duration of fertile life span (38.0 and 35.1 y, respectively; $P = 0.002$). The difference between the untreated CD and control groups in the number of pregnancies was not significant, but an index of pregnancies with poor outcome (ie, the sum of miscarriages and preterm births/number of pregnancies) was significantly higher in untreated celiac women than in control women (Table 3). The difference in the prevalence of dysmenorrhea was of borderline significance (high in the untreated CD group).

Regarding the effects of CD treatment, data about the comparison between untreated CD and treated CD groups indicated that the chronic treatment by GFD was associated with significant differences only in the age of menopause, the ratio of pregnancies with a poor outcome per pregnancy, and

TABLE 2. *CD and menopause: data about menopause-associated disorders from the MRS*

	Control group	Untreated CD group	Treated CD group
No. of women	45	33	25
Hot flushes	1.60 (1.27)	2.39 (1.52)[a]	1.80 (1.47)
Heart discomfort/palpitation	0.42 (0.92)	0.67 (1.05)	0.52 (0.96)
Sleeping problems	1.49 (1.49)	1.12 (1.34)	1.36 (1.25)
Muscle/joint problems	0.70 (0.79)	1.55 (1.18)[b]	0.82 (1.96)[c]
Somatic subscale score	4.80 (2.99)	6.23 (3.84)[d]	5.05 (3.43)
Depressive mood	0.91 (1.14)	1.39 (1.56)	1.14 (1.12)
Irritability	1.11 (1.00)	1.76 (1.20)[e]	1.40 (1.00)
Anxiety	1.16 (1.20)	1.48 (1.09)	1.18 (1.01)
Physical or mental exhaustion	0.98 (0.93)	1.23 (0.92)	1.14 (0.94)
Psychological subscale score	4.18 (3.60)	5.81 (4.14)[d]	4.77 (3.32)
Sexual problems	0.76 (1.05)	1.15 (1.46)	1.61 (1.62)
Bladder problems	0.67 (0.98)	0.42 (0.83)	0.76 (1.05)
Dryness of vagina	0.93 (0.97)	1.24 (1.12)	0.88 (1.09)
Urogenital subscale score	2.27 (1.77)	2.81 (2.75)	3.22 (2.68)
Total MRS score	11.16 (6.74)	14.45 (9.20)[d]	13.04 (7.05)

Data are mean (SD) of specific scores, subscale scores and total score.
ANOVA, analysis of variance; CD, celiac disease; MRS, Menopause Rating Scale.
[a] $P < 0.05$ vs control group using ANOVA.
[b] $P < 0.001$ vs control group using ANOVA.
[c] $P < 0.05$ vs untreated CD group using ANOVA.
[d] $P < 0.10$ vs control group using ANOVA.
[e] $P < 0.01$ vs control group using ANOVA.

TABLE 3. *CD and fertile life span: data about the fertile life span*

	Control group	Untreated CD group	Treated CD group
No. of women	45	33	25
Age of menarche, mean (SD), y	12.36 (1.32)	12.70 (1.55)[c]	13.32 (1.43)
Age of menopause, mean (SD), y	50.42 (3.82)	47.73 (3.99)[d]	49.76 (2.47)[f]
Length of fertile life span, mean (SD), y	38.06 (3.61)	35.03 (4.18)[c]	36.32 (3.36)
Pregnancies,[a] mean (SD)	2.66 (1.54)	2.85 (1.80)	2.48 (1.64)
Preterm birth/pregnancy, mean (SD)	0.05 (02)	0.08 (02)	0.07 (0.2)
Miscarriages/pregnancy, mean (SD)	0.08 (0.15)	0.15 (0.23)	0.19 (0.24)
Sum of preterm birth and miscarriages/pregnancy, mean (SD)	0.32 (0.6)	0.85 (1.5)[d]	0.80 (1.2)[e]
Women with regular menstrual rhythm, %	70.5	81.8	80
Women with menses of normal intensity of blood loss, %	73.3	78.8	72
Women with dysmenorrhea, %	29.9	48.5[e]	20[f]
Intensity of dysmenorrhea[b] (visual analog scale), mean (SD)	5.79 (3.40)	6.06 (3.43)	7.25 (2.21)
Women using analgesic drugs for dysmenorrhea, %	61.5	37.5	14.3
Contraception, %	20	15.2	8
Hormone therapy, %	8.9	9.1	20

CD, celiac disease; ANOVA, analysis of variance.
[a]Data are from women reporting pregnancies.
[b]Data are from women reporting dysmenorrhea.
[c]$P < 0.001$ vs control group using ANOVA.
[d]$P < 0.01$ vs control group using ANOVA.
[e]$P < 0.05$ vs control group using ANOVA.
[f]$P < 0.05$ vs untreated CD group using ANOVA.

the prevalence of dysmenorrhea. The difference in age of menopause was significant also in ANOVA with control for alcohol intake and smoking habits (adjusted means in untreated CD and treated CD groups, 47.7 and 49.8 y, respectively; $P = 0.02$). The ratio of pregnancies with poor outcome per pregnancy and the prevalence of dysmenorrhea were lower in the treated CD than in the untreated CD group.

