ORIGINAL ARTICLE

Increased risk of inflammatory bowel disease in women with endometriosis: a nationwide Danish cohort study

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ABSTRACT

Background An association between endometriosis and certain autoimmune diseases has been suggested. However, the impact of endometriosis on risk of inflammatory bowel disease (IBD) remains unknown.

Objective To assess the risk of Crohn's disease (CD) and ulcerative colitis (UC) in an unselected nationwide Danish cohort of women with endometriosis.

Design By use of national registers, 37 661 women hospitalised with endometriosis during 1977–2007 were identified. The relative risk of developing IBD after an endometriosis diagnosis was calculated as observed versus expected numbers and presented as standardised incidence ratios (SIRs) with 95% CIs.

Results Women with endometriosis had a increased risk of IBD overall (SIR=1.5; 95% CI 1.4 to 1.7) and of UC (SIR=1.5; 95% CI 1.3 to 1.7) and CD (SIR=1.6; 95% CI 1.3 to 2.0) separately, even 20 years after a diagnosis of endometriosis (UC: SIR=1.5; 95% CI 1.1 to 2.1; CD: SIR=1.8; 95% CI 1.1 to 3.2). Restricting analyses to women with surgically verified endometriosis suggested even stronger associations (UC: SIR=1.8; 95% CI 1.4 to 2.3; CD: SIR=1.7; 95% CI 1.2 to 2.5).

Conclusion The risk of IBD in women with endometriosis was increased even in the long term, hence suggesting a genuine association between the diseases, which may either reflect common immunological features or an impact of endometriosis treatment with oral contraceptives on risk of IBD.

Significance of this study

What is already known about this subject?

- Endometriosis is an inflammatory disorder suggested to be associated with autoimmune diseases such as multiple sclerosis, Sjögren syndrome and systemic lupus erythematosus.
- The risk of inflammatory bowel disease (IBD) in women with endometriosis remains unknown.

What are the new findings?

- Women with endometriosis are at increased risk of developing Crohn's disease and ulcerative colitis, even after more than 20 years of observation.
- This may reflect overlapping aetiological factors between endometriosis and IBD or an effect of endometriosis treatment on the risk of IBD.

How might it impact on clinical practice in the foreseeable future?

- A diagnosis of either endometriosis or IBD should not lead to the other diagnosis being disregarded and, hence, should not disqualify further clinical examination of patients with persisting abdominal or gynaecological symptoms.
- The role of treatment of endometriosis in risk of IBD needs further investigation.

INTRODUCTION

Both endometriosis and inflammatory bowel disease (IBD) are chronic inflammatory disorders with typical onset in young adulthood. Endometriosis is seen in up to 10% of women during their reproductive years,[1] whereas the prevalence of Crohn's disease (CD) and ulcerative colitis (UC) is about 0.5% in Western countries.[2 3]

Endometriosis is thought to result from retrograde menstruation leading to ectopic implantation of endometrium-like tissue,[1 4] which fails to be cleared by the immune system.[4 5] The immunological features of endometriosis include raised cytokine levels, decreased cell apoptosis, and B and T cell abnormalities, which are similar to those seen in autoimmune diseases, such as rheumatoid arthritis, psoriasis and IBD.[5] Also, women with endometriosis appear to be at a moderately increased risk of multiple sclerosis, systemic lupus erythematosus and Sjögren syndrome.[6]

Endometriosis and IBD do not only share immunological alterations. Both diseases may also affect the bowel and may cause abdominal pain.[7 8] Ileal endometriosis is a differential diagnosis of CD, since both diseases may cause inflammation, induration, thickening and stricturing of the small bowel.[7] Further, in approximately 4% of patients with biopsy-proven endometriosis the appendix is involved.[8] These features may lead to incorrectly disregarding one of the possible diagnoses if the alternative diagnosis is made. However, to our knowledge, no study has examined the association between endometriosis and IBD within the same subjects.

Hence, the aim of this study was to examine the risk of IBD in an unselected nationwide cohort of women with endometriosis.

