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ORIGINAL ARTICLE

Endometriosis in patients with irritable bowel syndrome: Specific symptomatic and demographic profile, and response to the low FODMAP diet

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Background: Women with endometriosis are frequently misdiagnosed with irritable bowel syndrome (IBS) for some time before a correct diagnosis is made. Visceral hypersensitivity is a key feature in both conditions.

Aims: To determine if there are distinct symptom patterns in women with IBS and endometriosis, and to determine the response of these women to a low FODMAP diet in comparison to those with IBS alone.

Materials and methods: A retrospective analysis of prospectively collected data from women attending a specialist IBS service in Christchurch New Zealand. Data from those who met Rome III criteria for IBS were sorted into two groups: concurrent endometriosis and those with IBS alone. Demographics and symptom patterns were identified from a prospective questionnaire. A low FODMAP (fermentable oligosaccharides disaccharides, monosaccharides and polyols) diet was taught to all women as the primary therapeutic intervention. Responses to the diet were noted against their ultimate disposition.

Results: Of the 160 women who met Rome III criteria for IBS, 36% had concurrent endometriosis. The presence of dyspareunia ($P > 0.0001$), referred pain ($P = 0.005$), bowel symptoms exacerbated by menstruation ($P = 0.0004$) and a family history of endometriosis ($P = 0.0003$) were associated with concurrent endometriosis. Seventy two percent of these women reported a >50% improvement in bowel symptoms after four weeks of a low FODMAP diet compared with 49% in those with no known endometriosis ($P = 0.001$, odds ratio 3.11, 95% CI, 1.5–6.2).

Conclusions: Women with concurrent endometriosis and IBS report a unique symptom phenotype. The low FODMAP diet appears effective in women with gut symptoms and endometriosis.

KEYWORDS

(MeSH) diagnostic error, diet, endometriosis, hypersensitivity, irritable bowel syndrome

INTRODUCTION

Endometriosis is a chronic condition affecting up to 10% of women.[1] It is associated with severe dysmenorrhoea, menorrhagia, and chronic abdominal pain and frequently bowel symptoms similar to those typically associated with irritable bowel syndrome (IBS).[1] The association between IBS and endometriosis is not new, with difficulties distinguishing the two conditions frequently raised as a clinical concern.[2] Many patients with endometriosis report abdominal bloating, diarrhoea and/or constipation, and are frequently told they have IBS before endometriosis is detected.[2] Classic symptoms of endometriosis include dyspareunia

and dyschezia,[1] symptoms also commonly reported by patients meeting Rome III criteria for IBS. Despite such concern, there is a paucity of studies on the association.

Over the last decade, the inception of the low FODMAP diet has changed the paradigm of management of people with IBS.[3] FODMAP is the acronym for fermentable oligosaccharides disaccharides, monosaccharides and polyols, a group of short-chain carbohydrates found in a variety of fruits, vegetables and grains.[4] FODMAPs are poorly absorbed, small molecules readily fermentable by bacteria. Their osmotic actions and gas production cause intestinal luminal distension inducing pain and bloating in patients with visceral hypersensitivity with secondary effects on gut motility. Visceral hypersensitivity, a hallmark of IBS,[5] is also found in women with endometriosis,[6,7] suggesting the low FODMAP diet might be an attractive therapy in this group.

A private community-based IBS clinic in Christchurch New Zealand saw patients referred by general practitioners and other healthcare professionals for identification and management of functional gut symptoms. This provided a unique opportunity to examine the various symptom clusters, associated concurrent diagnoses and responses to management strategies.

This study aimed to examine and compare symptom patterns in women with IBS and known endometriosis against women with IBS, but in whom endometriosis is not known, nor has been considered, and to determine the response of these women to a low FODMAP diet.

MATERIALS AND METHODS

Data accrual

Consecutive female patients referred to a private IBS clinic prospectively completed a structured symptom questionnaire, followed by assessment and examination by a nurse specialist. More intensive clinical interrogation, investigation and assessment by a gastroenterologist or colorectal surgeon were prompted by the presence of red flags and/or abnormal screening laboratory tests. At initial consult patients were given a symptom questionnaire to take home and complete and bring to their next visit. This 40-question tool collected data that included onset and duration of symptoms, symptom type and triggers, and co-existing conditions. Data were collected via tick boxes and visual analogue scales and stored on a spreadsheet alongside age, final diagnosis, management strategies and ultimate outcome. Patients were defined as having endometriosis if diagnosed either prospectively or retrospectively via laparoscopy by a consultant gynaecologist. This was determined by referral information, on history or noted on the questionnaire where a specific question is asked about a known diagnosis. The database was routinely prospectively entered in patient clinical care.

