

## Case control study

# High prevalence of post-partum depression in women with coeliac disease

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Received: June 19, 2014

Peer-review started: June 20, 2014

First decision: July 21, 2014

Revised: October 14, 2014

Accepted: October 29, 2014

Article in press: October 29, 2014

Published online: February 10, 2015

depression (PPD) in coeliac disease (CD).

**METHODS:** We performed a case-control study evaluating the prevalence of PPD in CD patients on gluten-free diet (GFD) compared to that of healthy subjects experiencing a recent delivery. All participants were interviewed about menstrual features, modality and outcome of delivery and were evaluated for PPD by Edinburgh Postnatal Depression Scale (EPDS).

**RESULTS:** The study included 70 CD patients on GFD (group A) and 70 controls (group B). PPD was present in 47.1% of CD women and in 14.3% of controls ( $P < 0.01$ ; OR = 3.3). Mean EPDS score was higher in CD compared to the controls (mean score: group A  $9.9 \pm 5.9$ ; group B  $6.7 \pm 3.7$ ;  $P < 0.01$ ). A significant association was observed between PPD and menstrual disorders in CD (69.7% vs 18.9%;  $P < 0.001$ ; OR = 3.6).

**CONCLUSION:** PPD is frequent in CD women on GFD, particularly in those with previous menstrual disorders. We suggest screening for PPD in CD for early detection and treatment of this condition.

**Key words:** Coeliac disease; Depression; Post-partum depression; Menstrual disorders; Gluten-free diet

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**Core tip:** Some studies have shown an increased prevalence of psychological symptoms and mental disorders in patients affected by coeliac disease (CD) and depression appears to be the most important condition in undiagnosed CD. On the other hands, focused data on post-partum depression are still lacking. In our mind, the present work is the first study mainly focused on this interesting and relevant topic.

## Abstract

**AIM:** To explore the prevalence of post-partum

Tortora R, Imperatore N, Ciacchi C, Zingone F, Capone P,

Siniscalchi M, Pellegrini L, De Stefano G, Caporaso N, Rispo A. High prevalence of post-partum depression in women with coeliac disease. *World J Obstet Gynecol* 2015; 4(1): 9-15 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v4/i1/9.htm> DOI: <http://dx.doi.org/10.5317/wjog.v4.i1.9>

## INTRODUCTION

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy precipitated by the exposure to dietary gluten in genetically predisposed individuals<sup>[1,2]</sup>. CD is the most common cause of enteropathy in the western world and affecting around 1% of the general population in both children and adults<sup>[3]</sup>.

Gluten consumption in these susceptible individuals leads to small bowel damage and the activation of immune responses which cause both intestinal and extra-intestinal manifestations of the disease.

About clinical features, as reported in a recent article by Ludvigsson *et al*<sup>[1]</sup>, classical CD is characterized by signs and symptoms of malabsorption (diarrhoea, steatorrhoea, weight loss, *etc.*), while non-classical CD presents with anaemia, osteopenia/osteoporosis, recurrent abortions, hepatic steatosis, dental enamel hypoplasia, hypertransaminasemia, recurrent aphthous stomatitis.

At present, CD diagnosis requires first of all a serological screening of patients with suspected CD using anti-tissue transglutaminase (a-tTG) and anti-endomysial antibodies and then, a duodenal biopsy to assess the intestinal damage in patients with positive serology<sup>[1]</sup>.

Many studies have shown an increased prevalence of psychological symptoms and mental disorders in patients affected by CD and depression appears to be the most important condition in undiagnosed CD<sup>[4-7]</sup>. In effect, Addolorato *et al*<sup>[8]</sup> reported that the prevalence of depression in CD patients was significantly higher than in the control group (57.1% *vs* 9.6%). In addition, recent reports have revealed a high prevalence of anxiety and sleep disorders in coeliac patients, so confirming the importance of exploring and treating mental aspects in this particular population<sup>[8,9]</sup>.

