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

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Abstract

Background: The relationship between subfertility 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 included 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. The relationship between subfertility and celiac disease has been well described and may be the only presenting feature of celiac disease. 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. Celiac disease or
gluten enteropathy are induced by dietary wheat gliadin and related proteins in genetically susceptible individu-
al.\textsuperscript{4,5} The clinical spectrum of the disease is extremely varied ranging from the classical presentation, char-
acterized by diarrhea with or without malabsorption, to the clinically silent form.\textsuperscript{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 preva-
ience of the disease among adult individuals is 0.5-
1.0%.\textsuperscript{4,5} Celiac disease has several extraintestinal
manifestations, one of which is an adverse reproduc-
tive outcome.\textsuperscript{6,7} The relationship between celiac dis-
ease 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 fer-
tility, more miscarriages and delayed menarche and early menopause than controls.\textsuperscript{8} In another study, the
prevalence of sub-clinical celiac disease in women with inferti-
lity or recurrent miscarriages was investigated by
using serological screening tests.\textsuperscript{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 infert-
ile women were found to have sub-clinical celiac dis-
ease. In the Mediterranean Island of Sardegna, the pre-
valence of celiac disease is known to be particularly
high (~10.6 per 1000).\textsuperscript{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 serological 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).\textsuperscript{11}
There is no consensus on this concept that celiac dis-
ease 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.\textsuperscript{12,13}

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 sci-
ences 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) exclu-
sion of all other etiologies of infertility (normal hor-
monal 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) infertil-
ity 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 me-
thod (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 bi-
opsy 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 con-
trol 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 duode-
nal biopsy in favor of celiac disease.

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

<table>
<thead>
<tr>
<th>Celiac disease</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>No. (%)</td>
<td>(%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Case</td>
<td>122(97.6)</td>
<td>3(2.4)</td>
<td>125</td>
</tr>
<tr>
<td>Control</td>
<td>125(100)</td>
<td>0(0)</td>
<td>125</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>247</td>
<td>3</td>
<td>250</td>
</tr>
</tbody>
</table>

Fisher’s exact test; $P$ value=0.247

According to the modified Marsh classification,
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. 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. In the present study, there was no statistically significant difference between the case and 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. 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. A few studies suggested that, celiac serologic tests should be considered for infertile patients. 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 suggestive manifestations such as iron deficiency anemia and chronic diarrhea.

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**Conflict of interest:** None declared.
Celiac disease in unexplained infertility

References