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Is endometriosis associated with irritable bowel syndrome? A cross-sectional study

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ABSTRACT

Objectives: Previous studies have found a high prevalence of irritable bowel syndrome (IBS). However, data on this relation in women without bowel endometriosis is limited. The aim of this study was to compare the prevalence of IBS in women with endometriosis to the prevalence in women without endometriosis and to investigate if the prevalence of IBS was associated with bowel involved endometriosis.

Study design: Information for this cross-sectional study was collected through an online questionnaire. A total of 373 women completed the questionnaire. After exclusions, 254 with endometriosis and 102 without endometriosis were included (N = 356). Endometriosis was identified by self-reported diagnosis. IBS was identified by; 1. self-reported diagnosis prior to the study and 2. fulfillment of ROME III diagnostic criteria in this study. Odds ratios were calculated to estimate the strength of the association between IBS and endometriosis. A separate analysis, restricted to women without bowel involved endometrioses, was conducted. Adjustment for potential confounders (age, gastroenterological comorbidities and length of education) was performed.

Results and conclusions: The prevalence of IBS was higher in women with endometriosis compared to the women without endometriosis (OR = 5.32 (CI: 2.88; 9.81)). In the analysis restricted to women without bowel involved endometriosis, the prevalence was also higher in women with endometriosis compared to women without endometriosis (OR = 6.54 (CI95% 3.22; 13.29)). Thus, this study found a higher prevalence of IBS in women with endometriosis compared to women without endometriosis. This finding seems to be unrelated to bowel involvement. This opens new perspectives in relation to treatment of endometriosis.

Introduction

Endometriosis is defined by the presence of endometrial-like tissue outside the uterus and occurs in 5–10% of women of reproductive age [1,2]. Symptoms include abdominal pain, altered bowel habits and infertility [3], with negative consequences for both patients and the community [4–7]. Symptoms do not always correspond to the extent of the disease. Animal studies indicate that this may be due to diffuse autonomic neural reflex mechanisms with decreased pain treshold in organs distant to the site of endometriosis lesion [8–11]. In accordance, many endometriosis patients suffer from a visceral syndrome with pain symptoms from several abdominal organs. This includes symptoms from the gastrointestinal tract, comparable with symptoms of irritable bowel syndrome (IBS) [11].

In IBS, abdominal pain associated with defecation or change in bowel habits are seen. Because no structural changes of the intestine can be found, IBS is a symptomatic diagnosis [12–14] Studies have found up to 2.5 times higher risk of IBS in women with endometriosis compared to women without endometriosis [11,15–20]. However, limitations of these studies include not using the internationally recognized diagnostic criteria and use of data from public health registries, which could underestimate the prevalence of IBS, as IBS is frequently overlooked. Moreover, most of these studies did not compare the risk of IBS in women with and without bowel involved endometriosis.

The aim of this study was to compare the prevalence of IBS in women with endometriosis with the prevalence of IBS in women without endometriosis, using prior IBS diagnosis and/or current fulfillment of the ROME III diagnostic criteria.

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Furthermore, we sought to clarify if any higher prevalence of IBS in women with endometriosis was restricted to patients with bowel disease.

Materials and methods

Study design

Data was collected through an online questionnaire (SurveyMonkey). The questionnaire was developed by the research group in autumn 2015 and was released from December 2015 to March 2016. The questionnaire was pilot-tested by eight people (board members of the Danish Endometriosis Patients Association). The questionnaire was sent to: 1. employees at a primary school, 2. employees in a call center, 3. employees at a City hall, 4. students at a social and health education center and 5. members of the Danish Endometriosis Patients Association. Participants were informed that the purpose was to investigate gastrointestinal problems in women, but were not informed about the potential relation between IBS and endometriosis. The mentioned places used intranet and mail to contact potential participants, while the Danish Endometriosis Patients Association used their electronic newsletter and Facebook group. It was not possible to obtain reliable information about the total number of individuals receiving the questionnaire. Once the needed number of participants was met, the survey was closed.

Inclusion criteria were women aged ≥18 years, who could read and understand Danish. Only participants, who completed the questionnaire, were included in the analysis. It was not possible to skip any question in the questionnaire.

Data description

The endometriosis diagnosis had to be based on laparoscopy and/or magnetic resonance imaging (MRI). If endometriosis was diagnosed by other means, the participant was excluded (n = 17).

IBS was identified by: 1. prior IBS diagnosis (diagnosed by health professional) and 2. fulfillment of IBS according to the ROME III criteria, which represented the latest version at time of inclusion [13].

Co-variates

Data on several demographic factors and gastroenterology comorbidities (Table 1) were collected.

