Coeliac disease and pregnancy outcomes

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Summary: Coeliac disease is a gluten-sensitive enteropathy affecting up to 1% of the population. An accumulating body of evidence supports the association of coeliac disease with adverse pregnancy outcomes, including increased risk of miscarriage and intrauterine growth restriction. Reports differ regarding the extent and severity of these associations, in addition to the exact pathophysiology underlying these associations. Overall, coeliac disease is believed to be a significant condition in pregnancy and reproductive medicine with some advocating the screening of coeliac disease in all pregnant women or some specific high-risk groups.

Keywords: coeliac disease, pregnancy, fertility, miscarriage

INTRODUCTION

Coeliac disease is a gluten-sensitive enteropathy resulting from an interaction between gluten and immune, genetic and environmental factors. In genetically predisposed persons the ingestion of gluten, the major storage protein of wheat, barley and rye, precipitates the disease. Coeliac disease is characterized by a chronic inflammatory state of the proximal small intestinal mucosa, which can impair digestion and absorption. Originally considered a rare malabsorption syndrome of childhood, coeliac disease is now seen as a common condition that may be diagnosed at any age and that may affect many organs. Treatment consists of adherence to a lifelong gluten-free diet; however, the response rate to therapy is poor in up to 30% of patients. Non-conformance to a gluten-free diet is the major cause of persistent or recurrent symptoms.¹

The prevalence of coeliac disease varies widely depending on the ethnicity and occurs at a rate of greater than 1% in the Irish population.² The disease is recognized not only throughout Europe but also in Asia, the Middle East, North Africa and South America.¹ Population-based studies have suggested that recognized cases of coeliac disease may only represent the tip of the coeliac iceberg with a large proportion of affected people remaining undiagnosed.³ The rate of diagnosis however is increasing. In common with other autoimmune conditions coeliac disease is thought to be two to three times more common in adult females than males.⁴

PATHOGENESIS

Coeliac disease results from the interaction of gluten, immune, genetic and environmental factors. The term 'gluten' refers to

the entire protein component of wheat; gliadin is the alcohol-soluble portion of gluten that accounts for the majority of the toxic components.¹ The ingestion of gluten results in the accumulation of undigested molecules of gliadin, which then interact with antigen-presenting cells in the lamina propria. A mucosal immune response follows, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy.

Coeliac disease has a strong genetic component evidenced by the strong family history of many patients with coeliac disease. The disease does not develop unless a person has alleles that encode for the HLA-DQ2 or HLA-DQ8 proteins, products of two of the HLA genes. The prevalence of coeliac disease is also influenced by family history. First-degree relatives have a prevalence of one in 10; second-degree relatives have a prevalence of one in 39.⁴

Environmental factors are also thought to play a role with factors such as breast feeding and rotavirus infection having negative and positive effects, respectively, in the development of coeliac disease.¹ Recent evidence has demonstrated an association between delivery by caesarean section and the subsequent development of coeliac disease in children.⁵ Alterations in the intestinal flora of the neonate after delivery by caesarean section are thought to impair the establishment of the host-microbe homeostasis and intestinal mucosal integrity, thereby contributing to the pathogenesis of enteric inflammatory diseases. This association may also be explained by the increased caesarean section rate observed in some studies in mothers with coeliac disease.⁶ Therefore, it is likely this association of delivery by caesarean section and subsequent development of coeliac disease in children has occurred secondary to the genetic nature of coeliac disease rather than being related to the mode of delivery.⁵

CLASSIFICATION AND DIAGNOSIS

With the increasing use of serological testing and the common use of upper endoscopy to aid diagnosis, the classification of

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coeliac disease has become more complicated. These tests have identified patients who appear to have the disease but have variable degrees of histopathological changes and/or symptoms. Several categories of coeliac disease now exist: classical, atypical, potential, latent and silent coeliac disease.

