SHORT REPORT

Undiagnosed coeliac disease does not appear to be associated with unfavourable outcome of pregnancy

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Background: In a previous hospital based study, we suggested that undiagnosed coeliac disease has a prevalence, among pregnant women, of 1:80, and is a cause of unfavourable outcome of pregnancy.
Aims: In order to confirm or dismiss this hypothesis, which has significant public health implications, we carried out a large population based study on a stratified sample from the whole Campania region.
Patients: During the period of the study, 5345 women were admitted to the OBS-GYN wards regional network: 5055 (95%) were enrolled in the study.
Methods: Antihuman IgA class antitissue transglutaminase (TGASE) antibodies were tested by an ELISA method. Endomysial antibodies (EMA) were investigated on thin sections of human cord blood by an immunofluorescence test. The HLA class II DQA1*0501/DQB1*02 and DQA1*0301/DQB1*0302 haplotypes were assessed using the Eurospital Eu-DQ kit. Duodenal biopsy was not considered feasible by the ethics committee for pregnant women near delivery.
Results: Fifty one of 5055 patients had confirmed positive results. We added to these 12 women with known coeliac disease, giving a prevalence rate for coeliac disease of 1:80 (exactly the value observed during the first study). Comparing the 51 TGASE positive with 4997 negative women, we did not observe an excess risk of abortion, premature delivery, small birth weight, or intrauterine growth retardation. Anaemia was more frequent in cases than controls.
Conclusions: Undiagnosed coeliac disease is frequent among pregnant women (>1%) but is not associated with an unfavourable outcome of pregnancy.

Several studies have suggested that coeliac women, before diagnosis and dietary treatment, experience an unfavourable outcome of pregnancy when they eventually do become pregnant: the relative risk of miscarriage is elevated[1–4] and the risk of low birth weight is also significantly increased.[3 4] Sher *et al* reported an increased risk of stillbirths in untreated coeliac women (7/120) compared with controls (1/161).

In a pilot hospital based study, we also showed[5] that more than 1% of pregnant women are affected by coeliac disease, the vast majority unrecognised; 70% of these had an unfavourable outcome of pregnancy, with several losses of babies. But when these women were correctly identified and placed on a gluten free diet, within 1–2 years they enjoyed a normal pregnancy.

However, it should be noted that most of these previous studies were carried out on a selection of coeliac women,[1–4] most retrospectively analysed. Thus the ''coeliac'' population under investigation in these previous studies (1970–1990) was in the vast majority of cases made up of patients with severe clinical symptoms.

Recently, due to the widespread use of effective screening tests, it has been recognised that many coeliacs are asymptomatic. However, whether these patients have significant health risks is a matter of debate. As these preliminary findings have significant public health implications, we conducted a population based study involving peripheral hospitals of the five provinces of the Campania region to control for previous referral bias.

PATIENTS AND METHODS

None of the cases previously investigated[5] participated in the new study. The eligible population were pregnant women admitted to one of 14 participating obstetric and gynaecology wards (stratified sampling by province) in the region of Campania, Italy, from 1 November 2001 to 31 January 2002. Exclusion criteria were: non-pregnant women, no informed consent, and admission lasting less than 24 hours. The total population of pregnant women admitted to the hospital network was 5345; the number enrolled was 5055, giving a participation rate of 94.64%. This sample represented approximately 30% of the total 16 500 births expected in the region over this period.

Total IgA deficiency screening was not planned after a negative cost-benefit analysis. In fact, approximately 10 cases of IgA deficiency in more than 5055 individuals would be expected in our population. Among these, one patient would be expected to have coeliac disease. Thus we would have to conduct 5055 total IgA screening tests, at a cost of approximately 60 660 Euros, to identify one case of coeliac disease with at least a 4% false positive rate.[6] IgA class antitissue transglutaminase (TGASE) was tested by an ELISA method using the Eurospital Eu-tTG kit. The sensitivity of the anti-TGASE is more then 93%.[7 8] Although the endomysial antibody (EMA) test has the greatest specificity, reaching almost 100%,[9] when the number of sera is high, the anti-TGASE ELISA can be used initially because of its technical simplicity, and positive results can then be confirmed by an EMA test. EMA were tested on thin sections of human cord blood using an indirect immunofluorescent method. HLA class II DQA1*0501/DQB1*02 (serologically named DQ2) and DQA1*0301/DQB1*0302 (serologically named DQ8) haplo-

Abbreviations: TGASE, IgA class antitissue transglutaminase; EMA, endomysial antibodies

Table 1 Anti-TGASE, anti-EMA, and HLA values

TGASE (IU)	n	EMA+	EMA−	DQ2+	DQ8+	DQ2/8−	Confirmed coeliacs
TGASE >9	48	48	0	43	4	1	48
TGASE >7 to <9	10	3	7	5	1	4	3
TGASE <7	4997	0					0
Total	5055	51	7	48	5	5	51

TGASE, IgA class antitissue transglutaminase; EMA, endomysial antibodies.

types were tested using the Eurospital Eu-DQ kit. DQA and DQB components of the DQ2 and DQ8 etherodimers were evaluated separately. Thus our data allowed selective estimation of cases having only DQB1*02, which is in linkage disequilibrium with DR7. It should be noted that the finding of ''half'' etherodimer in 6.65% of confirmed coeliacs has recently been confirmed in the European Cluster on the Genetics of Coeliac Disease.[10]

The ethics committee approved the study but discouraged endoscopy and biopsy for women in their third trimester of pregnancy. Delaying treatment of cases clearly identified as coeliac in order to perform duodenal biopsies several months after delivery was considered unacceptable by our ethics committee.