Post-partum depression (PPD) affects 10%-15% of new mothers being the most common complication of pregnancy in developed countries<sup>[10,11]</sup>. This condition is often unrecognized and when left untreated can be associated with potentially adverse consequences for the mother, her infant, and her family. In particular, PPD can lead to disruptions in maternal-infant interactions, and lower cognitive functioning and behavioural problems in children<sup>[12,13]</sup>. Even if PPD is underdiagnosed, a number of important risk factors (past depression, stressful life events, poor marital relationship, and social support) have been described and can be utilised as helpful risk factors for suspecting development of the condition<sup>[14-16]</sup>.

On the basis of these assumptions, consideration should be given to screening for PPD, although evidence in support of universal screening tools is lacking. However, women with known risk factors for PPD may

be selected for screening<sup>[17,18]</sup>. At present the most utilised tool for screening PPD is the Edinburgh Postnatal Depression Scale (EPDS) which consists in a 10-item self-rated questionnaire with a diagnostic cut-off of 10 (or greater) for possible PPD<sup>[19-22]</sup> even though the sensitivity and specificity varies across languages and cultures<sup>[23]</sup>.

Even if many studies have clearly shown the high prevalence of depression and other mental disorders in CD, specific data on PPD in CD women are still lacking.

Aim of this study was to explore the prevalence of PPD in women suffering from CD compared to that recorded in healthy subjects.

## MATERIALS AND METHODS

We performed a case-control study evaluating the prevalence of PPD in CD patients on gluten-free diet (GFD) in comparison with a control group of healthy subjects.

Between June 2010 and February 2013 we enrolled all coeliac women (Group A) followed-up at our Gastrointestinal Unit (tertiary centre for food intolerance and CD) who had given birth within the 8-wk period preceding their appointment at the Unit and had been on GFD for at least 1 year before pregnancy. CD patients were also classified in accordance with Oslo classification<sup>[1]</sup>. A group of consecutive healthy women who had given birth in the previous 8 wk were also recruited at two first-line obstetric Clinics as control group (Group B). The clinical interview was conducted postnatally by gastroenterologists not blinded on the clinical/pathological state of the subject. All women (CD patients and controls) with a diagnosis of active depression (based on DSM-IV criteria) formulated at least 3 mo before starting pregnancy and those already on treatment with anti-depressant drugs were excluded from the study.

A gynaecological evaluation explored menstrual cycle features, potential comorbidities, mode and outcome of delivery. Menstrual disorders were defined in presence of amenorrhoea, dysmenorrhoea, pre-menstrual syndrome, polymenorrhoea and oligo-menorrhoea in accordance with the gynaecological literature<sup>[24,25]</sup>. All women underwent a conventional serological evaluation comprising the detection of tissue anti-transglutaminase antibodies level.

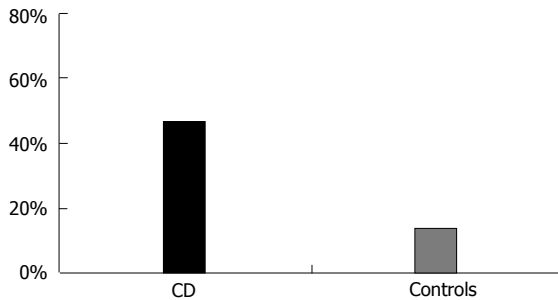
All participants were assessed blinded for PPD through clinical interview using the EPDS<sup>[19-22]</sup>.

Furthermore, quality of life as defined through the SF-36 questionnaire was examined in all patients and controls<sup>[26-29]</sup>.

All patients gave their written consent to participate in the study that was approved by local Ethical Committee.