All patients with a confirmed diagnosis of IBS (Rome III criteria[8]) were taught the low FODMAP diet by a nurse-specialist trained in the diet by an experienced dietitian. This comprised a one-on-one session. Patients completed a food and symptom diary for a week prior. Their diet and symptoms were discussed, and education on implementing the low FODMAP diet given. Educational resources, the Monash University Low FODMAP Diet digital application for iPhone and Android[9] was recommended and the low FODMAP diet booklet[10] provided. The first follow-up visit occurred four weeks after initial instruction, and patients reported their experience with the diet. A positive response was defined as a greater than 50% reduction in abdominal symptoms. Adherence to the diet was assessed by direct questioning where the patient reported either adherence all or most of the time, or non-adherence. Further instruction was given regarding reintroduction of FODMAPs in a gradual, systematic method according to individual responses, as per recommended guidelines.[11] Further follow up occurred as per individual needs.

Audit methodology

The current study represents an audit of female patients over a five-year period (January 2009 to December 2013). For the audit, the database was locked, data were de-identified and information evaluated. Only patients who returned for follow up were included in the analysis. Data were analysed according to the diagnosis (IBS or not), the presence of known endometriosis and the response to the low FODMAP diet. Results were expressed descriptively and analyses performed using Graph Pad Prism version 6.00 for Windows (Graph Pad Software, La Jolla, CA, USA). Categorical data were compared using χ^2 or Fisher's exact test, and odds ratio (OR) calculated together with 95% confidence intervals (CIs). Statistical significance was determined if the *P*-value was ≤ 0.05. As this audit conforms to the standards set by the National Health and Medical Research Council (NHMRC) for ethical quality review, ethics approval was not sought (NHMRC, 2003).

TABLE 1 Prevalence of endometriosis in women according to whether they fulfilled (positive) or not (negative) the Rome III criteria for irritable bowel syndrome

	Rome III positive, *N* = 160	Rome III negative, *N* = 71	*P* value	Odds ratio (95% CI)
Mean age (range)	37 (14–84) years	48 (17–84) years	<0.0001†	–
Endometriosis	59 (37%)	11 (15%)	0.001‡	3.02 (1.4–6.2)

†Wilcoxon signed rank test.
‡Fisher's exact test.

RESULTS

Prevalence of known endometriosis

Of the 231 eligible patients, 44 did not meet Rome III criteria for IBS, of whom 28 had another functional gastrointestinal disorder and another 16 had another organic condition. A further 27 met ROME III criteria for IBS but were diagnosed with an alternative condition following routine diagnostic blood or stool tests and investigation of red flags leaving 160 women with a confirmed diagnosis of IBS. Fifty-nine (37%) were found to have reported a history or recent diagnosis of endometriosis and 101 (63%) had no known diagnosis of endometriosis.

Characteristics associated with endometriosis

An analysis of demographics and symptoms in women with a final diagnosis of IBS stratified by presence/absence of endometriosis are shown in Table 2. Age, a family history of endometriosis and nulliparity were significantly associated with concurrent endometriosis. Only five women with known endometriosis were older than 55 years in comparison to 25 without a diagnosis of endometriosis ($P = 0.01$). Women with known endometriosis were more likely to have had a hysterectomy ($P = 0.06$). They were also significantly more likely to report dyspareunia ($P < 0.0001$), pain in the pelvis and back ($P = 0.005$) and bowel symptoms affected by menstruation ($P = 0.0004$), than those without a diagnosis of endometriosis. Interestingly, those without known endometriosis were more likely to report diarrhoea as the predominant symptom (20%) when compared with those with endometriosis (6%; $P = 0.008$). No differences were found between groups in terms of IBS type, frequency of bowel actions, responses to stress and to potential aggravators of pain.

Response to the low FODMAP diet

Adherence to the diet was high in both groups with only four (7%) in the endometriosis group and ten (9%) of the IBS alone group not adhering to the diet sufficiently to assess efficacy. Overall, the diet was reported as being effective (>50% improvement in symptoms) by 92 (58%) women meeting Rome III criteria for IBS (Table 3). A significantly higher proportion of patients with known endometriosis responded to the diet ($n = 43$, 72%) compared with those without ($n = 49$, 49%; $P = 0.001$) according to intention-to-treat. This represented a threefold increase in the likelihood of responding to the low FODMAP diet compared to those without known endometriosis (OR 3.11, 95% CI 1.5–6.2).

