Gastrointestinal Symptoms in Women With Endometriosis and Microscopic Colitis in Comparison to Irritable Bowel Syndrome: A Cross-Sectional Study

Malin Ek[1], *Bodil Roth*[1], *Mariette Bengtsson*[2], *Bodil Ohlsson*[1]

[1]Department of Internal Medicine, Skåne University Hospital, Lund University, Malmö, Sweden
[2]Faculty of Health and Society, Institution of Care Science, Malmö University, Sweden

Cite this article as: Ek M, Roth B, Bengtsson M, Ohlsson B. Gastrointestinal symptoms in women with endometriosis and microscopic colitis in comparison to irritable bowel syndrome: A cross-sectional study. *Turk J Gastroenterol.* 2021; 32(10): 819-827.

ABSTRACT

Background: *Gastrointestinal (GI) symptoms similar to irritable bowel syndrome (IBS) are often present in women with endometriosis and microscopic colitis (MC). The objective of this study was to estimate GI symptoms in IBS, endometriosis, and MC, to compare the clinical expression of the diseases.*

Methods: *Women with IBS, endometriosis, and MC were identified by diagnosis codes at a tertiary center. The patients had to complete the visual analog scale for IBS to estimate specific GI symptoms. Women fulfilling Rome III criteria for IBS were diagnosed as IBS (n = 109) and divided into subgroups depending on predominating symptoms. Women diagnosed with endometriosis (n = 158) and MC (n = 88) were evaluated whether they also fulfilled the Rome III criteria for IBS.*

Results: *Women with IBS experienced aggravated abdominal pain, diarrhea, bloating and flatulence, nausea and vomiting, the urgency to defecate, the sensation of incomplete evacuation and intestinal symptom's influence on daily life, and impaired psychological well-being, compared to women with endometriosis. When patients with endometriosis also fulfilled the criteria for IBS, all symptoms in the 2 cohorts, except intestinal symptom's influence on daily life, were equal. Women with IBS or diarrhea-predominated IBS experienced aggravated abdominal pain, bloating and flatulence, intestinal symptom's influence on daily life, and impaired psychological well-being compared to MC, but at equal levels as MC with IBS-like symptoms.*

Conclusions: *Women with IBS generally experience aggravated GI symptoms and impaired psychological well-being compared to endometriosis and MC. Patients with endometriosis or MC, in combination with IBS, express similar symptoms as patients with sole IBS.*

Keywords: *Endometriosis, gastrointestinal symptoms, irritable bowel syndrome, microscopic colitis, visceral hypersensitivity*

INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by abdominal pain and altered bowel habits, divided into subgroups based on the most predominant bowel habits.[1] The disease has a significant impact on healthcare utilization and health-related quality of life.[2] The pathophysiology of IBS is not clearly elucidated, but altered digestive secretion and motility, visceral hypersensitivity, and alterations in the endocrine, immune, and gut microbiota systems have been reported.[1,3]

Endometriosis is a benign, gynecological disease with chronic pelvic pain and dysmenorrhea as the main symptoms.[4] Women with endometriosis commonly experience symptoms similar to those of IBS, and they have been found to have 3.5 times higher risk to be diagnosed with IBS than controls.[4] The pathogenesis of the gastrointestinal (GI) symptoms has not yet been clarified, but suggestions include endometrial lesions in the bowel wall releasing prostaglandins altering bowel function.[4,5] A comorbidity between endometriosis and IBS may exist since both diseases are common in the population.[4,6]

Microscopic colitis (MC) presents itself with chronic nonbloody diarrhea as the main symptom. Other symptoms may include abdominal pain, fecal urgency, and weight loss. Women are affected more often than men, predominantly during middle-age.[7] Symptomatic overlap between MC and IBS, especially diarrhea-predominant IBS (IBS-D), has been described in several studies,[8] and a recently published meta-analysis concluded that one-third of patients with MC experience symptoms consistent with IBS.[9]

The similarities between symptoms of different diseases lead to extensive examinations with diagnostic delay

Corresponding author: ***Malin Ek****, e-mail:* ***malin.ek@med.lu.se***
Received: ***July 23, 2019*** *Accepted:* ***January 30, 2020*** *Available Online Date:* ***November 1, 2021***

DOI: 10.5152/tjg.2020.19583

from the onset of symptoms to an established diagnosis.[10] Studies examining the co-existence of different diseases often use diagnosis criteria from medical records or IBS classifications to characterize the diseases.[4,9] That is not enough, the patients' descriptions of their symptoms ought to be added. We hypothesized that specific GI symptoms differ between IBS, endometriosis, and MC. To address this, women with IBS, endometriosis, and MC were enrolled at a tertiary care center and completed the visual analog scale for irritable bowel syndrome (VAS-IBS). The aim of the present study was to estimate specific GI symptoms among women with IBS, endometriosis, and MC, to compare the clinical expression of the diseases.

