Coeliac disease and unfavourable outcome of pregnancy

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Abstract
Background—Up to 50% of women with untreated coeliac disease experience miscarriage or an unfavourable outcome of pregnancy. In most cases, after 6–12 months of a gluten free diet, no excess of unfavourable outcome of pregnancy is observed. The prevalence of undiagnosed coeliac disease among pregnant women is not known.

Aim—To determine the prevalence of untreated coeliac disease among women attending the obstetrics-gynaecological department.

Methods—Endomysial antibodies, which are specific and sensitive for coeliac disease, were evaluated in all women attending the obstetrics-gynaecology department of a large city hospital over a 90 day period.

Results—Of 845 pregnant women screened, 12 were identified as having coeliac disease. Three had previously been diagnosed but were not following a gluten free diet. The remaining nine underwent a small intestinal biopsy, which confirmed the diagnosis. The outcome of pregnancy was unfavourable in seven of these 12 women. Six healthy babies were born with no problems after the women had been on a gluten free diet for one year.

Conclusions—Overall, 1 in 70 women was affected by coeliac disease, either not diagnosed (nine cases) or not treated (three cases). Their history of miscarriages, anaemia, low birth weight babies, and unfavourable outcome of pregnancy suggests that testing for coeliac disease should be included in the battery of tests prescribed for pregnant women. Coeliac disease is considerably more common than most of the diseases for which pregnant women are routinely screened. Unfavourable events associated with coeliac disease may be prevented by a gluten free diet.

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The incidence of coeliac disease in the western world is higher than previously thought.[1][2] From 0.4% to 0.8% of populations screened have been found to be affected, and most patients are undiagnosed because they are asymptomatic or have symptoms unrelated to the disease.[2][3] Multiple population screenings suggest that a high rate of undiagnosed coeliac disease can be expected in any single western community, and there is an estimated one million cases in the European Union alone.[2][3] Regional differences are not significant, and are mostly due to observer bias and a variable threshold of clinical sensitivity.[4] Most undiagnosed patients are free from gastrointestinal symptoms, or suffer from mild complaints that do not lead to a correct diagnosis. This large cohort of patients includes subgroups affected by such conditions as epilepsy with cerebral calcifications,[5] dental disorders,[6] endocrine diseases,[7] arthritis,[8] and many others.[9]

A significant proportion of spontaneous abortions and unfavourable pregnancy outcomes have no specific cause.[10] Coeliac disease may be suspected from the finding of persistent iron deficiency and abnormal weight loss during a first, but more often, a second pregnancy. Women with undiagnosed coeliac disease seem to have an 8.9-fold relative risk of multiple abortions and low birth weight babies compared with treated patients.[11] A gluten free diet resulted in a 9.18-fold reduction in the abortion rate and a reduction in the prevalence of low birth weight babies from 29.4% to zero.[11] In another study, 15% of 68 women with untreated coeliac disease had miscarriages compared with 6% of controls, but after a gluten free diet, the miscarriage rate was similar in patients and controls.[12] Of 112 pregnancies in women with untreated coeliac disease, 20 ended in miscarriages compared with two of 22 in patients on a gluten free diet.[13] Similarly, six babies were stillborn in an undiagnosed group compared with none in a group on a gluten free diet.[14]

Notwithstanding this scenario and the high incidence of coeliac disease in the general population, there are no data about the prevalence of untreated coeliac disease in women who have experienced an unfavourable outcome of pregnancy. The aim of this study was to estimate the prevalence of untreated coeliac disease in the women attending the obstetrics-gynaecological department of a major city hospital, in an attempt to improve the mothers' reproductive status by diagnosing the condition and prescribing treatment.

