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Fertility disorder associated with celiac disease in males and females: fact or fiction?

Manouchehr Khoshbaten[1], Mohammad Rostami Nejad[5], Laya Farzady[2], Nasrin Sharifi[3], Sayyed Hassan Hashemi[4] and Kamran Rostami[6]

[1]*Liver and Gastrointestinal Disease Research Center and* [2]*Department of Infertility, Alzahra University Hospital and* [3]*Health and Nutrition Faculty, Tabriz University of Medical Sciences, and* [4]*Gastroenterologist and Hepatologist, Alinasab Hospital, Tabriz, and* [5]*Research Center for Gastroenterology and Liver Diseases, Shaheed Beheshti University M.C., Tehran, Iran; and* [6]*School of Medicine, University of Birmingham, Birmingham, UK*

Abstract

Aim: The association between celiac disease and infertility is controversial in the literature. The aim of this study was to determine the prevalence of celiac disease among the couples with unexplained infertility.

Material & Methods: Serum samples from 100 Iranian couples with unexplained infertility were evaluated for celiac disease by tissue transglutaminase antibody (tTGA). Two hundred couples not reporting reproductive problems and having delivered at least one uncomplicated birth served as controls. Total immunoglobulin A (IgA) was also obtained to investigate IgA deficiency. Those with IgA deficiency were tested with IgG tTG. Those cases with positive tTGA or tTGG (IgA deficients) underwent upper gastrointestinal endoscopy.

Results: Positive results of tTGA were detected in 13 infertile subjects (6.5%, 6 males and 7 females) and 11 controls (2.8%, 4 males and 7 females) ($P = 0.027$). The odds ratio of celiac disease in unexplained infertile couples was 2.39 (95% CI: 1.15–5.01) compared with fertile couples. IgA deficiency was identified in 14 infertile cases and 11 controls. Only 5/24 tTGA-positive and 4/24 IgA-deficient infertile subjects and controls accepted to undergo duodenal mucosal biopsy. Celiac disease was confirmed by biopsy in three (1.5%) of the unexplained infertile patients.

Conclusion: The results of this study show that there is a higher seroprevalence of celiac disease in those with infertility in comparison to those with normal fertility.

Key words: celiac disease, tissue transglutaminase antibodies (tTGA), unexplained infertility.

Introduction

Celiac disease may be accompanied with several extra intestinal manifestations/complications, with an adverse reproductive outcome.[1,2] Determining the cause of unexplained infertility is a challenge in reproductive medicine. When the results of standard infertility evaluation are normal, practitioners labeled the case as unexplained infertility.[3] Some cases of unexplained infertility may be due to systemic diseases that have subtle effects on the reproductive system,[4] among which celiac disease is of utmost importance. Some studies indicated that celiac disease may account for a significant percentage of unexplained infertility.[5] However, other studies did not find any association between the two conditions.[6]

The likelihood for a causal relationship between celiac disease and reproductive problems including infertility, recurrent abortions and intrauterine growth retardation has received support in a number of reports.[7] Some reports indicated a 4 to 8% prevalence of celiac disease in women with unexplained infertility;[8,9]

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Reprint request to: Professor Manouchehr Khoshbaten, Liver and Gastrointestinal Disease Research Center, Tabriz University of Medical Sciences, 5166615556, Tabriz, Iran. Email: mkhoshbaten@yahoo.com

others suggest that treating celiac disease with a gluten-free diet can improve fecundity.[10,11] Nevertheless, robust evidence has not yet been provided. Some researchers recommend that screening for celiac disease should be routine in all couples with unexplained infertility. Culturally, infertility is a significant health problem for young couples, while referring to infertility centers have been widely increased during the recent years. However, celiac disease has not found its role as a possible cause of unexplained infertility among couples. Therefore, we have evaluated the correlation of gluten-related auto-antibodies in infertile couples and assessed in which proportion celiac disease may account for unexplained fertility disorders between men and women.