### Screening for PPD

EPDS is a 10-item (scored on a scale of 0-3) self-reported scale assessing the symptoms of PPD. This questionnaire has been validated also in Italy<sup>[30]</sup> so that we were able to use it for the population in our study with high values on diagnostic accuracy. EPDS is routinely used in many



**Figure 1** Prevalence (%) of positive Edinburgh Postnatal Depression Scale for post-partum depression in coeliac disease women and controls.

clinical services to screen for probable distress in women, both antenatally and postnatally, with a diagnostic cut-off  $\geq 10$  (sensitivity 96%; specificity 92%)<sup>[51]</sup>. On these grounds, we established a cut-off  $\geq 10$  as highly indicative of possible PPD. CD patients and controls with a EPDS  $\geq 10$  were referred for psychiatric assessment. The screening for PPD was performed by an interviewer using the EPDS score with a  $\geq 10$  cut-off and a clinical interview performed by an expert psychiatrist according to the DSM IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision).

### SF-36 questionnaire

The SF-36 survey consists of a 36-item questionnaire that includes eight components: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional and mental health issues. These eight domains form two broader health dimension scales: the physical (PCS) and mental (MCS) component scales. The SF-36 subscales and composite scores can be summarised through means  $\pm$  SD, with higher scores indicating better health and well-being. Low scores on the PCS indicate limitations in physical functions and general health, and/or physical pain, while higher scores suggest no physical limitations, disabilities, or reductions in well-being. Similarly, low scores on the MCS suggest frequent experience of difficulties in psychosocial health, emotional problems and reduced vitality, while high scores indicate frequent positive affect and vitality, the absence of psychological distress and reduced or no limitations in daily social activities<sup>[26-29]</sup>.

### Sample size and statistical analysis

We estimated that a sample size of 67 participants would be able to offer a 80% power to detect a 20% difference between the two groups (when assuming a known PPD prevalence of 13% in general population)<sup>[10,11]</sup>.

Statistical analysis was performed by using  $\chi^2$ , Mann Whitney *U* test and odd ratio (OR) calculation when indicated; differences were considered significant with a  $P < 0.05$ . All statistical analyses were performed with software package SPSS for Windows (Rel SPSS 14.0; SPSS Chicago, IL).

**Table 1** Demographic and serological features of patients with coeliac disease and controls

	Group A Celiac women (# 70)	Group B Healthy subjects (# 70)	P value
Mean age (yr)	33.32 $\pm$ 2.88	32.32 $\pm$ 4.32	0.7
Level of instruction (yr)	11.06 $\pm$ 3.54	11.30 $\pm$ 3.58	0.9
Hb (gr/dL)	11.03 $\pm$ 2.46	11.21 $\pm$ 2.54	0.7
Cholesterol (mg/dL)	156.85 $\pm$ 35.82	149.68 $\pm$ 37.02	0.2
Anti-transglutaminase IgA (U/mL)	< 0.1	< 0.1	0.9
Type of childbirth			
Delivery by caesarean section	36/70	31/70	0.7
Vaginal delivery	34/70	39/70	0.7
Outcome of birth			
Live birth	70/70	70/70	1.0
Congenital malformations	0/70	1/70	0.9
Number of pregnancies			
First pregnancy	34/70	37/70	0.7
Second pregnancy	25/70	24/70	0.9
> 2 pregnancies	11/70	9/70	0.8
Weeks of gestation	37.7 $\pm$ 1.78	37.95 $\pm$ 1.43	0.9

## RESULTS

The study included 70 CD patients on GFD (group A) and 70 healthy controls (group B). According to the Oslo classification<sup>[1]</sup>, CD patients were classified as classical CD in 31 cases (44%), non-classical CD in 34 subjects (49%), asymptomatic CD in 5 patients (7%). About symptoms of CD patients, 30 subjects (43%) showed anaemia, 31 (44%) had diarrhoea, 33 (47%) presented weight loss, 26 (37%) showed abdominal pain and 28 (40%) asthenia.

Group A and Group B resulted well matched for age (group A: 33.3  $\pm$  2.9 years; group B: 32.3  $\pm$  4.3 years;  $P = \text{NS}$ ) and level of school education (group A: 11.1  $\pm$  3.5; group B: 11.3  $\pm$  3.9;  $P = \text{NS}$ ).