Methods
For 90 consecutive days, a 100 µl sample of serum was withdrawn from the serum collected for routine blood tests from all women admitted to the obstetrics-gynaecology department of our medical school. Only pregnant women or women in labour were considered.
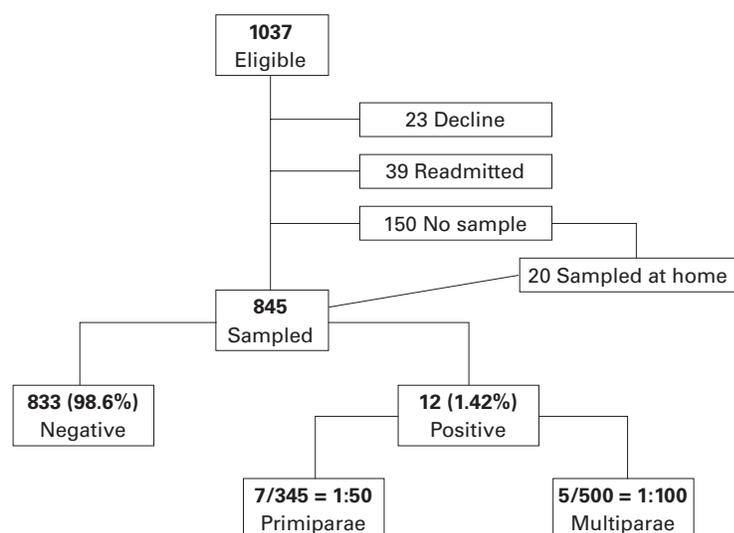
Figure 1   Outline of the sampling procedure and results.

The records of all admitted women were retrieved using a computerised system. To screen for coeliac disease, endomysium antibodies were determined as described by Ladinser and colleagues[15] and Volta and colleagues[16] on human umbilical cord sections. These antibodies are highly (>95%) specific and sensitive for coeliac disease, because they represent the autoantigen against the human tissue transglutaminase, which is the protein specifically involved in the gluten induced damage caused by the disease.[16] Evaluation of endomysium antibodies is age and sex independent and is not influenced by pregnancy.[16 17]

Of the 221 blood samples retested to verify the procedure, full concordance was obtained for 220 by two readers unaware of the first result. The remaining sample was judged to be dubious by one reader and negative by the other. This sample was retested and judged negative by both readers. Positive results were reanalysed three times. Patients with positive results were offered a complete gastroenterological examination, including a small intestinal biopsy, to confirm the diagnosis.

STATISTICAL PROCEDURES

Percentages were compared by rates and proportion; odds ratio with 95% confidence intervals are reported. We also used the corrected χ^2 test or Fisher's exact test to compare percentages, and the unpaired Student's t test to compare the means of normally distributed variables.

Results

A total of 845 serum samples were obtained from 1037 women admitted to hospital; 39 women were admitted twice during the three month period but were sampled only once; 23 declined to participate. For 150, no sample was available at the time of admission; 20 of these were recovered by taking a blood sample at home within 10 days of admission. Thus, the final number of samples was 845 (825 + 20) for an eligible population of 998 (1037−39 readmitted) (84.7%). Figure 1 gives an outline of the sampling procedure. The distribution of age, time of admission, and diagnosis in the 150 cases without a serum sample did not differ from those of the women with a sample, but the length of stay in hospital was considerably shorter in the former group because most were admitted to undergo single diagnostic procedures.

Table 1 shows the 12 samples with a positive test (confirmed three times). Eight other cases had one positive or dubious test not confirmed when repeated. Three of the 12 women with a positive test had been diagnosed with coeliac disease in childhood (by small bowel biopsy), but did not report the disease on admission and had not been receiving treatment for periods varying from 10 to 25 years. For these women (aged 21, 24, and 27 years), it was their first pregnancy; two had a breech presentation of the baby. None reported any gastrointestinal symptoms or was underweight.

The nine patients without a history of coeliac disease who had a positive result underwent a small intestinal biopsy. The specimens were evaluated by a pathologist unaware of the blood test results; severe to total villous atrophy, crypt hyperplasia, and lymphocyte infiltration were found in all cases. Of the nine newly diagnosed patients, one had a breech presentation, one suffered from pre-eclampsia, and a premature delivery was expected in two. Three babies died. An adverse neonatal outcome occurred in seven of the 12 diagnosed cases: five small for gestational age newborns (41%), and three preterm deliveries (25%). Among the multiparae, four out of five had experienced at least one miscarriage, and two had a history of two or more miscarriages. Four