MATERIALS AND METHODS

Study Design

Patients with IBS, endometriosis, and MC were recruited from a tertiary center to this cross-sectional study. After the identification of patients according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (Figure 1), the medical records were scrutinized. Controls and patients were contacted by mail with written information, a consent form, and the VAS-IBS questionnaire. Controls and most IBS patients returned their questionnaires by mail, whereas patients with endometriosis or MC had an appointment with ME or BR. At the meeting, questionnaires about medical history and the VAS-IBS were completed. Irritable bowel syndrome patients could also be recruited consecutively by MB or BO at their scheduled appointment at the Department of Gastroenterology. The diagnosis of IBS, or IBS-like symptoms in the case of MC since IBS per definition demands the absence of any organic alterations in the bowel, was set when the patients fulfilled the Rome III criteria with abdominal pain/discomfort weekly, associated with at least 2 of the following: onset of defecation, altered bowel consistency or altered bowel frequency.[11]

Patients

The overall inclusion criteria were an ability to comprehend Swedish or English the age above 18 years. The exclusion criteria were an uncertain diagnosis, inflammatory bowel disease, regular use of opioids, pregnancy, multiple co-morbidities, or severe mental illness. Men were excluded from all calculations due to a low prevalence. Controls were recruited from hospital staff and the Swedish population registry.

Irritable Bowel Syndrome

The majority of patients were identified retrospectively at the Department of Gastroenterology by the ICD

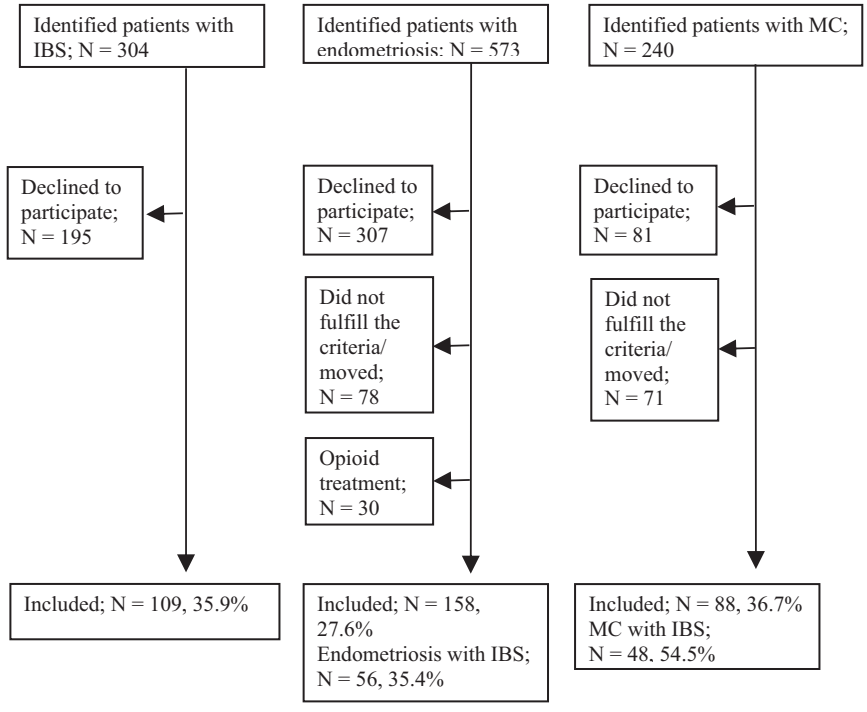

Figure 1. Flow-chart of inclusion of participants in the current study. IBS, irritable bowel syndrome.

classifications of functional GI disorders (K58.0, K58.9, K59.0, K59.1, K 59.9), but patients were also recruited consecutively when visiting the clinic due to abdominal pain and altered bowel habits. All patients referred to the Department were examined with blood and feces sampling including antibody analyses, endoscopy, and tests for bacterial overgrowth or malabsorption, according to clinical indications, to exclude any organic disease explaining GI symptoms. A total of 304 patients who fulfilled the Rome III criteria for IBS diagnosis[11] were identified during 2005 and 2010. Of these, 109 women (39 women, 35.8%, included prospectively) agreed to participate.[12,13] None of the patients were currently treated with opioids.

