FERTILITY DISORDERS ASSOCIATED TO COELIAC DISEASE-RETROSPECTIVE STUDY

Cosmin CIORA [1]
Mircea DICULESCU[2]

***ABSTRACT**: THE PURPOSE OF THIS STUDY IS TO EVALUATE THE ASSOCIATION BETWEEN COELIAC DISEASE AND MENSTRUAL CYCLE ABNORMALITIES , FERTILITY DISORDERS OR PREGNANCY ASSOCIATED COMPLICATIONS.*
***METHOD**: THIS WAS A CASE CONTROL STUDY IN WHICH 32 FEMALE PATIENTS WITH COELIAC DISEASE AND 44 HEALTHY CONTROLS WERE COMPARED, THE MAIN CHARACTERISTICS EVALUATED IN BOTH GROUPS BEING: THE PRESENCE OF MENSTRUAL CYCLE ABNORMALITIES, FERTILITY DISORDERS OR COMPLICATIONS DURING PREGNANCY.*
***RESULTS**: THE ANALYSED GROUP WAS COMPOSED OF 32 WOMEN WITH COELIAC DISEASE AND 44 HEALTHY WOMEN. THE MEAN AGE WAS 31.78 YEARS VS 32.29 YEARS IN CONTROLS. THE FREQUENCY OF AMENORRHEA WAS HIGHER IN THE COELIAC DISEASE GROUP VS CONTROLS (P=0.01). THE STRONGEST ASSOCIATIONS WERE OBTAINED BETWEEN COELIAC DISEASE AND COMPLICATIONS DURING PREGNANCY (P=0.00), MEAN AGE OF MENARCHE (13.65 YEARS VS 12,63 YEARS IN CONTROLS(P=0.00)), MEAN NUMBER OF PREGNANCIES (1.84 VS 2.39 (P=0.005)) .*
***CONCLUSIONS**: THE OCCURRENCE OF A SIGNIFICANT CORRELATION BETWEEN CELIAC DISEASE AND REPRODUCTIVE DISORDERS (MEAN AGE OF MENARCHE, AMENORRHEA, NUMBER OF PREGNANCIES OR COMPLICATIONS DURING PREGNANCY) COULD SUGGEST TO CONSIDER CELIAC DISEASE DIAGNOSTIC PROCEDURES (SEROLOGICAL SCREENING) IN WOMEN AFFECTED BY THESE DISORDERS.*

***KEY WORDS**: COELIAC DISEASE, FERTILITY DISORDERS, PREGNANCY ASSOCIATED COMPLICATIONS, MENARCHE*

INTRODUCTION:

Coeliac disease is an autoimmune chronic illness triggered by diet exposure to gluten, affecting genetically predisposed individuals (1). In general population the prevalence is aprox. 1 % (2) with a female: male ratio of 2.5: 1 (3). There are several studies in the literature reporting a higher prevalence of Coeliac disease in females with fertility disorders or in females with complications during pregnancy(4), the reciprocity being also described.

CELIAC DISEASE AND INFERTILITY

Coeliac disease is an autoimmune ilness affecting multiple organs but the symptoms are less specific, this being the cause for delayed diagnosis or even misdiagnosis. The diagnostic delay may lead to development of major complications in the long term. If once it was considered a rare disorder, nowadays 1 person in one hundred is estimated to suffer from

[1] Gastroenterology and Hepatology Center, Fundeni Clinical Institute; Assistant professor UMF Carol Davila Gastroenterology and Hepatology Center Fundeni; cioracsz@yahoo.com
[2] Gastroenterology and Hepatology Center, Fundeni Clinical Institute

this disease. Despite the high prevalence, more than 95 % of patients remain undiagnosed and this happens because almost 38 % of them are asymptomatic or are misdiagnosed given the nonspecific complainings.