Table 1   Features of cases of pregnant women with coeliac disease (CD)

Age (y)	Age at menarche (y)	History	Pregnancy	Haemoglobin (g/l)	Outcome	Weight of baby (g)	Apgar score at 1 and 5 minutes
33	16	–	Satisfactory	138	Spontaneous delivery at 41 weeks	3100	8–9
30	12.5	1 miscarriage	Twins, MPP	96	Pemature delivery at 24 weeks	450	Died
						350	Died
33	12.3	2 miscarriages	Satisfactory	85	Caesarean section at 39 weeks	2650	8–9
30	13	1 miscarriage	Satisfactory	109	Spontaneous delivery at 40 weeks	3030	8–9
29	12	–	Preeclampsia	106	Spontaneous delivery at 40 weeks	1820	8–9
31	12	–	Satisfactory	126	Spontaneous delivery at 40 weeks	3500	6–8
32	12.3	–	Breech	112	Caesarean section at 39 weeks	3520	8–9
25	13.2	2 miscarriages	MPP	104	Spontaneous delivery at 26 weeks	500	Died
33	13	–	MPP	71	Caesarean section at 36 weeks	1900	8–9
24	16	CD	Breech	104	Caesarean section at 39 weeks	2800	8–9
21	12.1	CD	Breech	95	Caesarean section at 37 weeks	2750	8–9
27	12	CD	Satisfactory	107	Spontaneous delivery at 40 weeks	3450	8–9

MPP, threatened premature delivery.

of the 12 women had a haemoglobin concentration below 100 g/l on admission, at 24, 36, 37, and 39 weeks of pregnancy.

COMPARISON BETWEEN PATIENTS WITH COELIAC DISEASE AND CONTROLS

To obtain a control group, an observer unaware of the aims of the study selected 206 pregnant women from the file of women with a negative coeliac disease test, using a computerised random number selection method. Age was similar (28 *v* 29 years) in the two groups, but menarche occurred later in the patients with coeliac disease: mean (SD) 13.03 (1.5) *v* 12.0 (1.3) years ($t = -2.99$; p<0.05).

A history of previous miscarriage was more common in women with coeliac disease than in controls; 8/12 (67%) reported no previous abortion compared with 161/206 (78.2%) of controls; two had one abortion (compared with 39 controls) and two had two or more abortions (compared with six controls) (χ^2 test 6.06; p = 0.04). Two of 206 controls had a stillbirth, another two suffered from severe perinatal disease, but no babies died after birth. Three of 13 babies born to women with coeliac disease died in the first week of life. All 12 pregnant women with coeliac disease reached delivery. The mean gestation at delivery was 36.75 weeks, which was similar to the controls (36.77 weeks), but four of the 12 patients (33%) terminated before the 37th week of gestation compared with 24/206 (11.6%) controls (odds ratio (OR) 3.79; 95% confidence interval (CI) 0.8 to 15). Breech presentation occurred in three of the 12 (25%) patients with coeliac disease and in three of 206 (1.4%) controls (OR 22.5; CI 3 to 170). The mean birth weight was lower for the patients with coeliac disease than for the controls (2601 *v* 3164 g; $t = 2.05$; p = 0.064) at the border of a 5% significance. The Apgar score at one minute was below 7 in three cases (21%) compared with 11 controls (5.8%) (OR 5.91; CI 1.1 to 29). Similarly, the score at five minutes was below 7 in two cases (17%) compared with one control (0.5%) (OR 41; CI 4.8 to 340; Fisher's exact test, p = 0.0081).

The anti human cord test was run on locally collected and prepared pieces of human umbilical cord. Each test cost about US$ 3.3. The total cost was: 845 single tests + 252 repeat tests = 1097 tests × US$ 3.3 = US$ 3620 to identify 12 cases—that is, each case was identified at a cost of US$ 301.6.