No significant difference was evident between the two groups in terms of laboratory variables: haemoglobin (group A: 11.03  $\pm$  2.46; group B: 11.21  $\pm$  2.54;  $P = \text{NS}$ ); cholesterol (group A: 156.85  $\pm$  35.82; group B: 149.68  $\pm$  37.02;  $P = \text{NS}$ ); glycaemia (group A: 80.6  $\pm$  10.3; group B: 79.81  $\pm$  13.3;  $P = \text{NS}$ ); alanine transaminase (group A: 25.41  $\pm$  12.6; group B: 24.18  $\pm$  11.9;  $P = \text{NS}$ ). Demographic and serological features of patients and controls are reported in Table 1. The level of anti-transglutaminase antibodies was normal for all participants (CD patients on GFD and controls).

Thirty-three subjects in Group A and 10 in Group B had EPDS scores higher than the selected cut-off (47.1% of CD patients *vs* 14.3% of controls;  $P < 0.01$ ; OR = 3.3). The Figure 1 shows the prevalence (%) of positive EPDS for PPD in CD women and controls. EPDS score was higher in CD women compared to the controls (mean score: group A 9.9  $\pm$  5.9; group B 6.7  $\pm$  3.7;  $P < 0.01$ ). After psychiatric assessment, 29 out of the 33 patients in Group A (prevalence 41%) and 8 out of the 10 people in the control group (prevalence 11%) with high EPDS scores received a diagnosis of PPD. These results confirmed the high sensitivity of EPDS in our country

**Table 2** Main results

	Group A Celiac women <i>n</i> = 70	Group B Healthy subjects <i>n</i> = 70	<i>P</i> value
EPDS score (mean $\pm$ SD)	9.94 $\pm$ 5.98	6.7 $\pm$ 3.73	< 0.01
Patients with EPDS score $\geq$ 10 (%)	33/70 (47)	10/70 (14)	< 0.01
PPD after psychiatric assessment	29/33	8/10	0.06
SF-36			
PCS (mean $\pm$ SD)	55 $\pm$ 12	66 $\pm$ 8	0.03
MCS (mean $\pm$ SD)	43 $\pm$ 11	56 $\pm$ 7	0.02

EPDS: Edinburgh postnatal depression scale; PPD: Post-partum depression.

(sensitivity 86%). The majority of patients suffered from a mild form of PPD received only active psychological support; only 6 patients (16%) needed anti-depressants and long-term psychiatric follow-up. Results are reported in Table 2.

Regarding the circumstances of delivery, no significant differences were observed between the two groups in terms of type of delivery (group A: caesarean section delivery 51.4%; vaginal delivery 48.6%; group B: caesarean section delivery 44.3%; vaginal delivery 55.7%;  $P = \text{NS}$ ) and birth outcomes (live birth: group A 100%; group B 100%; congenital malformations: group A 0%; group B 1.5%;  $P = \text{NS}$ ). On the contrary, a significant association was observed between the onset of PPD and a previous menstrual disorder in women suffering from CD. Among these, 23 women with and only 7 without previous gynaecological diagnosis of menstrual disorders were positive for PPD at EPDS (69.7% *vs* 18.9%;  $P < 0.001$ ; OR = 3.6); this association was not evident in the control group (25% *vs* 33%;  $P = 0.4$ ).

With regard to quality of life as measured by the SF-36, outcomes were significantly better in controls than in patients with CD in terms of both PCS (55  $\pm$  12 in Group A *vs* 66  $\pm$  8 in Group B;  $P = 0.03$ ) and MCS (43  $\pm$  11 in Group A *vs* 56  $\pm$  7 in Group B;  $P = 0.02$ ). These outcomes were significantly and inversely correlated with the presence of PPD ( $P = 0.02$ ).

## DISCUSSION

The present study, focused on PPD, has shown a higher prevalence of this condition in women affected by CD on GFD when compared to healthy subjects (47% *vs* 14%); after psychiatric assessment, the prevalence of PPD was 41% in CD patients compared to 11% of control group. To our knowledge, this is the first paper reporting a higher incidence of this kind of psychiatric condition in CD.