MATERIALS AND METHODS

Study population

All women with a diagnosis of endometriosis in the Danish National Hospital Register during 1977–2007 were identified. The register contains information on close to 100% of all non-psychiatric inpatient hospitalisations in Denmark since 1977 and outpatient hospital contacts since 1995.[9] Diagnoses are recorded in the register as either one 'primary diagnosis' or up to 20 'secondary diagnoses'. Women with endometriosis were identified using primary or secondary diagnosis codes 62530–62539 according to the 8th revision of the International Classification of Diseases (ICD-8) and code group N80 according to the 10th revision (ICD-10). Using the unique 10-digit personal identification number given to each Danish citizen at birth, we also retrieved information on surgical procedures in these women. Likewise, we identified patients diagnosed with IBD as either a primary or secondary diagnosis during 1977–2007 (CD: ICD-8 codes 56300–56309 and ICD-10 code group K50; UC: ICD-8 codes 56319 or 56904 and ICD-10 code group K51). To avoid diagnostic ambiguity, we excluded (in all separate analyses) patients who had a diagnosis of both CD and UC in the Danish National Hospital Register (9.4%).

Using the Danish Civil Registration System, a continuously updated national database on demographics in the Danish population,[10] we obtained information on sex and dates of birth, disappearance, emigration and death.

Statistical analyses

Patients with endometriosis were followed up from their first recorded date of hospital contact for endometriosis and until the date of IBD diagnosis, emigration, disappearance, death, or end of study (31 December 2007), whichever event occurred first. As a measure of relative risk, we calculated the standardised incidence ratio (SIR; observed/expected numbers of IBD) with a 95% CI. Expected numbers of IBD were calculated based on person-years at risk in the endometriosis cohort and age- and period-specific incidence rates of IBD among Danish women. Women with a diagnosis of IBD before endometriosis were excluded from all analyses. 95% CIs were calculated assuming a Poisson distribution of the observed cases (Wald's test was applied). We performed sensitivity analyses restricted to (1) women who underwent a surgical procedure (laparoscopy or laparotomy; national surgery codes, 402.40 or 402.20 or ICD-10 procedure codes, KJAH01 or KJAH00) in relation to the diagnosis of endometriosis, and (2) the calendar period 1980–2007 (to preclude prevalent cases). Comparison of SIRs across strata of explanatory variables was carried out using Wald's test for homogeneity in one-factor Poisson regressions on the observed cases with means proportional to the stratum-specified expected number of cases. All statistical analyses were conducted using SAS V.9.2 (SAS Institute). Stratification and aggregation was carried out using the SAS macros previously described by Rostgaard.[11]

Ethical considerations

The study was purely register based and followed the regulations set up by the Danish Data Protection Agency.

RESULTS

A total of 37 661 women had been diagnosed with endometriosis in a Danish hospital during 1977–2007 at a mean age of 38.6 years (±11 years; SD). The majority (87%) had been treated as inpatients. Characteristics of the endometriosis cohort are shown in table 1.

Table 1 Characteristics of women diagnosed with endometriosis in Danish outpatient and inpatient hospital settings during 1977–2007

Characteristics	Endometriosis cohort	
	All n (%)	Surgically verified n (%)
Total	37 661	9191
Age at diagnosis of endometriosis (years)		
<20	577 (1.5)	184 (2.0)
20–24	2635 (7.0)	1152 (12.5)
25–29	5343 (14.2)	2145 (23.3)
30–34	6169 (16.4)	2082 (22.7)
35–39	6277 (16.7)	1531 (16.7)
40–44	6815 (18.1)	1158 (12.6)
45–49	5552 (14.7)	595 (6.5)
50+	4293 (11.4)	344 (3.7)
Mean age (years)	38.6	33.7
Period of diagnosis of endometriosis		
1977–1979	2888 (7.7)	456 (5.0)
1980–1984	5472 (14.5)	1210 (13.2)
1985–1989	5156 (13.7)	1601 (17.4)
1990–1994	5064 (13.5)	1680 (18.3)
1995–1999	5611 (14.9)	1553 (16.9)
2000–2004	7967 (21.2)	1768 (19.2)
2005–2007	5503 (14.6)	923 (10.0)

Endometriosis and risk of IBD

During more than 492 000 person-years of follow-up (mean 13.1 years), 228 women were diagnosed with UC (SIR=1.5; 95% CI 1.3 to 1.7) and 92 with CD (SIR=1.6; 95% CI 1.3 to 2.0), yielding a combined risk of IBD of 1.5 (95% CI 1.4 to 1.7). Sensitivity analyses restricted to the calendar period 1980–2007 revealed similar estimates, whereas analyses restricted to women with surgically verified endometriosis showed even stronger associations (table 2).