Classical coeliac disease includes the following three features: villous atrophy, symptoms of malabsorption, including weight loss and steatorrhoea, and resolution of mucosal lesions and symptoms upon commencement of a gluten-free diet. Atypical disease (the commonest form) is characterized by fully developed villous atrophy associated with milder clinical features. Potential coeliac disease (most often seen in patients with a family history of coeliac disease) is that in which patients have serological changes consistent with coeliac disease but small bowel biopsy is inconsistent with the diagnosis of coeliac disease. Patients with silent disease will have no symptoms but characteristic intestinal lesions detected following small bowel biopsy. Finally, latent coeliac disease describes patients with a previous diagnosis of coeliac disease that responded to gluten withdrawal but retained normal villous architecture after gluten re-introduction.⁴

The gold standard for definitive diagnosis of coeliac disease is upper gastrointestinal endoscopy (with duodenal biopsy) plus positive serology. The first step in testing for coeliac disease is serological testing, and this should be conducted while patients remain on a gluten-rich diet for at least six weeks.⁷ IgA antitissue transglutaminase (tTG) and IgA endomysial antibodies are the first-line serological tests and have equivalent diagnostic accuracy, with high sensitivity and specificity. Antigliadin antibody tests are no longer routinely recommended because of their low sensitivity and specificity. In the general population, patients who screen positive with serological testing should undergo endoscopy with small bowel biopsy. Characteristic findings on endoscopy include scalloped or flattened folds, fissures and mosaic pattern. Mucosal inflammation, crypt hyperplasia and villous atrophy are the classic pathological features found on biopsy. The histological changes are classified using Marsh's classification of small-intestinal lesions.⁴ Endoscopy is not recommended in pregnant women. Investigations of gastrointestinal bleeding or obstructive jaundice are strong indications for endoscopy, but the risk of exposure to radiation and sedative drugs must be considered.⁸ Thus, screening for coeliac disease with serological tests may be appropriate during the pregnancy, with delayed endoscopy to confirm the diagnosis postnatally. Adherence to an exclusion diet is advisable once the diagnosis is suspected. Timing of the endoscopy should involve discussion with a gastroenterology specialist, as ideally the patient should be on a gluten diet for six weeks before the biopsy.

MANIFESTATIONS AND COMPLICATIONS OF COELIAC DISEASE

Although classically a disease of children, coeliac disease is now recognized to present at all ages with variable clinical presentations, while many patients are diagnosed incidentally following screening. Classical signs include diarrhoea and steatorrhoea while non-clinical manifestations include iron deficiency anaemia and metabolic bone diseases such as osteopenia and osteoporosis. Malignant diseases are more frequent in patients with long-term untreated classical coeliac disease. Small bowel adenocarcinoma, oesophageal and oropharyngeal

squamous cell carcinoma and non-Hodgkin's lymphoma occur more often than in healthy control individuals. Dermatitis herpetiformis is a cutaneous manifestation of gluten sensitivity in patients with coeliac disease. It is a severe pruritic bullous rash that affects the extensor surfaces. Treatment is with a gluten-free diet, but severe cases may require medical treatment with dapsone (diamino-diphenyl sulphone).⁴ Dapsone is classified as a Category C drug by the Food and Drug Administration in the USA. No reproduction studies in animals have been conducted. A study investigating carcinogenicity in pregnant mice and rats displayed limited evidence of an increase in mesenchymal tumours.⁹ Reported side-effects of dapsone include blood dyscrasias, haemolytic anaemia and peripheral neuropathy. Case reports of neonatal hyperbilirubinaemia after maternal dapsone therapy have been published. Sulphapyridine is an alternative treatment for dermatitis herpetiformis, but it is not recommended in pregnancy as it may be associated with congenital abnormalities and postnatal jaundice/kernicterus.

Undiagnosed coeliac disease also has a wide range of gynaecological and obstetric manifestations including delayed menarche, early menopause and secondary amenorrhoea. Increased rates of unexplained infertility, miscarriage and fetal growth restriction in women with undiagnosed coeliac disease are reported.¹⁰⁻¹⁴ We have reviewed the literature to assess the significance and importance of coeliac disease in these conditions, and the associated underlying pathology.