Lately, coeliac disease is considered a silent ilness , having few clinical manifestations or discrete gastrointestinal symptoms , such as moderate diarhhea. Females with fertility disorders or pregnancy associated complications have no other symptoms suggesting the background disease, some of them having as the only complaint a slight fatigue due to iron deficiency anemia. In many cases these fertility disorders , late menarcha, or early onset of menopause can be the only manifestations that can raise the suspicion of coeliac disease (6). These problems may be due to autoimmune complications or nutritional deficits associated with the disease (7). The highest prevalence of the disease is met in females during their reproductive life.

The "classical" ilness symptoms are gastrointestinal (chronic watery diarhhea,abdominal pain and bloating, nausea) and symptoms associated with malabsorption (weight loss despite normal apetite, growth stopping in children). Atypical disease is described in case of minimal or no gastrointestinal symptoms. In these cases the patient presents with iron deficiency anemia, growth deficit, osteoporosis, infertility. Atypical disease is more frequent than the classical one, but it is often misdiagnosed because of non gastrointestinal symptoms.

There are several data that sustain a positive correlation between nutritional deficits/inflammatory response and the appearance of fertility problems,although the pathogenesis is not fully known(8). The malabsorption leads to nutritional deficits that have a clear effect on reproductive function, although in females with coeliac disease this connection cannot be fully proven, so it is less probable that the malabsorption is the only implicated mechanism.(9)

METHODS: This was a case control study in which 32 female patients with coeliac disease and 44 healthy controls were compared, the main characteristics evaluated in both groups being : age of menarche, amenorrhea, number of pregnancies, complications during pregnancy, menstrual cycle abnormalities, number of misscariages and pregnancy duration.

Females between 18 and 50 years were included, with diagnosis of coeliac disease being set during pregnancy or postpartum , based on serologic testing : tTG IgA (1st choice in suspected CD according to latest guidelines) , AGA and anti DGP. 30 women out 32 included accepted gastrointestinal endoscopy as a method of diagnosis and in all cases the serological diagnosis was confirmed on biopsy. The other data were collected during a telephonic interview or from patients` datacharts.

The diagnosis was supported by tTGA positiviy in 26 cases (81%) , EMA in 8 cases (25%) and anti DGP in 12 cases (37 %). Gastroscopy was performed in 30 women out of 32, and the histological diagnosis was positive for coeliac disease in all cases. HLA testing was not performed. All patients were already following a gluten free diet when included in the study..

Statistical and graphical evaluations were performed with OriginPro8 programme. P Test (TTEST function- returns probability t`Student) is statistically significant when values are less or equal to 0.05.

RESULTS:

A number of 76 patients were investigated ,out of which 44 healthy controls (without coeliac disease) and 32 patients with coeliac disease. On the following presentation we will refer to 2 independent groups. We also mention the following:

Healthy controls group, n=44

Coeliac disease group , n=32

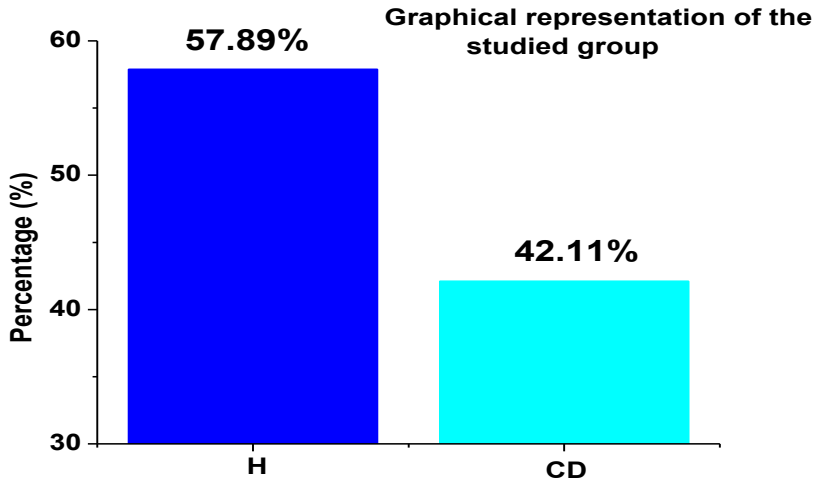

Figure 1. Procentual representation of the 2 groups components

The graphical design was performed using OriginPro8 programme.

