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Original Article

Prevalence of Celiac Disease in Unexplained Infertility in Shariati Hospital, Tehran, Iran

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Abstract

Background: The relationship between subfertiltiy and celiac disease has been well described and may be the only presenting feature of celiac disease. Therefore, this study was designed to show the prevalence of celiac disease in unexplained infertility among Iranian patients in Tehran, Iran.

Methods: This case-control study includes 125 patients with primary unexplained infertility and 125 fertile women as controls who referred to Shariati Hospital, affiliated to Tehran University of Medical Sciences Infertility Clinic. The total serum IgA and IgA anti-TTG were measured. In the case of positive TTG, a duodenal biopsy was performed to confirm the diagnosis.

Results: Four patients (3%) with unexplained infertility had positive TTG and in three (2.4%), biopsy of small intestine was compatible with celiac disease. None of the women in the control group had positive TTG.

Conclusion: A few studies suggest that celiac serologic tests should be considered for infertile patients. But the absence of a significant statistical difference in the incidence of celiac disease between subject and control groups in the present study suggests a need for further studies with large sample size to address the issue.

Keywords: Unexplained Infertility; Celiac Disease; Case-Control

Introduction

Subfertility is defined as a failure to conceive after one year of unprotected regular sexual intercourse. One in six couples have an unwanted delay in conception, with many factors being described as possible causes.[1] The relationship between subfertiltiy and celiac disease has been well described and may be the only presenting feature of celiac disease.[2] In the last decade, celiac disease has merited attention globally and also in Iran. The prevalence of celiac disease in Iran was $1/166$ in asymptomatic patients referred to Tehran Blood Transfusion Bank.[3] Celiac disease or

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gluten enteropathy are induced by dietary wheat gliadin and related proteins in genetically susceptible individuals.[4,5] The clinical spectrum of the disease is extremely variable ranging from the classical presentation, characterized by diarrhea with or without malabsorption, to the clinically silent form.[4,5] With the introduction of highly sensitive and specific serological tests, it has become apparent that most affected individuals have clinically indolent forms. Overall, the estimated prevalence of the disease among adult individuals is 0.5-1.0%.[4, 5] Celiac disease has several extraintestinal manifestations, one of which is an adverse reproductive outcome.[6,7] The relationship between celiac disease and reproductive problems including infertility, recurrent abortions and intrauterine growth retardation has been supported by a number of reports. In a case-control study, women with celiac disease had less fertility, more miscarriages and delayed menarche and early menopause than controls.[8] In another study, the prevalence of sub-clinical celiac disease in women with infertility or recurrent miscarriages was investigated by using serological screening tests.[9] In the present study, 150 fertile and 150 infertile women were evaluated and no cases of celiac disease were identified in the control group. On the other hand, 2.7% (4 out of 150) of infertile women were found to have sub-clinical celiac disease. In the Mediterranean Island of Sardegna, the prevalence of celiac disease is known to be particularly high (~10.6 per 1000).[10] Celiac disease was found to be more prevalent among the Arab population. In another case-control study, 192 Arab women with unexplained infertility and 210 fertile control individuals were tested for serologic markers of celiac disease, 2.65% of cases were found to be affected, that was five times higher than that in the controls (0.5%; 1 out of 210).[11] There is no consensus on this concept that celiac disease represents a risk factor for infertility. A recent large general population-based cohort study found that women with diagnosed celiac disease have fertility similar to that of the general population, though they tended to have their babies at an older age.[12-14]

Regarding the prevalence of celiac in Iran and the return of fertility after a gluten free diet in patients, it seems reasonable to carry out a study on patients with unexplained infertility.

Materials and Methods

In this case-control study, 125 patients with unexplained infertility who referred to Infertility Clinic of Shariati Hospital affiliated to Tehran University of Medical sciences were evaluated over a period of one year.

The inclusion criteria for infertile patients were 1) age under 35 years old, 2) regular menses, 3) exclusion of all other etiologies of infertility (normal hormonal markers, HCG: histerosalpingography; and sperm count and PCT: post-coital test), 4) no previous history of abdominopelvic surgery, 5) no systemic disease, 6) normal systemic examination and 7) infertility longer than 3 years. The inclusion criterion for the control group was having two or more children resulting from spontaneous pregnancy.

