PREVALENCE OF CELIAC DISEASE IN WOMEN WITH FERTILITY DISORDERS

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ABSTRACT:
BECAUSE SUBCLINICAL CELIAC DISEASE MAY DECREASE FERTILITY OR COMPLICATE PREGNANCY, WE SCREENED WOMEN WITH FERTILITY DISORDERS AND WOMEN WITH FUNCTIONAL DYSPEPSIA, FOR ANTI-TISSUE TRANSGLUTAMINASE ANTIBODIES IN SERUM TO FIND UNDIAGNOSED CELIAC DISEASE
***METHOD**: WE SCREENED WOMEN WITH RECURRENT MISCARRIAGE OF UNKNOWN AETIOLOGY (N = 36), UNEXPLAINED INFERTILITY (N = 46) AND WOMEN WITH FUNCTIONAL DYSPEPSIA (N = 112), FOR ANTI-TISSUE TRANSGLUTAMINASE ANTIBODIES IN SERUM TO FIND UNDIAGNOSED CELIAC DISEASE. ONE WOMAN (2.7%) WITH RECURRENT MISCARRIAGE, TWO WOMEN (4.35%) WITH UNEXPLAINED INFERTILITY AND ONE WOMAN IN THE CONTROL GROUP (0.9%), WERE CONSIDERED TO HAVE CELIAC DISEASE. ALL WOMEN WITH POSITIVE SEROLOGIC FINDINGS (4 CASES) UNDERWENT JEJUNAL BIOPSY AND OF THEM HAD HISTOLOGICAL EVIDENCE OF CELIAC DISEASE.*
***RESULTS**: THE PREVALENCE OF CELIAC DISEASE IN INFERTILE WOMEN SEEMS HIGHER (3 OUT OF 82, 3.65%) IN THE STUDY GROUP THAN IN THE GENERAL POPULATION (1 OUT OF 112, 0.9%), AND PARTICULARLY IN THE SUBGROUP WITH UNEXPLAINED INFERTILITY (2 OUT OF 46, 4.35%)*
***CONCLUSIONS**: UNDIAGNOSED CELIAC DISEASE IS A RISK FACTOR FOR INFERTILITY AND RECURRENT MISCARRIAGE OF UNKNOWN AETIOLOGY. WOMEN SEEKING MEDICAL ADVICE FOR THIS PARTICULAR CONDITION SHOULD BE SCREENED FOR CELIAC DISEASE. ADOPTION OF A GLUTEN-FREE DIET COULD HAVE A POSITIVE IMPACT ON FERTILITY IN THIS GROUP OF PATIENTS. IT SEEMS RATIONAL THAT SEROLOGICAL TESTS SHOULD BE PERFORMED AS ROUTINE INVESTIGATION IN THESE CASES. THE RECOMMENDED STRATEGY IS INDIVIDUALLY CASE-ORIENTED.*

KEY WORDS: CELIAC DISEASE, INFERTILITY, ANTI-TISSUE TRANSGLUTAMINASE ANTIBODIES, JEJUNAL BIOPSY, RECURRENT ABORTION

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INTRODUCTION: Celiac disease is a unique autoimmune disorder, unique because the environmental precipitant is known. The disorder was previously called celiac sprue, based on the Dutch word *sprue*, which was used to describe a disease similar to tropical sprue that is characterized by diarrhea, emaciation, aphthous stomatitis, and malabsorptin (1). Celiac disease is precipitated, in genetically predisposed persons, by the ingestion of gluten, the major storage protein of wheat and similar grains.

The prevalence of dyspepsia is up to 40% in population-based study. Functional dyspepsia is an exclusion diagnosis and it is classified as a chronic abdominal pain-related functional disorder, characterized by the presence of persistent or recurrent pain or discomfort centered in the upper abdomen, neither relief by defecation, nor association with the onset of a change in stool frequency or form (2). Celiac disease (CD) is a common autoimmune enteropathy, with a prevalence around 1% in the general population. The prevalence of CD is higher in patients with dyspepsia, but not in a statistically significant way (5).

