ISSN: 0067-2904
GIF: 0.851

The Relationship between Celiac Disease and Unexplained Infertility

Rana S. Aboud*
Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq

Abstract

To determine the relationship between celiac disease and reproductive complication, twenty five women with clinically definite unexplained infertility aged (22-35) have been investigated and compared to fifteen apparently healthy women. All the studied groups were subjected to measurement of anti-tissue transglutaminase antibodies IgA and IgG by ELISA technique and anti-endomysial antibodies IgA and IgG by IFAT technique .There was a highly significant elevation ($P< 0.01$) in the concentration of anti- tTG IgA Abs compared to control group, Also, there was significant elevation ($P< 0.05$) in the concentration of anti- tTG IgG Abs compared to control group .The results illustrated that the prevalence of anti-EMA IgA and IgG Abs were (5/25)20% and (3/25)12% respectively, and there was significant differences ($P< 0.05$) compared between studied groups. Frequency of HLA-DQ-8 by Real time PCR was (4/25)16% while no prevalence of HLA-DQ-2, and there was significant differences ($P< 0.05$) compared between studied groups. These results indicate that silent or sub- clinical celiac disease plays an important role in reproductive complication such as unexplained infertility.

Keywords: infertility, celiac disease, auto antibodies, reproductive complications

العلاقة بين مرض داء الزلاقي و العقم غير معروف السبب

رنا سعدي عبود*
قسم علوم الحياة، كلية العلوم، جامعة بغداد، بغداد، العراق

الخلاصة

لغرض تعيين العلاقة بين داء الزلاقي وتعقيدات التكاثر تم التحري عن 25 امرأة مصابة بالعقم الغير معروف السبب بعمر(22−35)سنة وتمت المقارنة مع (15) امرأة غير مصابة بالعقم عدت كسيطرة .خضعت جميع عينات الدراسة لقياس مستوى اضداد tTG الصنف ،(IgAIgG) باستخدام تقنية الامتزاز المناعي المرتبط بالانظيم وقياس مستوى أضدادEMA الصنف (IgA, IgG) باستخدام التألق المناعي غير المباشر. لوحظ هنالك ارتفاعا معنويا عاليا ($P< 0.01$) في تركيز أضداد IgA مقارنة بمجموعة السيطرة أيضا لوحظ ارتفاعا معنويا ($P< 0.05$) في تركيز أضداد IgG مقارنة بمجموعة السيطرة. أوضحت نتائج الدراسة بان تردد أضداد EMA الصنف IgA, IgG كانت(25/5)20% و(25/3) 12% على التوالي وهنالك فرقا معنويا($P< 0.05$) عند المقارنة بمجاميع الدراسة. كذلك كانت نسبة تكرار HLA−DQ8 باستخدام الزمن الحقيقي لتفاعل السلسلة البلمري(25/4)16% ولم يلاحظ تردد لل HLA−DQ 2 باستخدام نفس التقنية وكان هنالك فرقا معنويا ($P< 0.05$) عند المقارنة بين مجاميع الدراسة. تشير نتائج الدراسة بان مرض داء الزلاقي الصامت أو تحت ألسريري يلعب دورا مهما في تعقيدات التكاثر كحالات العقم غير معروف السبب.

الكلمات المفتاحية: العقم، مرض داء الزلاقي، الاضداد الذاتية، تعقيدات التكاثر.

*Email: drranasaadi@yahoo.com

Introduction:

Celiac disease is a chronic disease caused by a permanent intolerance to ingested gluten resulting in immunologically mediated inflammatory damage of the small-intestinal mucosa [1, 2]. Classically the disease is manifested by symptoms of diarrhea, flatulence and malabsorption, however, it is also associated with protean systemic manifestations including metabolic bone disease, diabetes, thyroid dysfunction and lympho-proliferative malignancies [3]. The path physiology 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 [4]. Celiac disease has been associated to several extra intestinal manifestations/ complications, one of which is an adverse reproductive outcome. The likelihood for a causal relationship between celiac disease and reproductive problems including infertility, recurrent abortions and intrauterine growth restriction has received support in a number of reports [5, 6, and 7]. Some series suggest a higher prevalence of undiagnosed celiac disease in patients with infertility. The prevalence in these series ranges from 2–6% as compared with almost 1% in the general population [8]. Celiac disease often affects women in their fertile period, and malabsorption may interfere with embryogenesis and fetal nutrition and growth. Latent celiac disease has been found to be associated with a number of gynecologic and obstetric disorders such as late menarche, early menopause, infertility, intrauterine growth restriction, recurrent spontaneous abortion, and stillbirth [9]. Women with infertility were 3.5 times more likely to have celiac disease than women who didn't have difficulty conceiving, the analysis found, based on a review of three studies including 449 women with infertility [10].

The aim of the present study attempts to determine the relationship between celiac disease and reproductive complication (women infertility).

Materials and methods

The study included (25) women suffering from well-established and clinically definite unexplained infertility aged 22-35 years. They were previously diagnosed and checked up for reproductive disorders in the department of obstetric and gynecology at the Teaching Baghdad hospital and kamal AL-Samarea hospital; 15 apparently healthy women donors aged 22-35 years, were taken as control groups .Blood samples (5 ml) were collected by disposable syringe into gel tubes and stand at room temperature until the coagulum was formed. Then the samples were centrifuged at 3000 rpm for 5 minutes Serum sample of each subjecte was were dispended onto seven Ependroff tubes. All samples were stored at (-20C) until were immunological examinations.

Serological markers:

Anti-tissue transglutaminase(tTG) anti-IgA,IgG antibodies levels quantification was achieved with the aid of commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit (Euroimmun)Germany; while anti-endomysial antibodies IgA,IgG were measured by immunofluorescence test IFAT(Euroimmun)Germany, according to the lefleat of kits [11].

Genetic markers:

Whole blood samples were tested to assess genetic susceptibility to celiac disease; the HLA-DQ8 and HLA-DQ-2 were assayed by using a Real time- polymerase chain reaction (Real time-PCR) with a commercially available kit (Bioneer, Germany).

Statistical analysis:

The statistical analysis used included Student t-test and Pearson chi-square test (x^2). The Statistical Package for Social Science V.13 (SPSS) was used. A p-value <0.05 was considered statistically significant [12].

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 Abs (1.217±0.266)RU/ml compared to control group (0.148±0.58)RU/ml, Also, there was significant elevation ($P< 0.05$) in the concentration of anti- tTG IgG Abs (1.066±0.231)RU/ml when compared to control group (0.333±0.77)RU/ml as shown in Figure-1.

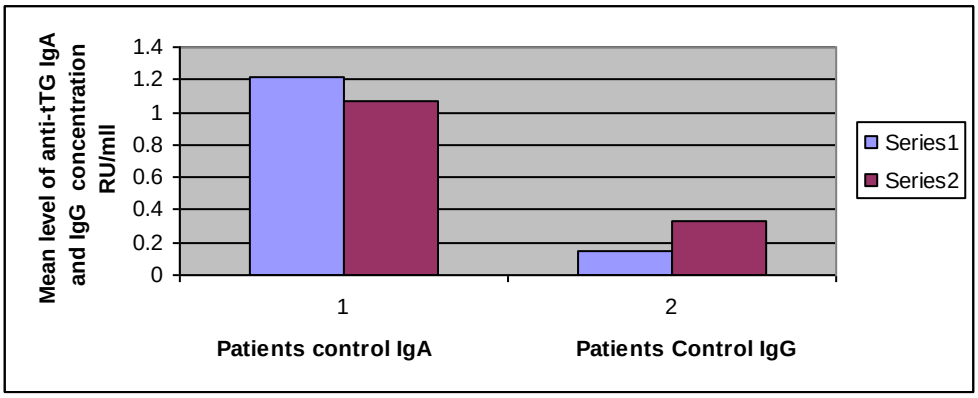

Figure 1- Mean level of anti-tissue transglutaminase IgA and IgG (RU/ml) in Sera of women with unexplained infertility and control groups.