Many studies have evaluated the psychiatric/mental aspects of CD<sup>[4,6,7]</sup>. In particular, a recent meta-analysis has clearly shown that depression is consistently more common and severe in adults with CD than in healthy adults<sup>[32]</sup>. After the diagnosis of CD, these patients must avoid foods containing grains (wheat, rye, and barley) for the rest of their life. From this point of view, depression

in adult CD may represent a non-specific disorder precipitated by adverse physical symptoms along with personal and social limitations imposed by the chronic disease and the related dietary restrictions.

In effect, in terms of clinical depression, adults affected by CD do not differ substantially from those with other types of physical illness. In addition, many reports have underlined the high prevalence in patients with CD compared to healthy control groups of other psycho-pathological conditions, such as anxiety and sleep disorders<sup>[5,8,9]</sup>.

In our study, a probable diagnosis of PPD identified on the basis of EPDS questionnaire scores was subsequently confirmed through psychiatric assessment in a majority of cases (sensitivity: 86%).

Although frequent, PPD was mild in most affected CD patients and was effectively treated by psychological support. This finding is in accordance with previous reports showing a high rate of missed diagnosis of PPD in the general population, especially if PPD presented in a mild form<sup>[33]</sup>. The screening approach led to early diagnosis and treatment in 43 women (33 CD, 10 controls) affected by PPD, potentially preventing negative consequences for mothers and their newborns.

The high prevalence of PPD in our CD population could be due to several causes. Firstly, PPD could be the expression of an underlying subclinical depression which develops features of PPD and clinical relevance during pregnancy or immediately after childbirth as a result of the heightened anxiety that can be typical of this period. This hypothesis is also in accordance with the low level of quality of life of CD patients compared to the controls<sup>[9,34]</sup>. On these bases, it is possible that a substantial proportion of the PPD cases were also mildly symptomatic during pregnancy so that the screening for and treating depression in CD patients during pregnancy might be more beneficial than waiting to screen them in the postnatal period. Many studies have highlighted the close relationship between low quality of life, anxiety and depression in patients with CD and, from this point of view, our findings are not surprising<sup>[4,9]</sup>. In addition, a woman suffering from CD may be concerned about the possible “genetic transmission” of CD to the newborn, thus worsening her anxiety.

Another explanation for our results could be found in inflammatory/autoimmune mechanisms. Many reports have investigated and underlined the possible role of inflammatory mediators in the pathogenesis of some variants of depression and of other mental problems such as sleep disorders<sup>[35,36]</sup>. Significant increase in pro-inflammatory cytokines and other inflammation-related proteins in major depression were found in plasma and cerebrospinal fluid. Furthermore, elevated levels of pro-inflammatory cytokines persist after clinical symptoms of depression are in remission and can also predict the onset of a depressive episode. Antidepressant treatment can lead to a normalization of elevated cytokine levels in major depression<sup>[35]</sup>. In effect, a recent meta-analysis has investigated the effect of some anti-depressants on the level of inflammatory cytokines. The results of this study



underlined that antidepressant treatment is able to reduce levels of IL-1 $\beta$  and possibly those of IL-6. Stratified subgroup analysis by class of antidepressant indicated that serotonin reuptake inhibitors may reduce levels of IL-6 and TNF $\alpha$ <sup>[36]</sup>. All these considerations could be considered an indirect demonstration of the pivotal role of inflammation in determining depression (and PPD) symptoms.

In our CD population the occurrence of PPD was significantly correlated with the presence of previous menstrual disorders<sup>[37]</sup>. This result could be the expression of a pre-existing underlying hormonal alteration which can also affect and/or contribute to the incidence of mental disorders<sup>[38,39]</sup>.