Endometriosis

Women who had sought treatment for endometriosis at the Department of Gynecology between 2009 and 2014 were retrospectively identified using the ICD-10 classification N80. A total of 307 women were identified, and 145 declined to participate, 49 had moved from the region and 4 denied the diagnosis, leaving 109 women available for the study. In a second inclusion period between September 2016 and March 2017, 266 women fulfilling the inclusion criteria were identified. Of those, 162 women declined to participate, 23 women had moved from the region, and 2 women had an uncertain diagnosis, leaving 79 women available.[14] Due to regular opioid treatment, 30 patients were excluded, leaving 158 patients included. Endometriosis was diagnosed using either laparoscopy or ultrasonography.[15] Women who stated that they had received a diagnosis of IBS or had symptoms according to the Rome III criteria were classified as suffering from IBS (n = 56).[6,11]

Microscopic Colitis

Women who were diagnosed at any Departments of Gastroenterology in Skåne, or found in the local register at the Department of Pathology in Malmö between 2002 and 2010, were retrospectively identified using the ICD-10 classifications for collagenous colitis and lymphocytic colitis (K 52.8). A total of 240 women were identified who had their diagnosis verified by colonic biopsy and histopathological examination.[16] Of these, 159 agreed to participate in the study. After the exclusion of 71 patients with transient symptoms, 88 patients were finally included in the study. Patients who fulfilled the Rome III criteria were classified as suffering from IBS-like symptoms (n = 48).[11,17] None of the included patients were in acute relapse of the disease or treated on high-doses of corticosteroids or opioids.[18]

Controls

Control data for calculation of Z scores were obtained from a study published in 2013.[19] A total of 248 subjects randomly acquired from the Swedish population registry were contacted, and after 1 reminder, 29 questionnaires were returned. Because the response rate was low, further controls were recruited among female hospital staff, and a total of 65 women, mean age 38.4 ± 7.4 years, representing the general population were recruited. The presence of IBS in controls was accepted, but all other diseases led to exclusion.

Questionnaires

Study Questionnaire

A study questionnaire about sociodemographic factors, family history, lifestyle habits, medical health, and pharmacological treatment was completed at inclusion by prospective enrolled patients with IBS, and all patients with endometriosis and MC.

Visual Analog Scale for Irritable Bowel Syndrome

The VAS-IBS is a psychometrical test for estimating GI complaints among individuals, validated against the gastrointestinal rating scale and the psychological general well-being index.[20] The items in the VAS-IBS address the symptoms of abdominal pain, diarrhea, constipation, bloating and flatulence, vomiting and nausea, psychological well-being, and the intestinal symptom's influence on daily life. The symptoms are measured on a scale from 0 mm to 100 mm, where 0 represents very severe symptoms, and 100 represents a complete lack of symptoms. Two additional questions, the urgency to defecate and sensation of incomplete evacuation after defecation, are answered by yes or no.[20] The item psychological well-being has been found to strongly correlate to positive and negative aspects of psychological well-being, anxiety in close relations, self-esteem, and coping skills.[21]

Statistical Methods

Statistical calculations were performed using SPSS© for Windows (release 24.0; IBM). Due to significant age differences between the study groups, the variables in the VAS-IBS were age-standardized using a linear regression model of the control group, to which age was added as a covariate, and values were expressed as Z-scores. The differences between groups were calculated using the 2-tailed Mann–Whitney *U*-test or Fischer's exact test. The values were expressed as the mean ± standard deviation, median and interquartile ranges (IQR), or number (n)

and percentage (%). Due to several comparisons, $P \leq .01$ was considered to be statistically significant.

RESULTS

Patient Characteristics

The IBS cohort was similar in age to the endometriosis cohort ($P = .197$), but younger than the MC cohort ($P \leq .001$). In the IBS cohort consisting of 109 women, 20 women had constipation-predominant IBS (IBS-C), 38 women had IBS-D, 39 women had mixed IBS, and 12 women had an unknown subtype of IBS. In the MC cohort, 56 women had collagenous colitis and 32 women had lymphocytic colitis. Approximately one-third of the women with endometriosis also fulfilled IBS-criteria, whereas almost half of the MC patients experienced IBS-like symptoms (Table 1).

In a drop-out analysis of the endometriosis patients, the mean age of the included patients was 37.3 ± 7.3 years (before exclusion of patients with opioid treatment), compared to 35.8 ± 6.9 years in the patients who declined to participate ($P > .05$). The reason for unwillingness to participate is not known. Not one of the invited patients was contacted a second time for response analysis, since this was not allowed according to the ethical review board.

