

Determination of the relationship between Celiac disease and recurrent spontaneous abortion

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ABSTRACT

To determine the relationship between celiac disease and reproductive disorder, twenty two women with recurrent spontaneous abortion (18-35) years have been investigated from the period 2017/11/1 – 2018/2/1 and compared with twenty two parentally healthy women. All studied groups were carried out to measure anti-tissue transglutaminase IgA and IgG antibodies by Enzyme linked immunosorbent assay (ELISA) technique, There were a highly significant differences ($P < 0.01$) in the concentration of anti TtG IgA and IgG Ab compared to control group, while there was non-significant differences ($P > 0.05$) in the concentration of anti TtG IgA according to the age group and there was a significant difference ($P < 0.05$) in the concentration of anti TtG IgG Ab according to the age group. The results indicate that the infection with celiac disease may play a role in the pathogenesis of recurrent spontaneous abortion.

Keywords: celiac disease, spontaneous abortion, anti-tissue transglutaminase, IgA, IgG

1. INTRODUCTION

Celiac disease (CD) is a multifactorial chronic autoimmune systemic disease triggered by gluten consumption in genetically predisposed individuals [1].

The pathophysiology of CD involves the environmental trigger gluten in genetically susceptible individuals. The HLA-DQ2 and DQ8 haplotypes are expressed on the surface of antigen-presenting cells in the gut lamina propria and bind activated gliadin peptides, eliciting an inflammatory reaction. This inflammatory state leads to changes in the small bowel mucosa architecture including increased infiltration of lymphocytes into the epithelial cells, villous atrophy and crypt distortion [2].

These intestinal changes can lead to malabsorption of macro- and micro- nutrients, resulting in symptoms of malabsorption such as weight loss and diarrhea. Additionally, CD is associated with a number of extra intestinal manifestations, and resultant morbidity and mortality [3]. However, many patients with CD may

have a clinically silent disease without any symptoms. A significant proportion of patients are diagnosed through screening populations such as family members of patients with CD and insulin-dependent diabetics [4].

Worldwide, the prevalence of CD in the general population is approximately 1%; female: male ratio is 2:1. In Europe, CD prevalence ranges between 0.5% in Germany and 2.4% in Finland. In Italy prevalence is between 0.55% and 1%. However, new epidemiological data indicate that CD is commonly found in Middle Eastern countries particularly Iran [5, 6, 7].

The accuracy of prevalence estimations of CD has been greatly improved with the development of reliable serological testing. Prevalence rates vary widely across different regions, which reflect varying population risks for disease. Serological based testing in the U.S. estimates prevalence of 1:105 (0.95%) in "not-at-risk" adults, 1:322 (0.31%) in children, and 1:133 overall

(0.75%) The male-to-female ratio of disease is roughly [8].

CD may be also associated with extra intestinal signs and symptoms and in women with reproductive disorders. CD has been associated with recurrent spontaneous abortion, intrauterine growth restriction, preterm delivery and low-birth weight. Infertility, delayed menarche, early menopause, and stillbirth .The risk of multiple abortions is 8 to 9 times higher in women with untreated CD than among treated patients. CD has also been associated with gynecologic disorders such as amenorrhea. These may even be the only presenting features and are considered atypical clinical forms of CD [9].

Several studies suggest a higher prevalence of undiagnosed CD in patient with infertility. In Europe, the prevalence of CD among infertile women varies between 4% and 8% [10-11]. Several mechanisms were reported through which CD potentially could affect a woman's fertility such as the presence of abnormal villous structure in the intestine and malabsorption of the nutrients leading to nutritional deficiencies (eg, in zinc, iron, folate, and selenium). These nutritional deficiencies are said to affect fertility, however, there is no conclusive evidence on the extent to which this may cause fertility problems in CD. A lower level of ghrelin and leptin in women with CD also has been reported to play a role in fertility problems. In addition, a shortened reproductive period with delayed menarche and early menopause also has been cited as an explanation for the reported increase in fertility problems related to CD [12].

The aim of the present study was to help clarify the association between CD and reproduction disorders such as (infertility).

