Turk J Gastroenterol *2015; 26: 484-6*

Is there any relationship between unrecognized Celiac disease and unexplained infertile couples?

INTESTINE

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Original Article

ABSTRACT

Background/Aims: Celiac Disease (CD) is a chronic autoimmune disease characterized by small intestinal malabsorbtion and diarrhea, triggered by the ingestion of food products containing gluten. There are studies reporting that some nutritional deficiencies and some factors related to immunity may cause a decrease in fertility as well as some problems in sperm parameters. The prevalence of CD in unexplained infertility (UEI) couples is not as high as that mentioned in some reports. There is no accurate knowledge about the prevalence of CD in a UEI couple.

Materials and Methods: A total of 68 couples with UEI who were admitted at Türk Diyanet Vakfı 29 Mayıs Hospital Center of in vitro fertilization (IVF) between January and June 2014 were included in this prospective pilot study. The diagnosis of UEI was made with basic infertility tests. A history of CD was questioned in the initial evaluation. Anti-gliadin, anti-endomysial, and tissue transglutaminase antibodies as well as total IgA were tested. Gastroscopy was performed in patients with positive serologic tests. Histopathological CD diagnosis was made according to Marsh criteria.

Results: The mean age of the study population was 33.40±4.59 years. Out of the 65 couples who were included into the study group, one of the five couples was positive for the autoantibodies (7.69%). Out of these 65 couples, none of them had autoantibody positivity at the same time in both partners. Anti-gliadin antibodies were found to be positive for two females out of five couples and in three male partners of the same group. Out of these five couples, only one male partner had all the antibodies as positive (1.5%). In the histopathological examination of patients with positive autoantibodies, only the patient in whom all autoantibodies were positive had findings compatible with Marsh IIIa gluten enteropathy. Only one couple had a diagnosis of CD (1.5%).

Conclusion: In many studies, CD was shown to affect the reproductive system of women. CD may also cause a decrease in fertility in men by affecting sperm motility and androgen levels. Our study is based on a limited sample size. Our data should be confirmed in a larger cohort of subjects. These results suggest that investigation of both couples with a diagnosis of UEI may be more beneficial in clarifying the etiology.

Keywords: Celiac disease, prevalence, unexplained infertility

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disease characterized by small intestinal malabsorbtion and diarrhea, triggered by the ingestion of food products containing gluten. Gluten is a protein complex found in wheat, rye, and barley. CD predominantly affects the mucosa of the small intestine; the injured small intestinal epithelium impairs digestion and absorption of the nutrients (1,2). CD may be classified as asymptomatic, classical, and atypical. Classic cases present with symptoms of malabsorbtion such as diarrhea, steatorrhea, flatulence, and deficiencies of ensuing nutrient and minerals (3). Atypical cases present with predominantly extraintestinal manifestations. Extraintestinal manifestations include dermatitis herpetiformis, aphthous stomatitis, neurologic dysfunction, osteopathy, and diabetes mellitus (4). Also, several studies have shown the implication of CD on reproductive disorders. Recurrent fetal loss, intrauterine growth retardation, preterm delivery, and low birth weight may be observed in untreated women with CD (5). There are studies reporting that some nutritional deficiencies (e.g., folic acid, zinc, and selenium) and some factors related to immunity (e.g., recurrent abortion, early menopause, and amenorrhea) may cause a decrease in fertility (6-8). Previous studies showed that CD is associated with androgen resistance, low levels of dehydroepiandrosterone

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Received: May 25, 2015 **Accepted:** August 10, 2015 **Available Online Date:** October 26, 2015

sulphate (DHEA-SO)$_4$, and marked reduction in sperm motility in men (6,9). All of these factors may be responsible in decreasing the fertility in female and male patients with CD.

Unexplained infertility (UEI) is defined as normal ovulatory functions with known current methods (ovarian reserve tests), normal tubal permeability (hysterosalphingography/laparoscopy), and normal semen analysis, which is present in 16% of the infertile couples (10,11). Although some studies have pointed that diagnostic methods used in the detection of the causes of infertility (endometriosis, tubal dysfunction, immunologic causes, and premature ovarian insufficiency) are not adequate (12) others have concluded that use of invasive methods that could detect these causes may not be helpful in clinical practice (11).

The aim of this study is to determine the prevalence of unrecognized CD in couples with UEI.

MATERIALS AND METHODS

A total of 68 couples with UEI who were admitted at 29 Mayıs Hospital assisted reproductive technology (ART) Center between January and June 2014 were included in this prospective pilot study. The study was approved by the instutional review board (IRB) of 29 Mayıs Hospital. Informed consents were obtained from each patient. The diagnosis of UEI was made by conducting basic infertility tests. For this aim, ovarian reserve tests (day 3 follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and/or antimüllerian hormone (AMH) levels) were conducted, thyroid stimulating hormone (TSH) and prolactine (PRL) were measured, and hysterosalpingography was performed for evaluating tubal permeability in female patients. FSH of 3–10 mIU/mL, LH of 2–12 mIU/mL, E2 of 20–50 pg/mL, TSH of 0.6–2.5 mIU/L, PRL of 3.5–20 ng/mL, and AMH of 1.5–4 ng/mL values were considered as normal. Patients with the normal appearances of uterine cavity and both tubes, with a normal peritoneal passage. In the evaluation of men, sperm specimens taken after a 3–4-day sexual fasting were investigated. Evaluation of semen parameters was performed according to WHO 2010 guidelines. Normal values in spermiogram were as follows: volume of >1.5 cc, count of >15,000,000/mL, progressive motility of >32%, and ≥4% were morphologically normal (13). A history of CD was questioned in the initial evaluation of infertile couples. Anti-gliadin antibodies (IgG and IgA), anti-endomysial antibodies (IgA and IgG), tissue transglutaminase antibodies (IgA and IgG), and total IgA were tested. Gastroscopic examinations were performed in patients with positive serologic tests, and biopsy specimens were obtained from the 2nd part of the duodenum for histopathological examination. Histopathological CD diagnosis was made according to modified Marsh criteria. Patients in whom the diagnosis was confirmed serologically and histopathologically, a gluten-free diet was started. Statistical analysis was performed by SPSS 16.0 program for Windows (IBM Corp., NY, USA).

