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Prevalence of Celiac in Fertile Women Due to Unexplained Infertility

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Abstract

Introduction: Celiac disease is an immune response to a gluten-based diet that affects the small intestines of people with a genetic predisposition to disease. Celiac has intra intestinal and extra intestinal manifestations. In recent years, celiac and infertility have been considered. The present study examines the effect of celiac disease and its treatment on the menstrual cycle, pregnancy and menopause. In this study, we compared the prevalence of celiac disease in fertile women with infertile women in Zahedan.

Materials and Methods: In this case control study, 150 patients with unexplained infertility from February 2016 to 2017 referred to Infertility Clinic of Ali ibn Abitaleb Hospital in Zahedan (Iran), were included in the study. Total IgA and IgA TTG were evaluated. If TTG is positive, for confirmation of diagnosis, biopsy is performed from the distal part of the duodenum. In control group, 150 fertile women with two or more children with the same characteristics were studied.

Results: Three patients with unexplained infertility (2%) were positive for TTG. Two of them (1/3%) were positive to celiac disease in small intestinal biopsy. None of the women in the control group had TTG positive ($p=0.49$).

Discussion and Conclusion: It seems that some infertile patients with unexplained infertility suffer from celiac disease, but with a ($p=0.49$), it seems that celiac screening as a cause of infertility with unexplained cause needs more studies with larger sample size in Iran

Keywords: Celiac disease; Infertility; Unexplained infertility

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Introduction

Celiac disease is an immune response to the gluten-containing diet that affects the small intestine of people who have the genetic potential of the disease and is eliminated by a gluten-free diet. Gluten is present in wheat and barley [1]. Celiac has intra intestinal manifestations and extra intestinal manifestations [2], classical manifestations of the disease include diarrhea, bloating, and malabsorption. Extra intestinal manifestations include herpetic dermatitis, depression, osteoporosis, osteomalacia, dental caries, diabetes, thyroid dysfunction and anemia [3,4].

In recent years, celiac and infertility have been considered. Many articles have been studied from 1966 to 2000 and have showed the effect of celiac disease and its treatment on the menstrual cycle, pregnancy and menopause, for example, untreated celiac disease will lead to abortion. In addition, the prevalence of preterm labor and low birth weight are greater in women with celiac disease [5]. These articles also showed that untreated celiac disease leads to delayed menarche, early menopause, and an increase in the incidence of amenorrhea [6,7]. Determining the

cause of infertility in the absence of other causes (male factor, tubal, ovarian and other factors) is an important challenge in fertility field. Sometimes, infertility is associated with systemic diseases of the mother or father, which affects the fertility system. A study in Europe found that celiac disease was the systemic disorder that included a significant percentage of unexplained infertility [1]. In a study conducted at Dr. Shariati Hospital of Tehran, the prevalence of celiac disease in women with unexplained infertility was 2.4% [2], as well as in study of McCann et al in 1988, prevalence of celiac disease in unexplained infertility was reported 8 percent [3].

In a study conducted by Janet M et al in the United States, the prevalence of celiac was reported 5.9% (4), and another study of Melony et al in Italy showed 3.03%. There is also evidence, has fertility in infertile women improved with gluten-free diet [6].

Measurement of anti-TGG antibodies in serological tests, HLA typing, duodenal biopsy with endoscopy and oral tolerance tests (xylose and lactose) are commonly used as diagnostic tests. Generally serological tests and biopsy of small intestine have the most accurate



diagnostic tests for Celiac disease. To diagnose this disease, assessment with serological tests is first performed, when the serologic test is positive, biopsy of small intestine should be performed to confirm the disease.

IgA Andomysial Ab (EMA) and IgA anti TTG tests among the serologic diagnostic tests of celiac disease are considered to be the most useful diagnostic tests and could be screen test with high sensitivity and specificity. Anti Andomysial antibodies (EMA) are autoantibodies which are produced against collagen matrix in human tissues.

Trans-glutaminase (TTG) is a cytosol, which provides cross-linking of various proteins of the extracellular matrix, and glyadine is the preferred substrate for it. Tissue transglutaminase is a target antigen for the production of antibodies with high sensitivity and specificity. In the case of IgA deficiency, its prevalence in celiac disease is 1.7% to 2.6%. Along with this disease, it should measure the anti-transglycemic IgG antibody. Anti-TTG antibodies are easily measurable by ELISA. Today, screening of celiac disease is suggested by anti-TTG antibodies, because EMA IgA is more expensive and more difficult. On the other hand, TTG IgA has been able to identify all cases that were false negative by EMA IgA. Antigliadin antibody has low sensitivity and specificity.

