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Review article

A systematic review and meta-analysis of the associations between endometriosis and irritable bowel syndrome

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ABSTRACT

Endometriosis and Irritable Bowel Syndrome (IBS) are common conditions among young women of reproductive age. The etiologies to the diseases are uncertain, but multifactorial pathophysiology has been proposed for each of them. Many studies have examined the two conditions separately, but the literature on the associations between endometriosis and IBS is sparse. However, there is an increasing amount of research on how endometriosis patients are likely to also have a diagnosis of IBS. Furthermore, endometriosis shares several features with IBS, such as low-grade inflammation and visceral hypersensitivity. This systematic review summarized published original articles in English that have compared associations between endometriosis and IBS. The inclusion criteria for articles in the review were: i) endometriosis was diagnosed by surgical methods, ii) gastrointestinal symptoms were examined in a structured manner and iii) IBS was diagnosed by Rome criteria. From the initial 254 publications identified on PubMed, Web of Science and EMBASE, 13 fulfilled the criteria and could finally be included in the summary. The findings from the review showed that women diagnosed with endometriosis seem to have a twofold or threefold risk to also fulfill the criteria for IBS. The summary risk estimate of the four studies included in the meta-analysis was 2.39 (95 % confidence interval: 1.83–3.11). In women initially diagnosed with IBS, some studies reported a threefold risk of having an endometriosis diagnosis. Despite the strong associations reported between the two conditions, this review also revealed a gap in adjusting for factors that may have affected the expression of gastrointestinal symptoms, e.g., phases of the menstrual cycle, medication and psychological aspects, which may have interpretation of the reviewed articles' results. The conclusion of this review is that there is a coexistence of gastrointestinal symptoms fulfilling the Rome criteria in patients with endometriosis, but it is uncertain whether there is a true comorbidity between endometriosis and IBS, or whether the gastrointestinal symptomatology in endometriosis depends on medication. Additionally, the adequacy of the Rome criteria to differentiate IBS from the shared symptomatology of other diseases with visceral hypersensitivity must be further evaluated.

Contents

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Introduction

Endometriosis is a chronic condition defined by the existence of endometrial tissue outside the uterine cavity [1]. It commonly presents with dysmenorrhea, menorrhagia, chronic pelvic pain and gastrointestinal symptoms [2,3]. Like any other chronic condition, early detection is the key in the management of endometriosis, to improve prognosis and enhance the patients' quality of life. However, prompt diagnosis of endometriosis is often delayed averaging 5–6 years, and patients often experience high disease burden related to costs of healthcare and poor physical health [4]. Before a concrete diagnosis is made, endometriosis patients receive several other diagnoses with one of the most common conditions being Irritable Bowel Syndrome (IBS) [3]. Though the two conditions are thought to have dissimilar pathophysiology, much debate exist on their close associations and common features such as low-grade inflammation, increased gut permeability and visceral hypersensitivity [5–8]. However, management of the two conditions are different. Hence, differentiating the two conditions is paramount [7,9]. Therefore, the challenge faced by medical practitioners, whether in general, gastroenterology or gynecology practice, is to differentiate the two conditions, which is often compounded by the nature of the diagnostic procedures.

The gold standard for diagnosing endometriosis involves surgical methods, which are often saved for specific cases, due to the associated invasive nature and costs of conducting laparoscopies [10]. Thus, pelvic examination and imaging techniques are conventional to be used, in place of surgical methods, to diagnose suspected endometriosis [6]. On the other hand, there is no one standard diagnostic procedure for IBS, with the commonest guidelines used being the Manning and Rome criteria [11,12]. As a result, a firm diagnosis of IBS may vary depending on the diagnostic criteria used [13]. It is therefore no surprise, that the gastrointestinal symptoms associated with endometriosis may be diagnosed also as IBS [8,14]. This further fuels the debate on whether the two conditions coexist together, or if IBS is a misdiagnosis of symptoms related to endometriosis. To our knowledge, no systematic review and meta-analysis has been performed to evaluate the associations between endometriosis and IBS. In continuance with this debate, this paper reviewed studies conducting comparisons between endometriosis and IBS, to shed more light on the need to distinguish the two conditions and outline the magnitude of the problem.