MENSTRUAL CYCLE, FERTILITY AND MISCARRIAGE

There have been conflicting reports regarding the effect of coeliac disease on a woman's reproductive life. Several studies have reported an increased frequency of reproductive abnormalities in women with coeliac disease including late menarche, premature menopause, secondary amenorrhoea, recurrent miscarriage and unexplained infertility.^{15,16}

Martinelli *et al.* reported a significant difference in the prevalence of menstrual cycle disorders in women with coeliac disease versus healthy controls. Although the study was small, the frequency of amenorrhoea was 19.4% versus 2.2% for women with coeliac disease versus controls, respectively ($P < 0.001$). While no difference was noted in the age of menarche, significant associations were observed between coeliac disease and other menstrual abnormalities including oligomenorrhoea, dysmenorrhoea and menorrhagia ($P < 0.05$).¹⁷

Studies concerning the association between infertility and coeliac disease are also contradictory and inconclusive.^{15,18} Two population-based cohort studies have been performed with similar results. Tata *et al.* found overall similar fertility rates between women with coeliac disease and controls. Age-specific fertility rates, however, showed that relative fertility between the two groups varied with age with women with coeliac disease more likely to have their children at an older age.⁶

The largest study of fertility in women with coeliac disease, conducted in Sweden, included 11,000 women of reproductive age with biopsy-proven coeliac disease. Zugna *et al.* reported that overall, coeliac disease was not associated with decreased fertility. Interestingly, fertility in coeliac disease was shown to be reduced in the two years preceding the diagnosis (fertility hazards ratio was 0.63 [95% CI 0.57-0.70]), and this returned to normal ranges following diagnosis and treatment.¹⁹

These two studies support the view that coeliac disease does not have a significant negative impact on fertility as was previously thought. In clinical practice however, women with coeliac disease should be informed that active disease may reduce fertility, but treatment with a gluten-free diet is likely to normalize fertility.¹⁹

Women with undiagnosed coeliac disease have been shown to have up to a nine-fold relative risk of recurrent miscarriage compared with treated patients.^{11,12} Other studies have demonstrated an association which is not as strong or statistically significant.^{6,17} Tata *et al.* reported that miscarriages were slightly more common in women with coeliac disease (RR 1.31 [95% CI, 1.06–1.61]).⁶ Martinelli *et al.* observed the miscarriage rate in women with coeliac disease to be almost twice that of controls, but this association was statistically insignificant.¹⁷ Adopting a gluten-free diet was shown to reduce the relative risk of miscarriage by approximately nine times in a study by Ciacci *et al.*,¹² but this case-control study was limited by small numbers. Another small case-control study conducted by Tursi *et al.*²⁰ demonstrated a similar positive outcome on pregnancy if a gluten-free diet was adopted.

COELIAC DISEASE AND PREGNANCY

Maternal coeliac disease is associated with adverse pregnancy outcomes such as low birthweight, small for gestational age/intrauterine growth restriction (IUGR) and preterm birth.^{10,12–14,21,22} IUGR is a major pregnancy complication responsible for a 5–20-fold increase in perinatal mortality and for considerable perinatal morbidity. IUGR may also have life-long consequences ranging from neurodevelopmental delay to an increased risk of developing hypertension, heart disease and diabetes later in life.^{23,24}

The association between maternal coeliac disease and IUGR varies considerably between studies with odds ratio between 1.6 and 6.0 reported.^{10,12,13} Variations also exist in the reported effect of treated versus untreated coeliac disease. Two large population-based cohort studies have been performed using data from Swedish and Danish population registries.

In the Danish cohort, Khashan *et al.* demonstrated that untreated coeliac disease was associated with a reduced mean birthweight of 100 g, with associated odds ratios for small for gestational age in multiparous women (adjusted OR = 1.27; [95% CI: 1.02–1.58]), very small for gestational age (adjusted OR = 1.54; [95% CI: 1.17–2.03]) and preterm birth (adjusted OR = 1.33; [95% CI: 1.02–1.72]). The magnitude of this effect was less than previously reported. There was no evidence to suggest an association between treated coeliac disease and reduced birthweight, small for gestational age, very small for gestational age or preterm birth.²¹

Ludvigsson *et al.* reported similar findings in a Swedish study. Undiagnosed coeliac disease was associated with a number of adverse pregnancy outcomes including an increased risk of IUGR (OR = 1.62; [95% CI: 1.22–2.15]), low birthweight (OR = 2.13; [95% CI: 1.66–2.75]), very low birthweight (OR = 2.45; [95% CI: 1.35–4.43]) and preterm birth (OR = 1.71; [95% CI: 1.35–2.17]). Again, these associations were not seen in the treated coeliac disease group.¹³

Using individualized birth ratios to account for the influence of factors such as maternal height and weight on fetal weight, McCarthy *et al.*²² demonstrated that women with undiagnosed coeliac disease had a significantly increased risk of delivering a

baby which was small for gestational age (adjusted OR 2.19; [95% CI 1.04–4.57]).

