

# Gluten-free diet: a new strategy for management of painful endometriosis related symptoms?

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**Aim.** Pelvic pain affects 4% to 39% of women and accounts for 10-40% of all outpatient gynecologic visits. The etiology of painful endometriosis-related has not been fully delineated. No studies have been published concerning gluten-free diet administered to achieved relief of painful symptoms endometriosis-related. The aim of this retrospective study was to evaluate the effectiveness for the outcomes of endometriosis-related pain and quality of life of gluten-free diet in a follow-up of 12 months in patients with chronic pelvic pain endometriosis-related.

**Methods.** Two hundred seven patients with severe painful endometriosis-related symptoms entered the study. At enrolment time, the baseline values of painful symptoms were assessed by Visual Analogue Scale (VAS) for dysmenorrhoea, non-menstrual pelvic pain, and dyspareunia. According to VAS, pain severity was scored from 0-10; 0 indicating the absence of pain, and 1-4, 5-7 and 8-10 mild, moderate and severe respectively. A gluten-free diet was submitted to all patients and a new evaluation was performed after 12 months of diet. Student t test was used for statistical analysis.

**Results.** At 12 month follow-up, 156 patients (75%) reported statistically significant change in painful symptoms ( $P < 0.005$ ), 51 patients (25%) reported not improvement of symptoms. No patients reported worsening of pain. A considerable increase of scores for all domains of physical functioning, general health perception, vitality, social function-

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ing, and mental health was observed in all patients ( $P < 0.005$ ).

**Conclusion.** In our experience, painful symptoms of endometriosis decrease after 12 months of gluten free diet.

Key words: Diet, gluten-free - Endometriosis - Celiac disease.

Pelvic pain is a major health problem and affects between 4% and 39% of women and accounts for 10-40% of all outpatient gynecologic visits.<sup>1</sup> Pelvic pain is a syndromic complex; universally it is the unpleasantness of the experience that characterizes pain, and this makes pain an emotional experience, not simply a sensory experience.<sup>2</sup> So, the constant presence of pain may be responsible for affective changes in dynamics, family, social and sexual attitude.<sup>3</sup>

Despite the high morbidity and health care cost associated with endometriosis, the etiology of painful endometriosis-related has not been fully delineated and few modifiable risk factors have been identified.<sup>4</sup>

Possible mechanisms causing pain in patients with endometriosis may include: shed menstrual blood in endometriotic implants;

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deep infiltration of endometriomas into surrounding tissues with tissue damage and deregulation of pelvic and central neural processes of generating impulse; deep intraperitoneal formation of adhesions and fibrotic tissue; peritoneal chronic inflammation and production of inflammatory mast cell-derived cytokines.<sup>5</sup>

Different drugs that have the function of interrupt or decrease the transmission of pain information might be beneficial on pain control but potential side effects, especially with chronic use, are significant, and careful observation is important.

Several studies have been published on the relation between nutritional factors and relief of pain and improvement of quality of life endometriosis-related.<sup>6,7</sup>

In this context, no studies have been published concerning gluten-free diet administered to achieved relief of painful symptoms endometriosis-related.

The aim of this retrospective observational trial was to evaluate the effectiveness for the outcomes of endometriosis-related pain and quality of life of gluten-free diet in a follow-up of 12 months in patients with chronic pelvic pain endometriosis-related.

## Materials and methods

### *Study population*

The present report refers to a retrospective observational case series of 330 patients with severe painful endometriosis-related symptoms, admitted to a network of the Office Endometriosis Center, between January 2008 and January 2010.

The study group included women in reproductive-age (median age of 28 years, range 18-40) with moderate-to-severe painful symptoms endometriosis-related such as dysmenorrhoea and/or non-menstrual pelvic pain and/or deep dyspareunia. All patients underwent ultrasonographic and magnetic resonance imaging to diagnose ovarian and/or pelvic endometriosis and laparoscopic diagnostic procedure has been performed to confirm the diagnosis of pel-

vic endometriosis. Symptoms graded  $\geq 4$  on a 10-point by visual analogue scale (VAS-score).<sup>8</sup> Clinical follow-up after restricted nutritional intake has been made.

