

# Puerperium and celiac disease: how to explain this association

## Abstract

**Introduction:** Celiac disease (CD) is defined as an immune-mediated disease consequent to the sensitivity to gluten ingestion and related proteins in genetically predisposed individuals.

**Objective:** Report the case of a young patient with CD during puerperium with a previous history of abortion.

**Method:** Data were collected in clinical history, physical examination and medical records, in addition to conclusive tests for a diagnostic definition.

**Case report:** A female patient presented chronic diarrhea from the 15th day after delivery for five months. It progressed to weight loss and vomiting. She was diagnosed with CD through serologic test and biopsy of the duodenum and terminal ileum.

**Discussion:** The exposure to gluten results in inflammatory injuries of the intestinal mucosa, triggering atrophy of the villi and malabsorption syndrome. Some patients develop a latent form of CD, which was the case of this study's patient, whose disease was developed in early pregnancy and was activated in the puerperium. Pregnancy is a significant factor in the unmasking of latent CD. CD is also associated with gynecological and obstetric disorders and the failure to recognize the disease has been associated with a worse outcome for the fetus.

**Conclusion:** Thus, it is important to list the undiagnosed CD as a relevant factor to preconception counseling under the title of unrecognized or pre-existing medical conditions. This case and others suggest that pregnancy and Puerperium should be added to the list of CD trigger factors.

**Keywords:** celiac disease, latent celiac disease, pregnancy, puerperium

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**Abbreviations:** CD, celiac disease; HULW, university hospital lauro wanderley

## Introduction

Celiac disease (CD) is defined as an immune-mediated disorder. It is related to the ingestion of gluten and proteins by genetically predisposed individuals. It is characterized by a variable combination of high contents of specific autoantibodies, inflammatory enteropathy with varying degrees of gravity and a wide range of gastrointestinal and/or systemic complaints.<sup>1</sup> Among gastrointestinal complaints, the most common are chronic diarrhea, abdominal pain and distension, vomiting, malnutrition and weight loss.<sup>1</sup> The extra-intestinal manifestations are becoming increasingly common and include dermatitis herpetiformis, enamel hypoplasia, recurrent oral thrush, anemia, osteoporosis, arthritis, neurological disorders, unexplained elevated transaminase levels and female infertility.<sup>2</sup> This enteropathy may occur at any age and it affects children and adults. It has a prevalence of about 1% in the general population, thus representing the most common genetic-based food intolerance in the world.<sup>2</sup> Celiac disease has been associated with systemic complications, including pregnancy complications such as infertility, premature birth and pre-eclampsia.<sup>3</sup> Several studies have shown a relation between CD and fertility disorders or disorders during pregnancy and puerperium. Thus, it may be considered as one of the potential causes of infertility problems.<sup>4-7</sup> Some reports indicate a 4-8% prevalence of CD in women with unexplained infertility.<sup>8</sup> In addition, clinical

and epidemiological studies have shown that women with CD have a higher risk of miscarriage.<sup>7,9</sup> The prevalence of undiagnosed celiac disease among pregnant women is 1:80. It may occur for the first time during pregnancy or during Puerperium.<sup>5,10</sup>

## Clinical case

A female patient, 27 years old, married, oral health assistant, born and living in João Pessoa, arrived at the gastroenterology clinic of the University Hospital Lauro Wanderley (HULW) with a diarrhea complaint five months ago. Approximately at the 15th day after delivery, she reported liquefied defecation with a yellow color, foul odor and no blood or mucus in stool. She had a defecation rate of approximately 5 to 10 times per day and started vomiting for a week. Concomitantly, the patient had abdominal distention and asthenia. She denied having fever, nausea and abdominal pain. However, she reported an 8-10 kg average weight loss over the last five months when the diarrhea had settled.

