BRIEF COMMUNICATION

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Reproductive aspects in Brazilian celiac women

Lorete Maria da Silva **KOTZE**[1], Andyara **MALLMANN**[1], Rebeca C **MIECZNIKOWSKI**[1], Kadija Rahal **CHRISOSTOMO**[2], Luiz Roberto **KOTZE**[1] and Renato **NISIHARA**[1,2,3]

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ABSTRACT – **Background** – Celiac disease (CD) is a chronic enteropathy in response to ingestion of gluten. CD was associated with gynecological disorders. **Objective** – In this retrospective study, we aimed to investigate the age of menarche, age of menopause, number of pregnancies and abortions in Brazilian celiac patients. **Methods** – We studied 214 women diagnosed with CD and as control group 286 women were investigated. **Results** – Regarding the mean age of menarche, a significant difference was found (12.6±1.40 in CD and 12.8±1.22 years in healthy group; *P*=0.04). Regarding abortions, in CD women 38/214 (17.8%) and 28/286 (9.8%) in the control group reported abortion (*P*=0.0092, OR:1.98; CI95%=1.1– 3.3). There was no significant difference in the mean age of menopause nor number of pregnancies per woman. **Conclusion** – In this study, we found that celiac women had a higher mean age of menarche and higher risk of spontaneous abortions.

HEADINGS – Celiac disease. Spontaneous abortion. Menarche.

INTRODUCTION

Celiac disease (CD) is a chronic enteropathy, characterized by permanent gluten intolerance in genetically predisposed people[1,2]. The disease affects about 1% of the world's population with a predominance of young adults[3,4]. To date, the only treatment is the strict gluten-free diet, which should be implemented only after laboratory confirmation of diagnosis[5,6]. Since 1970s, studies began to associate CD with gynecological disorders such as: infertility, complications in pregnancy, late menarche, early menopause, recurrent spontaneous abortions, prematurity and children with low birth weight[7]. Other studies suggest that CD may continue as a possible cause of these gynecological disorders[6-9].

In this study, we aimed to investigate the age of menarche, age of menopause, number of pregnancies and abortions in patients diagnosed with CD.

METHODS

This study has retrospective design and was approved by the ethics committee of the institution. We included women older than 18 years, with CD confirmed diagnosis and followed by at least five years. This study was performed at a single gastroenterology clinic in Curitiba, between January 2000 and December 2017.

All patients included in this study were diagnosed with CD based on clinical complaints, positive screening with autoantibodies and confirmation by histological findings of the duodenal mucosa[3].

A comparison group attended a gynecology clinic in Curitiba and were registered in a database. This group was composed by healthy women, of same geographic area and socio-economic status and with ages paired with the study group.

The following data were collected in the medical records: age of menarche and menopause, number of pregnancies and abortions. Patients with other diseases that might interfere with the fertility or chronic inflammatory diseases were excluded.

Data was collected in frequency and contingency tables. Comparison studies were done by Fisher and chi squared tests when data was nominal and unpaired t test when numerical, using Graph Pad Prism 5.0 A $P<0.05$ was considered statistically significant.

RESULTS

We included 214 patients with CD with mean age of 38.5±12.81 years (between 18 and 72 years). In control group, 286 patients were investigated with mean age 38.6±11.63 years (between 18 and 79 years).

Clinical data on patients with CD and the control group were available in TABLE 1. Regarding abortions, 38 (17.8%) celiac patients reported abortions, ranging from 1 to 5 abortions per woman. In the control group, 28 (9.8%) women reported abortion, ranging from 1 to 3 abortions per woman (*P*=0.0092, OR:1.98 CI 95%: 1.1–3.3).

TABLE 1. Clinical data from celiac patients and healthy controls studied.

	Healthy controls n=286	Celiac patients n=214	*P*
Mean age of menarche (years ± SD)	12.6±1.40	12.8±1.22	0.04
Mean age menopause (years ± SD)	49.0±1.56	48.3±1.82	0.37
Number of pregnancies (mean)	1.2	1.3	0.37
Percentage of women with abortion	9.8%	17.8%	0.0092*

*OR: 1.98; CI 95% = 1.1–3.3. SD: standard deviation.

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[1] Universidade Federal do Paraná, Hospital de Clínicas, Curitiba, PR, Brasil. [2] Faculdade Evangélica Mackenzie do Paraná, Departamento de Medicina, Curitiba, PR, Brasil. [3] Universidade Positivo, Departamento de Medicina, Curitiba, PR, Brasil.
Corresponding author: Prof. Dr. Renato Nisihara. E-mail: renatonisihara@gmail.com

DISCUSSION

Our study evaluated gynecological and reproductive aspects in celiac women from Southern region of Brazil, evidencing that the CD influenced significantly the age of the menarche and the number of spontaneous abortions. The greatest strength of the study is the large casuistic studied and the fact that the data collected evaluated a long period of follow-up.