Materials

Infertile couples referred to the Infertility Department of Alzahra Hospital (Tabriz University of Medical Sciences, Tabriz, Azerbaijan) were evaluated by a standard infertility protocol between October 2006 and September 2007. Endocrine status was evaluated using serum levels of follicle-stimulating hormone, luteinizing hormone, prolactin and thyroid hormone. Ultrasound, urinary luteinizing hormone and/or luteal phase progesterone confirmed the presence or absence of ovulation. Tubal patency was assessed with hysterosalpingography. Hysteroscopy or laparoscopy was performed, when appropriate. All male partners underwent semen analysis according to the World Health Organization criteria.[12] In the case of abnormal findings in the above-mentioned investigations, couples were labeled unexplained infertility. Using this protocol, 100 unexplained infertile couples were randomly selected.

The control group consisted of 200 apparently healthy couples lacking reproductive problems with at least one child delivered and attending the hospital or gynecology offices for routine screening visits. All subjects were requested to complete a questionnaire regarding infertility duration, drugs consumption, history of diabetes, abortion, infertility treatment, chronic diarrhea, anemia, autoimmune disease, hyper- and hypothyroidism and previous diagnosed celiac disease.

Five milliliters of fasting blood was obtained, and then serum was separated and divided into two aliquots and immediately stored at –20°C. Tissue transglutaminase antibodies (tTGA) were determined by enzyme-linked immunosorbent assay with human recombinant tTGA as antigen, using a commercial kit (Eu-tTG IgA, Eurospital, Trieste, Italy). Results were considered positive when higher than 7 AU/mL. tTGA is not appropriate for IgA-deficient patients and since 2–3% of celiac population is IgA-deficient,[13] the serum IgA level should be determined before the serological tests such as tTGA. This would eliminate false-negative results. The total serum IgA level was determined as described previously.[14]

The tTGA positive and IgA deficient subjects were asked to undergo an upper gastrointestinal endoscopy. Four biopsy samples, taking from distal duodenum, were evaluated by a pathologist who was unaware of the tTG test results. Intraepithelial lymphocytes, crypt hyperplasia and villous atrophy were classified according to Marsh–Rostami criteria.[15]

Symptomatic patients with positive serology and some degrees of mucosal abnormalities have been classified as celiac disease according to most recent studies.[16] Although histology has a non-specific nature, especially in those with mild abnormality, serology has a very high positive and negative predictive value and currently those symptomatic patients with positive serology (tTG and or endomysium antibodies [EMA]) with lymphocytic enteritis (Marsh I-II) should be treated as celiac disease.

The Statistical Package for Social Science version 11.5 (SPSS Inc, Chicago, IL, USA) was used for data analysis. Chi-squared *t*-test and logistic regression analysis were used, when appropriate. *P*-values < 0.05 were considered statistically significant.

The study protocol was approved by the Ethics Committee of the Tabriz University of Medical Sciences and an informed consent was obtained from each subject.

Results

Serological screening for celiac disease based on tTGA was performed on 100 unexplained infertile couples aged 29.06 ± 6.09 years and 200 fertile couples aged 29.91 ± 9.54 years (not significant). The mean duration of infertility in study group was 5.25 ± 3.94 years (a range, 1 to 20 years).

Positive results of tTGA were detected in 13 infertile subjects (6.5%, 5 males and 8 females) and 11 control (2.8%, 4 males and 7 females). The difference was statistically significant for tTGA-positive in cases compare to the controls ($P = 0.027$). IgA deficiency was identified in 14 (7%) infertile couples (six male and eight female) and 11 (2.8%) controls (four male and seven female); however, the difference did not reach a

Table 1 Clinical characteristics of unexplained infertile patients compared with healthy fertile controls