Endometriosis and Irritable Bowel Syndrome

Women with IBS experienced more severe symptoms than women with endometriosis with respect to abdominal pain, diarrhea, bloating and flatulence, vomiting and nausea, the urgency to defecate, and incomplete evacuation after defecation. They also experienced impaired psychological well-being, and their daily lives were more profoundly affected by their intestinal symptoms (Table 2).

When comparing patients with IBS and endometriosis who also fulfilled IBS criteria,[14] patients with IBS experienced a more profound effect by their intestinal symptoms on their daily lives (24 (4-48) vs. 40 (19-75) mm; $P = .005$), albeit each symptoms were non-significantly more severe in pure IBS (Table 2).

Microscopic Colitis and Irritable Bowel Syndrome

Women with IBS or IBS-D experienced aggravated symptoms regarding abdominal pain and bloating and flatulence compared to women with MC, with worse psychological well-being in IBS and more influence of intestinal symptoms on daily life in IBS-D. Diarrhea was more prominent in IBS-D compared to MC, and less prominent in IBS compared to MC with IBS-like symptoms. The degree of constipation was even less pronounced in IBS-D than in MC (Table 3).

DISCUSSION

Women with IBS experienced aggravated complaints about all GI symptoms except constipation, impaired psychological well-being, and more influence of intestinal symptoms on daily life, compared to women with endometriosis. When comparing patients with endometriosis who also suffered from IBS and patients with solely IBS, all differences disappeared, except the aggravating influence of intestinal symptoms on daily life. Abdominal pain and bloating and flatulence were more pronounced in women with IBS and IBS-D compared to women with MC, with worse psychological well-being and more influence of intestinal symptoms on daily life in IBS and IBS-D, respectively, compared to MC.

These results show similar symptoms in women with solely IBS and women with endometriosis and MC in combination with IBS/IBS-like symptoms. Although the Rome criteria have been shown to be safe to exclude organic diseases,[22] the present results demonstrate that we have to carefully exclude endometriosis and MC in women seeking for IBS or IBS-like symptoms, since symptom questionnaires do not differ between pure IBS and IBS or IBS-like symptoms in combination with endometriosis or

Table 1. Patient Characteristics

	Women with IBS N = 109	Women with Endometriosis N = 158	Women with MC N = 88	*P*
Age (years)	37.3 ± 12.3	37.4 ± 6.6	60.7 ± 9.7	
IBS/IBS-like symptoms (n, %)	109, 100	56, 35.4	48, 54.5	
Age of patients with IBS/IBS-like symptoms (years)	37.3 ± 12.3	36.3 ± 7.1	59.4 ± 11.1	

Values are presented as number and percentage and mean ± standard deviation. Comparison of age between IBS and endometriosis ($P = .197$) and MC (<0.001), respectively. Mann–Whitney *U*-test. $P \leq .01$ was considered statistically significant.
IBS, irritable bowel syndrome.

Table 2. Gastrointestinal Symptoms in Irritable Bowel Syndrome and Endometriosis

	Women with endometriosis	Women with Endometriosis end IBS	Women with IBS	*P* (IBS vs. Endometriosis/ IBS vs. Endometriosis and IBS)
	N = 158 Missing Value = 2	N = 56 Missing Value = 1	N = 109 Missing Value = 0	
Abdominal pain				
Absolute score	68 (37–95)	50 (27–70)	28 (18–60)	
Z score	−0.6 (−2.0 to 0.6)	−1.5 (−2.4 to −0.4)	−2.2 (−3.0 to −0.9)	<**.001**/.011
Diarrhea				
Absolute score	86 (51–100)	65 (29–96)	50 (24–90)	
Z score	0.2 (−1.0 to 0.7)	−0.4 (−1.8 to 0.5)	−1.2 (−2.1 to 0.3)	<**.001**/.219
Constipation				
Absolute score	80 (45–100)	51 (32–85)	81 (40–97)	
Z score	−0.1 (−1.5 to 0.6)	−1.2 (−1.9 to 0.2)	−0.2 (−1.8 to 0.4)	.450/.115
Bloating and flatulence				
Absolute score	49 (21–86)	30 (16–55)	26 (8–50)	
Z score	−0.8 (−1.7 to 0.5)	−1.5 (−1.9 to −0.6)	−1.6 (−2.2 to −0.7)	<**.001**/.245
Vomiting and nausea				
Absolute score	95 (70–100)	80 (50–98)	79 (38–97)	
Z score	0.3 (−0.7 to 0.5)	−0.4 (−1.7 to 0.4)	−0.7 (−2.3 to 0.4)	<**.001**/.335
Psychological well-being				
Absolute score	74 (41–95)	65 (30–78)	50 (27–75)	
Z score	−0.5 (−2.5 to 0.9)	−0.9 (−3.1 to −0.3)	−2.1 (−3.3 to −0.3)	<**.001**/.189
Influence on daily life				
Absolute score	66 (30–95)	40 (19–75)	24 (4–48)	
Z score	−0.5 (−1.9 to 0.5)	−1.6 (−2.5 to −0.1)	−2.3 (−2.8 to −1.2)	<**.001/.005**
Urgency to defecate (Yes/No/ Unknown)	49/100/9	21/31/4	57/48/4	**.001**/.127
Sensation of incomplete evacuation (Yes/No/Unknown)	78/74/6	32/20/4	81/27/1	<**.001**/.096