The risk of UC differed with respect to age at endometriosis diagnosis (test for homogeneity, p=0.02), with the highest risk found among women diagnosed with endometriosis at age 25–34 years (SIR=2.0; 95% CI 1.6 to 2.4) (table 2). The risk of CD was highest among women diagnosed with endometriosis below the age of 25 years (SIR=2.0; 95% CI 1.2 to 3.5), but overall age at endometriosis was not statistically significantly associated with risk of CD (table 2). The risk of IBD after a diagnosis of endometriosis did not apply to a specific age of patients at diagnosis of IBD (table 2).

The mean interval from diagnosis of endometriosis to diagnosis of IBD was 10.8 years for UC and 9.8 years for CD. In the first year of follow-up since a diagnosis of endometriosis, the SIR was 2.1 (95% CI 1.3 to 3.1) for UC and 1.7 (0.9 to 3.4) for CD (table 2). The SIR varied between 1.4 and 1.9 for UC and between 1.1 and 1.8 for CD during all subsequent intervals of follow-up (table 2), and remained significantly increased after ≥20 years of observation, both for UC (SIR=1.5; 95% CI 1.1 to 2.1) and CD (SIR=1.8; 95% CI 1.1 to 3.2). Also, analyses restricted to surgically verified endometriosis supported an increased risk for both UC (SIR=2.1; 95% CI 1.1 to 4.1) and CD (SIR=2.8; 95% CI 1.1 to 7.5) after more than 20 years of observation (table 2).

DISCUSSION

This nationwide cohort study of 37 661 women with endometriosis showed a 50% increase in the risk of IBD in women with endometriosis as compared with women in the general

Table 2 Observed and expected number of cases of ulcerative colitis (UC) and Crohn's disease (CD) among women with endometriosis, Denmark, 1977–2007

	Ulcerative colitis					Crohn's disease				
	Patient-years	Observed	Expected	SIR	95% CI	Patient-years	Observed	Expected	SIR	95% CI
All cases of endometriosis	492 199	228	150.1	**1.5**	**1.3 to 1.7**	493 555	92	57.1	**1.6**	**1.3 to 2.0**
Age at diagnosis of endometriosis (years)										
<25	38 704	17	13.1	1.3	0.8 to 2.1	38 732	13	6.4	**2.0**	**1.2 to 3.5**
25–34	146 188	92	46.2	**2.0**	**1.6 to 2.4**	146 830	29	18.5	**1.6**	**1.1 to 2.3**
35–44	180 432	66	50.9	**1.3**	**1.02 to 1.6**	180 786	30	18.6	**1.6**	**1.1 to 2.3**
45+	126 874	53	39.9	**1.3**	**1.01 to 1.7**	127 206	20	13.6	1.5	0.9 to 2.3
Test for homogeneity				p=0.02					p=0.84	
Age at diagnosis of UC/CD (years)										
<35	71 197	40	23.7	**1.7**	**1.2 to 2.3**	71 364	22	11.4	**1.9**	**1.3 to 2.9**
35–44	127 023	60	35.2	**1.7**	**1.3 to 2.2**	127 384	23	14.3	**1.6**	**1.1 to 2.4**
45–54	155 400	56	42.3	**1.3**	**1.02 to 1.7**	155 834	22	15.2	1.4	0.95 to 2.2
55–64	97 877	44	30.4	**1.4**	**1.1 to 1.9**	98 118	18	10.8	**1.7**	**1.1 to 2.7**
65+	40 702	28	18.6	**1.5**	**1.04 to 2.2**	40 855	7	5.4	1.3	0.6 to 2.7
Test for homogeneity				p=0.66					p=0.86	
Time since diagnosis of endometriosis (years)										
0	36 515	21	10.2	**2.1**	**1.3 to 3.1**	36 581	8	4.6	1.7	0.9 to 3.4
1–4	126 917	48	34.7	**1.4**	**1.04 to 1.8**	127 209	23	15.0	**1.5**	**1.02 to 2.3**
5–9	121 077	46	32.9	**1.4**	**1.05 to 1.9**	121 396	23	13.0	**1.8**	**1.2 to 2.7**
10–14	90 259	37	27.0	1.4	0.99 to 1.9	90 499	17	9.8	**1.7**	**1.1 to 2.8**
15–19	64 268	42	22.6	**1.9**	**1.4 to 2.5**	64 478	8	7.5	1.1	0.5 to 2.1
20+	53 163	34	22.7	**1.5**	**1.1 to 2.1**	53 391	13	7.1	**1.8**	**1.1 to 3.2**
Test for homogeneity				p=0.48					p=0.83	
Surgically verified cases of endometriosis	126 092	71	39.6	**1.8**	**1.4 to 2.3**	126 391	27	15.6	**1.7**	**1.2 to 2.5**
Time since surgical diagnosis of endometriosis (years)										
0	9023	7	2.6	**2.7**	**1.3 to 5.7**	9030	4	1.2	**3.2**	**1.2 to 8.5**
1–4	32 729	10	9.5	1.1	0.6 to 2.0	32 767	7	4.2	**1.7**	**0.8 to 3.5**
5–9	32 650	17	9.8	**1.7**	**1.1 to 2.8**	32 713	6	3.9	**1.5**	**0.7 to 3.4**
10–14	24 453	16	7.9	**2.0**	**1.2 to 3.3**	24 544	6	2.9	**2.1**	**0.9 to 4.6**
15–19	16 169	12	5.7	**2.1**	**1.2 to 3.7**	16 228	0	1.9	0	–
20+	11 068	9	4.2	**2.1**	**1.1 to 4.1**	11 109	4	1.4	**2.8**	**1.1 to 7.5**
Test for homogeneity				p=0.39					p=0.10	