CELIAC DISEASE AND INFERTILITY

The highest prevalence of the disease is met in females during their reproductive life (6). Celiac disease is seldom considered in the evaluation of infertility, and the link between the two has been referred to many times in the literature as a 'neglected clinical association'. It is estimated that approximately 7.4–14% of women are infertile in North America, with 15% of this infertility attributed to unexplained factors after hormonal and anatomical causes have been ruled out (3). Higher prevalence of CD in unexplained infertility was again demonstrated in an Italian study investigating the prevalence of CD in women undergoing assisted reproductive techniques (ARTs) (3). Undiagnosed CD may be particularly devastating in women who experience recurrent abortions and perinatal complications (4).

The increased proportion of nondiarrheal celiac disease has been attributed to the introduction of serologic testing and increased awareness among practicing clinicians. Women having unexplained infertility, recurrent abortions, stillbirths, or IUGR could have subclinical celiac disease, which can be detected by serologic screening tests. Therefore, consideration should be given to serologic screening for celiac disease in patients with poor reproductive performance.

Undiagnosed CD is in fact a risk factor for infertility. This may have a significant impact on the management of infertility, since women seeking medical advice for this particular condition should be screened for CD. Ultimately, adoption of a GFD could have a positive impact on fertility in this group of patients.

CELIAC DISEASE AND FUNCTIONAL DYSPEPSIA

Celiac disease is still under diagnosed in all age groups; the form with obvious symptoms is found in only a limited number of cases; in most patients, particularly adults, the disease has an atypical symptomatology or is completely silent. As regards mass screening, at the moment there is no evidence that supports this approach, since in the apparently healthy population the prevalence of CD varies in relationship with geographical areas [9]. Furthermore, a cost-effectiveness analysis in support of a mass screening program has not been performed. Case-finding is believed to be the most appropriate diagnostic approach to adopt for asymptomatic patients or for patients with subtle clinical features. This approach is particularly effective and becomes more so if in the selection of subjects to be investigated their family doctors are involved. The activation of a celiac awareness program in the primary-care setting focusing on selective serological screening of high risk groups has doubled the number of cases diagnosed from among the adult asymptomatic population.

It was recently observed that CD had a greater prevalence, with respect to the general population, in dyspeptic patients and that 30%-40% of CD patients have dyspeptic symptoms. Recent investigations have shown that most patients affected by CD, in particular adults, do not have the typical symptoms of the disease, thus they remain misdiagnosed, delaying the diagnosis until an older age. In a study conducted on paucisymptomatic patients over 65 years old that had seen both family doctors and specialists, it was documented that the correct diagnosis was made with an average delay of 28 years. Several studies performed celiac disease screening in patients with symptoms suggestive of dyspepsia, showing a biopsy-proved prevalence that ranged from 0.5% to 2% (5).

In a recent meta-analysis by Ford *et al* (14), the authors provided a pooled prevalence of biopsy-proven CD of 1.0%, similar to that in the general population, when duodenum biopsy was performed as first-line investigation.

METHODS: We screened women with recurrent miscarriage of unknown aetiology (n = 36), unexplained inferti lity (n = 46) and women with functional dyspepsia (n = 112), for anti-tissue transglutaminase antibodies in serum to find undiagnosed coeliac disease. One woman (2.7%) with recurrent miscarriage, two women (4.35%) with unexplained infertility and one woman in the control group (0.9%), were considered to have coeliac disease. All women with positive serologic findings (4 cases) underwent jejunal biopsy and all of them had histological evidence of coeliac disease. Infertility was attributed to unexplained factors after hormonal and anatomical causes have been ruled out (3,8).

Spontaneous pregnancy loss is a surprisingly common occurrence, with approximately 15% of all clinically recognized pregnancies resulting in pregnancy failure. Recurrent pregnancy loss (RPL) has been inconsistently defined. When defined as 2 consecutive pregnancy losses prior to 20 weeks from the last menstrual period, it affects approximately 1% to 2% of women.

Clinical evaluation for recognized causes of reccurent abortion was performed at the discretion of the physician and included testing for uterine abnormalities, parental karyotype defects, endocrinological abnormalities, antiphospholipid syndrome, luteal phase defects, and heritable thrombophilias. Women were excluded from the final analysis if testing indicated a potential etiology for their RPL. None had clinical features of celiac disease.