RESULTS

A blood sample was obtained from 5055 women. The results were analysed and are shown in table 1.

All 48 patients showing a TGASE level >9 IU had positive EMA antibodies and 47/48 had the HLA DQ2 (DQA1*0501/DQB1*02) and/or the DQ8 (DQA1*0301/DQB1*0302) haplotype. The remaining patient had the DR7 (DQB1*02) haplotype: these 48 women were considered to be coeliac cases. In the group of cases with TGASE levels 7–9 IU, we considered three women to be affected by coeliac disease because of confirmed EMA positivity and the presence of HLA DQ2 or DQ8. Thus a total of 51 cases were considered positive, and the actual prevalence rate of undiagnosed coeliac disease was at least 51/5055. To these we added 12 cases diagnosed with coeliac disease before pregnancy. These patients were on a gluten free diet and consequently their TGASE values were negative. Thus our sample was composed of 12 diagnosed and 51 previously undiagnosed cases, giving an overall prevalence rate of 63/5055 women (1.246%; 1 in 80 women). The prevalence of undiagnosed cases was 1% (1 in 100 women). The ratio of diagnosed to undiagnosed cases was 1:4.25.

Outcome of pregnancy of 12 coeliac cases known before screening

Of the 12 known coeliac cases, five had a normal pregnancy and delivery (42%), three had a normal pregnancy and caesarean delivery (25%), two aborted during the early months (16%), and two suffered threatened abortion but eventually had a good outcome (16%). None delivered a baby of less than 2500 g in weight (table 2).

Outcome of pregnancy in 51 new cases identified by screening

Of the 51 confirmed TGASE positive pregnant women:

- 29 had an uneventful pregnancy and delivered spontaneously (57%);
- 22 underwent caesarean section (43%);
- six women aborted, one because of an extrauterine pregnancy;
- four had a baby with a birth weight of less than 2500 g (7. 8%) (table 2).

Apart from severe anaemia (haemoglobin <9 g/dl) which was three times more frequent in coeliac women ($\chi^2 = 26$ $p = 0.0045$ after Bonferroni correction), none of these events was significantly different in the coeliac (undiagnosed or known) compared with the non-coeliac population. In the 51 undiagnosed coeliacs, there was a trend towards a reduced birth weight and a slightly higher abortion rate but these differences were not significant and it would require a much larger study to confirm these results (table 2).

DISCUSSION

The prevalence rate of coeliac disease (1.24% or 1:80) estimated in our large population based study was the same as that observed in a previous pilot study (1.26% or 1:80).[5] This prevalence rate was constant over the three months of the study: in each month we obtained the same rate as that overall. A limitation of the study was the lack of small intestinal biopsy which was not carried out in pregnant women close to delivery for ethical reasons. Undiagnosed coeliac disease is very common in the female general population: the rate observed in pregnant women is a good estimate of the actual prevalence rate in the overall female population. Possible bias may be in favour of a higher prevalence rate as infertile women and individuals with diseases were not considered.

Maki *et al* recently reported a population prevalence of ''coeliac condition'' (that is, positive serological test and

Table 2 Comparison of pregnancy outcome among undiagnosed, diagnosed, and non-coeliac women

Variable	Undiagnosed coeliacs (n = 51)	Known coeliacs (n = 12)	Non-coeliacs (n = 4997)
Age (y) (mean (SD))	29 (3)	28 (2)	27 (5)
Duration of pregnancy (weeks)	39	40	38
First pregnancy (n (%))	39 (76%)	6 (50%)	2798 (56%)
Spontaneous abortion (n (%))	6 (11.7%)	2 (16%)	390 (7,8%)
Anaemia (Hb <9 g/dl) (n (%))	18 (35%)	4 (33%)	564 (13,7%)
Vaginal delivery (n (%))	29 (57%)	5 (42%)	2334 (46,7%)
Caesarean section (n (%))	22 (43%)	3 (25%)	2189 (43,8%)
IUGR (n (%))	4 (7.8%)	0	251 (5.04%)
Birth weight (g) (mean (SD))	2800 (517)	3500 (413)	3220 (550)

IUGR, intrauterine growth retardation; Hb, haemoglobin.

specific HLA haplotype) of 1:67 individuals[11] whereas the prevalence of biopsy confirmed cases was approximately 1%. Our prevalence data are in line with these findings. It should be noted that the only woman in whom we did not detect the full DQ2 etherodimer did show a positive DQB1*02 without the DQA1*0501, which is compatible with coeliac disease.[10]

In this population based study, the actual prevalence rate of unfavourable events of pregnancy in coeliacs was not significantly different from that observed in the non-coeliac population. These findings do not confirm the suggestions of our previous hospital based study although the prevalence rate of coeliac disease determined in that study has been confirmed. Findings of previous case control studies were also not confirmed: this is not unusual when the study design is so different and may actually reflect the different populations screened (severe clinical cases on the one hand and asymptomatic patients on the other). A case control design is mainly suitable for estimation of the relative contribution of an aetiological influence (risk factor) to the total frequency of a disease whereas population based cohort studies are better for obtaining an unbiased account of the prevalence of a disease and his associated complications.[12]

In conclusion, our study does not deny the fact that undiagnosed and untreated disease may be a severe cause of discomfort, anaemia (also in the absence of clinical complaints), associated diseases, and unfavourable outcome of pregnancy in clinically evident patients.[13 14] In common with others,[15–17] we have previously shown that after one year on a gluten free diet the majority of these women enjoy a successful pregnancy. On the other hand, those cases identified only by screening, which are the majority, do not have major clinical complaints and hence it is expected that they may not manifest overt disease or severe complications in reproductive performance.

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