Material and methods

A systematic review of the English language literature on endometriosis and IBS was carried out according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [15]. The search term 'endometriosis and irritable bowel syndrome' was used to search for published articles in MEDLINE (PubMed), Web of Science and EMBASE during June until November 2019. Articles studying a combination of endometriosis and IBS were included if: i) surgical methods such as laparoscopy or laparotomy were used to diagnose endometriosis, ii) structured examinations of gastrointestinal symptoms were performed, iii) structured examinations of IBS symptoms using Rome questionnaire, or a specialist familiar with the Rome criteria, were performed to set the diagnosis IBS and iv) adjustment was done for medication that could affect gastrointestinal symptoms. After reading the titles and abstracts, only one article was found to fulfill all the inclusion criteria [8]. The inclusion criteria were therefore amended to include all previously mentioned criteria, except the specification on adjustment for medication. Two of the authors then conducted the review of articles based on these criteria according to the review protocol, available from the authors, independently of each other, and compared the results. In case of discordance between the authors, the articles were read again and after discussions, consensus were made. All reference lists of the included articles were scrutinized, to see whether additional articles could be found.

Articles that did not compare endometriosis and IBS, articles describing etiology and management of endometriosis or IBS, animal studies, case reports, commentaries, letters and review papers were excluded. Articles not in English and not accessible through Lund University libraries were also excluded from this review.

Quality assessment

One of the authors performed the quality assessment of the articles using the Newcastle-Ottawa Scale for cohort and case-control studies [16]. The scale was constructed to evaluate cohort and case-cohort studies, by questions regarding selection (n = 4), comparability (n = 1) and outcome (n = 3). A maximum of eight stars can be achieved.

Statistical analyses

The most fully adjusted risk estimates and 95 % confidence interval were used for the meta-analysis. Hazard ratios and other reported risk ratios were considered interchangeably. The pooled and weighted odds ratios were calculated using a random effect meta-analytic model, and statistical heterogeneity was assessed by means of the I^2 statistic, with values <50 % considered to be a low heterogeneity. Publication bias was assessed by generating a funnel plot and assessing its symmetry. We did not conduct further statistical testing (e.g., Egger's or Begg's test) because of the relatively low number of studies. When more than one group of patients was described in the same study, the subgroup with most severe disease, or IBS diagnosis after index date, was selected. Since some studies had endometriosis as the targeted cohort, and some studies used IBS as the targeted cohort, two research questions were raised: 1) what is the risk for patients with endometriosis to also have IBS and 2) what is the risk for patients with IBS to also have endometriosis? The meta-analysis and funnel plot were calculated on Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Publications assessed

The final search was conducted on 19th November 2019, and yielded 113 articles identified in PubMed, 234 articles in Web of Science and 357 in EMBASE. After exclusion of duplicates, reviews

and conference abstracts, 254 article remained for evaluation. After exclusion of 232 articles that did not meet the inclusion criteria, 22 articles were fully assessed for eligibility. Three articles were excluded due to reliance on the patients' self-reported diagnosis of endometriosis and IBS, while two studies were excluded due to no relevance, two studies did have a repeated cohort with another study, one study was a review article and in one study endometriosis was diagnosed with magnetic resonance imaging (MRI). After all the exclusions, the final list of 13 relevant articles was agreed upon by the authors. Scrutinizing the reference lists of these articles did not render any further articles to include. The flow diagram of the selection process is shown in Fig. 1. Two of the articles compared the relationship between endometriosis and IBS [8,17], nine focused on factors related to endometriosis [2,18–25], one focused on women with IBS [26], while one of the articles focused on assessment of pain in patients with chronic pelvic pain [27]. Details of the 13 articles that met the inclusion criteria are described in Table 1. All included studies scored six stars or more on the Newcastle-Ottawa Scale.