Before arriving at the University Hospital, the patient sought medical care at a Health Unit. She was treated with azithromycin and sulfamethoxazole, but without improvement. She did not report a history of similar conditions. There was not a history of smoking, drinking or drug use. She reported five previous hospitalizations due to the emergence of the condition, with a history of anemia since adolescence, two pregnancies and one abortion. She also reported a family history of breast cancer.

At the physical examination, the patient was in a regular general condition. She was lucid, well oriented, with a normal respiration rate of 16 bpm, acyanotic, anicteric, dehydrated (+/+4) and pale (+/+4). Cardiovascular and respiratory auscultation showed no changes; the heart rate was 88 bpm. The abdomen was flat, flaccid, and painless to superficial palpation, without visceromegaly and presence of bowel sounds. Extremities were well perfused and without edema.

The initial diagnosis hypothesis was chronic diarrhea due to celiac disease with an etiology basis. Therefore, the patient was sent to the hospital to establish the diagnosis and the clinical management. Laboratory tests showed altered coagulation tests, with an extended prothrombin time (27.8 seconds) and a reduced prothrombin activity (28.4% and a2.12 INR). She had AST and ALT slightly increased, 116 U/L and 84 U/L, respectively, a GAMA-GT of 45 and 143 of alkaline phosphatase.

The serology for celiac disease showed positive anti-gliadin IgG (>192) and IgM (>187), anti-endomysium IgG and IgM reagents, and positive IgG and IgA anti-transglutaminase. The serology suggested celiac disease. To assess tissue injury, an endoscopy was performed, showing no change. A colonoscopy showed the terminal ileum with micronodules and an apparent villous hypotrophy. A biopsy of both the terminal ileum region and the duodenum was performed. Its results were, respectively, chronic ileitis with mild edema and lymphoid hyperplasia in the chorion without impairment of the submucosal inflammation and no granulomas, as well as duodenal mucosa with a total villous atrophy, crypt hyperplasia and lymphocytic inflammatory infiltrate in the chorion. After confirming the diagnosis of the celiac disease, a treatment was administered to the patient. It consisted of the removal of gluten from her diet, achieving a significant improvement of diarrhea and a 17 kg weight gain after four months.

## Discussion

This study reports the case of a young patient with a previous history of abortion and one successful pregnancy, including a chronic diarrhea that started on the 15th day after delivery and that lasted five months. It gradually developed to a significant weight loss and vomiting. Then, a positive serology was found for celiac disease, in addition to a biopsy of the duodenum and the terminal ileum, confirming the diagnosis of celiac disease. The exposure to gluten results in damage to the mucosa, advancing to different stages of severity and causing atrophy of the intestinal mucosa, leading to poor digestion and malabsorption.<sup>6,11</sup> It is a multifactorial disease and, as such, it results from the interaction among genetic, environmental and immunological factors. It is being increasingly accepted that several environmental factors are related to it, among them microorganisms, the amount and time of the initial exposure to gluten, diet patterns and infections.<sup>12</sup>

The presence of gluten is a key factor, since there is no celiac disease without gluten. This disease results from the activation of cellular (mediated by T cells) and humoral (mediated by B cells) immune system responses to the exposure to the gliadin component of gluten. Thus, the current understanding is that celiac disease is an immunological disorder that is triggered by an environmental agent in genetically predisposed individuals. This genetic susceptibility is suggested by the high concordance between monozygotic twins (about 70%) and the association with HLA class II antigens: HLA DQ2 in about 90% of patients, and HLA-DQ8 in most of the remaining patients. This expression of HLA is necessary, although not sufficient, for the individual to develop the disease. The environment factor is also necessary for the development of the disease.

The presence of autoantibodies in the connective tissue around smooth muscle fibers (endomysium) is a highly specific factor for the celiac disease. The autoantigenic target contained within the endomysium is the enzyme tissue transglutaminase. This enzyme has a leading role in the pathogenesis of celiac disease due to the deamination of gliadin resulting in a great specific proliferative response of T cells and contributing to the inflammation of the mucosa and the subsequent activation of B cells with HLA DQ2 or DQ8.

