

# A gluten-free diet for endometriosis patients lacks evidence to recommend it



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Endometriosis is an estrogen-dependent chronic disease characterized by the presence of endometriumlike tissue outside the uterus and is often associated with symptoms, such as dysmenorrhea, dysuria, dyschezia, chronic pelvic pain, and infertility. Moreover, women diagnosed with endometriosis can report gastrointestinal symptoms, including bloating, constipation or diarrhea, and abdominal cramping, which can be associated with irritable bowel syndrome and can result in the misdiagnosis of endometriosis as irritable bowel syndrome at first. Treatment usually involves hormonal therapy, pain management, surgery, and/or assisted reproductive techniques in case of infertility. Nonetheless, these treatment methods can be insufficient for alleviating symptoms or can have unacceptable side effects, leading to noncompliance. Therefore, women often apply self-management strategies, including dietary interventions.

One of the diets frequently suggested as a tool to manage endometriosis-related symptoms on social media and patient forums is a gluten-free diet. Although a gluten-free diet has been proven effective in managing nonceliac wheat sensitivity or celiac disease, its effectiveness in endometriosis remains uncertain. The Nurses' Health Study II found it unlikely that gluten intake was a strong factor in endometriosis etiology and symptomatology. To the best of our knowledge, the most frequently cited and sole published intervention study on the efficacy of a gluten-free diet for endometriosis has several important limiting factors, including the absence of a control group. In addition, gluten consumption is highly susceptible to a placebo effect and a nocebo effect, where women might experience symptom relief after eliminating gluten and return of symptoms after they consume gluten again, solely because they believe that gluten is bad for them. Despite the inverse association between body mass index and endometriosis and between a gluten-free diet and increased body mass index, this is an association, and no causality was proven. In addition, other factors should be taken into consideration.

Of note, a gluten-free diet is expensive, has limited availability, and has a significant effect on quality of life. Moreover, without proper dietary guidance, it may adversely affect the gastrointestinal microbiome. Therefore, scientifically substantiated advice regarding the use of a gluten-free diet for endometriosis-related symptoms is currently not available, and a gluten-free diet should be discouraged unless there is an additional diagnosis of nonceliac wheat sensitivity or celiac disease.

**Key words:** dietary intervention, endometriosis, endometriosis diet, fiber deficiency, gastrointestinal symptom, gluten-free diet, high cost, insufficient evidence, irritable bowel syndrome, low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet, self-management, social isolation, quality of life

## Introduction

Endometriosis is an estrogen-dependent chronic disease characterized by the presence of endometriumlike tissue outside the uterus and is estimated to affect approximately 190 million women and

adolescents of reproductive age worldwide. This condition equals a prevalence between 1.9% and 5.7% of the global population.<sup>1-3</sup> Symptoms are often related to the menstrual cycle, can be progressive in severity, and include

dysmenorrhea, dyschezia, dysuria, dyspareunia, chronic pelvic pain, and infertility. However, women with endometriosis can also report gastrointestinal (GI) symptoms, which are associated with irritable bowel syndrome

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(IBS) and include bloating, constipation or diarrhea, and abdominal cramping. This can result in the misdiagnosis of endometriosis as IBS, thereby contributing to a diagnostic delay between 3 and 11 years.<sup>4,5</sup> Both the endometriosis-related symptoms and diagnostic delay can lead to reduced mental, physical, and social well-being and a lower quality of life (QoL).<sup>6,7</sup>

Treatment usually involves hormonal therapy, pain management, surgery, and assisted reproductive techniques in case of infertility. However, treatment may not alleviate all symptoms or may be accompanied by unacceptable side effects, leading to noncompliance.<sup>8,9</sup> Therefore, there is an increasing interest among women with endometriosis and healthcare providers in self-management strategies, including specific dietary interventions.<sup>10</sup> The current research on this subject has limitations, including short follow-up periods, inadequate control conditions, significant bias, and low to very low evidence quality scores. A critical review by Nap and de Roos<sup>11</sup> concluded that evidence regarding the effectiveness of dietary interventions in women with endometriosis is conflicting and that its effect on different endometriosis types remains unknown. In addition, the authors noted a lack of evidence regarding plausible biochemical mechanisms explaining the perceived effects of dietary interventions. Therefore, the 2022 endometriosis guideline from the European Society of Human Reproduction and Embryology does not provide recommendations for self-management strategies, such as dietary interventions, because of the lack of conclusive evidence regarding their benefits and risks.<sup>1</sup>

Nevertheless, previous studies have suggested that dietary adjustments and interventions could potentially affect endometriosis by reducing symptoms, shrink lesions, and prevent disease occurrence and/or progression.<sup>12,13</sup> Dietary adjustments include the supplementation of omega-3 and omega-6 and various vitamins and minerals. Popular dietary interventions for endometriosis management include the low

fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet (avoidance of rapidly fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), the so-called endometriosis diet (an avoidance diet where assumed symptom-triggering nutrients, such as red meat, dairy, and soy, which are removed from the daily diet), and a gluten-free diet. Recent studies found that the low-FODMAP diet is more effective in alleviating symptoms in women diagnosed with both endometriosis and IBS than in women diagnosed with IBS alone.<sup>4,14</sup> In addition, 1 study found specific benefits when adhering to either the low-FODMAP diet or endometriosis diet, where both diets alleviated bloating and contributed to improved QoL.<sup>15</sup>