Diagnosis of endometriosis and IBS

Ten articles relied on surgical methods for confirmation of the endometriosis diagnosis and included laparoscopy, laparotomy or surgery and histopathological confirmation [2,8,17–19,21,23,24,26,27]. Only one article also included endometriosis diagnosis using visual vaginal inspection in 3 % of patients, aside from using surgical methods [2]. Seven articles reported were relying on the Rome criteria to diagnose IBS [2,8,17,19,24,26,27], while three did not specify the criteria used, but the diagnoses were made by general practitioners, gastroenterologists or colorectal surgeons [18,20,21]. One study utilized the Visual Analogue Scale for IBS (VAS-IBS) [23]. Two large retrospective cohort studies and one large case control study that used the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) (applicable between 1978 and 1998 [28]) for endometriosis and IBS were also included, since the diagnoses were set by specialists in gynecology and gastroenterology/internal medicine at least twice and/or the endometriosis diagnosis was surgically confirmed. Thus, they were thought to be sufficient in meeting the inclusion criteria for this paper. Three articles reported used the ICD-9-CM code for endometriosis [20,22,25] and two articles used the ICD-9-CM code for IBS [22,25]. Three papers considered the patient's phase in the menstrual cycle [2,19,26].

Associations between endometriosis and IBS

Out of the 13 identified articles, nine of the studies primarily targeted women with gynecological issues [2,18–25]. Two papers targeted women with either endometriosis or IBS [8,17], another study recruited women with chronic pelvic pain [27], and another targeted female patients with IBS [26]. In all the studies reviewed, women with endometriosis reported a higher risk of being