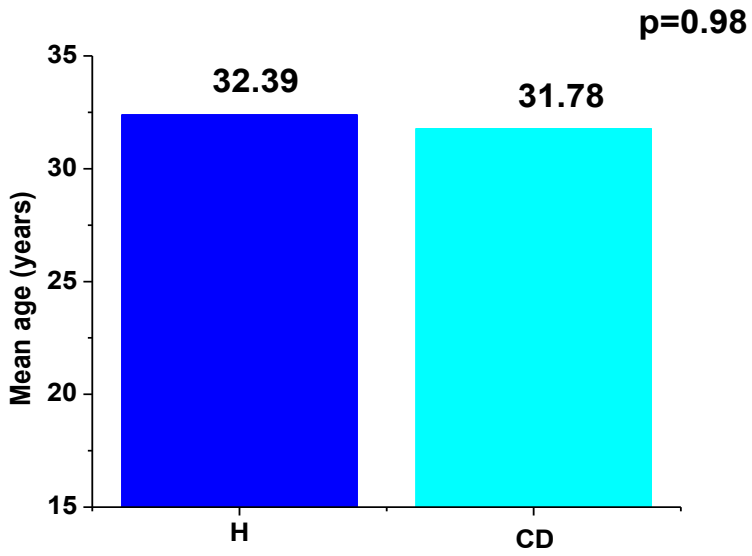

Figure 2. Median age in the 2 groups: healthy control group (marked as H) and coeliac disease group (marked as CD)

This graphic shows that the median age is similar in the 2 groups studied (p =0.98)

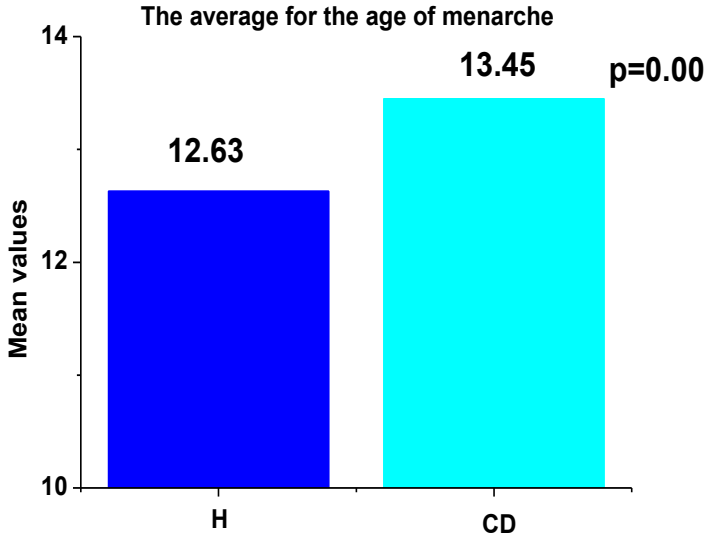

Figure 3. Age on menarche

Mean age on menarche is 12.63 in healthy females vs 13,45 in coeliac disease, suggesting late menarche in coeliac disease group is statistically significant. The late menarche and early menopause in coeliac disease is considered an indirect factor of infertility(13).

