Sealing the Diagnosis of Celiac Disease in Pregnancy

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INTRODUCTION

Celiac disease (CD) is an immune mediated condition that results from a reaction to dietary gluten and primarily affects the small intestine. Genetically predisposed individuals develop a chronic inflammatory state of the small intestine which leads to malabsorption. The disease is mediated by HLA DQ2 or DQ8 haplotypes, which bind the gliadin peptides of gluten, present the peptides to CD4+ T lymphocytes and trigger cytokine and B lymphocyte responses.¹

The prevalence of CD in the United States is approximately 1% and can reach up to 4-5% in at-risk groups.² Serologic study of asymptomatic elderly patients in the United Kingdom revealed a 1% prevalence rate of CD. The diagnosis of CD can be challenging in those without the classic malabsorptive symptoms of chronic diarrhea and bloating. Patients with silent CD vary in their presentation. In some cases, the diagnosis is made after a patient presents with iron deficiency anemia, osteoporosis, or an incidental finding of duodenal villous atrophy on endoscopy.^{3,4} Additionally, undiagnosed CD can increase long term risk of lymphoma, infertility, miscarriage, and complications in pregnancy.^{5,6} Mothers with untreated active CD are at higher risk of preterm labor, small for gestational age, or low birthweight infants.⁶ This case reinforces the importance of recognizing atypical presentations of CD in pregnancy to prevent maternal and fetal complications due to active disease.

CASE PRESENTATION

A 28-year-old G1P0 female of Italian and Irish descent with no prior medical history presented to her obstetrician at 15 weeks gestation with asymptomatic hypertension and transaminase elevation. Pertinent physical exam findings included gravid abdomen and trace pitting edema of the lower extremities. Laboratory data were significant for AST and ALT of 52 and 42, respectively. These values increased to AST and ALT of 221 and 203 at 30 weeks gestation and remained in the 100-200 range for the remainder of her pregnancy.

The differential diagnosis for the patient's transaminase elevation included pre-eclampsia, HELLP syndrome, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, autoimmune hepatitis, Wilson's Disease, CD, hereditary hemochromatosis, and nonalcoholic fatty liver disease. Initial workup for transaminase elevation was remarkable only for hepatic steatosis on abdominal ultrasound, with normal liver size, echogenicity and echotexture. Iron studies were consistent with iron

deficiency anemia. Serologic testing for etiologies of transaminase elevation including hepatitis A, hepatitis B, hepatitis C, auto-immune hepatitis, primary biliary cholangitis, Wilson's disease, and alpha-1 anti-trypsin deficiency were unremarkable. The patient was diagnosed with chronic hypertension and transaminase elevation secondary to superimposed preeclampsia. She delivered a 2850 gram female at gestational age of 37w1d. The patient's transaminases remained elevated up to three times the upper limit of normal post-partum which prompted re-evaluation. In addition to repeat testing for the aforementioned viral, auto-immune, and inherited causes of transaminase elevation, a Celiac antibody panel including endomysial antibody IgA, anti-tissue transglutaminase antibody (IgA tTG), and immunoglobulins was checked. She was ultimately found to have weakly IgA tTG of 6 units/mL (upper limit of normal is 3). Biopsy at the time of esophagogastroduodenoscopy (EGD) revealed duodenal mucosa with intraepithelial lymphocytosis and focal moderate villous blunting which met Marsh 3b criteria for CD. She was started on a gluten free diet with subsequent normalization of her transaminase levels.

DISCUSSION

There is an established connection between active CD and potential reproductive health repercussions including unexplained infertility, miscarriage, fetal growth restriction, delayed menarche, early menopause and secondary amenorrhea.⁷⁻¹³ Adherence to a strict gluten free diet has also been shown to curtail risk of fetal growth restriction, infertility and miscarriage.¹⁴ There are two leading hypotheses for the pathogenesis of adverse pregnancy outcomes in CD. One hypothesis is an antibody mediated process inferred by the close link between CD activity and reproductive failure. Potential mechanistic models have been proposed based on *in vitro* studies. The first is direct binding of anti-TG antibodies to trophoblasts of the embryo resulting in apoptosis and impaired trophoblast invasion.¹⁵ The second is anti-tTG antibodies inhibiting maternal endometrial angiogenesis by impairing the cytoskeleton structure of endometrial endothelial cells.¹⁶ Another hypothesis is based on an association between an increased rate of spontaneous abortion and certain vitamin and mineral deficiencies which have increased prevalence in CD.

Pregnancy and the postpartum period have a profound effect on autoimmune disorders transcending CD. The mechanism driving this is unclear. It has been proposed that pregnancy causes dysregulation of certain populations

of T-helper cells to allow for tolerance of paternal antigens introduced by the fetus. This is mediated by an increase in T-helper 2 type cells (Th2) over T-helper 1 type cells (Th1). Autoimmune diseases that are predominately Th1 regulated can improve in pregnancy, while those that are Th2 mediated may be exacerbated.²¹ Celiac disease is a Th1 mediated disease, therefore pregnancy may make detecting antibodies and successfully diagnosing the disease more challenging.²²

Given the implications of CD in several obstetric and gynecologic disorders, it's imperative to address how and who should be tested. The gold standard for diagnosing CD includes positive serology confirmed by duodenal biopsy via an upper gastrointestinal endoscopy. The spectrum of histological changes seen in the small intestinal architecture are categorized using Marsh's classification system.²³ However, given the risks of sedation, pregnancy is a relative contraindication to endoscopy. Thus, screening for celiac disease antepartum would occur with serological tests with postpartum endoscopy to confirm the diagnosis.

Presently, it is not recommended to screen for CD in asymptomatic patients in the general population, however serologic testing for CD is recommended in adults with gastrointestinal symptoms, extraintestinal manifestations or abnormal laboratory values associated with CD. While the prevalence of CD is approximated to be one percent of the American population, it can be as high as four percent in those with cryptogenic transaminase elevation.^{2,24} It has been demonstrated that patients with unexplained infertility, recurrent miscarriage or IUGR have a respective 5-, 6- or 8-fold risk of being afflicted by CD compared to the general population.²⁵ Additionally, patients with these reproductive disorders often do not present with the classic symptomology of CD. While serologic screening for CD is strongly suggested in cases of unexplained infertility, recurrent miscarriage, and IUGR there is still not enough evidence to recommend screening for CD in women with a history of small for gestational age child, preterm birth or pre-eclampsia. Given the adverse pregnancy outcomes associated with untreated CD it may be worth considering prenatal screening in high risk populations. Ultimately, CD should remain high on the differential when evaluating transaminase elevation in pregnancy.

CONCLUSION

Physicians should be aware that serologic screening for CD is strongly suggested in women with persistent elevation in serum aminotransferases, history of recurrent fetal loss, low birthweight offspring, or reduced fertility. Further research is needed to see if preconception screening for CD in high risk subgroups is cost-effective given the adverse pregnancy outcomes associated with untreated CD and high prevalence of asymptomatic CD.

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