All patients with serological diagnosis of celiac disease and/or affect by other known gastrointestinal and urologic disease and/or with a diagnosis of concomitant neoplastic diseases or chronic pelvic inflammatory disease were excluded from the study.

All the participants were interviewed using a structured questionnaire with questions regarding demographics, employment, prior medical conditions, menstrual pattern, pregnancy history, contraceptive methods, hormone use, tobacco and alcohol use, and family and personal history of endometriosis. During gluten-free diet period and until 12 months of follow-up all the patients were asked to keep a diary of daily dietary intake, painful symptoms as dysmenorrhoea, non-menstrual pelvic pain, deep dyspareunia graded between 0 and 10-point, and abdominal distension.

A gluten-free diet is a diet completely free of ingredients derived from gluten-containing cereals: wheat (including kamut and spelt), barley, rye, malts and triticale as well as the use of gluten as a food additive in some unexpected ways, for example as a stabilizing agent or thickener in products like ice-cream and ketchup.<sup>9</sup> Therefore, women were educated to follow a completely gluten free diet also taking into consideration the ingredients of any over-the-counter or prescription medications and vitamins and check the labels of medications before beginning a medication.<sup>10</sup> Also cosmetics such as lipstick, lip balms, and lip gloss may contain gluten and need to be investigated before use.

At enrolment time, the baseline values of painful symptoms were assessed by Visual Analogue Scale (VAS) for dysmenorrhoea, non-menstrual pelvic pain, and deep dyspareunia.<sup>8</sup> According to visual analogue scale, uni-dimensional measure of pain severity was scored from 0-10, with 0 indicating the absence of pain, and scores 1-4, 5-7 and 8-10 indicating mild, moderate and

severe pain, respectively. The data were reported as mean and standard deviation.

The response of treatment to life and health-related satisfaction with a gluten-free diet was assessed by improvement of physical functioning, general health perception, vitality, social functioning, and mental health.

### Statistical analysis

Statistical analysis was performed using the commercial statistical software Program/SPSS for Windows (version 10). One-way repeated-measures analysis of variance (ANOVA) was used to compare the treatment groups for selected baseline continuous variables. Statistical testing for visual analogue scale (VAS) was conducted by using Student *t*-test to evaluate treatment group changes from baseline. When appropriate, 95% confidence intervals (CIs) were calculated for the observed differences.  $P < 0.05$  was considered as statistically significant in any comparison.

## Results

Of 330 women referred, between January 2008 and January 2010, with dysmenorrhoea and/or non-menstrual pelvic pain and/or deep dyspareunia, 35 were excluded because they refused to participate.

No differences in baseline demographic and clinical characteristics of women enrolled in the trial, according to selected variables at trial entry was detected.

At two weeks after starting a gluten-free diet, as first step, only 207 patients (70%) with improvement of painful symptoms endometriosis-related follow the protocol for other 3 months and then for 6 months overall. The remaining eighty-eight patients withdrew because of side effects as abdominal symptoms due to other food intolerances. A total of 207 women completed the study protocol, and were analyzed for the primary and the secondary outcomes at 12 months follow-up.

At 12 month follow-up, 156 patients (75%) reported statistically significant

change from baseline in painful symptoms ( $P < 0.005$ ), whereas 51 patients (25%) reported not improvement of painful symptoms and abdominal distension. No women enrolled into the study reported worsening of pain and abdominal distension.

A considerable increase of scores for all domains of physical functioning, general health perception, vitality, social functioning, and mental health was observed in all women at 12 months' follow-up after starting gluten-free diet ( $P < 0.005$ ).

## Discussion

Chronic pelvic pain can be identified as a chronic nociceptive, inflammatory, and neuropathic pain characterized by spontaneous pain and an exaggerated response to painful and/or innocuous stimuli.<sup>11, 12</sup> This pain condition is extremely debilitating and usually difficult to treat.

