Celiac disease and endometriosis: an insidious and worrisome association hard to diagnose: a case report

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Summary

Background: Primary infertility is an unusual presentation of celiac disease (CD). When non-classical symptoms are present, the diagnosis is not easy and it becomes even more difficult when CD is associated with endometriosis, representing a diagnostic challenge for medical practitioners and gynecologists. *Case Report:* A 34-year-old patient presented to the authors' observation with primary infertility. Formerly she was treated for endometriosis and the diagnosis of CD was delayed. A favorable clinical and serological response following a gluten-free-diet (GFD) was achieved and a successful pregnancy was obtained. *Discussion:* This case report emphasizes the role of the CD in women's infertility and the possible association between CD and endometriosis. Even if the relationship between these two diseases is still unclear and further studies to address this issue are required, more attention from gynecologists is needed, considering that the later this association is diagnosed, the greater the probability of adverse outcomes of health developing.

Key words: Celiac disease; Endometriosis; Infertility; Pregnancy; Gluten-free-diet.

Introduction

Celiac disease (CD) is an immune-mediated enteropathy [1, 2] caused by the ingestion of foods containing gluten such as wheat, barley, and rye [1]. It is characterized by a damage of the small intestine with consequent micronutrient malabsorption and a wide clinical variability [1, 2]. The prevalence is estimated to be one percent in the general population [3] and it is often found in over two percent in women undergoing investigation for infertility [4], whereas other studies found that CD is about as prevalent in infertile women as in the general population [5, 6]. The disease is classically though to affect children under two years of age, but the epidemiology of CD has shifted over the years, and now the majority of patients are adults (40-50 years), with a wide array of symptoms, accounting for the high rate of missed diagnoses [7]. Besides the classical symptoms (diarrhea, abdominal pain, bloating, and weight loss) [8, 9], there are many non-specific, extra-gastrointestinal manifestations associated with CD, which do not promptly suggest to test for this disease [8], such as osteoporosis, malignancy, autoimmune disorders, infertility, recurrent abortions, and pregnancy complications (intrauterine growth retardation, low birth weight, and preterm birth) [10]. Another common cause of infertility is endometriosis, a chronic disease of the reproductive age characterized by the presence of active endometrial tissue outside the uterus and associated with various symptoms such as dysmenorrhea, dyspareunia, chronic pelvic pain, irregular bleedings, and infertility [11]. Endometriosis is found in 20% to 50% of all women with infertility and is associated with a lower pregnancy rate [12]. CD and endometriosis, when associated, may lead to difficult diagnosis due to the overlap of symptoms (abdominal pain, bowel changes, menstrual irregularities, spontaneous abortion, and infertility). To date, there are only two studies on the association between endometriosis and CD [2, 13], and further evidence is needed to definitively asses their shared pathogenesis and their possible association.

Case Report

A 34-year-old Caucasian woman presented to the authors' observation in 2010 with main compliants of primary infertility. Her clinical history revealed a normal physical and psychic development and lactose, yeast, and egg intolerance. She denied a history of smoking. She had menarche at the age of 13, her menstrual cycles were irregular since then, and had always been suffering from dysmenorrhea, dyschezia, chronic pelvic pain, and menometrorrhagia. In order to reduce the above-mentioned symptoms, she was treated with combined oral contraceptives (discontinuously administered) from 16 to 29 years of age. At the age of 29, after many years of bothersome symptoms such as constipation, bowel changes, abdominal pain, and dyschezia, which have always been attributed to irritable bowel syndrome, an ovarian cyst was detected in the left ovary with a transvaginal ultrasound during a medical examination. The ultrasound pattern of the cyst suggested endometriosis, thus Ca 125 was measured and resulted positive (83 U/ml) (normal value: < 35 U/ml). The cyst was laparoscopically removed and the histological examination of her specimen was reported as endometriosis. In the following three years, until 2008, she underwent other three laparoscopic surgeries to remove another cyst on the left ovary and some endometriotic lesions in the pelvic cavity. After each surgery she underwent six months cycle of gonadotropin-releasing hormone analogue (GnRH-a) to avoid possible relapses. Following the surgical treatments,

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she had been attempting to conceive for two years without success, and in 2010, when she came to the authors' observation, three cycles of ovarian stimulation with clomiphene and gonadotropins were performed, but the first intrauterine insemination (IUI) resulted in a spontaneous abortion. As a consequence of the failure of the assisted reproductive techniques (ART), the authors decided to perform another ovarian stimulation, but after further investigations her hemoglobin was 9.1 g/dl and the peripheral blood examination was suggestive of microcystic hypochromic anemia. In view of a history of bowel symptoms, menstrual irregularities, infertility, and the recent anemia, the authors decided to investigate the patient for CD. Her IgA tissue transglutaminase (tTG) antibodies were positive (84.57 U/ml) (normal value: < 4.0 U/ml), thus duodenal biopsies were performed and the histological examination revealed Marsh III atrophic mucosa, confirming the presence of CD. Following the diagnosis, the patient was placed on a gluten-free-diet (GFD). Three months later she was evaluated again and at that time, her hemoglobin was 12.3 g/dl and her IgA tTG levels decreased to 28.42 U/ml. The diet also led to an improvement in her celiac-related symptoms and within six months she spontaneously conceived. She had no complications during pregnancy and she delivered a healthy baby. To date, she is still on a GFD and she is continuing a careful follow-up.