Celiac disease is the result of the dysregulation of the innate and adaptive immune system. The innate immune system uses standard recognition receptors (DNA, RNA, lipopolysaccharide or viral proteins) to provide a first response to stimuli, in contrast to the adaptive immune system, which depends on the presence of the HLA antigen. In the celiac disease, gluten peptides have been implicated as triggers of innate immune responses in the intestinal epithelium and mononuclear cells. The activation of the adaptive immune system implies that gliadin (a toxic component of gluten) crosses the intestinal epithelium. Thus, the increased intestinal permeability is an early event in the pathogenesis of the disease.

The resulting impact of these responses is an inflammatory condition of the small intestine that causes a profound disruption to the mucosal architecture (flattening the villi), to the infiltration of lymphocytes in the epithelium and to the increase in the density and depth of crypts. These changes occur continuously from normal villi to a slow and progressive total flattening of the villi.<sup>12</sup>

In some cases, patients have the so-called latent celiac disease, and develop symptoms later in life.<sup>11</sup> Previous studies have suggested that pregnancy is a significant factor in the unmasking of the latent celiac disease and may cause a clinical relapse or an exacerbation in already diagnosed patients.<sup>10</sup> This study's patient probably had a silent CD that appeared with early pregnancy, and was active in the postpartum period. Although the reasons for the effect of pregnancy on the course of the disease are not yet entirely clear, a relation with extreme variations in the levels of female hormones, particularly prolactin, has been suggested.<sup>10,13</sup> During the puerperium, this hormone may play a role in the activation of subclinical CD. Another speculation is that the disease may result from maternal exposure to fetal antigens.<sup>14-18</sup>

Several studies have shown an association between CD and fertility disorders or pregnancy and puerperal disorders.<sup>5,7,19</sup> In the case of undiagnosed CD (as a cause of infertility) in women with a clinical sub-fertility, the prevalence is approximately 2.7-3%. The failure to recognize the disease has been associated with a worse outcome for the fetus.<sup>20,21</sup>

Moreover, studies have shown that CD is also associated with a great number of gynecological and obstetric disorders such as delayed menarche, premature menopause, intrauterine idiopathic growth restriction, gestational hypertension, placenta praevia, severe anemia, uterine hyperkinesia, recurrent miscarriage and fetal death, although this association is still very neglected in clinical practice.<sup>6,22-25</sup> It is possible that reproductive disorders are the first symptoms of the disease.<sup>26</sup>

Another study shows that the frequency of association between CD and amenorrhea is 19.4%, and the most observed disorders were oligomenorrhea, hypomenorrhea, dysmenorrhea and menorrhagia.<sup>6</sup> In contrast, a study stated that women with celiac disease have fertility levels similar to the female population in general. However, pregnancies occurred at an older age.<sup>26</sup>

The pathogenesis of reproductive disorders related to CD also awaits clarification and several hypotheses have been proposed. CD may induce malabsorption and micronutrient deficiencies such as iron, folic acid and vitamin K, which are essential to organogenesis and may therefore interfere with embryogenesis, fetal nutrition and fetal growth.<sup>22–24,26–28</sup> Furthermore, deficiencies of specific dietary elements could be involved in ovarian dysfunction.<sup>26,27</sup> Finally, it was suggested that gluten alone could explain these disorders, and malnutrition would aggravate the disease, leading to a vicious cycle.<sup>29</sup>

Thus, diagnostic procedures for celiac disease, such as serological screening, could be routinely performed in women with reproductive disorders as a potentially useful strategy to treat the disease and allow an early diagnosis in cases of unrecognized CD.<sup>6</sup> However, undiagnosed CD should be listed as an important factor for pre-conception counseling under the title of unrecognized or pre-existing medical problems.<sup>30</sup> Finally, this clinical case, along with other previous studies,<sup>14–18,31–35</sup> suggests that pregnancy and puerperium should be added to the list of CD triggers.

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## Conflicts of interest

The author declares there is no conflict of interest.

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