Age was considered a potential confounder, as young age a priori was identified as a risk factor for IBS in an epidemiological study [21] and is associated with endometriosis [6]. Gastroenterological comorbidities were also a priori considered potential confounders in this study, as the risk of IBS is higher in some gastroenterological disorders or have overlapping symptoms with IBS [19]. Length of education was also a priori considered a potential confounder, as low education is associated with poor general health [22].

Statistical analysis

Two main analyses were performed. The first analysis compared the prevalence of IBS in women with endometriosis to the prevalence of IBS in women without endometriosis, with *all* women with endometriosis included. The second analysis compared the prevalence of IBS in women with endometriosis

Table 1
Demographic characteristics for the study population, stratified by diagnosis of endometriosis (N = 356).

	Women with endometriosis (n = 254)		Women without endometriosis (n = 102)	
	n	%	*n*	%
Age				
18-25	11	4.3	33	32.4
26-35	78	30.7	19	18.6
36-45	116	45.7	20	19.6
46-55	41	16.1	12	11.8
56-65	6	2.4	17	16.7
66-75	2	0.8	1	1
Average age (years)	38.8	8.6	37.9	14.4
Level of education				
No vocational education	14	5.5	25	24.5
Skilled	38	15	13	12.7
Higher education, < 3 years	47	18.5	12	11.8
Higher education, 3-4 years	100	39.4	37	36.3
Higher education, > 4 years	46	18.1	12	11.8
Other education	9	3.5	3	2.9
Marital status				
Married / living together	194	76.4	69	67.6
In a relationship, living apart	12	4.7	16	15.7
Single	48	18.9	17	16.7
Gastroenterological comorbidity				
Food allergy	21	8.3	6	5.9
Food intolerance	16	6.3	6	5.9
Ulcer	12	4.7	3	2.9
Reflux	14	5.5	4	3.9
Inflammatory bowel disease	8	3.2	8	7.8
Celiac disease	2	0.8	2	19.6
Cancer	0	0	0	0
Disease in liver, bile duct or pancreas	7	2.8	1	1
At least one comorbidity	60	23.6	22	21.6
No comorbidity	194	76.4	80	78.4

Results are presented as numbers (*n*) or percentage (%), unless otherwise specified.

to women without endometriosis, restricted to women *without* bowel involvement.

Both first and second main analysis, consisted of three models. The first model included *all* women with IBS, that is both IBS diagnosed prior to the study *and* IBS diagnosed through this study based on the ROME III diagnostic criteria. The second model included only women, who fulfilled the ROME III diagnostic criteria in the study. The third model only included women with IBS diagnosed prior to the study.

Demographic data were compared using the chi^2 test for categorical variables. Odds ratio (OR) with 95% confidence interval (CI) were calculated by multiple logistic regression to describe the association between endometriosis and IBS, adjusting for potential confounding factors. A power calculation was performed prior to the study (90% power, 0.05 level of significance), showing that a minimum of 75 participants should be included in each group. Analyses were performed in Stata IC version 14.1.

Ethical considerations

The study was not reported to the local Ethics Committee, in accordance with Danish legislation on surveys of this character. The Data Protection Agency was contacted for review, but according to the rules of private data, it was not necessary to register the project, as it was part of a Master's degree. Informed consent was obtained, participants were informed of their rights and data analysis was performed with confidentiality.

Results

In total, 504 women initiated completion of the questionnaire, of which 373 (74%) completed the entire form. Out of these, 271 (73%) stated they had a diagnosis of endometriosis, and 102 (27%) stated they did not. Of the 271 participants, who stated they had endometriosis, 17 had undergone neither an MRI scan nor laparoscopy, and were therefore excluded. Thus, 254 participants were categorized as having endometriosis and 102 without endometriosis.

Demographic characteristics are shown in Table 1. Women with endometriosis were older, had higher level of education and were more often married or living with a partner compared with women without endometriosis. Apart from IBS, there was no difference in the prevalence of comorbidities between the two groups. The self-reported location of endometriosis is shown in Table 2.

The results from the first main analysis is shown in Table 3. Out of the 254 women with endometriosis, 57 (22.4%) had an IBS diagnosis prior to the study. Of the 102 women without endometriosis, 9 (8.8%) reported having an IBS diagnosis prior to the study. In the women with endometriosis, 152 (59.8%) fulfilled the ROME III diagnostic criteria. Similarly, 29 (28.4%) women without endometriosis fulfilled the ROME III diagnostic criteria.

Not all women, who had a prior diagnosis of IBS, fulfilled the ROME III criteria in this study. In women with endometriosis, 17 (6.7%) women had a prior diagnosis of IBS, but did not fulfill the ROME III criteria in this study. In women without endometriosis, the same was true in 3 (2.9%) women with a prior diagnosis of IBS.