The frequency of anti-tTG Abs IgA and IgG were (5/25)20% and (4/25)16% respectively, and there was a highly significant differences (P< 0.01) when compared between studied groups as shown in Figure-2.

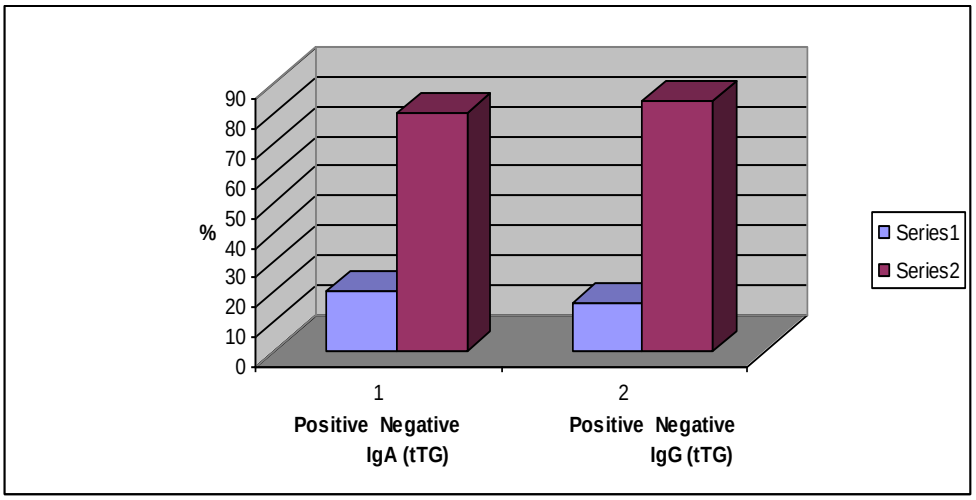

Figure 2- The percentage distribution of tTG Abs in sera of women with unexplained infertility.

The results of current study illustrated that the frequency of anti-EMA IgA and IgG Abs were (5/25)20% and (3/25)12% respectively, and there was significant differences (P< 0.05) when compared between studied groups as shown in Figure-3 and Figure-4a, b.

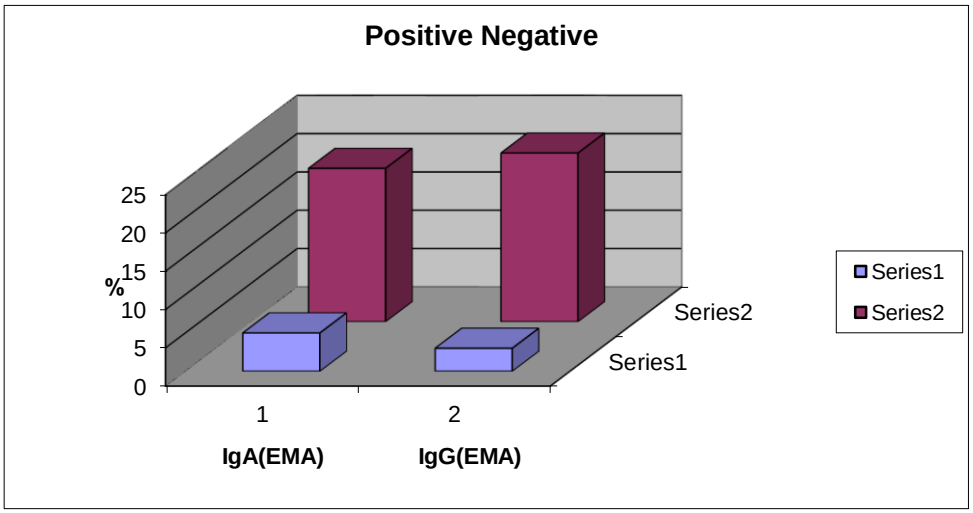

Figure 3- The percentage distribution of anti- EMA Abs in sera of women with unexplained infertility.