The age at menarche in patients with CD and FGD is decreased to age at menarche in mother's, but is higher in the untreated CD patients and mother's. These findings support the hypothesis that the age at menarche in girls with coeliac disease is regulated by gluten-free diet and by other genetic and environmental factors

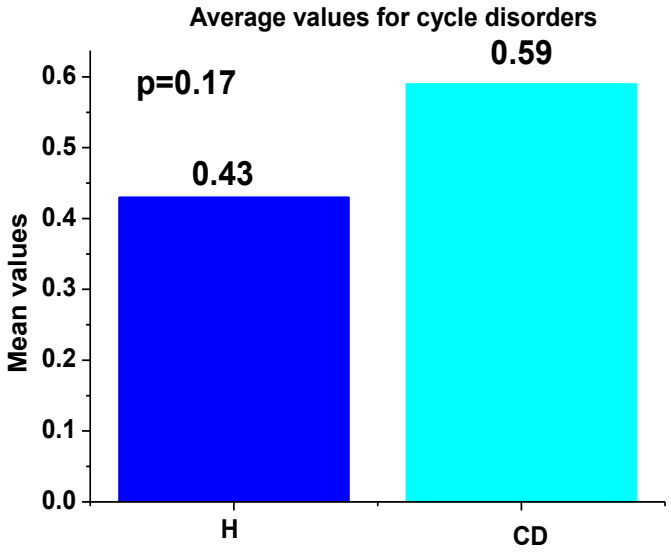

Figure 4. Menstrual cycle disorders (oligomenorrhea, hypomennorhea, metrorrhagies, premenstrual syndrome) were more prevalent in CD group (no statistical significance –p=0.17)

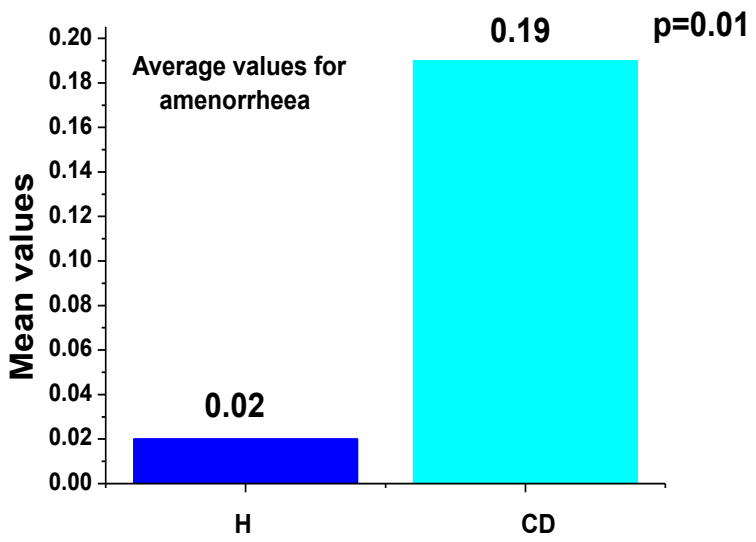

Figure 5. For p=0.01 amenorrhea-CD association is statistically significant.

It is known that higher prevalence of amenorrhea in women with celiac disease is a factor of subfertility. Amenorrhea may be the first manifestation of celiac disease. 19.4% frequency of amenorrhea was reported among celiac women versus 2.2% among healthy controls (14).

Celiac disease should be considered in patients presenting with malnutrition and primary amenorrhea.

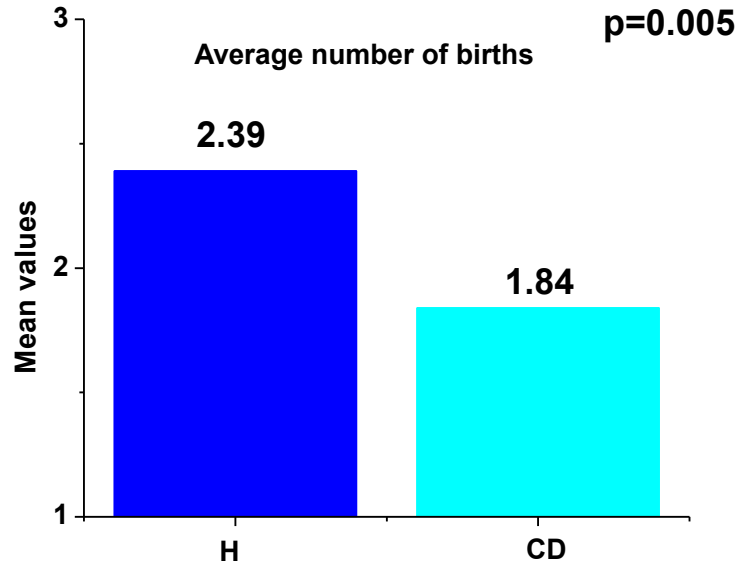

Figure 6. Number of pregnancies in the 2 groups studied

In this graphical representation it can easily be observed the difference between the 2 groups (p-0.005), concluding that the number of pregnancies is significantly lower in the