2. MATERIALS AND METHODS

2.1 Patient samples:

The study was carried out on twenty two women patients suffering from spontaneous abortion during first trimester of pregnancy that introduced to Baghdad hospital, during period 2017/11/1-2018/2/1. The ages of the patients were ranged from (18-35) years. The interviews were performed for each patient.

2.2 Control samples:

Twenty two samples of healthy femal individuals were studied as control groups of same age and sex. All samples were marked by the number of samples, names of patients and day of sample collection.

2.3 Blood samples collection:

Blood samples (5 ml) were collected by disposable syringe into gel tubes and stand at room temperature until the coagulant was formed. Then the samples were centrifuged at 3000 rpm for 5 min. and stored at (-20°C) until carried out to detect anti-tissue transglutaminase (IgA and IgG) according to the leaflet of the kit.

2.4 Immunological detection of the anti-tissue transglutaminase antibodies by ELISA method

All the studied patients group and apparently healthy individuals (control group) were submitted to estimate the anti-tissue transglutaminase antibodies IgA and IgG antibodies level by using ELISA test (Germany) according to a protocol of the kit as per method described in [3].

2.5 Statistical Analysis:

The Statistical Analysis System-SAS [14] program was used to study the difference factors in study parameters. T-test was used to compare between means in this study.

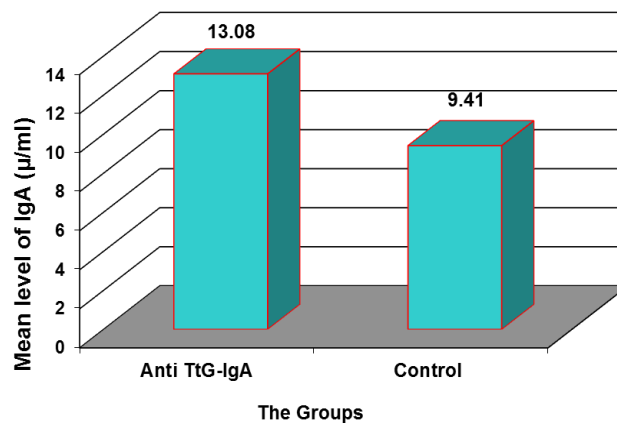


Figure 1. : Mean level of Anti TtG-IgA Ab(µ/ml) in sera of women with recurrent abortion and control group

3. RESULTS AND DISCUSSION

The results of the present study showed that there was a highly significant elevation ($P < 0.01$) in the concentration of anti TtG-IgA Ab ($13.08 \pm 1.23 \mu/ml$) compared to control group ($9.41 \pm 0.81 \mu/ml$).

Also, there was a highly significant elevation ($P < 0.01$) in the concentration of anti TtG-IgG Ab ($14.81 \pm 0.92 \mu/ml$) compare to control group ($7.37 \pm 0.52 \mu/ml$) as shown in figure (2)

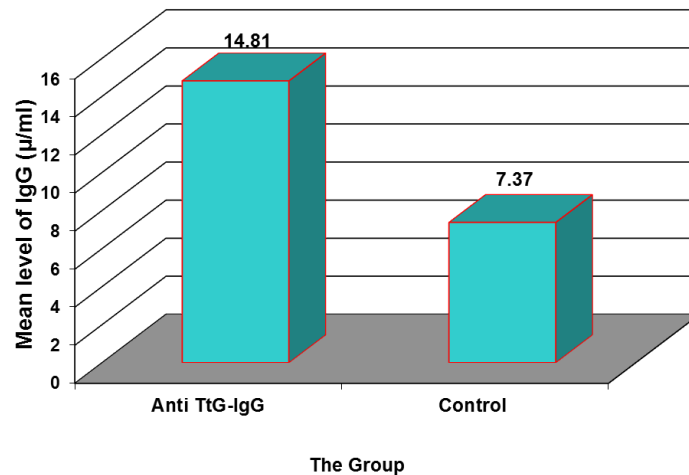


Figure 2. :Mean level of Anti TtG-IgG Ab(µ/ml) in sera of women with recurrent abortion and control group

The result of the present study revealed that there was non-significant difference ($P > 0.05$) in the concentration of anti TtG IgA Ab according to the age

group, while; there was significant difference ($P < 0.05$) in the concentration of anti TtG IgG Ab according to the age group as shown in table (3).