With a gluten-free diet, there is complete elimination of foods containing wheat, rye, or barley from the daily diet. Gluten represents a group of water-insoluble prolamin proteins that is composed of the largest protein fraction (70%–80%) in wheat.<sup>3,16,17</sup> Although they are mostly well digested by the human body, certain proline-rich peptides that are part of gluten can trigger hypersensitivities, such as wheat allergy and nonceliac wheat sensitivity (NCWS). In addition, it can trigger celiac disease (CD) in 1% to 2% of the population. Proteins in barley (hordein) and rye (secalin) share similarities with gluten, are considered “gluten proteins,” and are avoided when applying a gluten-free diet.<sup>18,19</sup> Recently, the gluten-free diet has gained popularity and has been mentioned on social media and patient endometriosis forums as a potential method to alleviate endometriosis-related symptoms. In addition, the elimination of gluten is widely considered part of a healthy diet. In this analysis article, we discussed the role of gluten and the application of a gluten-free diet in patients with endometriosis and addressed the uncertainties. More importantly, we will substantiate the reason why applying a gluten-free diet to manage endometriosis-related symptoms should be discouraged.

### A gluten-free diet and endometriosis

Endometriosis is associated with chronic, local, and systemic inflammations, prompting comparisons with other inflammatory conditions, such as rheumatoid arthritis.<sup>20</sup> Furthermore, there is a notable association between endometriosis and GI conditions, such as ulcerative colitis, Crohn disease, NCWS, CD, and IBS.<sup>20–22</sup> Previous studies found a positive association between CD and endometriosis and a 2- to 3-fold risk of IBS in women with endometriosis.<sup>20,21</sup> This has led to the hypothesis that a gluten-free diet could provide relief for endometriosis-related symptoms, in which the cytokine network and thereby the immune response—related symptoms could be affected by inhibiting the inflammatory response and gluten-mediated immunomodulation.<sup>23</sup> Although a gluten-free diet is frequently mentioned as an effective tool for endometriosis-related symptom management, it is important to note that this is speculative and that causality remains unproven. In addition, the overlap between IBS, CD, and endometriosis raises the possibility that GI symptoms in women with endometriosis may be related to IBS rather than directly linked to endometriosis. Therefore, it is possible that a gluten-free diet only affects FODMAP fermentation-related symptoms, not necessarily endometriosis-related symptoms.

In 2022, Schwartz et al<sup>24</sup> published the Nurses' Health Study II, a prospective cohort study with a follow-up period of 24 years and data from 81,961 premenopausal women. Of these women, 3810 had a laparoscopically confirmed diagnosis of endometriosis over the 24 years of follow-up. Although the authors found that gluten intake was associated with a lower risk of endometriosis, the results did not remain significant in their sensitivity analyses. Therefore, Schwartz et al<sup>24</sup> stated that their results should be interpreted with caution and considered it unlikely that gluten intake was a strong factor in endometriosis etiology and symptomatology. To the best of our knowledge, the study by Marziali et al<sup>25</sup> is the most frequently cited and sole published

intervention study on the effect of a gluten-free diet on endometriosis-related symptoms. They demonstrated a significant improvement in symptoms after 12 months of adherence to a gluten-free diet. However, 88 participants withdrew from the study after adherence to the diet for 2 to 3 weeks because of abdominal side effects. Only participants who reported a positive response to the diet were analyzed, thereby potentially introducing bias. Furthermore, the primary limitation is the absence of a control group, which potentially influences the positive results.<sup>25</sup> This is because gluten consumption is highly susceptible to a placebo effect and a nocebo effect, where women might experience symptom relief after eliminating gluten from their daily diet and a return of symptoms after they consume gluten again. This can purely be because they believe they are avoiding a harmful nutrient and not because gluten causes the symptoms.<sup>26–28</sup> The influence of a nocebo effect on gluten intake was confirmed in a recently published international multicenter study by De Graaf et al<sup>28</sup> with a double-blind and placebo-controlled design. The expectancy to eat gluten-rich bread (E<sup>+</sup>) or not (E<sup>-</sup>) and consuming gluten-rich bread (G<sup>+</sup>) or not (G<sup>-</sup>) were combined to create 4 groups (E<sup>+</sup> G<sup>+</sup>, E<sup>-</sup> G<sup>+</sup>, E<sup>+</sup> G<sup>-</sup>, and E<sup>-</sup> G<sup>-</sup>). De Graaf et al<sup>28</sup> found that the expectancy of gluten intake and actual gluten intake had the largest effect on overall and several individual GI symptoms, highlighting the presence of a nocebo effect. Moreover, the study by Crawley et al<sup>29</sup> with a similar design found no significant difference in reported GI symptoms between their control group and intervention group who unknowingly added gluten to their diet.