According to clinical finding that as with all medications potential benefit of medical therapy must be balanced with potential risk, it has been suggested a dietary supplementation to treat chronic pain that is poorly responsive to prescription drugs or in which therapeutic options are limited.<sup>13</sup>

Several studies suggest that smooth muscle contractility, estrogen levels, inflammation, prostaglandin metabolism and menstrual cyclicity are some of the factors that may contribute to endometriosis and can be influenced by diet.<sup>14, 15</sup> For example, specific dietary fatty acids are known to influence the circulating levels of IL-6 and other inflammatory markers found in higher levels among women with endometriosis.<sup>16</sup> Also, an inverse relation between fish oil supplementation and circulating levels of series 2 prostaglandins and inflammatory symptoms have been observed.<sup>17</sup>

Moreover, antioxidants, vitamins (B6, A, C, E), and omega-3 and omega-6 fatty acids (fish oil), have a suppressive effect on the endometrial-cell survival in combined endometrial and stromal cell cultures, by involving cell adhesion, secretion and modulation of inflammatory cytokines, re-

cruitment and activation of macrophages.<sup>18</sup> This evidence may provide a basis for their clinical use in the treatment of painful symptoms endometriosis-related.

In addition, a recent research suggests that specific types of dietary fat are associated with the incidence of laparoscopically confirmed endometriosis, and that these relations may indicate modifiable risk.<sup>4</sup>

This is the first trial that provides evidence to support gluten-free diet in the management of severe painful endometriosis-related symptoms.

At present, gluten-free diet is the only medically accepted treatment for coeliac disease, the related condition dermatitis herpetiformis and wheat allergy.<sup>20</sup>

Celiac disease is a small intestinal disorder caused by adaptive and innate immune responses triggered by the gluten proteins present in wheat in genetically susceptible people.<sup>21</sup>

Coeliac disease is an extremely common condition with potentially serious consequences and also extradigestive complications to long-term health.<sup>22</sup> Between 50% and 90% of people with coeliac disease remain undiagnosed in the community with mild symptoms and in this population group there are many women with chronic pelvic pain.<sup>23</sup> The severity of symptoms varies widely, but there are only limited and unconvincing data that link the severity of symptoms to the risk of developing long-term complications.<sup>24</sup>

The overall evidence suggests that untreated coeliac disease adversely affects female reproduction and celiac disease patients can be a group particularly susceptible to reproductive toxicants and to endocrine disorders as the deficiencies of specific trace elements on ovarian function.<sup>25</sup> Clinical and epidemiological studies show that female patients with celiac disease are at higher risk of an unfavourable outcome of pregnancy probably due to malabsorption and deficiency of factors essential for organogenesis, (*e.g.* iron, folic acid and vitamin K, and micronutrients) as well as recurrent spontaneous abortions, low birth weight of the newborn, and short-breast feeding period.<sup>26, 27</sup> Moreover, the prevalence of coeliac disease among

women with unexplained infertility is 2.5-3.5%, higher, although not always significantly, than control population.<sup>28</sup> However, the pathogenesis of celiac disease-related reproductive disorders still awaits clarification. At present, like the other pathologies associated with celiac disease, the possible prevention or treatment of reproductive effects can only be achieved through a life-long maintenance of a gluten-free diet.<sup>29</sup>

It may be supposed that relief of painful symptoms observed in women who take complete absence of gluten in the diet may be due to inhibition of gluten mediated immunomodulation and inflammatory response by modulating cytokine network.<sup>30</sup> There is growing evidence that gluten is partially degraded into the intestine and modified, which results in gluten peptides that bind with high affinity to HLA-DQ2 or HLA-DQ8 and trigger an inflammatory T cell response.<sup>31</sup> Simultaneously, gluten exposure leads to increased production of interleukin 15, which induces the expression of NKG2D on intestinal lymphocytes and its ligand MICA on epithelial cells, leading to epithelial cell destruction.<sup>32</sup>