Estimates in bold reflect SIRs with 95% CIs which do not include 1.0 ($p<0.05$).
SIR, standardised incidence ratio; CI, confidence interval.

Danish population. The increased risk persisted after 20 years of follow-up. Restricting analyses to women with surgically verified endometriosis resulted in even stronger risk associations.

This study had several strengths. First, the risk of IBD following a diagnosis of endometriosis has to our knowledge not previously been assessed in an unselected nationwide cohort of women with endometriosis diagnosed in a country with free access to healthcare and thorough registration of citizens and medical diagnoses. We determined whether the diagnosis of endometriosis had been made in relation to surgery and we obtained information on diagnoses of UC and CD, which are known to be accurate and almost complete in the Danish National Hospital Register.[12] Also, using national registries with prospectively collected data, the study was not limited by recall bias. Further, we adjusted for any effect of age and calendar period by use of age- and period specific rates for IBD occurrence in the general population, and we had a considerable follow-up time (mean 13.1 years), allowing for analyses of the long-term effect of endometriosis on the risk of IBD.

Our study also had potential limitations. First, the results of the study applied to women diagnosed with endometriosis in Danish hospitals and hospital outpatient clinics, whereas milder cases diagnosed in ambulatory settings outside Danish hospitals were not assessed. However, surgically verified endometriosis represents the most valid diagnosis, and such cases were all included in this study.

Another potential limitation is the risk of ascertainment bias, since information on both exposure (endometriosis) and outcome (IBD) was retrieved from the Danish National Hospital Register. This approach increases the possibility for observation of falsely high associations. However, since a diagnosis of IBD (treated as the outcome) relies on fairly severe symptoms and strict diagnostic criteria, resulting in contact with a hospital in 91% and 99% of UC and CD cases (unpublished data from a recent Danish inception cohort study[13]), it is not likely that ascertainment bias would constitute a large problem in this study.

Another possible limitation is the rather high mean age of the women diagnosed with endometriosis (mean age 38 years). Endometriosis normally has its onset in early adulthood, but has a known fairly long delay from onset to diagnosis (of around 9 years).[14] The mean age in this study may, furthermore, reflect that a diagnosis of endometriosis in Danish inpatient and outpatient hospital settings in some cases (18% in this material) is made in relation to referral for infertility. The relatively high mean age at diagnosis of endometriosis implies that we have assessed the risk of IBD at a stage, where women had lived approximately half of their risk time for developing IBD, which might have resulted in somewhat conservative risk estimates. Women with surgically verified endometriosis, who probably represent those with the most severe symptoms, were on average 4 years younger at their first hospital contact for

endometriosis. Evidence for an increased risk of IBD in this group of women was even stronger.