RESULTS

A total of 68 couples with a mean age of 33.40±4.59 years were included in this study (Females: 31.68±4.45; Males: 35.12±4.59). Three of the couples were excluded as their test results could not be obtained. The mean duration of infertility of these couples was 4.91±2.91 years. A total of 53 couples (82%) had primary infertility and 12 couples (18%) had secondary infertility. We summarized the characteristics of the couples in Table 1. When the patients were questioned on the presence of malabsorption clinical features (steatorrhea, weight loss, and fatigue) of classical CD, no positive findings could be detected. Only one couple had a diagnosis of CD (1.5%).

Out of the 65 couples who were included into the study group, one of the five couples was positive for the autoantibodies (7.69%). Out of these 65 couples, none of them had autoantibody positivity at the same time in both partners. Anti-gliadin antibodies were found to be positive for two females out of five couples and in three male partners for the same group. Out of these five couples, only one male partner was positive for all the antibodies (1.5%). We summarized these results in Table 2. In the histopathological examination of patients with positive autoantibodies, only the patient in whom all autoantibodies were positive had findings compatible with Marsh IIIa gluten enteropathy. Out of the 65 couples, only one male partner had been diagnosed with CD. In the semen analysis of the patient with a diagnosis of CD, volume was 2.1 cc, sperm count was 82 million/mL, motility was 68%, and 5% was found to be normal in the morphological examination.

DISCUSSION

As the CD is an immune-mediated disorder, the patients have an increased sensitivity against gluten proteins and intolerance against it. There is an intestinal mucosal damage caused by the immunological reaction against gluten proteins (1,2). Also, CD is a genetically transmitted disease that affects 0.5%–1% of the general population in North America and Europe (14). Presence of the class II human leucocyte antigen DQ2 and DQ8 confers an increased risk of developing CD (15). In patients in whom there is a suspicion of CD, anti-endomysium antibody IgA serologic test is used for screening. The definitive diagnosis of CD is with biopsy (16). The mainstay of treatment is a gluten-free diet.

Table 1. Clinical characteristics of couples

N (Couples)	65
Mean age (year)	33.40±4.59
Age of females (year)	31.68±4.45
Age of males (year)	35.12±4.59
Duration of infertility (year)	4.91±2.91
Type of infertility (primary/secondary)%	82/18

Table 2. Characteristics of couples with seropositive and diagnosed CD

Couples	F/M	AGA	AEA	tTGA	BX
1	–/+	+	–	–	–
2	+/–	+	–	–	–
3	–/+	+	–	–	–
4	+/–	+	–	–	–
5	–/+	+	+	+	Marsh IIIa

F: female; M: male; AGA: anti-gliadin antibody; AEA: anti-endomysium antibody; tTGA: tissue transglutaminase antibody; BX: biopsy

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Although enteropathy is the most frequently seen presentation, CD may involve other organ systems (3). In many studies, CD was shown to affect the reproductive system in women (5-8). Untreated CD may cause maternal complications such as recurrent fetal loss, intrauterine growth retardation, preterm birth, and low birth weight (5,17). An association between CD and gynecological disorders, such as endometriosis and amenorrhea, is shown (18,19). CD may also cause a decrease in fertility in men by affecting sperm motility and androgen levels (6,9).

The prevalence of undiagnosed CD in infertile women was found to be higher than that in the general population. The prevalence of CD in infertile women is 2%–6%, which is approximately 1% in the general population (20). On the other hand, there are studies reporting an absence of an increased prevalence (21). In the present study, four in five patients had positive anti-gliadin antibodies that have a low sensitivity and specificity; findings of CD could not be found in their histopathological examination. In the patient in whom all autoantibodies were positive, CD was also diagnosed histopathologically. The prevalence of CD in the group as a whole was 0.8%, which increases to 1.5% when couples are taken into consideration.

In former studies, prevalence of CD was usually investigated in women among couples with a diagnosis of UEI. Also, there is no any data about Turkish population in Pubmed. Unlike other studies, we included women without tubo-ovarian factor and men with normal spermiograms to investigate the prevalence of undiagnosed CD and found a slightly higher rate than that reported in the medical literature (14-16). However, our study is based on a limited sample size. Our data should be confirmed in a larger cohort of subjects.

As we can see from our study, when couples get studied male population can have CD positivity. We believe that the investigation of both couples with a diagnosis of UEI may be more beneficial in clarifying the etiology.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of IRB of 29 Mayıs Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.K., R.Y., C.K.; Design - N.K.; Supervision - C.K.; Resource - N.K., L.A.; Materials - N.K., R.Y., L.A.; Data Collection and/or Processing - N.K., R,Y., L.A.; Analysis and/or Interpretation - N.K., G.B.; Literature Search - N.K., G.B., C.K.; Writing - N.K., C.K.; Critical Reviews - C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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