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Increased Prevalence of Celiac Disease in Patients with Unexplained Infertility in the United States: A Prospective Study

Janet M. Choi, M.D.,
Columbia University, Center for Women's Reproductive Care, 1790 Broadway, 2nd floor, New York, New York 10019, jmc30@columbia.edu, Phone: 646-756-8282, Fax: 646-756-8280

Benjamin Lebwohl, M.D., M.S.,
Celiac Disease Center at Columbia University, Harkness Pavilion, 180 Fort Washington Avenue, Suite 934, New York, New York 10032, bl114@columbia.edu

Jeffrey Wang, M.D.,
Columbia University, Center for Women's Reproductive Care, 1790 Broadway, 2nd floor, New York, New York 10019, jw781@columbia.edu

Susie K. Lee, M.D.[1],
Celiac Disease Center at Columbia University, Harkness Pavilion, 180 Fort Washington Avenue, Suite 934, New York, New York 10032, gisusie@yahoo.com

Joseph A. Murray, M.D.,
Mayo Clinic, 200 First Street, SW, Rochester, Minnesota 55905

Mark V. Sauer, M.D., and
Columbia University, Center for Women's Reproductive Care, 1790 Broadway, 2nd floor, New York, New York 10019, mvs9@columbia.edu

Peter H. R. Green, M.D.
Celiac Disease Center at Columbia University, Harkness Pavilion, 180 Fort Washington Avenue, Suite 934, New York, New York 10032, pg11@columbia.edu

Abstract

Celiac disease is an autoimmune disorder which can present with a variety of non-gastrointestinal manifestations. In women, it may manifest with an assortment of gynecologic or obstetric disorders. Some reports have linked female infertility with undiagnosed celiac disease. Though there are a number of studies from Europe and the Middle East, only two prior American studies have examined the prevalence of "silent" celiac disease in a female infertility population. We prospectively performed serologic screening for celiac disease in 188 infertile women (ages 25–39). While we did not demonstrate an increased prevalence of celiac disease in our overall infertile female population, we were able to detect a significantly increased prevalence (5.9%) of undiagnosed celiac disease among women presenting with unexplained infertility (n=51). Our findings suggest the importance of screening infertile female patients, particularly those with unexplained infertility, for celiac disease.

Keywords

Female infertility; celiac disease

Correspondence to: Janet M. Choi.
[1]Present address: Saint Barnabas Hospital, Department of Gastroenterology, 4422 Third Avenue, Bronx, New York 10457

Introduction

Celiac disease is a chronic autoimmune disorder triggered by the ingestion of gluten, the protein found in wheat, barley and rye. 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[1]. With improvements in screening serology for celiac disease, more patients are being diagnosed due to non-gastrointestinal presentations.

Several studies have demonstrated implications of celiac disease on the reproductive health of women. For instance, untreated maternal celiac disease may be associated with recurrent fetal loss, [2, 3] intrauterine growth restriction, preterm delivery and low-birth weight. [4, 5, 6, 7] Reports have also suggested an association between gynecologic disorders such as endometriosis[8] or amenorrhea [7,9,10] and celiac disease.

Some series suggest a higher prevalence of undiagnosed celiac disease in patients with infertility.[3, 11, 12, 13, 14] The prevalence in these series ranges from 2–6% as compared with almost 1% in the general population.[14] Other authors do not show an increased prevalence. [15,16] Establishing the actual prevalence of celiac disease in infertile populations would be an important step in determining if any sub-groups of infertile patients should be screened for the presence of celiac disease.

Overall, celiac disease is considered to occur in about 1% worldwide, with some variations in different populations; higher rates being observed in European, Middle Eastern and North African regions and much lower rates in Southeast Asian countries.[17,1,18] Given the prevalence variability and given that most of the earlier studies examining celiac disease prevalence in infertile women were conducted in Europe (only two studies to date have been conducted in the United States [14, 15]), we attempted to determine the prevalence of celiac disease in a more heterogeneous population of infertile North American women. Identifying infertile woman with celiac disease would potentially be beneficial if a gluten-free diet could improve fertility and pregnancy outcomes.

Methods

We enrolled 191 patients, ages 25–39, who presented to our center for care of either primary or secondary infertility of at least 12 months duration. Patients were recruited on a volunteer basis after study approval was obtained from our university's Institutional Review Board. We compared the prevalence of celiac disease in this infertile population to the expected prevalence of celiac disease in this age range based on a well-defined population in the United States (Olmstead County, Minnesota; J Murray, personal communication). For our entire screened sample, we calculated the point prevalence of celiac disease with 95% confidence intervals. We then repeated this prevalence estimate and comparison restricted to those subjects who were deemed to have unexplained infertility.

