Unexplained Infertility and Undiagnosed Celiac Disease: Study of a Multiethnic Canadian Population

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Abstract

Objective: The aims of this study were to examine the prevalence of Celiac disease (CD) in Canadian women with unexplained infertility versus women with an identifiable cause of infertility and to assess the sensitivity of the point-of-care Biocard Celiac Test Kit versus standard serum serologic testing.

Methods: In this prospective cohort study, women aged 18 to 44 who were evaluated for infertility between February 2010 and May 2012 at a tertiary academic care fertility clinic in Toronto, ON, were invited to participate. They were categorized as having unexplained infertility (Cases) or infertility secondary to a known cause (Controls). Women on a gluten-free diet or previously diagnosed with CD were excluded. Outcome measures were the Celiac Questionnaire, serum testing for tissue transglutaminase IgA antibody (anti-tTG IgA), serum IgA levels, and Biocard Celiac Test Kit.

Results: Of 685 women approached, 1.2% (4/326) with unexplained infertility and 1.1% (4/359) with an identifiable infertility cause were newly found to have CD. Biocard testing revealed the same results as standard serologic IgA and anti-tTG IgA testing.

Conclusion: CD was not more common in women with unexplained infertility than those with an identifiable cause of infertility. These results do not support the routine screening of Canadian women with infertility for CD.

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INTRODUCTION

Infertility affects 1 in 6 Canadian couples. In many couples, an identifiable cause, whether isolated female factor, male factor, or a combination of both, can be found. In 10% to 15% of couples, despite extensive evaluation, no obvious etiology for infertility is identified. These couples are categorized as having unexplained infertility and often find themselves spending time and emotional and financial resources pursuing a diagnosis and undergoing treatment. The most effective treatment available, IVF, is costly and results in a live birth in 41% of cycles started in good prognosis patients.[1]

Systemic illness may cause infertility, possibly by subtle effects on the reproductive system. Celiac disease (CD), also known as gluten enteropathy, is a common multifactorial autoimmune disease estimated to affect 1 in 133 Canadians.[2] CD is more common in individuals and families in whom other autoimmune diseases are present, as well as in those of specific ethnic origins. Although those with CD may present with gastrointestinal symptoms or nutritional deficiencies, many affected individuals may have very subtle symptoms mimicking other common disorders. Because of the variability in presentation, CD often goes undiagnosed.

The diagnosis of CD generally begins with screening blood tests for highly sensitive and specific markers. Endomysial IgA antibody (IgA-EMA) and tissue transglutaminase IgA antibody (anti-tTG IgA) are considered the most sensitive serologic screening tests with sensitivities of greater than 90%.[3] Positive screening test requires confirmation by endoscopy and small bowel biopsy. Once the official diagnosis is made, treatment is lifelong adherence to a gluten-free diet.

Over the last number of years, researchers have been investigating the impact of CD on reproductive function. Several studies have suggested that subclinical CD may be a cause of infertility and that institution of a gluten-free diet in such cases may hasten conception.[4–8] Some[5,9–12] but not

all studies[13,14] have demonstrated an increased prevalence of CD in women with unexplained infertility. To date, no studies have assessed prevalence of CD in a Canadian population of women with infertility. As CD occurs at varying rates in different populations, we felt it was important to determine the prevalence of CD in a multiethnic Canadian population to determine if screening should be instituted as a routine part of a fertility evaluation, particularly given that, with a diagnosis of CD, dietary changes alone may improve fertility.

Recently, a simple, rapid (5–10 minutes) and affordable point-of-care ELISA-based CD detection kit that uses a drop of whole blood from a fingertip puncture has been approved for use by Health Canada as a screening tool for the diagnosis of CD (Biocard Celiac Test, 2G Pharma, Canada). In at least one European controlled study, this test has been used with a high degree of specificity and sensitivity (93.5% and 96.7% respectively) compared with traditional serum-based serologic screening tests.[15] Although approved for use in Canada, the sensitivity and specificity of Biocard compared with traditional serum serology has not been determined as a screening test for CD in a Canadian population.

The primary objective of this study was to determine the prevalence of CD in Canadian women with unexplained infertility versus women with an identifiable cause of infertility. A secondary objective was to assess the sensitivity of the "point-of-care" Biocard Celiac Test Kit versus standard serum serologic testing.

METHODS

Women aged 18 to 44 with infertility who were referred to Mount Sinai Fertility at Mount Sinai Hospital in Toronto were approached to take part in the study. Infertility was defined as a lack of conception after a minimum of 12 months of unprotected intercourse. All eligible patients received information about the study. Those who agreed to participate provided written informed consent. Women were excluded if they were currently on a gluten-free diet, had a previous diagnosis of CD, or had IgA deficiency. Enrolment took place between February 2010 and May 2012.

A standard reproductive, general medical, and surgical history was obtained. In addition, a detailed personal and family history of symptoms and conditions associated with a higher prevalence of CD was collected (Celiac Questionnaire). A targeted infertility workup was performed. This included determining the presence of regular ovulation (day 3 FSH, TSH, and Prolactin, menstrual history, luteal phase progesterone levels, and/or cycle monitoring by LH, estradiol determinations, and transvaginal ultrasound follicular tracking); confirmation of at least one patent fallopian tube by hysterosalpingogram, laparoscopy, or sonohysterogram as clinically appropriate; and normal semen analysis.[16] Women were categorized as having either a diagnosed cause of infertility (Controls) or unexplained infertility (Cases). Participants were asked their ethnicity as categorized by the Canadian Census Questionnaire.[17]

Enrolled participants were asked to fill out the Celiac Questionnaire and have a non-fasting blood sample drawn for determination of anti-tTG IgA and serum IgA levels (assays run at reference laboratory, Hospital for Sick Children, Toronto, ON). Concurrently, the participants performed the Biocard point of care Celiac Test kit under the supervision of a clinical research assistant.

Statistical Analysis

Descriptive statistics were used to describe the two populations and the incidence of CD was calculated. Statistical analysis was performed using SPSS (version 22, IBM Corporation, USA).

Sensitivity and specificity of the Biocard Test kit was determined by comparison of results of the test with serum anti-tTG IgA antibody screening results.

Sample Size Determination

With a conservative estimate of a 1% prevalence of CD in women with known infertility and in order to detect a three-fold increase in the incidence of CD in the population with unexplained infertility (3%), we calculated this would require 424 participants (212 per group), assuming a power of 80% and type 1 error of 5%. We assumed a dropout rate of 5%, leaving 445 participants (223 in each group) needing to be recruited.

Ethical Approval

Local research ethics board approval was obtained from the Mount Sinai Hospital Research Ethics Board prior to participant enrollment (REB Protocol 09-0239-E).

RESULTS

A total of 685 patients were approached to take part in the study. Of the women approached, three with unexplained infertility and four with a known cause for their infertility had already been diagnosed with CD and were excluded. An additional nine women with unexplained infertility approached had not been officially diagnosed with CD; however, they were on a gluten-free diet by choice. Eight