In this context, interleukins have many biologic functions as induce the synthesis of inflammatory prostaglandins and promote fibroblast proliferation, collagen deposition, and fibrinogen formation, which can contribute to the pathophysiology of chronic painful symptoms.<sup>33, 34</sup>

Therefore, a recent research suggests that sensory ganglionopathy can be a manifestation of gluten sensitivity.<sup>35</sup> The term gluten sensitivity describes a spectrum of diseases having in common an immune response to the ingestion of gluten, but with diverse manifestations such as an enteropathy, dermatopathy, and neurological disorders.<sup>36</sup>

The most common type of neuropathy seen in the context of gluten sensitivity is sensorimotor axonal as demonstrated by inflammation in the dorsal root ganglia with degeneration of the posterior columns of the spinal cord on autopsy tissue.<sup>37</sup>

In patients followed-up for a number of years in dedicated gluten sensitivity/neurology and neuropathy clinics has been

detected that neurological disease may respond to a strict gluten-free diet.<sup>35</sup>

This evidence supports the hypothesis that gluten-free diet is involved in mechanisms of nociceptive pain also implied in chronic pelvic endometriosis-related.

In women with painful symptoms peripheral and central sensitisation leads to abnormal perception of both painful and non-painful stimuli contributing to visceral hyperalgesia and allodynia.<sup>38</sup> Temporal and spatial summation of pain stimuli is also thought to be important in the development of hyperalgesia at the site of an irritated organ that develops as a result of enhanced excitability of respective neuronal soma within the dorsal root ganglia.<sup>38</sup>

However it was found that starting a gluten-free diet had marked adverse psychological effects to lifestyle with feelings of isolation and envy towards peers.<sup>39</sup> Consequently, after starting a gluten-free diet, compliance can be expected to be poor at long time.<sup>40</sup>

## Conclusions

Symptomatic endometriosis cannot be indicated as an extraintestinal manifestations of coeliac disease but gluten-free diet appears able to successfully improve endometriosis-related symptoms even in the absence of enteropathy.

The specific immune response and mechanisms of nociceptive pain implied on relief of painful endometriosis-related symptoms after gluten-free diet for 12 months remain unclear.

Further adequately designed, large-scale controlled clinical trials with larger series and long-term follow-up are required to confirm our results.

## Riassunto

*Alimentazione priva di glutine: una nuova strategia di gestione del dolore associato a endometriosi*

**Obiettivo.** Il dolore pelvico è un problema che affligge dal 4 al 39% delle donne in età fertile ed è la

causa di circa il 40% delle visite ginecologiche. L'endometriosi è una delle possibili cause di dolore pelvico cronico, che può avere intensità variabile fino ad essere invalidante e compromettere in maniera considerevole la qualità della vita delle donne. Non esistono studi in letteratura che correlano una dieta priva di glutine al miglioramento della sintomatologia dolorosa nel dolore pelvico cronico associato ad endometriosi. Lo scopo di questo studio retrospettivo è stato quello di valutare il miglioramento della sintomatologia dolorosa e della qualità della vita, nelle pazienti affette da endometriosi e dolore pelvico cronico, dopo la somministrazione di una dieta priva di glutine.

**Metodi.** Duecentosette pazienti hanno partecipato allo studio e sono state seguite in un follow up di 12 mesi. L'intensità del dolore è stata valutata con la scala analogica VAS ed i dati statistici sono stati elaborati con il test t di Student.

**Risultati.** Al termine del follow-up il 75% delle pazienti ha presentato un miglioramento statisticamente significativo della sintomatologia dolorosa ( $P < 0,005$ ) ed il 25% non ha avuto alcun beneficio dalla privazione di glutine nella dieta.

**Conclusioni.** Nella nostra esperienza una dieta priva di glutine può contribuire alla diminuzione del dolore pelvico cronico in pazienti affette da endometriosi; tuttavia sono necessari ulteriori studi ed una casistica più ampia per confermare questo dato.

Parole chiave: Dieta priva di glutine - Endometriosi - Celiachia.

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