The false positive results of this test are common. Antiglyadine antibodies are found in other diseases such as cow's milk intolerance, Crohn's disease, anti-eosinophilic and also in 5 to 10% of healthy people. However nowadays, this test is not applicable for early diagnosis and screening. Although the diagnosis of Celiac disease may be based on clinical symptoms and laboratory findings, but intestinal biopsy is still introduced as a gold standard in the diagnosis process, that sampling, usually are performed from the second part of the duodenum and should be interpreted by a expert pathologist.

Material and Methods

In this case-control study, 150 patients with infertility were studied who referred to the Infertility Clinic of Ali ibnAbiTaleb Hospital in Zahedan in 2016 to 2017

Inclusion criteria for the infertile group including: age 20 -35, not having of systemic illness and abdominal or pelvic surgery history, not having of all the specific causes of infertility, regular menstrual period, duration of infertility over 2 years,

Inclusion criteria of the Fertility Group including women with the same general characteristics of the infertile group that had more than two children with NVD. After receiving informed consent, blood samples were collected from patients and examined for Total IgA and IgA TTG. If positive, confirmation of diagnosis was performed with biopsy of the distal part of the duodenum.

Results

2 out of 150 (1.3%) women with unexplained infertility had celiac

disease (positive TTG and celiac biopsy), none of the women of control group had celiac disease ($p=0.49$ chi-squaretest) (Table1). One patient with celiac disease was asymptomatic, one of whom reported bloating symptoms and intermittent diarrhea (Table 2) and total IgA was normal in the control group. Two patients with celiac disease classified according to modified marsh classification, one at stage I and one in stage II. Both patients were on a gluten-free diet and are currently in follow-up. The difference in menarche age was significant between the control and case groups ($p<0.001$) Mean age of menarche was 12.22 years in case group and was 12.12 years in control group. The mean age of the menarche in the unexplained infertility group with celiac disease was greater than unexplained infertility without celiac disease. But p value was not significant. The mean age of the menarche in the unexplained infertility group for celiac disease was 14/50 and 12/32 years for unexplained infertility without celiac disease.

Discussion

Celiac disease (an enteropathy caused by gluten sensitivity) is an autoimmune disease that is caused by inflammatory lesions of the intestinal mucosa due to contact with gluten [7]. The disease involves a wide range of clinical symptoms that including malabsorption typical syndrome or the patient may be completely asymptomatic [8], and only with complications from the disease, including early menarche, premature menopause, recurrent pregnancy loss, or unexplained infertility [9-11]. The mechanism of infertility in celiac disease is unclear, but may be due to malnutrition (iron deficiency, folate, zinc, selenium, fat-soluble vitamins for reproductive function).

In some studies, the relationship between unexplained infertility and celiac disease has been confirmed (Italian study) [5]. Unfortunately, few studies have been done in this field. In Iran, a study by Dr. Ashraf Al Yassin et al. was conducted in Dr. Shariati Hospital of Tehran in 2001 to 2002, although there was not a significant difference between the control and case groups ($P=0.08$)but it showed that a number of patients with unexplained infertility suffered from celiac disease in Iran [2].

Significant differences were found in the US study ($p=5.9$) and Italian study ($p=0.02$), but the absence of this significant difference in our study ($p=0.49$) may be related to the outbreak of celiac disease in other countries, the other reason for this difference can be from the small sample size in our study, however, in studies conducted in the above countries, the number of samples was the same ,the difference in the sensitivity of laboratory kits may be another cause of this difference. Therefore, in view of the prevalence of asymptomatic celiac disease in Iran, it seems that the screening of celiac disease as a cause of unexplained infertility requires more studies and more sample size.

Conclusion

According to this study and similar studies, it is believed

Table 1. Incidence of celiac disease among subjects.

Groups(Infertile vs fertile)	N	Age	BMI	Menarche age(SD)	Celiac Disease (Diagnosis)%	P-Value
Unexplained infertility	150	4/8 ± 27/56	25/8	Dec-80	1.30%	0.49
Fertile	150	5/1 ± 29/53	26/5	10-Dec	Zero	-

Table 2. Infertile women with unexplained cause and celiac disease.

Patients	Age	Celiac Manifestations	Menarche Age	Infertility duration	Marsh classification
1	24	+	14	4	2
2	27	-	15	5	1



that a number of patients with unexplained infertility suffer celiac disease. But the screening of celiac disease in these patients requires more extensive studies in larger sample sizes. Considering that few studies have been done in this area, it is recommended that similar studies be carried out in larger volumes in other areas.

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