Z score = standard score. Gastrointestinal symptoms were measured on the Visual Analog Scale for Irritable Bowel Syndrome scale, where 0 represents very severe symptoms and 100 mm represents a complete lack of symptoms. Mann–Whitney *U*-test was used for calculations of Z scores and Fischer's exact test for dichotomous variables. Values are expressed as median and IQR, and number. $P \leq .01$ was considered statistically significant.
IBS, irritable bowel syndrome.

MC. Nevertheless, the treatments of these 3 conditions differ markedly.[1,4,7]

Women with MC and IBS-like symptoms have aggravated diarrhea compared with patients with IBS. This is not surprising since diarrhea is the cardinal symptom of MC.[7] However, there was no difference in reported diarrhea compared with IBS-D. A recent meta-analysis concluded that one-third of MC patients report symptoms compatible with IBS,[9] and in the present study, more than half of MC patients fulfilled the Rome III criteria.[11] It is therefore important to acknowledge and provide

Table 3. Gastrointestinal Symptoms in Irritable Bowel Syndrome and Microscopic Colitis

	Women with MC N = 88	Women with MC and IBS N = 48	Women with IBS N = 109	*P* (IBS vs. MC/IBS vs. MC and IBS)	Women with IBS-D N = 38	*P* (IBS-D vs. MC/ IBS-D vs. MC and IBS)
Abdominal pain	–					
Absolute score	70 (47-88)	58 (35-74)	28 (18-60)		22 (14-38)	
Z score	−1.1 (−2.1 to −0.2)	−1.8 (−2.8 to −0.9)	−2.2 (−3.0 to −0.9)	<**0.001**/0.276	−2.5 (−3.1 to −1.9)	<**.001**/.022
Missing value	4	2	0		0	
Diarrhea						
Absolute score	54 (23-80)	37 (19-69)	50 (24-90)		24 (7-42)	
Z score	−1.3 (−2.4 to −0.2)	−1.9 (−2.5 to −0.6)	−1.2 (−2.1 to 0.3)	0.120/**0.005**	−2.1 (−2.7 to −1.5)	**.001**/.136
Missing value	4	3	0		0	
Constipation						
Absolute score	95 (86–98)	96 (87–98)	81 (40–97)		96 (92-100)	
Z score	−0.1 (−0.4 to 0.1)	−0.1 (−0.4 to 0.1)	−0.2 (−1.8 to 0.4)	0.801/0.865	0.4 (0.2 to 0.7)	<**.001**/<**.001**
Missing value	7	4	0		0	
Bloating and flatulence						
Absolute score	52 (30–82)	40 (25–70)	26 (8–50)		26 (8-50)	
Z score	−0.9 (−1.7 to 0.2)	−1.3 (−1.8 to −0.3)	−1.6 (−2.2 to −0.7)	<**0.001**/0.056	−1.6 (−2.2 to −0.7)	**.001**/.074
Missing value	4	2	0		0	
Vomiting and nausea						
Absolute score	95 (77–99)	88 (63–98)	79 (38–97)		83 (21-98)	
Z score	−0.2 (−0.9 to 0.0)	−0.5 (−1.6 to 0.0)	−0.7 (−2.3 to 0.4)	0.681/0.932	−0.3 (−2.9 to 0.4)	.984/.846
Missing value	4	2	0		0	
Psychological well-being						
Absolute score	76 (46–89)	52 (42–86)	50 (27–75)		48 (31-80)	
Z score	−0.6 (−2.4 to 0.2)	−2.0 (−2.7 to 0.0)	−2.1 (−3.3 to −0.3)	**0.003**/0.355	−2.1 (−3.1 to −0.1)	.047/.640
Missing value	2	2	0		0	
Influence on daily life						
Absolute score	58 (24–82)	41 (30–41)	24 (4–48)		16 (3–40)	
Z score	−1.4 (−2.7 to −0.5)	−2.0 (−2.9 to −0.9)	−2.3 (−2.8 to −1.2)	0.025/0.779	−2.7 (−2.8 to −1.5)	**.006**/.219
Missing value	2	2	0		0	
Urgency to defecate (yes/no/unknown)	46/37/5	37/9/2	57/48/4	0.884/0.207	26/10/2	.104/.635
Sensation of incomplete evacuation (yes/no/ unknown)	54/31/3	30/15/3	81/27/1	0.113/0.537	24/13/1	1.000/.137