DISCUSSION

The main finding of the present study is that fertile life span is shorter in untreated celiac women than in control women because of the combination of late menarche and early menopause. In celiac women, CD diagnosis and subsequent treatment with GFD at least 10 years before menopause seem to delay the onset of menopause. Untreated and treated celiac women report low physical exercise and, before GFD, an increased perception of some menopause-associated disorders in comparison with control women. Our study reveals that, in untreated celiac women, the early onset of menopause is not related to drinking or smoking habits and that the period of life deprived of estrogens is longer in untreated celiac women than in control women. The observed reduced length of fertile life span of celiac women due to late menarche and early menopause may be related to altered hormonal levels. The levels of follicle-stimulating hormone or other clinical records were not available for most of the women; therefore, we cannot exclude hypothalamic amenorrhea at the time of menarche or menopause with absolute certainty, although for the latter, the age of the women is not suggestive of hypothalamic amenorrhea.[31] GFD seems to lengthen the fertile life span of treated celiac women, becoming similar to that of control women. This datum indicates that dietetic treatment may be efficacious in reporting the hormones to normal level by ameliorating the nutritional and/or the inflammatory status.

Another new finding of our study is that, at menopause in untreated celiac women, the subjective perception of intensity of muscle/joint problems, hot flushes and irritability is significantly more severe than in control women. Physical activity can influence the menopause-related symptoms through its effects on the perception of physical self.[27,28] Data from the present study show that the IPAQ score of the untreated CD group was lower than that of the control group, indicating low physical exercise. One possible explanation is that the chronic fatigue frequently experienced by celiac women before the diagnosis[32] could play a role. The treated CD group reported an IPAQ score similar to that of the control group; this could be related to the fact that GFD positively affects the perception of physical self of celiac women, who "discover" a well-being never experienced before. The present study collected information on the characteristics of menses, its symptoms, and pregnancy outcomes in celiac women. Although the frequency of dysmenorrhea was higher in untreated celiac women than in control women and the intensity of pain is similar, the control women reported a more frequent usage of drugs for menstrual pain than did the celiac women. This may be due not only to the reticence of celiac women to take drugs if not strictly necessary but also to the recall bias of the untreated celiac women because they reported symptoms and drug intake while still having menses, at least 10 years before. In our series, smoking and drinking habits were analyzed as known causes of dysmenorrhea.[29,30] Although the control women reported greater alcohol consumption, they showed a lower frequency of dysmenorrhea compared with the untreated celiac women. The analysis of pregnancy outcomes showed that the number of miscarriages and preterm births taken together in untreated celiac women was significantly higher than in control women, as already reported.[2-10] When the comparison for this datum was performed between the untreated and treated CD groups, no differences between the groups were found. It is possible

that, in treated celiac women, because of the late diagnosis (ie, after the proliferative years), GFD may be sufficiently effective in prolonging the length of the fertile period but scarce to determine any effect on the reproductive outcomes of celiac women. The hypothesis made is that the lower BMI of untreated celiac women compared with controls at the moment of menopause indicates less adipose tissue implicated in the creation of sexual hormones; on the other hand, in treated celiac women, BMI at menopause was also lower than in control women. Another possibility is that the reduced physical exercise and/or the poorer quality of life frequently reported by celiac women not yet treated with GFD[33] might reduce the tolerance and increase the subjective perception of perimenopausal symptoms and also be the cause of muscle/joint problems. And yet another possibility is that arthritis reported in CD[34] may play a role in the increased muscle/joint problems. Previous studies differently addressed the fertile life span of celiac women.[2-12] The pathogenesis of the alterations of reproductive aspects in celiac women is still unknown.[10] The hypothesis is that the lack of macro/micronutrients (ie, zinc, selenium, and folic acid)[35,36] and/or autoimmunity may play a role in late menarche. The enzyme transglutaminase is involved in different functions such as the assembling of extracellular matrix, the cellular adhesion, and migration[37]; the presence of maternal antitransglutaminase antibodies may exert an adverse effect on the placenta, both in nutrient transport and in decidualization, besides having a negative effect on fetal growth[38,39] and therefore influence pregnancy outcome. Autoimmunity, inflammation, and low BMI may be associated with early menopause.

To the best of our knowledge, the present study is the first that investigates a group of women who received the diagnosis of CD after menopause, thus describing the natural history of the fertile life span of undiagnosed celiac women.

Some limitations of the study are that untreated celiac women were asked to answer a self-administered questionnaire on their fertile life when they were already in menopause and that, in most cases, we could not check their answers against medical records. The finding of an early age of menopause in untreated celiac women is in keeping with previous studies.[10]

CONCLUSIONS

This study indicates that the fertile life span of untreated celiac women is shorter than that of control women because of late menarche and early menopause. GFD started at least 10 years before menopause delays the onset of menopause. Therefore, an early diagnosis of CD can lengthen the fertile life span, delaying the onset of menopause. This study also indicates that, in celiac women, as in the general population, the menopausal period is critical for its aftermath on social and private life, with a reduction in the quality of life[40,41] because of the increased perception of menopause-associated symptoms. Life expectancy is increasing in the general population, especially in women, and therefore, the life span after menopause is longer at present than in the past. This is also true for treated celiac women, and our study suggests that researchers and practitioners should incorporate strategies that help enhance the physical self-perceptions of celiac women and optimize menopausal symptom management as a way of maximizing improvements in the quality of life. A definite evaluation of the effect of a strict adherence to a GFD started before the menarche on the characteristics of fertile lifespan and particularly on pregnancy's outcomes and menopause will be feasible when the large number of children diagnosed in the past years with celiac disease will reach menopausal age and complete their fertile age.

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