Coeliac disease group when compared with the general population. This difference is no longer seen when free-gluten diet is adopted. Also, some studies attest a higher age of the mother when the first child is born in coeliac disease group compared to the general population.(7)

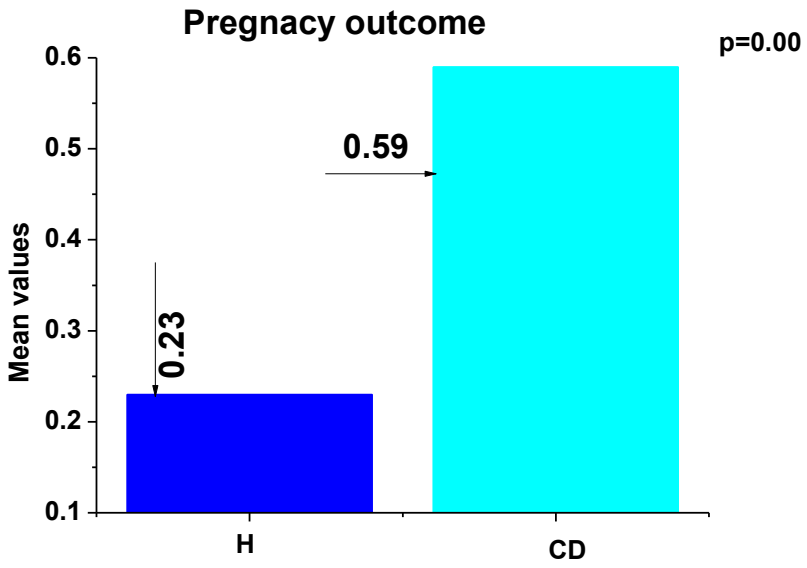

Figure 7. Pregnancy disorders associated with celiac disease are statistically significant p = 0.00. The association is statistically significant in this study. This association is reported by several studies in relation to nutritional deficiencies or immune-mediated mechanisms.

The number of misscarriages is higher in the celiac disease group , but this theory has no statistical significance(p 0.39). The pregnancy duration is lower in CD, this also having no statistical significance (p 0.11). Premature birth was defined as giving birth before 37 weeks of pregnancy.

DISCUSSION

Coeliac disease is rarely considered as a diagnosis when evaluating infertility , and the literature term for this connection is “neglicted clinical association”. In North America 7-14 % of the women are infertile. Among these ,aprox 15 % have idiopathic infertility, once the anatomic and endocrine causes are excluded(10). This leads to the conclusion that aprox 1 % of women suffer from idiopathic infertility. Female patients with Coeliac disease may present with amenorrhea, repeated spontaneous misscarriages, iron deficiency anemia, premature births, low weight babies on birth, but sometimes they may be completely asymptomatic (11). If we consider the mean age on diagnosis as 40-50 years and the delay in diagnosing, we can say that most of the women suffering from Coeliac disease un diagnosed when they are close to menopause. This means that most of their reproductive life can be affected by a undiagnosed coeliac disease (12).

There are several studies in the literature evaluating the association between coeliac disease and menstrual cylce disorders, fertility problems and complications during pregnancy (3).

In this study the age on menarche was significantly higher in coeliac disease patients comparing to healthy controls. This is also available for females complaining of menstrual cycle abnormalities. Most of the patients described thes disturbance as first manifestation of disease.