Patients underwent basic infertility screening including ovarian reserve testing (day 2 estradiol and FSH and/or Anti-Mullerian Hormone (AMH) levels), hysterosalpingogram (HSG), TSH, prolactin, and a semen analysis for the male partner. Several patients also underwent laparoscopy to screen for endometriosis. Etiologies for infertility included decreased ovarian reserve (MIS <0.4ng/ml or day 2 FSH >=12mIU/ml); male factor (if semen analysis demonstrated at least one of the following: concentration <20million/ml, motility<50%, morphology< 10%, using the Kruger comparison where normal >=15%); tubal factor (if one or both of the tubes were occlued on HSG or if the patient reported a prior history of ectopic); uterine factor, endometriosis, ovulatory dysfunction (either due to polycystic ovarian syndrome or hypotholamic dysfunction) as well as unexplained (for

patients who had normal results on basic infertility screening). The age range and types and etiologies of infertility are shown in Table I.

All participating patients completed a questionnaire regarding the presence of gastrointestinal symptoms.

Patients who were recruited into this study then underwent serologic screening for tissue transglutaminase (TTG IgA, ELISA) and endomysial antibodies (EMA IgA). Due to the known association of celiac disease with IgA deficiency, measurement of total IgA and anti-gliadin antibodies (both AGA IgG and IgA) was performed to allow for the serologic identification of potential subjects with coeliac disease and IgA deficiency. All serologic testing was performed by Prometheus Laboratories (San Diego, California, United States).

Patients who tested positive on any of the celiac screening tests were informed of their results and advised to seek follow up care with a gastroenterologist and undergo confirmatory diagnosis with endoscopy and small intestinal biopsies. Histologically the degree of villous atrophy was classified according to the modified Marsh criteria.[18] Patients with biopsy confirmed celiac disease underwent nutritional counseling on how to maintain a gluten-free diet.

Results

Among the 191 patients, 3 were excluded because of missing laboratory data. The demographic information and etiologies of infertility for the remaining 188 patients are shown in Table I. Unexplained infertility was present in 51 patients (27%). Gastrointestinal symptoms were common, reported by 55% of the cohort. The most common reported gastrointestinal complaint was bloating (65%), however constipation was reported by 54%, diarrhea 52%, nausea 26% and abdominal cramping 1%. A prior history of an irritable bowel syndrome (IBS) diagnosis was reported by 8%. The prevalence of IBS in the patients diagnosed with celiac disease was 50% in contrast to the 3% IBS prevalence in the remaining 184 infertile patients (p=.0069, Fisher's exact test).

Four of the 188 patients were diagnosed with celiac disease (Table II). The prevalence of previously undiagnosed celiac disease in the cohort of 188 patients was 2.1% (95% CI, 0.8%–5.4%). The expected prevalence for CD in a similarly aged female population from Olmtead County, MN, was 1.3%. A sub-group analysis of celiac disease prevalence in women with unexplained infertility demonstrated a prevalence of 5.9% (95% CI, 1.5%–17.2%). The expected prevalence based on the age distribution of these 51 patients was 1.3%.

Among the four patients with celiac disease, three were identified because of positive anti-tTG IgA antibodies, while one patient with selective IgA deficiency had minimally elevated AGA IgG. Symptoms, serology and endoscopic biopsy results for these four patients are recorded in Table II.

All four patients underwent nutritional counseling concerning the gluten-free diet. All four conceived within a year of their celiac diagnosis and diet changes. Patient A conceived naturally within a month of her diagnosis and diet change. She delivered a healthy daughter at term via primary Cesarean delivery due to fetal intolerance of labor. One month prior to her celiac diagnosis and diet change, patient B underwent an abdominal myomectomy for a rapidly enlarging intramural myoma (20cm in diameter). She conceived naturally four months post-operatively and delivered a healthy daughter at term via primary Cesarean section. Patient C conceived on her third cycle of gonadotropin/IUI therapy, eight months after her celiac diagnosis and delivered a healthy term daughter via normal spontaneous

vaginal delivery. Patient D conceived ten months after her celiac diagnosis through a frozen embryo transfer cycle. She delivered healthy twin boys at 35+weeks via primary Cesarean delivery after she experienced premature preterm rupture of membranes.

Additionally, there were 8 patients who tested positive for either AGA IgG or AGA IgA; they were also advised to follow up with a gastroenterologist. None of these or other patients in the cohort underwent endoscopy.