Table 3: Effect of age group in IgA and IgG concentration of anti TtG among studies groups

Age group (year)	Mean \pm SE (μ/ml)	
	IgA	IgG
Less than 25	10.73 \pm 0.82	10.29 \pm 0.80
≤ 25	13.09 \pm 2.01	13.78 \pm 1.85
T-test	3.748 NS	3.599 *
P-value	0.2105	0.0478

* ($P < 0.05$), NS: Non-Significant.

The results of the present study was in agreement with several other studies- , recent studies have demonstrated that the rate of spontaneous abortions was 50.6% (124 of 245 women) in the CD group, which was significantly ($P = 0.01$) higher than the rate of 40.6% (198 of 488 women) in the control group [15].

In the surveys we included 91 celiac women; 61.5% of them reported menstrual cycle disorders. 47/91 reported at least one pregnancy and 70.2% of them reported problems during pregnancy. From the HDRs and the registry of exemption, we selected 4,070 women with CD; the proportion of women hospitalized for infertility was higher among celiac women than among resident women in childbearing age (1.2% versus 0.2%) [16].

In other study up to 50% of women with untreated CD refer an experienced miscarriage of an unfavorable outcome of pregnancy. Sher, *et al.* noted an increased incidence of spontaneous abortions. In adult patients with CD, the disease has insidious clinical manifestation with few symptoms and the pregnancy may be considered a "trigger" to unmask the disease, that it may be considered as "latent" [17].

Molteni, *et al.* noted an increased percentage of recurrent spontaneous abortions in untreated celiac patients, not correlated to clinical severity and biochemical alteration of the pathology [18]. The first description of an association between CD and reproductive abnormalities was made by Morris, *et al.* in 1970 when they described three patients with untreated CD and infertility, who became pregnant after starting the gluten free diet (GFD) [19].

The prevalence of CD in unexplained infertility may be as high as 4-8%. The infertility in untreated CD may be related to malabsorption of Iron and/or Folate, and vitamins deficiency. The diagnosis of CD is often done in women without classic malabsorption symptoms. The "silent" Presentation causes a diagnostic delay with a prolonged dietary gluten exposure that may lead to a reduction of the fertile life period [20].

Zinc deficiency may determine impaired synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) that lead to the abnormal ovarian axis, secondary amenorrhea, spontaneous abortion, and pre-eclampsia. Selenium deficiency

affects the synthesis and secretion of FSH and LH. Folic acid is an essential vitamin in nucleic acid metabolism and its deficiency has a negative impact on rapidly proliferating tissue in the embryo, especially in neuronal cell development [21].

CD patients on free-diet generally show increased blood levels of autoantibodies, in particular anti transglutaminase (antiTtG) antibodies. anti TtG could be directly involved in placental-related pregnancy complication. Enzyme TtG is expressed in many different tissue and organs such as intercellular or extracellular. TtG is also expressed in endometrial cells, stromal and trophoblast placental cells with higher levels in late pregnancy. TtG is involved in extracellular matrix assembly and cell adhesion, spreading and migration in diverse tissue. TtG localized on syncytiotrophoblast may be a target of material autoantibodies in CD. The binding of circulating anti TtG antibodies to placenta cells could be an immunologic mechanism that may interfere with pregnancy outcome in CD patients. Normal development and function of the placenta requires the invasion of maternal decidua by extra villous trophoblasts (EVT) followed by abundant and organized vascular growth. EVTs produce a large amount of basic proteins and hormones involved in the maintenance of pregnancy. It is likely that increased apoptosis of EVTs may contribute to the pathophysiology of human miscarriage and intra uterine growth retardation (IUGR) in celiac women on free-diet due to an increased apoptosis of EVT in placenta with a subsequent low birth weight of newborns. Anti TtG antibodies may cause an inhibition of syncytial TtG, with impairment of placental development [22-23].

4. CONCLUSION

Celiac disease may play a trigger role in the pathogenesis of reproduction disorders such as recurrent spontaneous abortion.

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