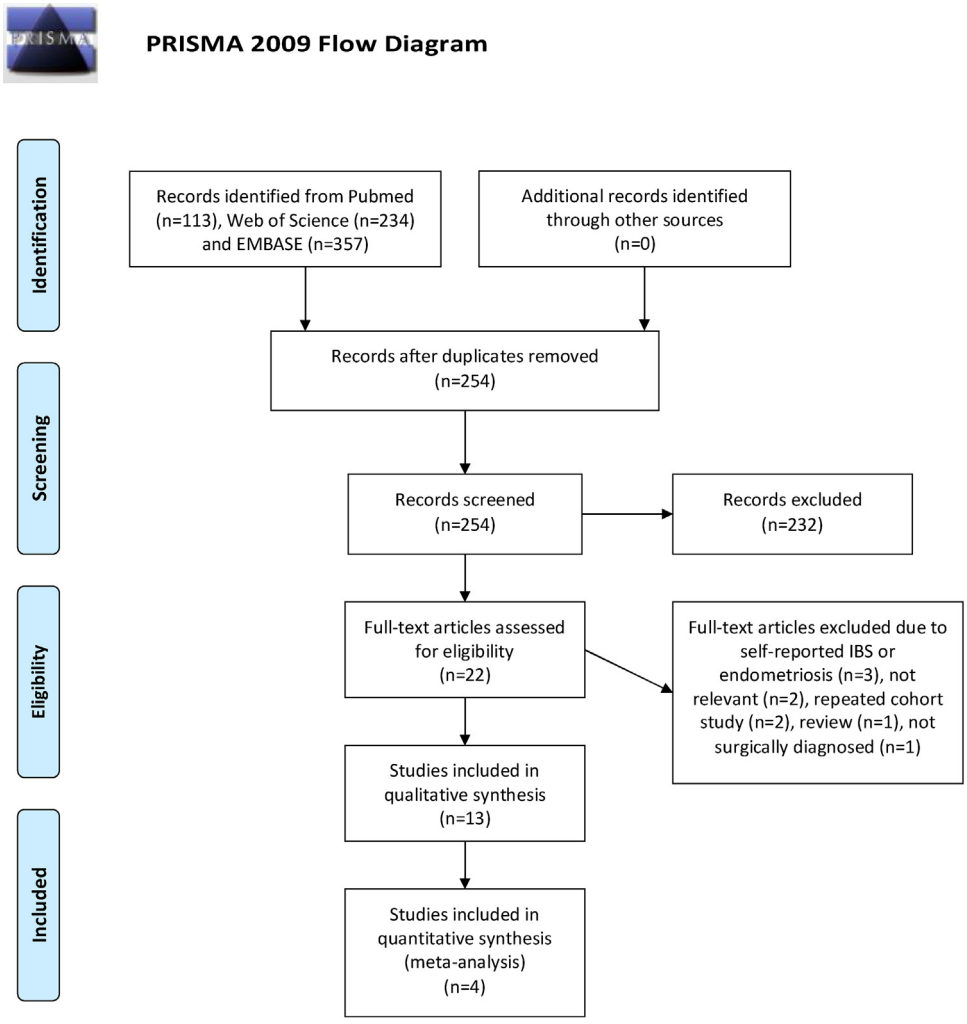

Fig. 1. Flow chart over the selection process according to PRISMA.

Table 1
Narrative data of fully reviewed articles on endometriosis and IBS.

Study	Country	Study design	Target group	Diagnosis criteria IBS	Diagnosis criteria endometriosis	Sample size	Health outcome/ associations
Yantiss et al., 2001 [18]	USA	Cohort study	Endometriosis patients	Unknown Rome Criteria	Surgical	44 endometriosis patients	2 out of 44 women with endometriosis had IBS as a differential diagnosis.
Lea et al., 2004 [17]	UK	Case cohort study	Women presenting with lower abdominal pain diagnosed with IBS, endometriosis or pelvic inflammatory disease	Rome I	Surgical	−50 IBS patients -51 gynecology patients	30 % of gynecology patients had symptoms suggestive of IBS
Remorgida et al., 2005 [19]	Italy	Cohort study	Women with chronic pain for more than 6 months of suspected endometriotic origin undergoing surgery	Rome II	Surgical	362 endometriosis patients	−2 (4.4 %) and 1 (2.2 %) patients with stage 0 bowel endometriosis had IBS-D and IBS-C respectively. - 4 (17.4 %) and 3 (13.0 %) women with stage 2 bowel endometriosis had IBS-D and IBS-C respectively. -16 (5.4 %) and 9 (3.1 %) women without bowel endometriosis had IBS-D and IBS-C respectively.
Seaman et al., 2008 [20]	UK	Case control study	-Cases: Women with endometriosis diagnosis code -Controls: Women without endometriosis matched on year of birth	Unknown Rome Criteria	ICD-9-CM Endometriosis codes	5540 endometriosis cases 21240 Controls	−702 (3.3 %) controls and 587 (10.6 %) cases had a history of IBS diagnosis before index date. OR 3.5 (95 % CI: 3.1–3.9) -828 (3.9%) controls and 529 (9.5%) cases had a history of IBS diagnosis after index date. OR 2.6 (95% CI: 2.3–3.0)
Meurs-Szojda et al., 2011 [2]	Netherlands	Cohort study	Endometriosis patients	Rome III	Surgical	98 endometriosis patients	15 (15 %) had IBS symptoms; 9 (9 %) had IBS-C, 2 (2 %) had IBS-D and 2 (2 %) mixed/ un-subtyped IBS
Droz et al., 2011 [27]	USA	Retrospective cohort study	Patients evaluated for chronic pelvic pain in the pelvic pain and endometriosis clinic	Rome II	Surgical	83 IBS patients 108 endometriosis patients	−34 (41 %) of IBS patients had endometriosis concomitantly. -34 (31 %) of endometriosis patients had IBS concomitantly
Issa et al., 2012 [8]	UK	Case cohort study	-Patients undergoing laparoscopic investigation found to have endometriosis. -Comparison groups: i) patients with normal pelvis, laparascopically negative abdominal pain ii) laparascopically normal healthy patients due for sterilization iii) women with firm diagnosis of uncomplicated IBS	Rome III	Surgical	20 controls 20 minimal-mild endometriosis patients 20 moderate-severe endometriosis patients 20 laparoscopy negative endometriosis patients 20 IBS patients	-In 20 patients with minimal to mild endometriosis, 13 found to be Rome positive; in 20 patients with moderate to severe endometriosis, 11 were Rome positive, in 20 with laparoscopy negative abdominal pain, 17 were Rome positive.
Smorgick et al., 2013 [21]	USA	Retrospective cohort study	Adolescent endometriosis patients	Unknown Rome Criteria	Surgical	138 endometriosis patients	25 % of the patients had IBS
Wu et al., 2015 [22]	Taiwan	Retrospective case control study	Patients with endometriosis (cases) and without (controls)	ICD-9-CM IBS codes	ICD-9-CM Endometriosis codes	6076 endometriosis cases 30380 controls	−256 (4.2 %) cases and 670 (2.2 %) controls were diagnosed with IBS. -IBS incidence density in 5 years was 8.67 per 1000 patient-years in cases compared to 4.46 in controls. -In 5 years, Incidence rate ratio for IBS in cases was 1.95 (95 % CI: 1.68–2.25) -Crude HR was 1.94 (95% CI 1.68–2.25), adjusted HR for event occurrence was 1.79 (95% CI 1.55–2.07) in 5 years.