When looking at model 1 (women with *both* IBS diagnose prior to the study *and* fulfillment of ROME III diagnostic criteria in this study), the prevalence of IBS was higher in women with endometriosis compared to the women without endometriosis (OR = 5.32 (CI: 2.88;9.81)). A higher prevalence was also found in model 2 (only women, who fulfilled the ROME III diagnostic criteria in the study) and model 3 (only women with IBS diagnosed prior to the study).

Table 4 shows the results from the second main analysis. In the second main analysis, restricted to women without bowel involved endometriosis (n = 128), the proportion of IBS in the second main analysis was 68%, compared to 67% in the first main analysis that included all women with endometriosis. Similar to the first main analysis, the prevalence of IBS was higher in women with endometriosis (without bowel involvement) compared to the women without endometriosis (OR = 6,54 (CI: 3,22;13,29). A higher prevalence was found in all three models.

Table 2
Location of endometriosis for the participants with endometriosis (n = 254).

	n (%)
Peritoneum of the pelvis	91 (35.8)
Abdominal peritoneum	84 (33.1)
Ovaries	159 (62.6)
Fallopian tubes	118 (46.5)
Bowels	126 (49.6)
Vagina	44 (17.3)
Urinary bladder	35 (13.8)
Uterine wall	112 (44.1)
Elsewhere	55 (21.7)
Don't know	33 (13.0)

Results are presented as numbers and percentage (%).

Discussion

In this study, we found a five times higher prevalence of IBS in women with endometriosis compared to women without endometriosis. The prevalence of IBS still was higher in women with endometriosis, when bowel involved endometriosis was excluded.

The purpose of setting up three models in the two main analyses was to compare the association between endometrioses and IBS when using different methods to identify IBS. We believe that the most valid method to identify IBS in this study was to combine prior diagnosis with current fulfillment of the ROME III criteria, as there is a risk of underestimating the prevalence of IBS, if only prior diagnosis is included. On the other hand, only using ROME III criteria could also underestimate the prevalence, as our analyses showed that not all women with prior diagnosis of IBS fulfilled the ROME III criteria at time of the study. These women may have found an adequate treatment and therefore no longer fulfill the diagnostic criteria.

Although the possible causal link between endometriosis and gastrointestinal symptoms is still unclear, several explanations has been suggested. One explanation may be that inflammatory activity and local prostaglandin release caused by endometriosis lesions may alter bowel function [23,24]. It has also been suggested that low-grade mucosal inflammation might be a contributing factor in the pathogenesis of IBS [25,26]. In fact, research on inflammation in endometriosis almost completely mirrors that observed in IBS, suggesting shared pathogenic factors [20]. Although this is a likely explanation for gastrointestinal symptoms in women with bowel involved endometriosis, it may not explain symptoms in women with endometriosis lesions no near the bowel. Visceral hypersensitivity has also been observed in both patients with endometriosis and IBS [18,27]. Interestingly, visceral hypersensitivity does not seem to be associated with the location or severity of endometriosis [18].

It is a prevailing theory that the affected bowel function in endometriosis is due to changes in the autonomic nervous system caused by sensory impulses from endometriotic tissue. Among other things, the autonomic nervous system controls the intestines and receives sensory impulses from endometriotic tissue. This can trigger diffuse nerve signals that interfere with bowel function and alter the pain threshold in the intestines – a phenomena referred to

Table 3
Prevalence and odds ratio (OR) for IBS in participants with and without endometriosis.

	Women with endometriosis *n (%)*	Women without endometriosis *n (%)*	OR (95% CI) Unadjusted	*p*	OR (95% CI) Adjusted*	*p*
Number of participants	254	102				
Model I: ROME III and prior diagnosis** Women with IBS	169 (66.5)	32 (31.4)	4.35 (2.66;7.12)	<0.001	5.32 (2.88;9.81)	<0.001
Model II: ROME III*** Women with IBS	152 (59.8)	29 (28.4)	3.75 (2.28;6.17)	<0.001	4.15 (2.27;7.57)	<0.001
Model III: Prior diagnosis Women with IBS	57 (22.4)	9 (8.8)	2.99 (1.42;6.30)	0.004	4.48 (1.81;11.06)	0.001

* There was adjusted for age, education and gastroenterological comorbidity.
** This analysis included both prior diagnosis of IBS prior and IBS diagnosed in this study according to the ROME III diagnostic criteria.
*** This includes participants, who prior to the study had received an IBS diagnosis.

Table 4
Prevalence and odds ratio (OR) for IBS in participants with and without endometriosis, where women with bowel endometriosis are excluded from the analysis.