Z score = standard score. MC = microscopic colitis. Gastrointestinal symptoms were measured on the Visual Analog Scale for Irritable Bowel Syndrome scale, where 0 represents very severe symptoms and 100 mm represents a complete lack of symptoms. Mann–Whitney *U*-test was used for calculations of Z scores and Fischer's exact test for dichotomous variables. Values are expressed as median and interquartile range (IQR), and number. $P \leq .01$ was considered statistically significant. IBS, irritable bowel syndrome.

treatment for additional GI symptoms in patients with MC, and not only diarrhea.

IBS symptoms severely impair health-related quality of life, and patients with IBS have higher levels of anxiety and depression than the average population.[23] Accordingly, the current IBS patients had both worse psychological well-being and experienced a greater influence on the daily life of their intestinal symptoms, than patients with endometriosis and MC without IBS. Patients with IBS often face stigmata, which could be due to the fact that the etiology behind IBS is poorly understood.[24] In contrast, patients with endometriosis or MC have verified, organic explanations for their complaints. Additionally, psychological factors are moderators of symptom severity, and pain perception in IBS has been shown to be strongly determined by psychological factors.[23] Thus, aggravated GI symptoms in patients with IBS may partially be explained by psychological factors. However, increased prevalence of mood disorders and anxiety have also been reported in endometriosis,[25] and patients with MC have impaired psychological well-being compared to controls,[17,18] which, however, are most evident in the subgroup of patients with concomitant IBS.[17]

Although similar symptoms, the etiology, and pathophysiology of IBS/IBS-like symptoms may vary.[1,3] Since this was a cross-sectional study, we cannot know whether IBS or IBS-like symptoms are secondary to endometriosis and MC, or if it is co-existence of 2 common diseases. GI symptoms were not related to localization of endometriosis lesions or other characteristics in this cohort,[6] which make it difficult to identify predictors and etiology to GI symptoms in endometriosis.[4,5] On the other hand, bowel lesions can be difficult to diagnose, and lesions may be present although not identified. The findings of antibodies against gonadotropin-releasing hormone (GnRH) in serum in IBS, but not in endometriosis and MC, support a neuron degeneration in a subgroup of patients with IBS.[14,17]

In endometriosis, there is an inflammatory activity with systemic effects,[10] whereas the supposed inflammation in IBS and MC is more related to the bowel wall with increased numbers of lymphocytes and mast cells.[7,26] Inflammation is one explanation to visceral sensitization, which means an exaggerated pain sensation related to visceral organs,[27] and may contribute to the IBS symptoms since it has been described in both IBS and endometriosis.[1,3,28] There is close proximity between the visceral organs and their innervation, through the convergence of afferent pathways at the level of the spinal cord and at higher brain centers.[27] This convergence contributes to the co-existence of pain states affecting more than 1 organ, the so-called cross-reactivity.[29] Low pain thresholds in endometriosis patients during rectal balloon distention test due to central sensitization,[28] suggest that visceral hypersensitivity and cross-reactivity may explain the GI symptoms in this entity.[29] Further research regarding underlying mechanisms and how to manage and treat GI symptoms among women with IBS, endometriosis, and MC is warranted.

This study has several limitations. Many declined to participate, but the frequency of inclusion is comparable with other studies. Only women were included, leading to difficulties to extrapolate the results to men. The phase of the menstrual cycle at the time of symptom registration was not recorded. However, the vast majority of MC patients were in menopause, and about half of the patients in the endometriosis group were on current hormonal treatment.[14] Still, symptoms in both endometriosis and IBS may be influenced by the menstrual phase. Furthermore, the statistical calculations were not adjusted for current drug treatment, which could affect GI symptoms. We have previously described that about 15-20% of these 3 patient groups are treated with anti-depressant drugs.[14,18] Due to the lack of this information in the current IBS patients, we could not adjust for medication, more than that all patients with known opioid treatments were withdrawn. Since the frequency and regimes of current treatments were equal between groups,[14,18] the influence should be similar and not affect differences between groups. In the future, questionnaires of GI symptoms should be completed before the start of any treatment, to better describe the native states of diseases.