Moore et al., 2017 [26]	New Zealand	Retrospective cohort study	Female patients referred to a private IBS clinic	Rome III	Surgical	160 Rome positive patients 71 Rome negative patients	59 (37 %) Rome positive patients had endometriosis. 11 (15 %) Rome negative patients had endometriosis. OR 3.02 (95 % CI: 1.4–6.2)
Ek et al., 2018 [23]	Sweden	Case cohort study	Patients with endometriosis (cases) and without (controls)	Visual Analogue Scale for IBS	Surgical	172 endometriosis cases 117 controls	–32 (18.6 %) endometriosis cases had IBS compared to 14 (12.3 %) controls. Crude OR 1.63 (95 % CI: 0.83–3.22), Adjusted OR 2.58 (95% CI: 1.01–6.63). -73 (42.4%) endometriosis patients suffered IBS-like symptoms
Lee et al., 2018 [24]	Canada	Cohort study	Endometriosis patients	Rome III	Surgical	373 endometriosis patients	194 (52 %) endometriosis patients had IBS.
Surrey et al., 2018 [25]	USA	Retrospective case control study	Patients with incident endometriosis (cases) and without (controls)	ICD-9-CM IBS codes	ICD-9-CM Endometriosis codes	26961 endometriosis cases 107844 controls	-IBS Crude incidence in cases was 21.3 compared to 10.7 in controls. Adjusted HR 2.3 (95 % CI: 2.2–2.5) -IBS Crude incidence in laparascopically confirmed cases was 25.1 compared to 9.8 in controls. Adjusted HR 2.9 (95% CI: 2.5–3.5)

CI = Confidence interval, IBS = Irritable bowel syndrome, ICD-9-CM = International Classification of Diseases, 9th revision, clinical modification, HR = Hazard ratio, OR = Odds ratio. Number within brackets reflect the number in the reference list of the paper.