PATERNAL COELIAC DISEASE

The evidence concerning the effect of paternal coeliac disease on preterm birth and birthweight is conflicting.^{25–27} Khashan *et al.* conducted a large population-based cohort study, which found no significant association between untreated paternal coeliac disease and birthweight or preterm birth. For treated paternal coeliac disease there was some evidence for an association with birthweight (adjusted mean difference = –81 g; [95% CI –161, –3]).²⁷ However, further research is needed to confirm and explain this association.

UNDERLYING PATHOPHYSIOLOGY

Coeliac disease may lead to adverse pregnancy outcomes through a number of mechanisms.

The negative influence on nutritional status, due to malabsorption from mucosal inflammation, has been postulated to be the likely pathogenesis for both reproductive and pregnancy complications. Undiagnosed coeliac disease may cause folic acid, vitamin B₁₂, fat-soluble vitamin and iron deficiencies, which may further adversely impact on outcome. However, malnutrition has not been a consistent trait among women with coeliac disease and adverse fetal outcome.^{12,15,16} Gliadin may also induce an inflammatory reaction with associated cytokine production,¹³ which may adversely affect the fetus.²⁸

Recent research has demonstrated that maternal autoantibodies bind to placental tTG. Such effects could include compromised nutrient transfer, altered cell dynamics through effects on apoptotic shedding, immune dysregulation and altered secretory function of the placenta.²⁹ Di Simone *et al.*³⁰ additionally demonstrated impaired invasiveness, reduced ability to migrate and interact with the extracellular matrix, and altered apoptosis when trophoblastic tissue was exposed to anti-tTG IgG. These data suggest a possible pathogenesis for early pregnancy loss and IUGR in untreated maternal coeliac disease. Adherence to a gluten-free diet has been shown to reduce circulating autoantibodies and the risk of fetal growth restriction during pregnancy.¹³

SCREENING

Coeliac disease is a common condition affecting up to 1% of the population. Coeliac disease has been shown to be associated with adverse pregnancy outcomes, the majority of which appear to be reversed following implementation of a gluten-free diet. Much rarer conditions are routinely screened for in pregnancy. Management with a gluten-free diet is an acceptable treatment for most and can reduce adverse pregnancy outcome. A screening test that is both sensitive and specific, acceptable to the patient and accessible is currently available. Thus, it may be appropriate to consider routine screening in pregnancy, followed by confirmation of the diagnosis with endoscopy and tissue biopsy after delivery.

Where resources are limited, a compromise may be to consider targeted screening for high-risk groups. For example, in those with a first-degree relative, known autoimmune disease (diabetes mellitus, thyroid disease), weight loss, iron deficiency

anaemia or when IUGR is detected. Although it seems likely that screening for coeliac disease would be both cost-effective, (anti-tTG costing approximately \$45³¹ compared with the average cost of one day's care in the neonatal intensive care nursery of approximately \$1250–\$2000)³² and beneficial in terms of improved outcomes, appropriately conducted prospective randomized controlled trials are needed to demonstrate these assumptions conclusively.

CONCLUSION

Untreated coeliac disease is associated with adverse pregnancy outcomes, particularly the serious complication of IUGR. Treatment with a gluten-free diet appears to ameliorate the risks associated with undiagnosed coeliac disease. Much rarer diseases than coeliac disease are routinely screened for in pregnant women and pregnancy may provide us with an optimal time to screen and treat women improving fetal outcomes as well as the long-term health of our female population. Further research is needed, ideally with prospective cohort or randomized controlled trials, to conclusively demonstrate these associations and the safety and cost-effectiveness which may be associated with screening and treatment.

DECLARATIONS

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