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ENDOMETRIOSIS AND COELIAC DISEASE – WHAT IS THE LINK?

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Abstract

Endometriosis is a common gynaecological condition known to cause dysmenorrhea, dyspareunia, and pelvic pain. It is a common cause of infertility in women. Coeliac disease classically causes abdominal pain and weight loss but can remain undiagnosed in many who present with atypical symptoms. The precise aetiology of endometriosis remains uncertain, but there are distinct similarities between the pathophysiology of coeliac disease and endometriosis, in that endometriosis also has an inflammatory component as well as links with autoimmunity. The purpose of this article is to review the literature to ascertain whether there is a relationship between the conditions.

Keywords: Endometriosis, Coeliac disease, Gluten Free, infertility, autoimmunity, inflammation

الملخص:

بطانة الرحم هو حالة أمراض النساء الشائعة المعروفة بأنها تسبب عسر الطمث ، وعسر الهضم ، وآلام الحوض .وهو سبب شائع للعقم لدى النساء .مرض كولياك يسبب عادة آلام في البطن وفقدان الوزن ولكن يمكن أن تظل غير مشخصة في العديد من الذين يعانون من أعراض غير نمطية .لا تزال المسببات الدقيقة لبُعَد الرحم غير مؤكدة ، ولكن هناك أوجه تشابه متميزة بين الفيزيولوجيا المرضية لمرض كولياك وبصلة الرحم ، في بطانة الرحم تحتوي أيضًا على مكون التهابي بالإضافة إلى روابط مع المناعة الذاتية .الغرض من هذه المادة هو مراجعة الأدبيات للتأكد من وجود علاقة بين الشروط .

الكلمات المفتاحية: بطانة الرحم، مرض كولياك، الغلوتين خالية، العقم، المناعة الذاتية، الالتهاب

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1. Introduction

Endometriosis is characterised by ectopic growth of endometrial tissue outside the uterine cavity. This can lead to dyspareunia, dysmenorrhea, infertility and in some women, it can be a cause of debilitating pelvic pain. It can be difficult to distinguish between other non-gynaecological causes of pelvic pain which can lead to a delay in diagnosis of endometriosis. [1] The estimated prevalence of endometriosis is 10%. [2] In contrast the presence of endometriosis is as high as 50 % in those being investigated for infertility.[3] The aetiology of endometriosis still remains under debate and not fully understood. Although retrograde menstruation is widely accepted as a cause of endometriosis, it is a common occurrence in most healthy menstruating women. Therefore, there must be additional factors that contribute to development of the condition, such as a genetic component, as there is a five times increased risk of endometriosis within siblings. [4] There is also discussion around possible environmental factors [5] that could contribute to the condition as well as a link with diet and endometriosis. [6]

Coeliac disease is an immunological disorder characterised by sensitivity to gluten. Diagnosis is confirmed by jejunal biopsy which shows the presence of chronic inflammation of the small intestine resulting in flattened villi which eventually leads to malabsorption. Classical gastrointestinal symptoms include loose stools, malabsorption resulting in weight loss and abdominal pain. Atypical features such as anaemia, neurological symptoms and dermatological manifestations have been well documented. [7] The extraintestinal symptoms can add to the diagnostic challenge of detecting the condition, adding to the delay in diagnosis. [8] Screening those patients for coeliac disease who only have classical symptoms is known to lead to underestimation of prevalence of disease. Given that disease more common in first degree relatives and those with underlying autoimmune diseases should prompt screening in these cohorts. Undiagnosed coeliac disease is common and many patients suffering with coeliac disease may have mild symptoms such as fatigue, anaemia, or slight weight loss, some may have no symptoms at all. [9]

Both sufferers of endometriosis and coeliac disease can present with vague and non-classical symptoms. Both conditions have some overlap of symptoms, such as abdominal pain and bowel symptoms. Certainly, endometriosis does share similarities with coeliac disease, in that there is an association with autoimmune conditions and there is an underlying inflammatory process. [10] A potential explanations to link endometriosis with coeliac disease include shared etiological factors such as immune and genetic links. Also, coeliac disease-mediated inflammation of the gut and the nutritional deficiencies that can contribute to some gynaecological symptoms.