Functional dyspepsia (FD) is a condition commonly seen in gastroenterological practice. With the introduction of Rome III criteria in 2006, a new approach for categorizing patients has been recommended (9),

Table 1. Rome III Diagnostic Criteria for Functional Dyspepsia

Functional Dyspepsia
At least 3 months, with onset at least 6 months previously, of 1 or more of the following: 1. Bothersome postprandial fullness 2. Early satiation 3. Epigastric pain 4. Epigastric burning 5. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

The diagnosis was supported by tTGA positiviy in all cases. Anti-tTG have a high specificity and sensitivity in the screening of celiac disease, while requiring a second method of confirmation (13). Gastroscopy was performed in 4 women out of 4, and the histological diagnosis was positive for coeliac disease in all 4 cases. HLA testing was not performed. All patients were following a normal 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 194 patients were investigated, out of which 112 healthy controls (without celiac disease) and 82 patients with infertility disorders- 36 with recurrent miscarriage of unknown aetiology (n = 36), unexplained infertility (n = 46). On the following presentation we will refer to 3 independent groups.

We also mention the following:

Healthy controls group, n=112

Recurrent miscarriage of unknown aetiology, n = 36

Unexplained infertility, n = 46

The graphical design was performed using OriginPro8 programme.

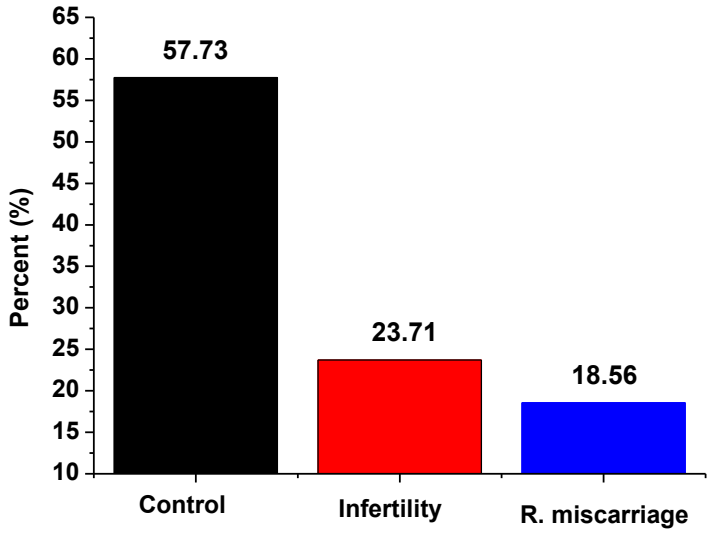

Figure 1. Procentual representation of the 3 groups components

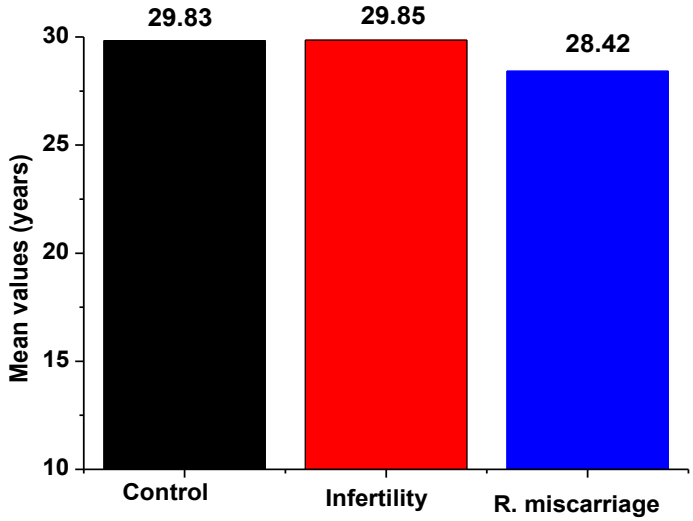

Figure2. The mean age of women with a history of recurrent spontaneous abortion were 28.42 years, of women with infertility 29.85 years, and of control women 29.83 years respectively.