The study also proved the association of coeliac disease with complications during pregnancy. The misscarriage rate was double in the coeliac disease group compared to the healthy controls, but the association was not statistically significant, and this may be due to reduced number of cases. The rate of complications during pregnancy (severe anemia, uterine hiperkinesia, intrauterine growth deficit, miscarriage imminence, pregnancy related hypertension) was significantly higher in Coeliac disease as in healthy controls. Also, a shorter duration of pregnancy was observed in patients affected by the disease, but this observation was not proven to be statistically significant.

The number of babies born by coeliac disease affected females was significanlty lower than the one of healthy ones.

Most of the females cu coeliac disease had a histological confirmed diagnosis (30 of 32) and this percentage is so high probably because the illness was diagnosed in a tertiary center of Gastroenterology.

The study described a significant association between late menarcha, number of pregnancies, amenorrhea and complications during pregnancy , suggesting the fact that coeliac disease is a potential cause for all these fertility related problems. As serological screening is easily performed and its cost is not high compared with all the other tests performed in investigating feritilty disorders, it seems rational that serological tests should be performed as routine investigation in these cases. The recommended strategy is individually case-oriented.

REFERENCES

1. Review Celiac disease. Karandish E, Hachem C. Mo Med. 2009 Sep-Oct; 106(5):346
2. Characteristics of adult celiac disease in the USA: results of a national survey.Green PHR, Stavropoulos SN, Panagi SG, Goldstein SL, Mcmahon DJ, Absan H, Neugut AI
3. Coeliac disease.Review. Green PH, Jabri B. Lancet. 2003 Aug 2; 362(9381):383-91
4. Celiac disease and its effect on human reproduction: a review. Soni S[1], Badaw J Reprod Med. 2010 Jan-Feb;55(1-2):3-8.y SZ
5. Dyspepsia and celiac disease: Prevalence, diagnostic tools and therapy. Petrarca L, Nenna R, Mastrogiorgio G, Florio M, Brighi M, Pontone S. World J Methodol. 2014 Sep 26;4(3):189-96. doi: 10.5662/wjm.v4.i3.189. eCollection 2014.
6. Ginekol Pol. 1999 May;70(5):359-62. [Age at menarche in girls with celiac disease].Rujner J
7. Reproductive life disorders in Italian celiac women. A case-control study. Domenico Martinelli, Francesca Fortunato, Silvio Tafuri, Cinzia A Germinario, BMC Gastroenterol 2010; 10:89.
8. Review [Reproductive aspects of celiac disease]. Stazi AV, Trinti B. Ann Ital Med Int. 2005 Jul-Sep; 20(3):143-57.
9. Anti-tissue transglutaminase antibodies from celiac patients are responsible for trophoblast damage via apoptosis in vitro.Di Simone N, Silano M, Castellani R, Di Nicuolo F, D'Alessio MC, Franceschi F, Tritarelli A, Leone AM, Tersigni C, Gasbarrini G, Silveri NG, Caruso A. Am J Gastroenterol. 2010 Oct; 105(10):2254-61.
10. **Stephen EH, Chandra A**. Declining estimates of infertility in the United States: 1982–2002. Fertil.Steril 2006;86(3):516–523. [PubMed: 16952500
11. Clinical Utility of Serologic Testing for Celiac Disease in Asymptomatic Patients.An Evidence-Based Analysis.Ont Health Technol Assess Ser. 2011; 11(3): 1–63.
12. Reproductive changes associated with celiac disease. Hugh James Freeman. World J Gastroenterol. Dec 14, 2010; 16(46): 5810–5814.
13. From menarche to menopause: the fertile life span of celiac women.Santonicola A[1], Iovino P, Cappello C, Capone P, Andreozzi P, Ciacci C. Menopause. 2011 Oct;18(10):1125-30.
14. A risk factor for female fertility and pregnancy: celiac disease.Stazi AV[1], Mantovani A. Gynecol Endocrinol. 2000 Dec;14(6):454-63.