The control group was recruited from hospital staff, and it is likely that these women were healthier than average women. However, controls were used only for calculations of Z-scores. The ages between the study groups were not matched. To minimize the impact of this factor, comparisons were made using age-standardized values. Irritable bowel syndrome is a disease that is mainly managed by primary care facilities; however, the IBS cohort in this study was recruited from a tertiary center, and it is likely that these women had more severe symptoms than other patients with IBS.[30] However, all of the patients were recruited at the hospital, which explains why the same bias is present in the cohorts with IBS, endometriosis, and MC. The IBS patients were properly examined at

the Department of Gastroenterology. However, we cannot exclude that some of these patients still suffered from endometriosis.

CONCLUSIONS

Women with IBS generally experience aggravated GI symptoms and impaired psychological well-being compared to women with endometriosis or MC. Women with endometriosis or MC and IBS/IBS-like symptoms have similar symptoms as women with pure IBS. These findings underline that careful examination of women with GI symptoms is necessary, to exclude endometriosis and MC before a final diagnosis of IBS is set.

Ethics Committee Approval: This study was performed at Skåne University Hospital, Malmö, in accordance with the Declaration of Helsinki, and was approved by the Regional Ethics Review Board of Lund University; LU 510-02 (12), 2011/209 (17), 2010/386 (13), 2012/56 (6), and 2011/44 (19).

Informed Consent: All subjects provided written, informed consent before participating in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.O., M.B., M.E.; Design - B.O., M.B., M.E.; Resource - B.O.; Materials - B.O., M.B.; Data collection and/or Processing - B.O., B.R., M.B., M.E.; Anaysis and/or interpretion - B.O., M.B., M.E.; Literature Search - B.O., M.E; Critical Reviews - B.O., B.R., M.B., M.E.

Acknowledgments: We thank Dr Oskar Hammar for the data collection of the controls. We also thank Dr Per Ekström and Dr Lil Valentin for data collection of the endometriosis cohort.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This research was funded by the Albert Påhlsson Foundation, Bengt Ihre Foundation, and the Development Foundation of Region Skåne.

