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Infertility and coeliac disease

P Collin, S Vilska, P K Heinonen, O Hällström, P Pikkarainen

Abstract

***Background*—Coeliac women may suffer from gynaecological and obstetric complications. It is possible that these complications are the first symptom of coeliac disease.**

***Aims*—To investigate the occurrence of subclinical coeliac disease in patients with infertility or recurrent miscarriages.**

***Subjects*—Women of reproductive age who were attending the hospital because of either primary or secondary infertility, or two or more miscarriages. Women undergoing sterilisation served as control subjects.**

***Methods*—The diagnostic investigation for infertility included the endocrine status, diagnostic laparoscopy, investigation of tubal patency, postcoital test, and semen analysis of the partner. Circulating antibodies against IgA class reticulin and gliadin were used in screening for coeliac disease. In positive cases, the diagnosis was confirmed by small bowel biopsy specimens.**

***Results*—Four (2·7%) of 150 women in the infertility group, and none of the 150 control subjects were found to have coeliac disease (p=0·06). All four women with coeliac disease suffered from infertility of unexplained origin. Altogether 98 women had no discoverable reason for infertility. Thus, in this subgroup the frequency of coeliac disease was 4·1% (four of 98), the difference from the control group being statistically significant (p=0·02). None of the coeliac women had extensive malabsorption, but two had iron deficiency anaemia. One women with coeliac disease has had a normal delivery. None of the 50 women with miscarriage had coeliac disease.**

***Conclusion*—Patients having fertility problems may have subclinical coeliac disease, which can be detected by serological screening tests. Silent coeliac disease should be considered in the case of women with unexplained infertility.**

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Keywords: coeliac disease, infertility, gliadin antibodies, reticulin antibodies.

Department of Medicine, Tampere University Hospital, and Medical School, University of Tampere, Finland
P Collin
P Pikkarainen

Department of Obstetrics and Gynaecology, Tampere University Hospital, and Medical School, University of Tampere
S Vilska
P K Heinonen

Department of Microbiology, Tampere University Hospital
O Hällström

Correspondence to:
Dr P Collin,
Medical School, University of Tampere, PO Box 607, FIN-33101 Tampere, Finland.

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The classic symptoms of coeliac disease are diarrhoea and malabsorption. Nowadays, however, many patients have only subtle manifestations, and the disease may even be silent, with no symptoms at all.[1] Some coeliac patients present with atypical non-abdominal symptoms. Such clinically silent or atypical forms of the disorder can be detected using reticulin, endomysium, and gliadin antibody tests as screening methods.[2 3]

Many studies have shown that coeliac women are susceptible to reproductive difficulties such as infertility and miscarriages.[4–6] There are no reports, however, on the occurrence of silent coeliac disease among patients with reproductive disorders. In this study we applied serological screening tests to detect coeliac disease among women suffering from infertility or miscarriages.

Methods

The study group comprised 150 successive women examined for infertility, and 50 women having two or more spontaneous abortions. The control group comprised 150 women with a normal obsetetric history who had undergone laparoscopic sterilisation. All patients were treated at the Department of Obstetrics and Gynaecology, Tampere University Hospital, Finland, between February 1993 and December 1994.

The aetiology of infertility was evaluated, and considered unexplained when no obvious reason could be found. The presence of ovulation was assessed by endometrial biopsy and serial measurements of serum progesterone. Further evaluation of the endocrine status included determinations of pituitary gonadotropins, prolactin, and adrenocortical and thyroid functions. Diagnostic laparoscopy and hysteroscopy were carried out, and tubal patency was investigated by chromopertubation. Postcoital testing was performed to assess the role of a cervical factor in infertility, and the male factor was excluded by semen analyses. The tubal factor was the reason for infertility in 29 cases and hormonal factors in 23 cases. In 98 women the aetiology was considered to be unexplained.

All patients were screened for coeliac disease using serum IgA class reticulin and gliadin antibody tests. The sensitivity of IgA class reticulin antibody test has in recent studies been 90%, and the specificity 99–100%.[7 8] IgA class gliadin antibody test has shown the sensitivity of 90%, and the specificity of 85%.[8] Reticulin antibodies were determined by an indirect immunofluorescence test[7]; the screening dilution was 1:5. Gliadin antibodies were investigated by enzyme linked immunorsorbent assay (ELISA)[9]; the results were obtained from a standard curve established according to dilutions of a positive reference serum and converted to concentrations of arbitrary ELISA units per millilitre (EU/ml). Serum samples exhibiting gliadin antibodies in higher concentrations of EU/ml than known healthy age matched controls, plus two standard deviations were considered positive. This

resulted in a cut off level of IgA class gliadin antibodies at 0·20 EU/ml. This cut off level finds childhood and adolescent coeliac disease at a rate of 90% but gives at the same time 30% positive results in subjects with normal jejunal mucosa.[10]

Patients positive in one or both of these screening tests underwent upper gastrointestinal endoscopy, including biopsy specimens taken from the descending part of the duodenum. The diagnosis of coeliac disease was based on subtotal or severe partial small bowel villous atrophy and crypt hyperplasia on duodenal biopsy. Women having villous atrophy started a gluten free diet. A control biopsy specimen was taken after they had maintained a gluten free diet for six to 12 months.

The study protocol was approved by the ethics committee of the University Hospital of Tampere.