Lastly, it might be considered a limitation that 9.4% of patients were registered in the Danish National Patient Register with both a diagnosis of CD and UC. However, former regional Danish studies based on prospective follow-up of unselected patient cohorts have shown that 9.6% of patients diagnosed with UC change diagnosis to CD during follow-up, whereas 1.9% change diagnosis from CD to UC.[15]

No previous systematic assessment of the association between endometriosis and IBD has been made. The two disease entities have been discussed as potentially differential diagnoses[7 16 17] and have therefore been described in case reports of one disease mimicking the other.[18 19] An initial diagnostic mistake between endometriosis and IBD is possible, as endometriosis normally presents with pelvic pain as the most predominant symptom.[5 20] Also, ileal and sigmoid endometriosis may mimic Crohn's disease with inflammation and stricturing of the bowel.[7] However, the differential diagnostic problem primarily lies in a primary diagnosis of CD with an atypical clinical course or medical response, which may turn out to be endometriosis at a later stage,[7] a situation that does not explain the observed increased risk of IBD decades after a diagnosis of endometriosis. Interestingly, a Belgian case series reported on eight female patients, who underwent surgery for complicated CD and were diagnosed with intestinal endometriosis in the ileum (n=6), colon (n=1), and ileum and rectum (n=1) in addition to simultaneous classical features of CD in endometriosis-free parts of the intestine, leading the authors to suggest that co-occurrence of the two diseases is possible.[21]

The observation of a persistently increased risk of IBD more than 20 years after a diagnosis of IBD also strengthens the possibility of a true association rather than reflecting initial differential diagnostic problems. Endometriosis is believed to result from retrograde menstruation, which is common in all women, but assumed to persist only in women with immunological impairment.[5] The immunological alterations in women with endometriosis have been suggested to involve both cell-mediated and humoral immunity, including increased levels of autoantibodies, and endometriosis has been suggested to fulfil the classification criteria of an autoimmune disease.[5] Further similarities with autoimmune diseases include peritoneal inflammation (including elevated tumour necrosis factor α levels), a role of adhesion molecules causing invasive features, a role for matrix metalloproteinases and deregulation of apoptosis, potentially explaining why ectopic endometrium avoids cell death and why autoreactive lymphocytes are not eliminated.[5] In a former study of Danish women with endometriosis, we observed a moderately increased risk for multiple sclerosis, Sjögren syndrome and systemic lupus erythematosus,[6] which in combination with the present findings might favour a more general link between endometriosis and autoimmune diseases.

An alternative explanation for the increased risk of IBD is the treatment of endometriosis, which includes oral contraceptives, gestagens, progestins, gonadotropin-releasing hormone agonists and, to some extent also, non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors.[20] Interestingly, oral contraceptive use has been associated with development of IBD, an association suggested to be explained by multifocal microvascular infarctions.[22] A meta-analysis of 14 studies based on 75 815 patients with IBD (36 797 exposed and 39 018 unexposed to oral contraceptives) showed a significantly increased risk of both UC and CD among current oral contraceptive users.[23] Hence, our findings reflect the possible existence of common underlying immunological features between endometriosis and IBD and possibly, in some cases, the IBD might be a consequence of the treatment of endometriosis.

As an alternative to oral contraceptives, it has been suggested that endometriosis should be treated as an autoimmune disease with immunomodulators already in use for diseases such as IBD, rheumatoid arthritis and psoriasis.[5] One may hypothesise that such drugs might decrease the subsequent risk of IBD or other autoimmune diseases in women with endometriosis, either by changing the unfavourable immunological mechanisms related to endometriosis or by decreasing the use of oral contraceptives in these women. Further investigation is obviously needed to examine these possibilities.

Future perspectives of this new finding of an association between endometriosis and IBD are several. First of all, considering the novelty of our findings, they need confirmation in other populations. The possibly shared immunological background between endometriosis and autoimmune diseases, such as IBD, needs investigation, and future studies should characterise the IBD phenotype in patients with concomitant endometriosis and determine how this phenotype may differ from that of other patients with IBD. It is also of both immunological and clinical interest to know whether patients with IBD with endometriosis have a different prognosis from that of other IBD patients. Lastly, there is still a need for large-scale unselected cohort studies to confirm the influence of oral contraceptive use on the short- and long-term risk of IBD, not least in the context of concurrent endometriosis.

In conclusion, this study of a nationwide cohort of 37 661 women with endometriosis showed a significantly increased risk of IBD in women with endometriosis, which was most pronounced in women with surgically verified endometriosis and persisted after 20 years of follow-up. This association may be explained by shared immunological features between endometriosis and IBD, or it may reflect a hitherto little appreciated impact of endometriosis treatment on future risk of IBD.

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