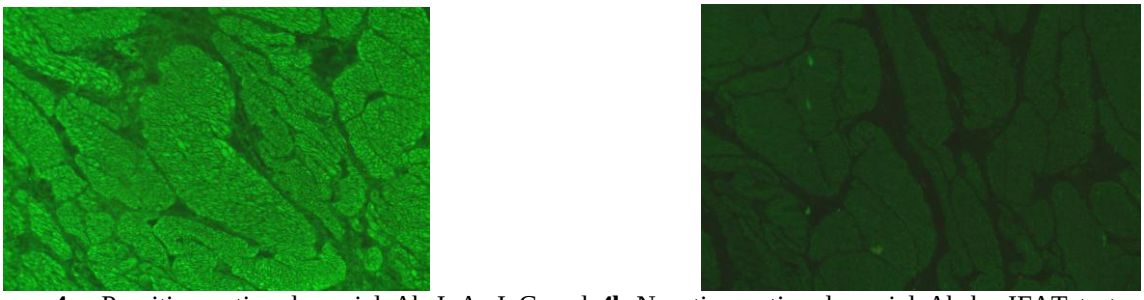

Figure 4a- Posaitive anti-endomysial Ab IgA, IgG and **4b-**Negative anti-endomysial Ab by IFAT test on primate esophagus in sera of women with unexplained infertility (200x**).**

The frequency of HLA-DQ-8 by Real time PCR were (4/25)16% while no frequency of HLA-DQ-2 with significant differences (P< 0.05) compared between studied groups Figure-5 and 6.

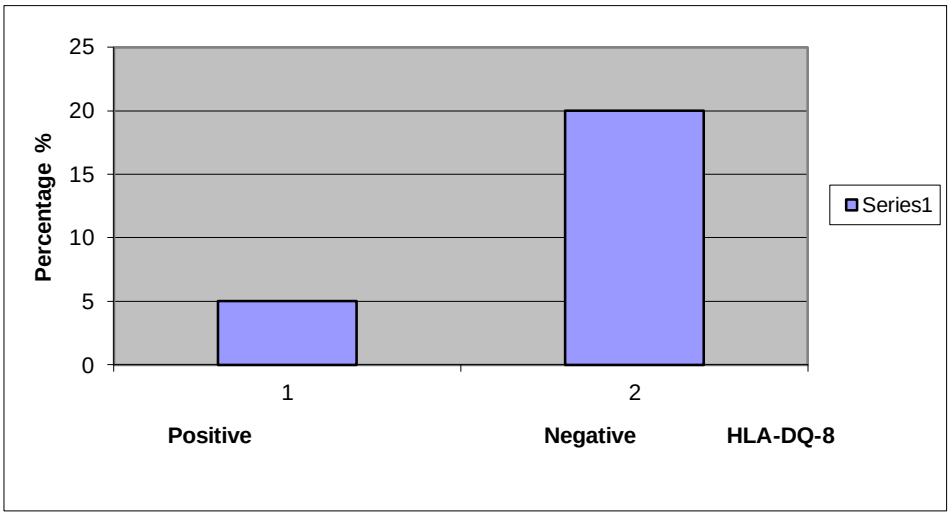

Figure 5- The percentage distribution of HLA-DQ8 by using HLA-DQ8 Real –Time PCR for blood of women with unexplained infertility.