Interestingly, a recent paper by Buttner *et al*<sup>[39]</sup> has highlighted the significant association between previous menstrual disorder and depression with a twofold increased risk of PPD in women with menstrual irregularities<sup>[40]</sup>. In our control population this kind of association was not evident, probably because of the small number of controls with PPD (10 patients). Nevertheless, one could postulate that this association may be related to the range of alterations characterising the spectrum of gynaecological/obstetric manifestations of CD<sup>[41,42]</sup>. Unfortunately, our work did not include investigations for the measurement of sexual and other hormones and this hypothesis remains therefore unanswered. On the other hand, no significant association was seen between PPD and type/outcome of delivery between the two groups of subjects. About this issue, our work confirmed once again the very high percentage of caesarean delivery performed in South of Italy<sup>[43,44]</sup>.

Our work presents some limitations. First of all, we included all CD patients on GFD in our study; the full compliance to GFD was confirmed by the negative level of anti-transglutaminase antibodies in all CD patients. We decided to exclude patients with new/recent diagnosis of CD (who would be patients on free diet) because the majority of patients followed-up at our Centre consisted of individuals with previous diagnosis of CD and already on GFD. Hence, in order to recruit a homogenous population to the study, we decided to exclude patients who had recently been diagnosed with CD and were on free diet. However, thanks to the composition of our sample, we were able to document that PPD in patients suffering from CD is not directly related to active gluten ingestion. Further studies (ideally multicentre) are needed to define the prevalence of PPD in CD women on free diet (*e.g.*, diagnosed with CD during their pregnancy or immediately after childbirth).

We used healthy subjects as control group. This methodological approach is necessary to demonstrate the real increase of PPD in patients with CD compared to the general population; however, it does not determine whether the high prevalence of PPD is related to CD specifically or to a non-specific "illness status". In effect, as mentioned earlier<sup>[32]</sup>, adults affected by CD do not differ substantially in terms of incidence of depression from those with other types of physical illness and the

same could be true of PPD. In view of this, only a study directly comparing prevalence of PPD in patients with CD with that in patients suffering from other diseases (*e.g.*, inflammatory bowel diseases, rheumatologic diseases) could clarify this aspect.

However, the high prevalence of PPD in patients suffering from CD and the clinical relevance of this psychiatric condition justify the routine use of the EPDS questionnaire in women with CD who have recently given birth.

In conclusion, post-partum depression is a frequent condition in women affected by CD on GFD, particularly in those with history of menstrual disorders. We suggest screening for PPD in all women with CD for early detection and prompt treatment of this condition.

## ACKNOWLEDGMENTS

Many thanks to Giovanna Affinito, our nurse of endoscopy, for her precious support and contribution. Many thanks to Dr Sara Donetto (King's College London - National Nursing Research Unit) for her unique technical and intellectual support.

## COMMENTS

### Background

Celiac disease (CD) is an autoimmune enteropathy gluten-related, characterized not only by gastrointestinal symptoms, but also by an increased prevalence of psychological symptoms and mental disorders, specially depression, anxiety and sleep disorders.

### Research frontiers

Focused data on post-partum depression (PPD) in celiac women are still lacking.

### Innovations and breakthroughs

In this case-control study, the authors evaluate, for the first time in the literature, the prevalence of PPD in CD patients on gluten-free diet compared to that of healthy subjects experiencing a recent delivery.

### Applications

The authors demonstrated that PPD was present in 47.1% of CD women and in 14.3% of controls ( $P < 0.01$ ; OR = 3.3). In the CD population the occurrence of PPD was significantly correlated with the presence of previous menstrual disorders. The authors suggest screening for PPD in all women with CD experiencing delivery for early detection and prompt treatment of this condition.

### Terminology

PPD is a psychiatric disorder affecting women after pregnancy and leading to disruptions in maternal-infant interactions, and lower cognitive functioning and behavioural problems in children.

### Peer review

In this manuscript, the authors present psychiatric disorders - showing higher incidence of PPD in patients with CD in comparison to healthy women controls. From the gastrological point of view this is a well written paper, but it should be evaluated by a psychiatrist to assess accuracy of psychological tests used for the assessment of depression.

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