### Negative effects of a gluten-free diet

There are several challenges and high costs associated with lifelong adherence to a gluten-free diet. Of note, 1 study found reduced QoL because of the lifelong dietary restrictions among children and adults with CD who applied a gluten-free diet.<sup>30</sup> Furthermore, the diet can result in a lower intake of dietary fiber, thereby minimizing the diversity

of fiber-fermenting microbiota (eg, *Bifidobacterium* and *Lactobacillus* genera) and metabolism, which play a key role in immunity and general health.<sup>31–33</sup> When inadequately balanced with healthy alternatives to gluten-rich nutrients, adherence to a gluten-free diet may elevate the risk of obesity and increase body mass index (BMI), impair glucose and lipid metabolisms, and increase the likelihood of developing metabolic syndrome.<sup>17,34</sup> Previous studies have found a complex relationship between BMI and endometriosis involving genetic and environmental factors. High BMI is associated with inflammation and hyperestrogenemia, potentially facilitating endometriosis pathogenesis. However, obesity might disrupt ovulation, causing oligomenorrhea or amenorrhea and potentially suppressing endometriosis activity.<sup>35</sup> Of note, 2 studies not only found an inverse association between BMI and endometriosis but also noted that stage I (minimal) endometriosis was reduced in women with obesity.<sup>35,36</sup> Although this finding could suggest that adherence to a gluten-free diet and a potential increase in BMI might lead to a decreased risk of endometriosis, it might also influence the severity of the disease. In addition, although this is an association between BMI and endometriosis, no causality can be proven, and other factors should be considered. Finally, high BMI negatively affects general health; increases the risk of diabetes mellitus type II, cardiovascular disease (CVD), female hypertension, and certain types of cancer (eg, ovarian and endometrial); and ultimately increases the risk of death.<sup>37,38</sup> In contrast, regular consumption of whole grain foods is strongly associated with a significant reduction in diabetes mellitus, CVD, intestinal inflammatory disorders, intestinal dysbiosis, and colon cancer risk and better weight management.<sup>39–42</sup> This underlines the importance of dietary guidance when a gluten-free diet is applied to ensure a full-fledged diet and has resulted in a globally supported recommendation by the food authorities to regularly consume whole grains as part of a healthy diet and lifestyle.<sup>43</sup>

Furthermore, natural and certified gluten-free foods can still contain gluten and may have low nutritional quality.<sup>44</sup> Substituting gluten-rich products with flours from corn, rice, potato, and tapioca often leads to reduced micronutrient, dietary fiber, and protein contents and a higher glycemic response. In addition, the production process of gluten-free food often involves more saturated fats, trans fats, and salt, making it less healthy.<sup>33,45,46</sup> In addition, gluten-free foods are expensive and have limited availability and choices. Singh et al<sup>47</sup> found that only 41% of wheat-based foods had gluten-free alternatives, which were 76% to 518% more expensive. Arias-Gastelum et al<sup>48</sup> found an even greater price difference, with gluten-free options being up to 1088% more expensive than wheat-based versions. Finally, avoidance of FODMAP rather than gluten may be the key factor influencing endometriosis-related symptoms and GI distress. This is substantiated by studies that employed challenge tests with gluten or FODMAPs and found that individuals with self-reported NCWS and IBS reacted primarily to rapidly fermentable fructans (a type of FODMAP) in grains rather than to gluten itself.<sup>29,49</sup> Therefore, a low-FODMAP diet rather than a gluten-free diet could be effective in reducing endometriosis-related symptoms.

### Conclusion

Currently, providing evidence-based recommendations regarding the application of a gluten-free diet to manage endometriosis-related symptoms is impossible. Schwartz et al<sup>24</sup> found it unlikely that gluten intake was a strong factor in endometriosis etiology and symptomatology. Moreover, the positive effect of a gluten-free diet on endometriosis-related symptoms was solely based on the study by Marziali et al.<sup>25</sup> This study has several important limitations that call their results into question, most notably the absence of a control group. To the best of our knowledge, studies evaluating the effect of a gluten-free diet on endometriosis-related symptoms are lacking. Therefore,

adherence to a gluten-free diet for endometriosis management should be discouraged. Alternatively, emphasis should be placed on general healthy eating guidelines, including the avoidance of trans-fatty acids and limited alcohol, meat, and salt consumption. There are indications that the low-FODMAP diet and the so-called endometriosis diet could be effective in reducing endometriosis-related symptoms and improving QoL. However, further studies regarding their efficacy are needed, and the importance of dietary guidance for all dietary interventions should be underlined. Finally, when evaluating dietary interventions, considering the placebo and nocebo effects is crucial.<sup>28,29</sup> ■

### CRedit authorship contribution statement

**Annelotte P. van Haaps:** Writing – original draft, Data curation, Conceptualization. **Fred Brouns:** Writing – review & editing, Visualization, Data curation. **Anneke M.F. Schreurs:** Writing – review & editing. **Daniel Keszthelyi:** Writing – review & editing. **Jacques W.M. Maas:** Writing – review & editing, Conceptualization. **Velja Mijatovic:** Writing – review & editing, Visualization, Supervision.

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