Table 2 Risk factors and outcome of pregnancy

Condition	Prevalence	Symptomatic newborns (%)
Congenital rubella	0.01/1000 deliveries	80
Congenital syphilis	0.015/1000 deliveries	Variable with care
HIV infection	0.1/1000 deliveries	20
Congenital toxoplasmosis	0.2–2/1000 births	10
Fetal neural tube defects	1–2/1000 pregnancies	100
Group B streptococcal infection	1–3/1000 births	20
Cytomegalovirus infection	2–22/1000 deliveries	10
Urogenital chlamydia	5–30/1000 deliveries	10
Haemolytic disease of the newborn	10–30/1000 deliveries	1
Undiagnosed coeliac disease	12/1000 deliveries	30

Discussion

Undiagnosed coeliac disease has been reported to increase the risk of an unfavourable outcome of pregnancy.[11] As the incidence of coeliac disease in the western gluten-consuming population can be expected to be high (from 0.4 to 1%), the occurrence of unfavourable outcome of pregnancy and poor neonatal outcome resulting from undiagnosed coeliac disease is probably relevant. Our results provide the first evidence for this. The overall prevalence of 1.42% is slightly higher than the prevalence expected in the screened general population, but the incidence of coeliac disease is higher in women than men. Undiagnosed cases are usually called "silent". Although the condition is silent from the gastrointestinal viewpoint, the term is not appropriate for women who experience such a severe non-gut complaint as an unfavourable outcome of pregnancy.

The risk attributable to undiagnosed coeliac disease is not trivial. In this study, 41% of the 12 pregnancies resulted in small for gestational age babies, and three babies died. Table 2 lists the conditions most often related to an unfavourable outcome of pregnancy.[10] Undiagnosed coeliac disease is more common than most of the widely screened conditions that may lead to an unfavourable outcome of pregnancy. Coeliac disease, unlike most screened conditions, is easily treatable: dietary treatment is simple and effective and it reduces or abolishes the excess of unfavourable outcomes of pregnancy.[11] However, coeliac disease has never been included in the screening tests for pregnant women, neither has it been looked for in groups with at risk pregnancies or in those with a previous unfavourable outcome.

None of the 12 cases observed here had overt signs of malnutrition, apart from low haemoglobin in four; there was no stunting and no patients were underweight. Therefore nutritional factors were probably not of major importance in the unfavourable outcomes. Malabsorption or malnutrition was not a consistent feature in women affected by coeliac disease who had an adverse outcome of pregnancy.[11 12 15] The patients examined by Stewart and Willoughby[17] "had met the nutritional burden of pregnancy". Ciacci and colleagues[11] reported that the adverse outcome of pregnancy in their patients was not related to the clinical condition of the patient or to the severity of the coeliac disease symptoms.

During the period over which this paper was being revised, we followed up the 12 women identified during the study. One was lost to follow up. Three had no further pregnancies; these were on a gluten free diet and healthy. Eight had a further pregnancy: one is still in progress, and seven reached term. Of these seven, six, five of whom were on a strict gluten free diet, gave birth to healthy babies, above 2500 g in weight, with no problems. The seventh had a baby with a major cardiac malformation; she was the only one on a gluten-containing diet.

Dysregulation of the immune system has been evoked to account for the adverse outcome of pregnancy in apparently healthy

women with only relatively minor nutritional disturbances.[12 17]

Coeliac disease is an autoimmune disorder associated with the production of an autoantibody, anti-endomysium, which is an antibody against the ubiquitous human tissue transglutaminase.[18 19] Early expression of anti-endomysium is observed in the cultured small intestinal mucosa of patients with coeliac disease exposed to gliadin.[20] Obviously, the later that coeliac disease is diagnosed, the greater the probability of complications of the disease developing. More than 25% of patients diagnosed after the age of 15, and hence after prolonged exposure to gluten, develop an autoimmune disease.[21] The interaction between tissue transglutaminase and gliadin produces a neoepitope that is recognised by the HLA moiety specific for coeliac disease. This finding provides a new approach to exploring why and how the autoantibody and the T cell mediated reaction provokes a series of ill conditions, including unfavourable outcome of pregnancy.[22]

In conclusion, consideration should be given to screening for coeliac disease in pregnancy, because of the high incidence of avoidable outcomes and the chance of reversibility through consumption of a gluten free diet.

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