DISCUSSION

The prevalence of endometriosis is high, affecting up to 10% of women of reproductive age.[1] Many patients with endometriosis experience abdominal bloating, diarrhoea and/or constipation. Such symptoms are commonly seen in IBS, which itself affects up to 15% of the population.[11] When a woman presents with chronic abdominal and/or pelvic symptoms, defining the cause – endometriosis, IBS or both – can be challenging. This dilemma may in part contribute to the average delay of between 6 and 11 years before an eventual diagnosis of endometriosis is made.[12,13]

To date no accurate clinical markers of endometriosis have been found,[14] diagnosis requires invasive investigation, the gold standard being laparoscopy.[15] As such, defining a symptom profile in patients presenting with otherwise non-specific abdominal symptoms that predicts the presence of endometriosis is valuable. It has been reported that first-degree relatives of women

TABLE 2 Demographics and symptoms in women with concurrent IBS and a diagnosis of endometriosis in comparison to those with IBS alone. Significance set at 0.005 after Bonferroni correction for multiple comparisons

	Endometriosis			
	Known	**Not known**	***P*-value†**	**Odds ratio (95% CI)**
Number	59 (37%)	101 (63%)	–	–
Mean age (range) years	28 (16–65)	38 (13–84)	0.006	–
Age > 55 years	5 (8%)	25 (25%)	0.01	0.2 (0.10–0.78)
Family history of endometriosis	11 (19%)	2 (1.9%)	0.0003	11.3 (2.4–53.2)
Nulliparous	40 (68%)	51 (50%)	0.04	2.1 (1.1–4.0)
Hysterectomy	17 (29%)	16 (15%)	0.06	2.1 (0.98–4.6)
Dyspareunia	28 (47%)	13 (12%)	<0.0001	6.1 (2.8–13.2)
Pain referred to back and pelvis	53 (90%)	71 (70%)	0.005	3.7 (1.44–9.6)
Menses affecting bowel symptoms	46 (78%)	50 (49%)	0.0004	3.6 (1.74–7.4)
Nocturnal symptoms	27 (46%)	33 (32%)	0.12	1.7 (0.89–3.36)
Pain main symptom	26 (44%)	33 (32%)	0.06	1.9 (0.99–3.67)
Diarrhoea main symptom	4 (6%)	23 (22%)	0.008	0.2 (0.08–0.75)
Bloating main symptom	14 (23%)	15 (14%)	0.20	1.7 (0.79–4.0)

†Fisher's exact test.

TABLE 3 Adherence and response to the low FODMAP diet

	Endometriosis, *N* = 59	No reported endometriosis, *N* = 101	*P* value	Odd's ratio (95% CI)
Adherence to low FODMAP diet	55 (93%)	91 (90%)	0.57	1.5 (0.45–5.05)
Success with low FODMAP diet	43 (72%)	49 (49%)	**0.001**	**3.11 (1.5–6.2)**

with endometriosis have an 8–11-fold increased risk of the disease.[16] In the current study, women with known endometriosis were 11 times more likely to report a family member with the disease than those without a diagnosis of endometriosis, supporting this statement. The present study found specific symptoms – dyspareunia, menstruation affecting bowel symptoms and pelvic pain were more frequently reported in those with known endometriosis. This is consistent with a previous study that found these symptoms are suggestive of a diagnosis of endometriosis[15] and more likely misdiagnosed as IBS.

In light of these findings, it is thus proposed that the presence of such symptoms in patients suspected of having IBS, combined with a family history of endometriosis, be included in the list of indices that might direct targeted investigation for the presence of endometriosis. Such symptoms should be added to the list of 'red flags'. Reasons for highlighting the need to diagnose endometriosis include the increased risk of infertility or subfertility with endometriosis[15] and the possibility that delay in diagnosis may contribute to a poorer outcome. Certainly, in the current study, patients with endometriosis were more likely to be nulliparous than those with no known endometriosis, although reasons for this were not addressed.