Discussion

Menstrual and reproductive disorders are now known to be among the atypical symptoms of CD. These disorders include late menarche, early menopause, secondary amenorrhea [1, 9], menstrual irregularities [10], infertility, recurrent miscarriages, intrauterine growth restriction [1, 9, 10], lower birth weight of celiac women babies, and preterm birth [1, 10]. Many times patients with CD are completely asymptomatic, aside from infertility or they may have none of the symptoms classically attributed to CD. For this reason, the diagnosis on average is delayed up to ten years and many women are only diagnosed in their adulthood [10]. CD can induce malabsorption and deficiencies of micronutrients such as iron, folic acid, vitamin K, zinc, and selenium, which are essential for organogenesis and ovarian function and their deficiency may lead to celiac-associated infertility [14, 15]. The rate of menstrual and reproductive disorders is reduced with early diagnosis and treatment with a GFD [9, 10]. However, studies on the association between CD and infertility are often inconclusive and contradictory. The prevalence of CD in women undergoing investigation for infertility was often found in over two percent [4], whereas other studies found that CD was about as prevalent in infertile women as in the general population [5, 6]. Overall, it is not possible to draw any definitive conclusion on this issue and there are no guidelines for CD testing in patients with infertility or in women with a history of adverse pregnancy outcomes [10]. Nevertheless, given the likelihood that the GFD improves pregnancy and fertility outcomes and the low cost of serological screening compared with the great medical expense associated with infertility and complications of pregnancy, CD testing should be strongly considered [10], especially among women with unexplained infertility. As it is commonly known, endometriosis is associated with infertility, however, the etiology of this association is unclear, thus complicating management. Several mechanisms have been proposed to explain the endometriosis-related infertility, such as [16-18]: distorted pelvic anatomy, altered peritoneal function, altered hormonal and cell-mediated function, endocrine and ovulatory abnormalities, impaired implantation, oocyte and embryo quality, and abnormal utero-tubal transport. Some women with endometriosis will conceive without difficulties, however others may encounter a substantially longer time to conception. Several controlled trials have suggested reduced fecundity in women with endometriosis ranging from two to ten percent [19]. The impact of endometriosis on oocyte quality has been suggested by studies evaluating the donor oocytes of patients with and without endometriosis and implantation rates in recipients. Specifically, in a retrospective analysis women who received embryos from endometriotic ovaries had significantly reduced implantation rates [17]. To the authors' knowledge, there are only two studies addressing the association between endometriosis and CD. In one study, Aguiar *et al*. screened 120 women with endometriosis and 1,500 controls with CD serology followed by a small intestinal biopsy where indicated. CD was confirmed in 3/120 (2.5%) cases with endometriosis and in 10/1500 (0.66%) controls, but the difference was not statistically significant [2]. In the other study, Stephansson *et al*. found similar results and endometriosis seemed to be associated with prior CD [13]. Shared etiological factors are possible explanations for the positive association between the two diseases. Endometriosis is associated with chronic inflammation as well as CD [20] and it is possible that the two diseases share certain pathways of inflammation. Indeed, major increases in interferon-γ and interleukin-6 are seen in both CD [21] and endometriosis [22]. Moreover, CD and endometriosis are both considered immunologically mediated diseases [2]. In addition, it has been demonstrated that HLA-DQ7 is twice as common in patients with endometriosis [23], and it may also influence the risk of future CD [24]. As an alternative, assuming that there is a casual link between CD and endometriosis, a common genetic/immunologic link is more likely than a possible nutritional deficit. The association of CD and endometriosis is still unclear and represents a challenge for medical practitioners and gynecologists due to the overlap of symptoms, such as infertility, abdominal pain, constipation, diarrhea, menstrual irregularities, amenorrhea, and multiple spontaneous abortions. Furthermore, some of these conditions may be mistaken for irritable bowel syndrome, remaining misdiagnosed for years.

Conclusion

In the past, CD was considered as a solely gastrointestinal disease of infancy, whereas nowadays many patients present with the disease in adulthood and experience a wide range of non-classical symptoms, some of which are specifically relevant to women's health, such as infertility and unfavourable pregnancy outcomes. It is recommended, according to the authors' experience and on the available literature on the subject, that all women with unexplained infertility and a history of adverse pregnancy outcomes should be tested for CD. The diagnosis may be very difficult when CD is associated with endometriosis and it represents a diagnostic challenge for physicians. The presented case report sheds additional light on the role of the CD in women's infertility and on the possible association between CD and endometriosis. Even if the relationship between these two diseases is still unclear and further studies to address this issue are required, more attention from gynecologists is needed, considering that the later this association is diagnosed, the greater the probability is of adverse health outcomes to develop.

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