Characteristics	Unexplained infertile patients	Control group	*P*
Number	200	400	
Age (mean ± SD§)	29.06 ± 6.09	29.91 ± 9.54	0.1†
tTGA¶ positive	13 (6 males and 7 females)	11 (4 males and 7 females)	0.027‡
IgA deficiency	14 (4 males and 10 females)	11 (4 males and 7 females)	0.15
History of chronic diarrhea	1 (0.5%)	0	0.3
History of anemia	5 (2.5%)	20 (5%)	0.14
History of hyperthyroidism	2 (1%)	1 (0.2%)	0.21
History of autoimmune disease	2 (1%)	1 (0.2%)	0.22

†Student's *t*-test. ‡χ^2 test. §Standard deviation. ¶tTG, tissue transglutaminase. IgA, immunoglobulin A; SD, standard deviation.

Table 2 Tissue-transglutaminase antibodies, IgA deficiency and histological aspects in infertile patients underwent duodenal mucosal biopsy

Case	Gender (male/female)	Clinical symptoms	tTGA	IgA deficiency	tTGG	Histological aspects	Endocrine status			
							FSH	LH	PL	TH
1	Female	Bloating	Positive	Negative	–	Marsh IIIb	2.6	8.1	12.6	2.2
2	Male	None	Positive	Negative	–	Normal	–	–	–	–
3	Female	Constipation	Positive	Negative	–	Normal	1.2	18.9	19.8	0.7
4	Male	Abdominal pain	Positive	Negative	–	Marsh I	–	–	–	–
5	Female	None	Positive	Negative	–	Normal	7.2	4.6	9.4	0.4
6	Female	None	Negative	Positive	–	Normal	4.8	10.2	8	0.3
7	Female	Abdominal pain	Negative	Positive	Positive	Marsh I	5.4	8.2	16.4	0.9
8	Female	Abdominal pain, weight loss	Negative	Positive	Positive	Marsh I	3.7	8.5	10.8	3.1
9	Female	None	Negative	Positive	Positive	Normal	6.7	9.2	17.3	1.3

IgA, immunoglobulin A; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PL, prolactin; TH, thyroid hormone; tTGA, tissue transglutaminase immunoglobulin A; tTGG, tissue transglutaminase immunoglobulin G.

statistically significant level. Three of 14 infertile cases (three females) with IgA deficiency and three of 11 controls (two females and one male) were serologically positive for tissue transglutaminase IgG (tTGG). The odds ratio of celiac disease in unexplained infertile couples was 2.39 (95% CI: 1.15–5.01) when compared with fertile couples based on serological screening adjusted for age. There was no significant association between positive tTGA results and gender in either case or control group.

Table 1 represents results of serologic screening together with age and extra intestinal manifestations of celiac disease in cases and controls.

Totally, five tTGA-positive and four IgA-deficient cases underwent duodenal mucosal biopsy (three tTGA-positive and two IgA-deficient belonged to infertile patients and two tTGA-positive and two IgA-deficient patients were from control group). Due to no remarkable clinical presentation, the rest of seropositive patients were unwilling to undergo duodenal mucosal biopsy. The biopsy samples revealed Marsh IIIb in one of tTGA-positive and Marsh I in two IgA-deficient subjects in infertile patients and Marsh I in one tTGA positive subjects in control group (Table 2). Therefore, celiac disease was suggested by biopsy and auto-antibodies test in three (1.5%) cases of unexplained infertility compared to one (0.25%) in control group. All infertile celiac disease patients were female compared with those in control group who were male.