It has been suggested that IBS may, in many, be a manifestation of endometriosis,[2] with up to 90% of women with histologically confirmed endometriosis having gastrointestinal symptoms.[17] IBS symptoms may relate to the presence of bowel or recto-vaginal endometriosis,[18] commonly affecting the sigmoid colon or recto-vaginal space. Small bowel involvement may also produce non-distinct symptoms of bloating, flatulence and pain, often mistaken for IBS.[19] Importantly, gastrointestinal symptoms frequently occur even in the absence of overt bowel involvement with endometriosis[17] suggesting the disease may also indirectly affect enteric nervous system function leading to secondary changes in visceral sensitivity or motility. Pain fibres in visceral organs may be linked (viscero-visceral hyperalgesia) via afferent and efferent nerve reflex arches, sharing painful stimuli.[6,20] This is supported by studies which have found that visceral hypersensitivity is present regardless of the severity of endometriosis.[6] Nevertheless, the mechanism behind this is not known, although inflammation and local prostaglandin release in response to endometrial deposits has been suggested.[21] Pain transmission pathways are also known to be affected by female gonadal hormones. Certainly, the association of endometriosis with visceral hypersensitivity has been established,[7] suggesting that, contrary to current understanding, the presence of visceral hypersensitivity may be a hallmark of endometriosis rather than IBS alone.

As luminal distension is a major stimulus for symptom genesis in visceral hypersensitivity, the role of diet is likely to be just as important for symptom control in endometriosis as it is in IBS. There are few studies that explore diet and endometriosis. It has been suggested that a high dairy intake and vitamin D may have some preventive effect,[22] but no studies have looked at diet having a therapeutic effect. This is the first study to show a therapeutic benefit of a low FODMAP diet in patients with endometriosis. The putative major mechanism of action of FODMAPs in triggering symptoms is via luminal distension from water retention due to osmotic effects and gas production from its fermentation in the large bowel.[23] Indeed, in the current study, the low FODMAP diet was beneficial in a substantially higher proportion of patients with endometriosis than in those in whom such a diagnosis had not been made. This difference in response rates between those with known and unknown endometriosis requires explanation. Responses to the low FODMAP diet in cohorts with IBS have varied from 52 to 80%.[4,5,11,20] Possible reasons for the range of response rates include method of assessment of response and the quality of the teaching, although these are unlikely to account for differences observed between cohorts in the present study. Adherence to the diet was reported subjectively by the patient, the determination of which may create a responder bias,[24] and hence, if those with endometriosis were more conscientious, may have influenced the outcomes. In the current cohort, a known diagnosis of endometriosis conferred a threefold greater chance of responding to the diet. This might then represent the first clinically useful predictor of response to the low FODMAP diet. Such an association has not been examined before. Sex-related differences in response have not been reported, but most cohorts have been small in number and the majority of participants were women, (54–93%)[24] in whom at least one-third may have endometriosis.

There are several limitations to this study. First, not all patients underwent laparoscopy to exclude endometriosis. This is a major limitation to this study as it reduces confidence that the control group is a true negative control. The characterisation of the patient cohort with respect to endometriosis depended upon an established diagnosis. However, endometriosis is commonly missed clinically and hence it is possible that some patients in the IBS-alone group did have concurrent endometriosis as a contributor to their symptomatology. Nevertheless this study has merit, as it highlights the increased prevalence of endometriosis in the IBS population (37% in IBS vs 15% without IBS).[6] In addition it identifies potential

clinical features that should promote further investigation and consideration of endometriosis with the hope that the diagnosis is missed in fewer patients in the future. Furthermore, prospective studies using laparoscopy as the gold standard for diagnosis are in progress. Secondarily, as a retrospective audit of a single centre, the generalizability of the findings is not known. Some of the other limitations of a retrospective study, such as the completeness and veracity of the data, were not issues since the data were collected prospectively. Patient selection was biased toward higher socioeconomic groups as the study was performed within private practice.

The intervention was also not placebo-controlled, but this does not detract from the sub-group analysis where it might be predicted that placebo responses were roughly similar. The use of a non-validated tool for symptom data collection does reduce the validity of the study; however, the tool was an adaptation of various validated questionnaires with additional questions around data we wanted to gather. Unfortunately, changes in individual symptoms in response to a low FODMAP were not gathered, although previous studies have uniformly shown improvement of all IBS symptoms associated with the diet.

In conclusion, endometriosis appears common in women with IBS. Historical clues, including dyspareunia, low pelvic pain and a family history of endometriosis, should lead to investigation and treatment that may assist in reducing complications from endometriosis, such as infertility. The low FODMAP diet is beneficial in reducing bowel symptoms in women with endometriosis. Indeed, the presence of endometriosis may be a clinical predictor of a higher likelihood of response to the low FODMAP diet, presumably because of the causal association with visceral hypersensitivity.

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