Upon completion of the questionnaire, 6 ml of blood was provided from each patient in order to measure the total IgA and IgA TTG by ELISA method (Bois system-Spain) (TTG≥7positive).

In any patient with positive TTG antibody, endoscopy and biopsy from distal end of duodenum were performed and tissue samples were evaluated for any evidence of celiac disease. Difficulties and limitations of this study were limited size of the sample, refusal of the patients to enter the control group, and the patient drop out.

Data were analyzed using SPSS software (version 11.0; Chicago, IL, USA). Fischer's exact test and t-Test were used for comparison. A P value less than 0.05 was considered significant.

Results

Three out of 125 women with unexplained infertility (2.4%) had celiac disease (TTG was positive and biopsy compatible with celiac disease) while no patient in the control group suffered from the disease (*P*= 0.247; Table 1). The disease in the three patients was asymptomatic (Table 2). In all patients (case and control groups), the total serum IgA was normal. Four (3%) out of 125 patients had a positive IgA-TTG and 3 patients with positive IgA-TTG had positive duodenal biopsy in favor of celiac disease.

Table 1: Incidence of celiac disease in case and control groups.

Celiac disease Group	Yes No. (%)	No No. (%)	Total
Case	122(97.6)	3(2.4)	125
Control	125(100)	0(0)	125
Total	247	3	250

Fisher's exact test; *P value*=0.247

According to the modified Marsh classification,

Table 2: Characteristics of the patients with unexplained infertility and celiac disease.

Patients	Age	Symptoms of celiac disease	Age of menarche	Duration of infertility	Marsh classification
1	30	--	14	9	1
2	29	--	16	7	1
3	28	--	13	5	2

two patients were in stage I and 1 in stage II. The difference in the mean age of menarche between case and control groups was statistically significant (*P*=0.00003). The mean age of menarche in unexplained infertility group with celiac disease was higher than that in unexplained infertility group without celiac disease but the *P value* was not significant (P= 0.06). The mean age of menarche in patients with unexplained infertility and celiac disease was 14.33% and in patients with unexplained infertility but without celiac disease was 12.88% (Table 3).

Discussion

The possible correlation between celiac disease and infertility has been the subject of a number of investigations.[8, 9,11-14] Our study showed that few patients with unexplained infertility had celiac disease (2.4%) but failed to show a significant difference (*P value*=0.08) with the control group. This is in contrast with similar studies in Finland and Italy that showed a significant *P value*.[9,13] In the present study, there was no statistically significant difference between the case and the control groups to show that our findings can only be regarded as indicative of a trend. The lack of statistical significance is likely to reflect an insufficient size of sample, or low prevalence of celiac disease in our country.

In the present study, the mean age of the study group was not significantly higher than that in the control group. A relationship between the age and fertility of women with celiac disease was reported by Tata *et al.*[14] when comparing the patients with the general population. They showed that women with celiac disease had a lower fertility at younger ages that recovered at older ages.

Underlying mechanisms for infertility in celiac disease are still unknown. Several hypotheses have been proposed to explain the causes of infertility in patients with celiac disease. Deficiency of essential nutrients such as folic acid or vitamin B12 can have adverse effects on fertility in these patients. Another finding in a few studies is shortened reproductive period with delayed menarch and early menopause in infertile patients with celiac disease.[16,17] A few studies suggested that, celiac serologic tests should be considered for infertile patients.[4,6,7,15] But the absence of a significant difference in the incidence of celiac disease between the study and control groups in our study suggests a need for further studies with large sample size to address this issue.

Regarding the significant relationship between celiac disease and unexplained infertility and the return of fertility by assignment of a gluten free diet; it is prudent to consider celiac disease in the differential diagnosis of unexplained infertility in the presence of suggestivte manifestations such as iron deficiency anemia and chronic diarrhea.

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Conflict of interest: None declared.

Table 3: Comparison of age, BMI and menarche age between case and control groups.

Variables	Group	No. of patients	Mean±SD	T value	*P Value*
Patients age	Case	125	28.78±5.1	2.43	0.015
	Control	125	30.32±4.9		
BMI	Case	125	24.6± 3.7	1.54	0.123
	Control	125	26.9±16.2		
Menarche age	Case	125	12.86±1.4	4.21	0.00003
	Control	125	12.14±1.3		

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