Celiac disease is not more prevalent in patients undergoing in vitro fertilization and does not affect reproductive outcomes with or without treatment: a large prospective cohort study

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Objective: To study the prevalence of celiac disease in the infertile population undergoing in vitro fertilization (IVF) and assess outcomes.
Design: Prospective cohort study.
Setting: A single infertility center from January 2016 to March 2017.
Patient(s): Women 18–45 years of age participating in IVF.
Intervention(s): Patients had serum tissue transglutaminase (tTG) and endomysial (EMA) IgA testing to screen for celiac disease and completed a 10-question "yes or no" survey to assess their medical history, previous testing, dietary habits, and pertinent symptoms.
Main Outcome Measure(s): IVF cycle outcomes were compared between seronegative and seropositive patients.
Result(s): Of 1,000 patients enrolled, 995 completed serologic screening and 968 underwent oocyte retrieval. Eighteen patients screened positive for both tTG and EMA (1.8%) and 10 additional patients (1.0%) screened positive for one of the two antibodies. The number of mature oocytes retrieved, fertilization rates, and blastulation rates were equivalent between seronegative and seropositive patients. There were 987 patients who completed the questionnaire (98.7%), and 84 reported being gluten free (8.5%). Those who reported being gluten free were no more likely to be antibody positive than the general population. Furthermore, a low-gluten diet was not associated with markers of ovarian reserve, oocytes retrieved, fertilization, blastulation, sustained implantation and pregnancy loss rates.
Conclusion(s): The prevalence of seropositive celiac disease was consistent with that of the general population (2.8%). Patients who were seropositive for celiac disease–related antibodies had outcomes equivalent to seronegative patients, and patients with a gluten-free diet did not have improved outcomes. (Fertil Steril® 2018;110:437–42. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Celiac disease, gliadin, IVF, gluten

Celiac disease is a systemic autoimmune disease affecting primarily the small intestines; it occurs in genetically susceptible patients and is provoked by the ingestion of gluten. The prevalence of celiac disease is reported to be <1%, although the proportion that screen positive is slightly higher, at ~2%. Women are disproportionately affected in a 3:1 ratio (1–3). The pathogenesis is related to an immune reaction against gliadin, which is a protein found in a diet consisting of wheat, barley, and rye (4).

Although celiac disease has its most well characterized influence on the small intestine, there may be systemic manifestations of inflammation, with many investigators reporting associations between extra-intestinal disorders and celiac. The classic form is most common and presents in childhood with

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diarrhea, anemia, abdominal bloating, and growth retardation. Atypical adult-onset celiac disease occurs in as much as 45% of cases and presents with abdominal pain and bloating, osteoporosis, and nutritional deficiencies (5, 6). From a gynecologic perspective, menstrual irregularities and amenorrhea have been reported. It has also been hypothesized that celiac disease may be involved in the pathogenesis of infertility or subfertility, although the prevalence of disease and its overall role in inducing infertility in the infertile population remain unknown (5–7).

A recent meta-analysis of five studies showed a pooled prevalence of celiac disease of 2.3% in the general population (8). Of note, this particular group of papers made the diagnosis based on a duodenal biopsy showing villus atrophy, not on serology alone. Intestinal biopsy, though the criterion standard for diagnosis, is invasive and extremely impractical for routine clinical use in assisted reproduction patients.

Several strategies for serologic screening have been described, but they typically consist of tissue transglutaminase IgA (tTG) and endomysial IgA (EMA) (6, 9). In fact, the positive predictive value of serologic screening approaches 99% (10). Although serologic diagnosis is slightly more likely to overestimate prevalence, it is much less invasive and more straightforward to incorporate into clinical care. Given that the intervention is simply a change in diet, it seems reasonable to perform the least invasive screening paradigm that is also sensitive and specific.

Beyond the direct evaluation of the relationship of celiac disease and infertility, many individuals are now advocating a gluten-free diet even in the absence of a specific pathologic diagnosis. The concept is not new. The first report of the link came in an early case series of three individuals who initiated a gluten-free diet and had subsequent success conceiving (7). However, there are been many conflicting reports in studies with larger patient populations. The present study therefore sought to study the prevalence of a gluten-free diet in our population in women with no evidence of celiac disease and then to determine if following a gluten-free diet has any measurable impact on clinical outcome.

In summary, this prospective study sought to evaluate the relationship between celiac disease, gluten ingestion, and treatment success in the infertile population undergoing in vitro fertilization (IVF). These might then be used to assess the value, if any, of celiac screening or to determine if there is an indication for advocating a gluten-free diet in the infertile population.

MATERIALS AND METHODS

Population

To answer these questions, a prospective cohort study was performed at a single academically affiliated private practice. The study was approved by the Institutional Review Board, and all patients who were enrolled completed the informed consent process.

Women 18–45 years of age participating in IVF from January 2016 to March 2017 were consecutively recruited for participation. The exclusion criteria included those couples with a sole diagnosis of male-factor infertility and those who were using donor gametes or a gestational carrier. All samples were collected at the time of routine phlebotomy performed as part of routine care.

Defining Celiac Disease and Gluten Exposure

Patients had serum tissue tTG (>20.0 U/mL was considered to be positive) and EMA testing (>20.0 U/mL was considered to be positive) to screen for celiac disease and were divided into two groups: 1) those who displayed serologic evidence of celiac disease; and 2) those who did not. The enzyme immunoassays AntihutransG (Generic Assays) and CeliAK EMA human (Generic Assays) were used for tTG and EMA testing, respectively, following the manufacturer's instructions. To apply the most liberal definition of seropositivity for celiac disease, a patient was considered to be seropositive for the disease if either one of the antibodies was positive. Although the diagnosis of celiac disease is less certain, including these individuals in the celiac group was performed to assure the greatest opportunity to identify a relationship between seropositivity and IVF outcomes. All data were recorded prospectively and analyzed after each patient's treatment was completed.

Patients were invited to complete a 10-question "yes or no" survey to assess their medical history, previous testing, dietary habits, and pertinent symptoms. Patients were divided into two groups: 1) those who reported being gluten free; and 2) those who admitted to gluten ingestion. IVF outcomes were recorded prospectively and compared.

Statistical Analysis

Statistical analysis included both parametric and nonparametric tests for both categoric and continuous data when appropriate, where an alpha error of 0.05 was considered to be significant. Parametric continuous data was compared with the use of Student *t* test and proportions compared with the use of chi-squared and Fisher exact tests as appropriate. Logistic regression was used to create models to control for potential confounding factors for patient, embryo, and cycle characteristics. The main outcome was ongoing clinical pregnancy because patients are discharged from our clinic at 8 weeks of pregnancy. Live birth data were collected and reported where available. Secondary outcomes included clinical loss (defined as loss after documented fetal heart rate).

RESULTS

There were 1,000 patients enrolled in the study. Of these, 995 patients completed serologic screening. Demographics are presented in Table 1. Twenty-four patients tested positive for tTG (2.4%) and 22 positive for EMA (2.2%). Of those, 18 tested positive for both (1.8%). Therefore, in the most liberal definition, a total of 28 patients were considered to be seropositive for celiac disease (2.8%). A total of 968 patients underwent vaginal oocyte retrieval.