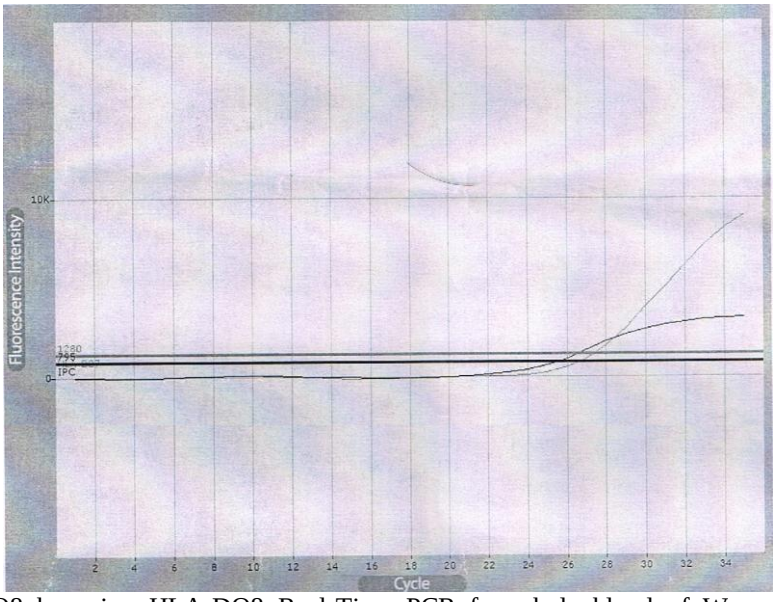

Figure 6- HLA-DQ8 by using HLA-DQ8 Real-Time PCR for whole blood of Women with unexplained infertility.

Statistical analysis revealed that there were highly significant differences (P< 0.01) in correlation coffient between anti-EMA and anti-tTG Abs in affected women as shown in Table-1.

Table 1- Pearson Correlation between anti-EMA and anti-tTG Abs in affected women

Correlations		Anti tTGA	Anti EMA
Anti tTGA	Pearson Correlation	1	.999**
	Sig. (2-tailed)		.001
	N	4	4
antiEMA	Pearson Correlation	.999**	1
	Sig. (2-tailed)	.001	
	N	4	4
****. Correlation is significant at the 0.01 level (2-tailed).**			

In this study we have tried to determine the association between unexplained infertility and autoimmune celiac disease. The results of the present study were agreed with other studies. One study showed that women with celiac disease had higher percentage of reproductive complication than control groups (50.6% vs. 40.6%,p=0.01)[13].While[14] revealed that there were a significant increased prevalence(5.9%) of undiagnosed celiac disease among women presenting with unexplained infertility. Another study demonstrated that women with CD had a normal fertility, but their fertility was decreased in the last two years preceding CD diagnosis [15]. Other research showed that in subgroup of unexplained infertility, the prevalence was 10.3 %(3 out of 29)[16], while in another study, positive results of tTGA were detected in 13 infertile subjects 6.5%[17]. While some other study showed that women with celiac disease did not have clinically recorded fertility problems more frequently than women without celiac disease [18]. CD has been reported to have a number of reproductive complications [19]. Silent celiac disease may represent a risk factor for infertility, but the underlying mechanisms are still unknown. Several hypotheses have been proposed to explain the cause of infertility in patient's with CD. Deficiency of essential nutrients can have an adverse effect on fertility such as selenium, folate, iron, vitamin A, K and D. [20]. Also, anemia can wreak havoc on women reproductive system, leading to an erratic menstrual cycle, missed periods, and interrupted ovulation. All of these dramatically reduce the chances of conception. [20]. this silent presentation of CD combined with delayed diagnosis may result in prolonged dietary gluten exposure and an extended effect of the disease on women's fertile life span [19]. A gluten-free diet would be an attractive infertility treatment option because of the relatively low cost and absence of significant adverse effects compared to other infertility treatments [21].

Conclusion: This study indicates that silent or sub clinical celiac disease plays an important role in reproductive complication.

Recommendation: Women with fertility disorder have to examine for celiac disease.