The mean age of celiac patients was about 40 years, ranging from 18 to 70 years. Therefore, it was possible to include several age groups of adult women, being possible to evaluate stages of reproductive life, such as menarche, pregnancy and for some menopause. Currently, menarche occurs on average at 12.65 ±2 years, termed late after 16 years[10]. Menopause is the last menstrual period after 12 months of amenorrhea, due to the progressive loss of the capacity of the ovary to produce hormones and to promote ovulatory cycles, it occurs on average at 50 years and is called precocious before age 40[11]. In our study, there was a significant delay in the age of menarche in celiac patients in relation to the control group, which is similar to the results observed by Santonicola et al. (2011)[9] and Sher and Mayberry (1996)[12]. There is few information in the literature that attempts to explain this finding, but may be a change in hormone levels[9], possible zinc and selenium deficiency affects the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), modifying the hypothalamic-pituitary-ovarian axis[13], causing the delay in menarche. Conflicting data were found by the study Sferlazzas et al. (2008)[14], where the authors suggest that menarche delay is not related to the lack of treatment of CD and that it is influenced by the age of the maternal menarche.

Regarding the number of spontaneous abortions, in our study the frequency of this finding was significantly higher in celiac patients when compared to the control group. Tersigni et al. (2014)[7] suggest that nutritional deficits are the main cause of gynecological disorders and adverse outcomes of pregnancy in CD. Other authors have reported that, in addition to anemia caused by atrophy of intestinal villi, there is low absorption of zinc, selenium, and folic acid[15,16]. The decrease in the absorption of these elements influences the regulation of the hypothalamic-pituitary-ovary axis, affecting pregnancy maintenance and fetal development[8]. On the other hand, it is observed that the clinical manifestations of patients with CD have changed in recent years. Previously frequently, in the first consultation, the patient presented with a severe deficit due lower intestinal absorption. Currently, the patients usually presented oligosymptomatic clinical condition. Therefore, it is not possible to explain gynecological disorders present in celiac patients based only by absorption deficit, as already suggested by other authors[14]. In recent years, new immunopathogenic mechanisms that may influence the fetal and placental development of celiac women have been investigated[7]. The gluten intake by celiac patient increases the levels of serum autoantibodies against tissue transglutaminase. Some authors have investigated the relationship between the presence of these antibodies and alterations in the female reproductive system[7,17]. Tissue transglutaminase is expressed in endometrial cells, as well as in stromal and trophoblastic placenta cells, it is possible that there is binding of circulating anti-transglutaminase antibodies in the syncytiotrophoblast cells, inducing their apoptosis[7,18]. Endometrial angiogenesis, decidualization and trophoblastic invasion are necessary for successful implantation and pregnancy outcome.

A meta-analysis study showed that patients with infertility of unknown causes or recurrent abortions are six times more frequently in CD than general population[7]. It is important to value the symptoms such as fatigue, anemia with iron deficiency, menstrual irregularities and other findings that may suggest the diagnosis of CD. In these cases, laboratory tests are suggested to investigate CD.

This study has limitations related to a retrospective research and not allowed analysis nutritional aspects of the disease, demographic and clinical aspects adherence to restricted gluten diet, and aspects before and after diet introduction. These aspects could influence the study results.

Concluding, celiac women had a higher mean age of menarche and more spontaneous abortions. The age of menopause and the number of pregnancies in patients with CD were similar the control group.

Authors' contribution

Kotze LMS, Mallmann A: protocol/project development, data collection or management, manuscript writing/editing. Miecznikowski RC: protocol/project development, manuscript writing/editing. Chrisostomo KR, Kotze LR: data collection or management, manuscript writing/editing. Nisihara R: protocol/project development, statistics analisys, manuscript writing/editing.

Orcid

Lorete Maria da Silva Kotze: 0000-0003-2683-6132
Andyara Mallmann: 0000-0001-8232-9106
Rebeca C Miecznikowski: 0000-0002-9074-9992
Kadija Rahal Chrisostomo: 0000-0001-9845-9925
Luiz Roberto Kotze: 0000-0001-8456-4361
Renato Nisihara: 0000-0002-1234-8093.

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RESUMO – **Contexto** – A doença celíaca é uma enteropatia crônica em resposta à ingestão de glúten e já foi associada a distúrbios ginecológicos. **Objetivo** – Neste estudo retrospectivo, visamos investigar a idade da menarca, idade da menopausa, número de gestações e abortos em pacientes celíacas brasileiras. **Métodos** – Foram estudadas 214 mulheres com diagnóstico de doença celíaca e no grupo controle, 286 mulheres foram investigadas. **Resultados** – Em relação à média de idade da menarca foi encontrada diferença significativa (12,6±1,40 na doença celíaca e 12,8±1,22 anos no grupo controle; *P*=0,04). Em relação aos abortos, nas mulheres com doença celíaca 38/214 (17,8%) relataram ter tido pelo menos um abortamento espontâneo, enquanto que 28/286 (9,8%) no grupo controle relataram aborto (*P*=0,0092, OR: 1,98; IC95% = 1,1–3,3). Não houve diferença significativa na idade média da menopausa nem no número de gestações por mulher. **Conclusão** – Neste estudo, constatamos que as mulheres celíacas apresentaram maior idade média de menarca e maior risco de abortos espontâneos.

DESCRITORES – Doença celíaca. Aborto espontâneo. Menarca.

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