Discussion

In the present study, the frequency of celiac disease autoantibodies among unexplained infertile patients serologically was 8% (13 tTGA+ and 3 tTGG+) which was significantly higher than controls (3.5%, 11 tTGA+ and 3 tTGG+). Furthermore, the likelihood of celiac disease in infertile patients was 2.39 times higher than controls. We used tTGA for screening which is a highly sensitive and specific serological marker.[17]

Similarly, an increased prevalence of celiac disease in infertile patients has been reported in previous studies in Europe and the Middle East.[6–9,18,19] Collin *et al*. in Finland investigated the prevalence of sub clinical

celiac disease in women with infertility or recurrent miscarriage by serological screening tests.[9] In their series, no cases of celiac disease were identified in the control group of 150 fertile women, however, 2.7% (four of 150) of infertile women were found to have sub clinical celiac disease. When infertile couples in Italy were evaluated for subclinical celiac disease, an increased prevalence of 3% was found (3/9). This rate of disease was much higher compared with the general population (17 cases among 1607 women; 1.06%).[8] Celiac disease has also been found to be more prevalent among the Arab infertile female. When a group of 192 Arab women suffering from unexplained infertility were tested for serologic markers of celiac disease, 2.65% were affected. This figure was five times higher than the controls (0.5%).[18] A study from Israel investigated pregnancy outcome in patients with celiac; no statistically significant differences were noted between the groups regarding fertility treatments (0% among patients with known celiac vs 2.5% among patients without known celiac sprue; $P = 0.267$).[19] Tiboni *et al*.[20] investigated the prevalence of celiac disease in women undergoing assisted reproduction techniques by tTGA. Five (2.5%) cases and 2 (1.0%) controls were revealed to have celiac disease ($P = 0.44$). In a cohort study among women with unexplained infertility in a United States population, tTGA and EMA were assessed and among those, EMA was positive only in one (0.8%), which is approximately as prevalent as the general population in the United States (<1%).[6]

In the present study, none of the infertile patients with celiac disease had remarkable gastrointestinal complaints consistent with studies performed by Tiboni *et al*.[20] and Collin *et al*.[9] Moreover, there was no significant association between positive TGA results and gender. Regardless of risk factors such as GI symptoms, individuals experiencing unexplained infertility could significantly benefit from awareness of disease status as management has demonstrated improved fertility outcomes.[7] There are growing evidence to prove that celiac disease may affect reproduction at various points in both men and women. Farthing's study[21] of men with celiac disease demonstrated an increased incidence of hypogonadism, sexual dysfunction and poor semen quality in almost half of his cohort, resulting in an increased incidence of infertility. Women with celiac disease can also have major menstrual problems. One report from Italy showed 34 newly diagnosed celiac women suffered from significantly delayed menarche (13.5 vs 12.1 years of age; $P = 0.000$), more frequent secondary amenorrhea (38.8% vs 9.2%; $P = 0.001$) and a trend towards earlier menopause (45.5 vs 49.5 years of age).[22] In our study the prevalence of celiac disease was not the same in males and females and all of the confirmed cases of celiac disease in the infertile group were female.

Two recent studies by Kurppa *et al*. have elegantly demonstrated that even those who are serology positive but having no villous abnormality do respond to a gluten-free diet.[23,24] Likewise, some studies have suggested that treating celiac disease with a gluten-free diet can improve fecundity in these patients.[10,11] In a study examining the effect of celiac disease on reproduction, patients on a normal diet were found to be at increased risk for infertility in comparison to patients on a gluten-free diet.[11] The potential of a gluten-free diet to exert a positive effect on reproduction is rationalized by the possibility that nutritional imbalance, especially malabsorption of selective nutrients including zinc, selenium, iron and folate, may underlie celiac disease-mediated reproductive disorders.[2] There is little doubt that untreated celiac disease adversely affects both male and female reproduction. It also seems that patients with minimal symptoms have a considerably increased risk of problems. However, good evidence exists regarding the effectiveness of gluten-free diet in returning reproduction to normal. Several studies have indicated a potential association between celiac disease and infertility,[6,10,11,19,25] often recommending celiac disease screening of some or all patients with unexplained infertility.

The present study, in agreement with prior reports, showed higher frequency of celiac disease among unexplained infertile couples compared with fertile couples in Tabriz, Iran.

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