Discussion

In our screened population of infertile women 2.1% had celiac disease. This was not significantly different from the prevalence in an aged matched North American population. However, there was a statistically significant increased prevalence of celiac disease in patients with unexplained infertility. The prevalence in this subgroup (5.9%) contrasts with the findings of a recent American prospective cohort study which showed no increased celiac disease prevalence in women with unexplained infertility (0.8%).[15] Differences in the ethnic background of patients in the two cohorts may partly explain this disparity. In our study, all four patients who were diagnosed with celiac disease were Caucasian, and only 15% of the screened patients were of East Asian descent while 5% were of South Asian background. In the Jackson series from northern California, 28% of the patients were of general Asian descent. The prevalence of celiac disease is believed to be lower in Asian populations than European or Middle-Eastern populations.[18] But the prevalence appears to be elevated in certain South Asian populations. [17, 18] Our findings are not dissimilar to those from a very large (n=13, 145) study examining the prevalence of undiagnosed celiac disease in American patients of both genders. That study reported a 6.25% prevalence of celiac disease in patients presenting with “idiopathic” infertility though the genders of those patients were not specified.[14]

Our findings raise the possibility that celiac disease is an important association of unexplained infertility. All four patients with celiac disease in our series either reported gastrointestinal symptoms (bloating, diarrhea, constipation) that are known to occur in those with celiac disease, or prior history of IBS. In fact, there was a significantly increased prevalence of IBS in the patients diagnosed with celiac disease compared to the IBS prevalence in the infertile patients without celiac disease. Patients with IBS are known to have an increased rate of celiac disease[20] and it is considered to be cost effective to screen for celiac disease.[21] Therefore, it may be useful to inquire after these symptoms in patients initially presenting for an infertility evaluation. For those patients presenting with both unexplained infertility and any gastrointestinal complaints or history, screening for celiac disease would be appropriate. In fact, given the significantly increased prevalence of celiac disease found in our patients with unexplained infertility (as well as the supporting findings in several previous studies), it may now be reasonable to screen any patient presenting with unexplained infertility, regardless of the absence or presence of gastrointestinal symptoms.

Identifying celiac disease in infertile woman would be beneficial if institution of a gluten-free diet could improve fertility and pregnancy outcomes. This hypothesis is plausible and has been suggested by case reports[22] and small prospective studies [23, 12]. However, this theory has not been rigorously evaluated in clinical trials. 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. Identification of celiac disease in infertile woman would also be helpful given the higher rate of serious illnesses and mortality in patients with untreated celiac disease .[24]

We believe that our testing protocol accurately identified patients with celiac disease. Early generation screening tests that identified antibodies to gliadin, the chief antigenic agent in gluten, were low in both sensitivity and specificity. Current tests for antibodies against tissue translutaminase (TTG IgA) and endomysium are highly sensitive (90%–97%) and specific (96%–100%) [25]. Because up to 2.6% of patients with celiac disease will also have selective IgA deficiency, our assays included a measurement of total IgA as well as AGA IgG antibodies[26]. Patients with abnormal antibodies suggestive of celiac disease were advised to seek expert gastroenterological evaluation.

Our study has several limitations. Despite the large volume of patients seen in our clinic, many patients were reluctant to undergo further testing beyond their standard fertility evaluation. Therefore, our sample size was limited. Since screening was voluntary and not consecutive, there may be significant selection bias. Therefore the findings may not be generalizable to other populations. However, our findings support the hypothesis that celiac disease may be a potentially modifiable risk factor for unexplained infertility and strong consideration should be given to screening all women presenting with unexplained infertility for celiac disease. In the future, a large scale multi-center study prospectively evaluating the prevalence of celiac disease in infertile woman could further clarify these issues.

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Table 1

Patient Demographics and Clinical Diagnosis

Number of Patients Enrolled *(N)*	188
Female Age *(years)*	
Mean±SEM	33.8±0.2
Range	25–39
Female Patient Ethnicity *N (%)*	
Caucasian	119 (63.3%)
East Asian	28 (15%)
Hispanic	17 (9%)
Indian-Asian	10 (5.3%)
Black	10 (5.3%)
Middle Eastern	4 (2.1%)
Etiology of Infertility *N (%)*	
Primary infertility	116 (62%)
Secondary infertility	72 (38%)
Male factor	53 (28.2%)
Unexplained	51 (27.1%)
Ovulatory dysfunction	25 (13.3%)
Decreased ovarian reserve	23 (12.2%)
Endometriosis	18 (9.6%)
Tubal	14 (7.5%)
Uterine	4 (2.1%)

Table II

Clinical Characteristics of Patients Diagnosed with Celiac Disease

Patient	Female Age	Gravidity Parity	Infertility Etiology	GI symptoms	AGA IgG (nl<10U/ml)	AGA IgA (nl<5U/ml)	Total IgA (44–441mg/dl)	TTG IgA (nl<4U/ml)	EMA (nl:-)	Endoscopic findings
A	33	G0	unexplained	bloating, constipation	10.7	0.5	<6.7	0.6	−	Marsh IIIa
B	39	G2P0	uterine	bloating, constipation, diarrhea, history of IBS	3.2	1.6	198	11.8	+	Marsh IIIb
C	38	G1P1	unexplained	none	7.6	1.2	140	9.3	+	Marsh IIIb
D	38	G0	unexplained	bloating, constipation, diarrhea, history of IBS	8.9	2.1	197	4.2	+	Marsh IIIb