References:

1. Kumar, A. , Meena, M. , Begum, N. , Kumar, N. , Gupta,R. K. ,Aggarwal, S.,Prasad,S.and Batra,S. **2011**. Latent celiac disease in reproductive performance of women. *Fert. Ster*, 95 (3), pp:922-927.
2. Guandalini, S. and Assiri, A. **2014**.Celiac disease: a review. *JAMA. Pediatr*, 168 (3), pp:272-278.
3. Fasano, A.and Catassi,C. **2012**.Celiac disease.*N.Eng.J.Med*,367,pp:2419-2426.
4. Kupfer, S.S. and Jabri, B. **2012**.Celiac disease pathophysiology.*Gastrointest.Endosc.Clin.N.Am*, 22(4),pp:10-1016.
5. Tiboni, G. M., Vita, M.G., Faricelli, R., Giampietro, F. and Liberati, M. **2005**. Serological testing for celiac disease in women undergoing assisted reproduction techniques. *Hum.Repro.Advan.Acc*, 13,pp:1-4.
6. Melonil,G.F., Dessole, S., Vargiu, N.,Tomasi, P.A. and Musumecil,S. **1999**.The prevalence of celiac disease in infertility.*Hum.Reprod*,14(11), pp:2759-2761.
7. Martha. **2011**. Unexplained infertility higher in woman with gluten sensitivity. *Glu.Free.Soci*, 8, pp:1-9.
8. Jackson, J.E., Rosen, M. and McLean, T. **2008**.Prevalence of celiac disease in a cohort of women with infertility.*Fert.Ster*,89, pp:1002-1004.

9. Gasbarrini, A., Torre, E.S., Trivellini, C., De Carolis, S., Caruso, A. and Gasbarrini, G. **2000**.Recurrent spontaneous abortion and intrauterine fetal growth retardation as symptoms of celiac disease. *Lanc*, 356, pp: 399-400.

10. Rapaport, L. **2015**. Celiac disease might explain fertility problems. *J.Clin.Gastroenterol*, 145, pp:1-2.

11. SAS. **2012.** Statistical Analysis System, User's Guide. Statistical. Version 9.1th ed. SAS. Inst. Inc. Cary. N.C. USA.

12. Schyum, A.C. and Rumessen, J.J. **2013**. Serological testing for celiac disease in adult.*United. European.Gastroenterol. J*, 1(5), pp:319-325.

13. Moleski, SM., Lindenmeyer, C.C., Veloski , J.J., Miller, R.S., Miller, C.L, Kastenberg, D. and DiMarino , A.J. **2015**. Increased rates of pregnancy complications in women with celiac disease. *Ann.Gasstroenerol*, 28(2), pp:236-240.

14. Choi, J.M., LebwohlB., Wang , J., Lee , S.K., Murray, J.A.,Sauer, M.V. and Green, P.H. **2011**. Increased prevalence of celiac disease in patients with unexplained infertility in the United States. *J. Reprod. Med*, 56(5-6),pp:199-203.

15. Zugna, D., Richiardi, L., Akre, O., Stephansson, O., Ludvigsson, J. **2010**.Women with undiagnosed celiac disease have lower fertility. *Gut*, 59(11), pp:1471-1475.

16. Machado, A.P., Silva, L.R., Zausner , B., Oliveira , A., Diniz , D.R. and Oliveira , J. **2013**. Undiagnosed celiac disease in women with infertility. *J. Reprod . Med*,58 (1-2),pp: 61-66.

17. Khoshbaten , M.., Nejad , M.R., Farzady , L., SHarifi , N., Hashemi , S.H. and Rostami , K. **2011**. Fertility disorder associated with celiac disease in males and females: fact or fiction?.*J. Obstet. Gynecol.Res*,37(10),pp:1308-1312.

18. Dhalwani, N.N. **2014**. Celiac disease not associated with increased risk for fertility problems in women.*Gastroenterol*, 147, pp:1267-1274.

19. Riddle, M.S., Murray, J.A. and Porter, C.K. **2012**. The incidence and risk of celiac disease in a healthy US adult population. *Am.J. Gastroenterol*, 107, pp: 1248-1255.

20. Schuster, D.B and Doula, C.H.**2014**. Celiac disease increases risk of infertility.*Nat.Fer.Web.Site.*

21. Ludvigsson, J.F., Montgomery, SM. and Ekom, A. **2009**. Small-intestinal histopathology and mortality risk in CD. *JAMA*, 302, pp: 1171-1178.