diagnosed with IBS or also presenting with IBS-like symptoms compared to controls (Table 1). The highest IBS prevalence reported amongst endometriosis patients was 52 % [24]. When dividing the patients into minimal to mild, or moderate to severe endometriosis, the prevalence of IBS was 65 % and 55 %, respectively [8]. The highest adjusted odds ratios reported of being diagnosed with IBS amongst endometriosis patients compared to the controls was 2.58 [23], and the corresponding adjusted hazard ratio was 2.9 [25]. The increased risk of being diagnosed with IBS persisted even after a confirmed endometriosis diagnosis [20]. When patients were thoroughly investigated and all kinds of gastrointestinal disorders were considered, the prevalence of IBS was only 2 cases out of 44 [18]. In the meta-analysis, which only could include four articles, the pooled odds ratio was 2.39, with 95 % confidence interval 1.83–3.11 (Fig. 2). There was a high statistical heterogeneity of 86 %, which would be indicative of the variations in the study outcomes and methodological differences between studies. Visual inspection of the funnel plot provided evidence of publication bias due to asymmetry of the plot (Supplemental Fig. 1).

Droz et al. [27] reported that 41 % of patients diagnosed with IBS were concomitantly diagnosed with endometriosis. Similarly, Moore et al. [26] reported that 37 % of the Rome positive patients had endometriosis, whereas only 15 % of the Rome negative patients had endometriosis (Table 1). Since only one study targeted patients with IBS, no meta-analysis could be performed to study the second research question: “what is the risk for patients with IBS to also have endometriosis?”.

Discussion

To the best of the authors’ knowledge, this is the first study to systematically review articles comparing the associations between endometriosis and IBS. This systematic review and meta-analysis has found that the literature report an increased risk of endometriosis patients to also having an IBS diagnosis. This risk is inherent after a surgically confirmed endometriosis diagnosis [20]. However, the assessment of the associations between endometriosis and IBS in the available literature need to be interpreted with caution. Due to the reliance on self-reported symptoms to guide the diagnosis of IBS, and in some cases endometriosis, it would be prudent to consider different aspects that may also affect the symptomatology.

Drug treatments, such as opioids and gonadotropin-releasing hormone (GnRH) analogs used in the treatment of endometriosis, have been found to increase the severity of gastrointestinal symptoms [23,29–31]. As noted in this review, only one article took into consideration the medication prescribed to patients [8], which may affect interpretation of the current study findings. As such, all the other studies that used the Rome criteria to assess bowel symptoms, and did not adjust for the drug treatments, may have been over-reporting symptoms due to side-effects from medications. For example, Seaman et al. [20] reported that the risk of an IBS diagnosis after confirmed endometriosis diagnosis is doubled in the cases compared to the controls. Yet, drug prescription histories were not accounted for [20].

Given the increased prevalence of IBS amongst women, the effect of the patient’s phase in their menstrual cycles is another important factor to consider. Moore et al. [32] described in a review, that abdominal pain related to endometriosis and bowel symptoms, in both functional and non-functional bowel disorders, are often worsened during menstruation. In this current review, only three papers considered the patient’s phase in the menstrual cycle [2,19,26]. Moore et al. [26], and Remorgida et al. [19], both reported that menstruation worsened bowel symptoms in endometriosis patients. Meurs-Szojda et al. [2] found that 80 %

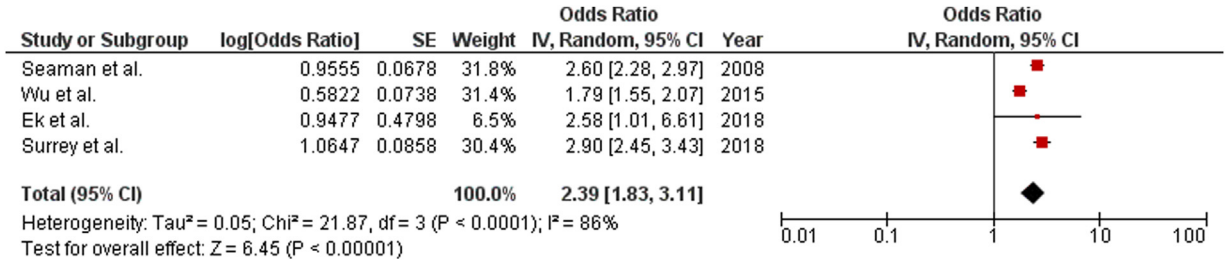

Fig. 2. Meta-analysis over the four articles included, where hazard ratios or odds ratios were given, ref No 20, 22, 23, 25. CI = confidence interval.

of the endometriosis patients with IBS experienced an exacerbation of intestinal symptoms during menstruation. It is therefore concerning that the findings of the other ten studies in this review did not adjust for the menstrual cycle. Thus, the derived associations may possibly be exaggerated.