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2. Impact of diet

Endometriosis is an oestrogen dependant condition and there is much evidence describing the impact of diet on other oestrogen dependant illnesses such as the dietary factors that have been implicated in breast [11] and endometrial cancers. [12] There are also studies observing the influence of fibre as well as fat intake on oestrogen levels. [13] Dietary fibre has been shown specifically to have an impact on the severity of dysmenorrhea [14] and adolescents suffering with dysmenorrhea were found to eat significantly lower amounts of fruit, fish and eggs.[15] A higher intake of green vegetables and fresh fruit can lower the risk of endometriosis whereas the intake of beef or red meat and ham can increase risk [16]

3. The link with inflammation and endometriosis

Coeliac disease is defined as an immune mediated inflammatory condition. There are underlying inflammatory processes involved in the development of endometriosis. The underlying physiology of menstruation involves an inflammatory process, the cyclical endometrial breakdown is a related to the release of cytokines and chemokines. [17]

Endometriosis sufferers have abnormal levels of immune cells present in endometrial and peritoneal tissue.[18] Prostaglandin E2, a potent cytokine and inflammatory mediator has been linked to the development of endometriosis. Its impact on macrophages is of interest in endometriosis. Macrophages are involved in the elimination debris in the peritoneum which includes endometrial tissues deposited via retrograde menstruation. Patients with endometriosis were found to have macrophages with reduced capacity and the uptake of debris was also reduced. [19, 20]

T cells are known to produce inflammatory signals which results in the activation and migration of neutrophils in endometriotic tissue. [21] When compared to disease free women, those with endometriosis have an abundance of regulatory T cells in the secretory phase of menstruation. It is suggested that the regulatory T cells reduce the ability to recognise and target endometrial antigens which leads to the survival of shed endometrial cells. [22]

The cytokine interleukin-1 has a significant impact on the regulation of inflammatory responses and endometriosis sufferers have increased levels of interleukin 1 in the peritoneum. [23] Tumour necrosis factor has also been found to be elevated in the peritoneal fluid, with higher concentrations correlating to advanced disease [24]

4. Endometriosis and Autoimmune conditions

It is known that there can be considerable comorbidity of autoimmune conditions. Patients suffering with primary biliary cirrhosis have up to 20 times more prevalence of autoimmune conditions like systemic lupus erythematosus and autoimmune thyroid diseases. [25] Families with Sjögren syndrome are more likely to report thyroid disease and rheumatoid arthritis. [26] There is also an association between type 1 diabetes and thyroid disease. [27]

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Endometriosis has been linked with a range of autoimmune diseases including systemic lupus erythematosus and Sjögren syndrome. [28] A statistically significant association has been established between endometriosis and at least one autoimmune disease such as rheumatoid arthritis, celiac disease, multiple sclerosis or inflammatory bowel disease. [29]

A Danish epidemiological study looking at the comorbidity of autoimmune conditions found that coeliac disease was linked to numerous conditions.[30] It is suggested that the comorbidity associated with coeliac disease may be related to the damaged and permeable intestine which allows for the passage of antigen like substances as well as food proteins, bacterial products and endotoxins leading to autoimmune diseases affecting multiple organ systems. [31]

5. Infertility and Coeliac disease

Endometriosis can lead to the presence of pelvic adhesions, there can be change in the physiology of the endometrium itself and the condition is known to have a negative impact on embryos as well as gametes, all of which contribute to the infertility associated with the condition. [32] Women with coeliac disease are known to suffer with gynaecological problems such as menstrual irregularities, recurrent miscarriages and obstetric complications. [33] A less frequently considered diagnosis of unexplained infertility is coeliac disease. It is possible that infertility is one spectrum of extraintestinal coeliac disease. There have been reported cases where the first symptoms of coeliac disease are menstrual or obstetric complications and studies to suggest that patients with unexplained infertility or recurrent miscarriage have increased incidence of coeliac disease.[34]

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6. Evidence suggestive of the link between Endometriosis and Coeliac disease

Caserta et al. report a case study of a patient presenting with primary infertility and endometriosis. [35] The patient had no classical symptoms of coeliac disease but was found to have microcytic anaemia and was offered antibody testing. Subsequent endoscopy confirmed the diagnosis of coeliac disease. The patient was able to conceive following a gluten free diet.