N total	Mean	Standard Deviation	SE of mean	Lower 95% CI of Mean	Upper 95% CI of Mean	Minimum	Median	Maximum
112	29.83036	4.72274	0.44626	28.94607	30.71465	21	29	41
46	29.84783	4.16316	0.61382	28.61152	31.08413	22	29	37
36	28.41667	4.12224	0.68704	27.0219	29.81143	21	28	37

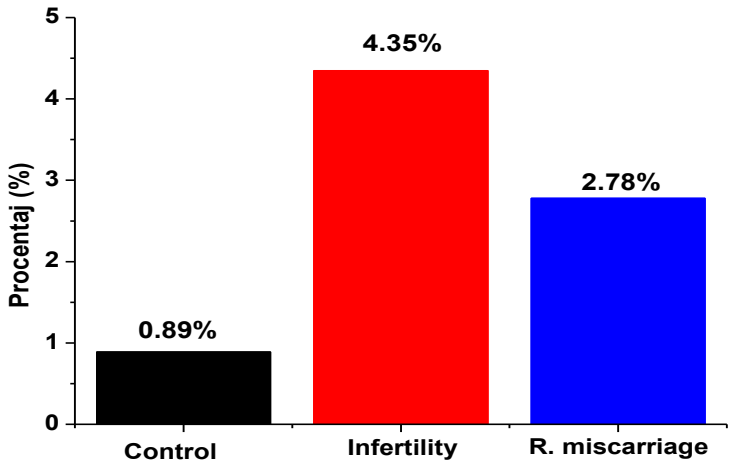

Figure3. One (2.78%) of 36 subjects in the group with recurrent spontaneous abortion 2 (4.35%) of 46 women in the group with infertility, and 1 (0.89%) of 112 in the control group were tested positive for IgA tTG

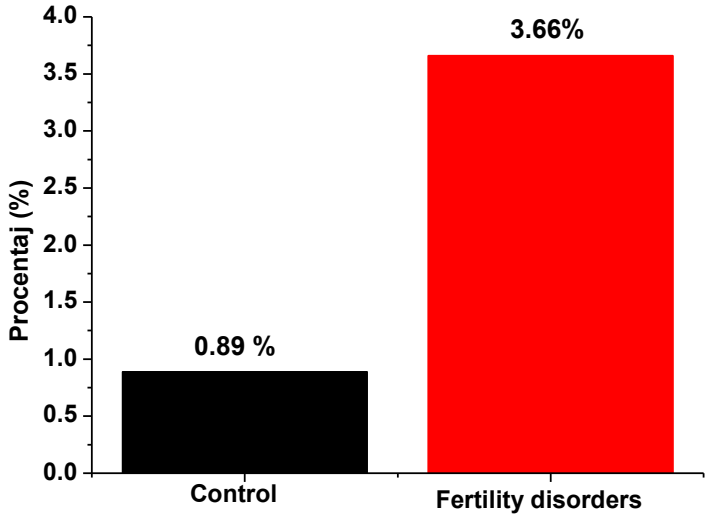

Figure 4. Three (3.66%) of 82 subjects in the group fertility disorders (recurrent spontaneous abortion and idiopathic infertility, and 1 (0.89%) of 112 in the control group were tested positive for IgA tTG

The prevalence of anemia in IgA tTG–seropositive women in the group with recurrent spontaneous abortion was 100%, in the group with infertility 50%, and in the control group 0%

None of the 4 IgA tTG–seropositive women had overt signs of malnutrition, showed stunting of growth, or were underweight. Therefore, nutritional factors were probably not of major importance in unfavorable pregnancy outcomes.

Agreater prevalence of positive serology for celiac disease was seen in patients with hemoglobin<12 gm/dL (15). Iron and folate deficiency anemia are seen more often in patients with celiac disease because these nutrients are absorbed in the upper two parts of the intestine where damage can occur in earlier stages. Anemia without other clinical clues of intestinal malabsorption is one of the most common extraintestinal manifestations of celiac disease (15, 16). The number of seropositive subjects with anemia is too small to draw any significant conclusion.

DISCUSSION

Celiac disease is rarely considered as a diagnosis when evaluating infertility (6), and the literature term for this connection is “neglicted clinical association” (7). 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 celiac 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 (11,18). 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 presently no guidelines for CD testing in patients with infertility or in women with a history of adverse pregnancy outcomes, although CD prevalence has been shown to be

higher in these groups than in the general population (8). Owing to the higher risk of CD in these populations, and the likelihood that the GFD improves pregnancy and fertility outcomes, we argue that given the low cost of serological screening compared with the great medical expense associated with infertility and complications of pregnancy, CD testing should be strongly considered.

Undiagnosed CD is in fact a risk factor for infertility. This may have a significant impact on the management of infertility, since women seeking medical advice for this particular condition should be screened for CD. Ultimately, adoption of a GFD could have a positive impact on fertility in this group of patients.

„ACKNOWLEDGEMENT: This paper is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/132395”

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