REFERENCES

1. Bellini M, Gambaccini D, Stasi C, et al. Irritable bowel syndrome: A disease still searching for pathogenesis, diagnosis and therapy. World J Gastroenterol. 2014;20(27):8807-8820. [CrossRef]
2. Soares RL. Irritable bowel syndrome: A clinical review. World J Gastroenterol. 2014;20(34):12144-12160. [CrossRef]
3. Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Irritable bowel syndrome: A microbiome-gut-brain axis disorder? World J Gastroenterol. 2014;20(39):14105-14125. [CrossRef]
4. Seaman HE, Ballard KD, Wright JT, de Vries CS. Endometriosis and its coexistence with irritable bowel syndrome and pelvic inflammatory disease: Findings from a national case-control study--Part 2. BJOG. 2008;115(11):1392-1396. [CrossRef]
5. Roman H, Ness J, Suciu N, et al. Are digestive symptoms in women presenting with pelvic endometriosis specific to lesion localizations? A preliminary prospective study. Hum Reprod. 2012;27(12):3440-3449. [CrossRef]
6. Ek M, Roth B, Ekström P, et al. Gastrointestinal symptoms among endometriosis patients—A case-cohort study. BMC Womens Health. 2015;15:59. [CrossRef]
7. Bouma G, Münch A. Microscopic colitis. Dig Dis. 2015;33(2):208-214. [CrossRef]
8. Ozdil K, Sahin A, Calhan T, et al. The frequency of microscopic and focal active colitis in patients with irritable bowel syndrome. BMC Gastroenterol. 2011;11:96. [CrossRef]
9. Kamp EJ, Kane JS, Ford AC. Irritable bowel syndrome and microscopic colitis: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14(5):659-68.e1; quiz e54. [CrossRef]
10. Fassbender A, Burney RO, F. O D, D'Hooghe T, Giudice L. L: Update on biomarkers for the detection of endometriosis. BioMed Res Int. 2015;2015:1-14. [CrossRef]
11. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. J Gastrointestin Liver Dis. 2006;15(3):237-241.
12. Bengtsson M, Hammar O, Mandl T, Ohlsson B. Evaluation of gastrointestinal symptoms in different patient groups using the visual analogue scale for irritable bowel syndrome (VAS-IBS). BMC Gastroenterol. 2011;11:122. [CrossRef]
13. Bengtsson M, Sjöberg K, Candamio M, Lerman A, Ohlsson B. Anxiety in close relationships is higher and self-esteem lower in patients with irritable bowel syndrome compared to patients with inflammatory bowel disease. Eur J Intern Med. 2013;24(3):266-272. [CrossRef]
14. Ek M, Roth B, Valentin L, Nordengren J, Ohlsson B. Autoantibodies common in patients with gastrointestinal diseases are not found in patients with endometriosis: A cross- sectional study. Eur J Obstet Gynecol Reprod Biol. 2019;240:370-374. [CrossRef]
15. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Donnez J. Deep endometriosis:definition, diagnosis, and treatment. Fertil Steril. 2012;98(3):564-571. [CrossRef]
16. Lazenby AJ. Collagenous and lymphocytic colitis. Semin Diagn Pathol. 2005;22(4):295-300. [CrossRef]
17. Roth B, Ohlsson B. Gastrointestinal symptoms and psychological well-being in patients with microscopic colitis. Scand J Gastroenterol. 2013;48(1):27-34. [CrossRef]
18. Roth B, Bengtsson M, Ohlsson B. Diarrhoea is not the only symptom that needs to be treated in patients with microscopic colitis. Eur J Intern Med. 2013;24(6):573-578. [CrossRef]
19. Hammar O, Roth B, Bengtsson M, Mandl T, Ohlsson B. Autoantibodies and gastrointestinal symptoms in infertile women in relation to in vitro fertilization. BMC Pregnancy Childbirth. 2013;13:201. [CrossRef]
20. Bengtsson M, Ohlsson B, Ulander K. Development and psychometric testing of the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS). BMC Gastroenterol. 2007;7:16. [CrossRef]
21. Bengtsson M, Ohlsson B. The brief Visual Analogue Scale for irritable bowel syndrome questionnaire can be used to evaluate psychological well-being in patients with irritable bowel syndrome. Eur J Intern Med. 2013;24(7):e82-e83. Epub 2013/06/19. [CrossRef]
22. El-Salhy M, Halwe J, Lomholt-Beck B, Gundersen D. The prevalence of inflammatory bowel diseases, microscopic colitis, and colorectal cancer in patients with irritable bowel syndrome. Gastroenterol Insights. 2011;3(1). [CrossRef]
23. Fond G, Loundou A, Hamdani N, et al. Anxiety and depression comorbidities in irritable bowel syndrome (IBS): A systematic review

and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2014;264(8): 651-660. [CrossRef]
24. Taft TH, Keefer L, Artz C, Bratten J, Jones MP. Perceptions of illness stigma in patients with inflammatory bowel disease and irritable bowel syndrome. Qual Life Res. 2011;20(9):1391-1399. [CrossRef]
25. Laganà AS, Condemi I, Retto G, et al. Analysis of psychopathological comorbidity behind the common symptoms and signs of endometriosis. Eur J Obstet Gynecol Reprod Biol. 2015;194:30-33. [CrossRef]
26. Ohman L, Simrén M. Pathogenesis of IBS: Role of inflammation, immunity and neuroimmune interactions. Nat Rev Gastroenterol Hepatol. 2010;7(3):163-173. [CrossRef]
27. Bielefeldt K, Lamb K, Gebhart GF. Convergence of sensory pathways in the development of somatic and visceral hypersensitivity. Am J Physiol Gastrointest Liver Physiol. 2006;291(4):G658-G665. [CrossRef]
28. Issa B, Onon TS, Agrawal A, et al. Visceral hypersensitivity in endometriosis: A new target for treatment? Gut. 2012;61(3):367-372. [CrossRef]
29. Pezzone MA, Liang R, Fraser MO. A model of neural cross-talk and irritation in the pelvis: Implications for the overlap of chronic pelvic pain disorders. Gastroenterology. 2005;128(7):1953-1964. [CrossRef]
30. Polster AV, Palsson OS, Törnblom H, et al. Subgroups of IBS patients are characterized by specific, reproducible profiles of GI and non-GI symptoms and report differences in healthcare utilization: A population-based study. Neurogastroenterol Motil. 2019;31(1):e13483. [CrossRef]

Author Queries

JOB NUMBER: 20190583

JOURNAL: TJG

Q1 Please provide the significance of the bold characters in Tables 2 and 3.