Santoro et al. [36] conducted a case control study to review the link between endometriosis and coeliac disease. Women with laparoscopically confirmed endometriosis were screened for coeliac disease via IgA endomysial and transglutaminase antibodies. A diagnosis of coeliac disease was made following endoscopy and biopsy of positive cases. The authors also noted the frequency of miscarriage, infertility and the presence of other autoimmune diseases in these women. Coeliac disease was diagnosed in 2.2% of women with endometriosis compared to 0.8% of the control group. The results suggest an increased prevalence of coeliac disease in this group although this study did not show a statistically significant increase in prevalence.

Stephansson et al. [37] conducted a cohort study of over 11, 000 cases of coeliac disease. Data regarding endometriosis was then retrieved and estimation of hazard ratio for endometriosis was calculated and compared to age matched controls. Patients with coeliac disease were found to have an increased risk of endometriosis.

Aguiar et al. [38] conducted a study on women with laparoscopically confirmed endometriosis who were tested for coeliac disease antibodies and those with positive results offered intestinal biopsy. The results were compared to a control group of healthy women. Coeliac disease prevalence in endometriosis group was 2.5% and 0.66% in the control group.

7. Discussion

The vague and sometimes atypical symptoms that both endometriosis and coeliac disease patients present with can cause diagnostic delays which can have a detrimental impact on patient care. The considerable clinical overlap of symptoms including abdominal pains, change in bowel habit and the impact on fertility that both conditions can have, should prompt clinicians to consider a diagnosis of coeliac disease in patients with endometriosis and vice versa.

Coeliac disease is a condition which is almost exclusively managed by dietary changes and in a climate where the impact of diet in the management of chronic conditions has been under scrutiny more than ever before, it would be sensible to consider dietary factors influencing endometriosis also. Given that there is considerable comorbidity between autoimmune conditions, establishing these links can be fundamental in managing associated conditions. As demonstrated by a case study reported by Valentino et al. [39] in which a patient who was known to suffer with autoimmune thyroid disease and Addison's disease was screened and diagnosed with coeliac disease. After adopting a gluten-free diet, the patient showed a marked clinical improvement and subsequently could discontinue thyroid substitutive therapy.

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8. Conclusion and recommendations

There are limited number of largescale studies that specifically investigate the risk of coeliac disease in endometriosis. The retrospective cohort study conducted by Stephansson et al[37] was a large study involving over 11,000 patients which showed patients with coeliac disease had a statistically significant increased risk of endometriosis. (HR = 1.39 P less than 0.001) [28] The study conducted by Aguiar et al.[38] found a higher frequency of coeliac disease in endometriosis suffers. Unfortunately, it was a small study population and the results were not statistically significant. However, in this particular study one patient refused a biopsy and had they been positive, the P value would have been statistically relevant.

Despite the lack of sufficient studies, there are several reasons to consider screening for asymptomatic coeliac disease in endometriosis patients. Currently there is there is no curative treatment for endometriosis and the mainstay of treatment is aimed at managing pain. Often this is with the use of hormonal contraception, but it can include invasive surgical intervention, for which the recurrence of pain and lesions is common.[40] Both hormonal and surgical options may not be acceptable to some women, particularly for those who are younger and those wishing to preserve fertility. Coeliac disease can easily be managed with dietary intervention and the effect on disease activity, including reduction of pelvic pain in endometriosis and favourable outcome in fertility treatment can be life changing.

It is not yet known whether these two conditions share pathophysiological mechanisms even if they arise independently and further research is still needed to establish the link.

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