Results

Four (2·7%) of 150 women in the infertility group, and none in the control group were found to have coeliac disease (p=0·06) (Table I). All women with coeliac disease were categorised in the group of unexplained infertility. Thus, in this subgroup coeliac disease was detected in four (4·1%) of 98 women. The difference from the control group (none of 150) was statistically significant, p=0·02. No coeliac disease was detected among 29 women with tubal infertility, 23 with hormonal infertility, and 50 women with miscarriages.

Of the four women with coeliac disease, two had iron deficiency anaemia, but no apparent gastrointestinal symptoms; two women had asymptomatic coeliac disease (Table II). None had folic acid deficiency. Their mean (SD) age at menarche was 14·7 (1·5) years. All four started gluten free diet, and the control biopsy showed mucosal recovery in every one. Two patients have conceived during the follow up, one at the time she was starting the gluten free diet, the outcome of pregnancy being normal, and the other had had one unsuccessful 'in vitro fertilisation and embryo transfer' (IVF-ET) earlier while on a normal diet. She conceived with IVF-ET, after being on six months of gluten free diet. She had, however, to have induced abortion due to fetal malformation.

All four women with coeliac disease had gliadin and three had reticulin antibodies. Normal small bowel mucosa despite positive gliadin antibodies was found in six women with infertility, in two with spontaneous abortions, and in two women undergoing sterilisation. One woman in the control group had positive reticulin antibodies, but normal small bowel mucosa.

TABLE I *Incidence of coeliac disease among various study groups*

Study group	*Number of patients*	*Median age (range)*	*Menarche age (SD)*	*Coeliac disease, number (%) of patients*	*p Value**
Infertility, all	150	31 (22–42)	12·9 (1·4)	4 (2·7%)	0·06
tubal factor	29	34 (27–42)	12·6 (1·4)	0	
hormonal	23	29 (22–42)	13·3 (1·7)	0	
unexplained	98	31 (22–42)	12·9 (1·4)	4 (4·1%)	0·02
Miscarriages	50	31 (22–46)	12·8 (1·4)	0	
Control group†	150	38 (26–45)	13·0 (1·3)	0	

*Compared with the control group, Fisher's exact test. †Women undergoing laparoscopic sterilisation.

TABLE II *Women with unexplained infertility and coeliac disease*

Patient	*Age*	*Symptoms of coeliac disease*	*Menarche (age)*	*Duration of infertility (years)*	*Number of deliveries*	*Therapeutic intervention*	*Outcome of infertility on gluten fre diet*
1	39	No	13	6	0	IVF*	Induced abort
2	43	No	14	6	1†	None	Not conceived
3	32	Iron deficiency anaemia	16	7	0	None	Not conceived
4	36	Iron deficiency anaemia	16	4	1†	None	Normal delivery

*In vitro fertilisation and embryo transfer. †Investigated due to secondary infertility.

Discussion

This study shows that some women suffering from unexplained infertility have clinically silent coeliac disease. The observed frequency of 4·1% is at least 10 times higher than the prevalence of coeliac disease in the population. According to population screening studies, the estimated prevalence figure for adult coeliac disease in Europe is approximately 0·3%.[3 11 12]

In choosing screening methods, some of their characteristics have to be considered. The reticulin and endomysium tests are both tissue antibody tests; their titre correlates well and they can thus be used alternatively in clinical practice.[7 10] These tests are highly specific for coeliac disease.[7] The combination of reticulin and gliadin antibody tests here resulted in better sensitivity. However, using the gliadin antibody test in screening for silent coeliac disease, one can expect to have to carry out more endoscopic examinations with normal small bowel mucosal findings.[13] This was seen in this study as well.

Silent coeliac disease seems to be a risk factor for infertility, but the aetiology remains so far unknown. A deficiency in essential nutrients can have an adverse effect on fertility. Even though coeliac disease patients in this study did not have overt malabsorption, iron deficiency was present in two patients.

Coeliac patients taking a normal diet have a shortened reproductive period with delayed menarche and early menopause.[4–6] Even in the present series, the mean (SD) age at menarche was older in coeliac patients (14·7 (1·5)) than in other groups (Table I). Gonadal dysfunction has been demonstrated in coeliac men.[14] Such hormonal abnormalities have not been reported in women, however.[15]

Coeliac patients have an increased frequency of endocrinological and autoimmune diseases.[16] Moreover, coeliac disease patients are subject to extraintestinal manifestations such as liver diseases,[17] dental enamel defects,[18] and neurological complications.[19] It is possible that infertility is one spectrum of extraintestinal gluten intolerance.

There are several reasons justifying screening for asymptomatic coeliac disease among women with infertility. Successful deliveries after starting a gluten free diet have been reported.[4 20] It seems that a gluten free

diet retrieves the relative infertility in women with coeliac disease.[6] Ferguson *et al*[4] and Sher *et al*[6] have shown that in untreated coeliac disease the risk of stillbirths is increased. Obviously patients with undiagnosed coeliac disease also run an increased risk of miscarriages,[4 5] even though we did not detect silent coeliac disease among 50 women with recurrent abortions. Patients with untreated coeliac disease are susceptible to osteoporosis.[21] The risk of developing malignant lymphoma is increased in coeliac disease, and treatment with gluten free diet can prevent this complication.[22]

To summarise, silent coeliac disease should be considered among patients suffering from unexplained infertility. The positive effect of gluten free diet treatment should not be dismissed, even if its impact on infertility remains so far equivocal.

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