	Women with endometriosis *n (%)*	Women without endometriosis *n (%)*	OR (95% CI) Unadjusted	*p*	OR (95% CI) Adjusted*	*p*
Number of participants	128	102				
Model I: ROME III and prior diagnosis** Women with IBS	87 (68.0)	32 (31.4)	4.64 (2.65;8.12)	<0.001	6.54 (3.22;13.29)	<0.001
Model II: ROME III*** Women with IBS	80 (62.5)	29 (28.4)	4.19 (2.39;7.34)	<0.001	5.16 (2.58;10.30)	<0.001
Model III: Prior diagnosis Women with IBS	31 (24.2)	9 (8.8)	3.30 (1.49;7.31)	0.003	5.25 (1.94;14.22)	0.001

* There was adjusted for age, education and gastroenterological comorbidity.
** This analysis included both prior diagnosis of IBS prior and IBS diagnosed in this study according to the ROME III diagnostic criteria.
*** This includes participants, who prior to the study had received an IBS diagnosis.

as “cross-organ effect”. The process probably includes morphological changes of the autonomic nervous system [8–10]. Our findings of higher prevalence of IBS in women with endometriosis, even without bowel involved endometriosis, support this theory.

A weakness in the studies in the area is that not all of them distinguish between the location of the endometriotic tissue. A study by Remorgida et al indicated that the prevalence of IBS was increased in both patients with and without bowel involved endometriosis, but the majority of the patients with bowel involved endometriosis experienced significant improvement in their IBS symptoms after surgery [28]. This is probably because there are some separate reasons why endometriosis in the bowel may induce IBS-symptoms, of which some can be improved by surgery. Our analyses indicated that increased risk of IBS still was present, when patients with bowel involved endometriosis were excluded from the analysis. These findings support the theory about cross-organ effect.

The number of participants calculated in the power calculation was met, but it was not possible to assess the overall number of potential participants. Therefore, the response rate could not be calculated, which implies a risk of information- and selection bias. Strengths include that participants were asked about the ROME III diagnostic criteria for IBS and not only prior IBS diagnoses. This approach may give a more realistic estimate of the prevalence of IBS than found in registry studies.

Due to practical and legal limitations, it was not possible to validate diagnoses of endometriosis and IBS by review of medical reports. However, only cases where the diagnosis of endometriosis was based on laparoscopy or MRI and diagnosis of IBS was, were included in our study. For IBS, only 20 participants with this reported diagnoses did not meet the ROME III criteria in this study. We believe that the reliability of these self-reported diagnoses is acceptable in this type of study, as we see no reason for the participants to report their diagnosis incorrectly.

Selection bias are likely, as we expect fewest answers from women without endometriosis and without IBS, which can lead to an underestimation of the association between IBS and endometriosis. A possible underestimation will however only emphasize our findings of a higher prevalence of IBS in women with endometriosis. However, there is probably an over-representation of participants with gastrointestinal problems in this study, since the participants were informed about the purpose of the study. Although it was not disclosed that the study referred to IBS in woman with endometriosis, it is possible that women with endometriosis were more likely to participate, because they may be more likely to participate in studies of diseases, and because some of the participants were recruited through the Danish Endometriosis Patients Association. This might lead to an overestimation of the prevalence of IBS in women with endometriosis. Although the prevalence of bowel endometriosis in this study was high (50%), we do not believe this had led to selection bias. Moreover, an association between endometriosis and IBS of equal size was also found in women without bowel involvement.

Furthermore, as endometriosis is frequently overlooked, and a diagnostic delay of 6–11 years has been observed [29], patients with endometriosis may tend to overestimate their symptoms to get heard. Thus, there is a risk of information bias, and that the observed association between IBS and endometriosis may be overestimated. However, our findings support the results of previous register studies without the same risk of bias, although the estimates of the association in these studies were slightly lower than in our study [15,19,20].

Because the symptoms overlap, there is a risk of misdiagnosis between the two conditions. Seaman et al (2008) investigated the prevalence of IBS before and after diagnosis of endometriosis. They found the risk of IBS decreased after a diagnosis of endometriosis was given, but the risk of IBS was still increased in women with endometriosis compared to women without [15]. This supports the findings in our study.

Other potential confounders cannot be excluded. For example, data about lifestyle factors and anthropometry were not collected.

These factors can trigger and worsen IBS symptoms, but are probably not risk factors for IBS. Kay et al (1994) found that lifestyle and BMI had only a weak association with IBS [21]. Moreover, it is generally believed that lifestyle isn't the primary risk factor for IBS [12,30], but it may be a potential effect modifier.

This study together with several others indicates a higher prevalence of IBS in women with endometriosis compared to women without this diagnosis, and that this higher prevalence is unrelated to bowel involvement. The results emphasize a new understanding of endometriosis and a need to investigate treatment of endometriosis-related IBS.

Conflict of interests

The authors have no financial or non-financial conflicts of interest.

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