Both endometriosis and IBS are related to chronic stress and psychological disorders, and the severity of gastrointestinal symptoms correlate with the degree of psychological well-being [23,33]. Visceral hypersensitivity, which is common in both diseases [8,34], may be caused by peripheral mechanisms, e.g. inflammation, but may also be caused by central mechanisms [35,36]. Thus, the existence of gastrointestinal symptoms may not only be related to a primary gastrointestinal disorder, but may be the consequence of psychological and psychosomatic aspects [33]. Whether the impaired psychological well-being is primary or secondary to chronic pain is difficult to determine.

Due to the considerable symptom overlap between endometriosis and IBS, the use of questionnaires alone may be insufficient to differentiate between the two conditions. With the number of Rome positive patients reported to have a history of, or concurrent endometriosis diagnosis, it is difficult to determine whether the two conditions are coexistent [24,26]. The Rome criteria could possibly be too general and vague to differentiate between IBS and endometriosis symptoms. Revision of the Rome criteria to the current version IV, has led to a marked reduction of the prevalence of IBS [13]. Estimation of IBS according to Rome IV could possibly lead to different results in relation to endometriosis, than the actual comparison with Rome I-III. Issa et al. [8] noted, that although many endometriosis patients may fulfill the Rome criteria, the criteria used are unable to differentiate between visceral hypersensitivity causing bowel symptoms specifically related to endometriosis or IBS. Similarly, due to the shared symptoms of celiac disease and IBS, the Rome criteria alone are insufficient to differentiate the two conditions [37,38]. Analysis of antibodies related to celiac disease needs to be performed. Nevertheless, gastrointestinal symptoms remain to be a significant finding in women with histologically confirmed endometriosis and are almost as frequent as the gynecological symptoms [3]. Therefore, further development of better diagnostic tools to differentiate the symptomatology of endometriosis and IBS are crucial for an optimal health care. The finding of low prevalence of IBS in endometriosis patients when considering all types of gastrointestinal disorders, and not only relying on symptom questionnaires, further underlines the need for proper examinations in addition to questionnaires to set final diagnoses [18].

The strengths of this paper include the independent review of published articles by the authors, and reliance on structured diagnostic criteria for endometriosis and IBS to select relevant articles. Additionally, this review included several case-control or case-cohort studies, which were able to find associations between endometriosis and IBS. The main limitation is the lack of adjustment of important confounders in most of the reviewed papers, such as drug treatment, menstruation and psychological aspects. Other limitations include very few relevant publications regarding the topic, especially available for meta-analysis with its great heterogeneity, and presence of significant symptom overlap, which may have contributed to misdiagnoses of the two conditions in the studies reviewed. Publication bias, with omitting to publish articles not showing an increased association between the two diseases, cannot be excluded.

Conclusion

This review has shown the complex nature of endometriosis and IBS and the difficulty medical practitioners are faced with when diagnosing the two conditions in women. It is paramount that endometriosis is excluded in young women presenting with gastrointestinal symptoms. Given the close association of the two conditions and increased risk of being diagnosed with both, there is a need to investigate the management of endometriosis-related IBS. As a result, gastroenterologists and gynecologists ought to collaborate and develop effective diagnostic and treatment options for these women to avoid medical mismanagement. Further research within this area is needed.

Declaration of Competing Interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.01.031.

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