Endometriosis and its coexistence with irritable bowel syndrome and pelvic inflammatory disease: findings from a national case–control study—Part 2

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Accepted 5 July 2008. Published OnlineEarly 19 August 2008.

Objective To investigate whether the increased chances of having a diagnosis of irritable bowel syndrome (IBS) and pelvic inflammatory disease (PID) in women with endometriosis is due to misdiagnosis or co-morbidity.

Design A case–control study of women aged 15–55 years with endometriosis and matched controls.

Setting Data from the UK’s General Practice Research Database for the years 1992–2001.

Sample A total of 5540 women aged 15–55 years, diagnosed with endometriosis, each matched to four controls without endometriosis. The index date was defined as the date of diagnosis.

Methods Data were analysed to determine whether women with endometriosis were more likely to receive a diagnosis of PID or IBS than women without endometriosis. Odds ratios were calculated for endometriosis associated with IBS and PID before and after the index date.

Main outcome measures Diagnosis of IBS or PID before and after the index date.

Results Compared with the controls, women with endometriosis were 3.5 times more likely to have received a diagnosis of IBS (OR 3.5 [95% CI: 3.1–3.9]). Even after women had been diagnosed with endometriosis, they were still two and a half times more likely to receive a new diagnosis of IBS when compared with the controls (OR 2.5 [95% CI: 2.2–2.8]). Similarly, women with endometriosis were more likely than those without endometriosis to have been treated for PID both before (OR 5.9 [95% CI: 5.1–6.9]) and after (OR 3.8 [95% CI: 3.1–4.6]) being diagnosed with endometriosis.

Conclusions Women with endometriosis are more likely to be diagnosed with IBS and PID than controls, even after a definitive diagnosis of endometriosis has been reached.

Keywords Co-morbidity, diagnostic error, endometriosis, irritable bowel syndrome, misdiagnosis, pelvic inflammatory disease.

Introduction

The symptoms of endometriosis are typically chronic pelvic pain (CPP), severe dysmenorrhea, deep dyspareunia, ovulation pain, and dyschezia.1 Indeed, in part 1 of these two papers,2 we demonstrated that women with a diagnosis of endometriosis commonly reported these symptoms to the GP. These typical endometriosis symptoms, however, also feature in patients with other conditions such as irritable bowel syndrome (IBS) and pelvic inflammatory disease (PID). Classic symptoms of IBS are abdominal pain that is relieved by defecation, abdominal pain that is associated with a change in the frequency and/or consistency of the stools, and abdominal bloating.3 Typical symptoms of PID are lower abdominal pain and tenderness, deep dyspareunia, abnormal vaginal or cervical discharge, cervical excitation and adnexal tenderness, motion, and pyrexia.4 These overlapping symptoms create potential diagnostic difficulties, not least of all because there are no simple noninvasive diagnostic tests that can be carried out. A definitive diagnosis of endometriosis and PID can only be made at surgery1,4 and a diagnosis of IBS is one of exclusion, made only after other organic disease has been ruled out.5

In part 1 of these two papers, we report finding that women with endometriosis were more likely to have a diagnosis of IBS and PID than women without a diagnosis of endometriosis.2 Since PID and IBS are largely diagnosed and treated within
Primary Care, a misdiagnosis of these conditions may be a key contributor to the delayed diagnosis of endometriosis, which is currently reported to be 9 years.6

We were only able to find one study that considered the possible coexistence of endometriosis and IBS and PID.7 This study looked at self-reported symptoms among 50 women with a confirmed clinical diagnosis of IBS and 51 women with laparoscopy-confirmed PID or endometriosis. The investigators reported that the only gynaecological features that were more common in women with PID or endometriosis were intermenstrual bleeding, premenstrual exacerbation of pain and vaginal fornical tenderness on pelvic examination. However, this study excluded 20 women with coexisting disease and the respondents were not asked about experiencing pelvic pain and dysmenorrhoea, the classic symptoms of endometriosis.

In this article, we report the results of an analysis of women with endometriosis compared with matched controls without endometriosis from UK general practice. We have investigated whether the apparent association between endometriosis, IBS and PID represents misdiagnosis in the presence of endometriosis or true co-morbidity.

Methods

As described in detail in part 1 of these two papers, this is a national case–control study that uses data retrieved from the General Practice Research Database (GPRD). The study population was comprised of women aged 15–55 years registered with practices contributing to the GPRD. The cases are 5540 women with a diagnosis of endometriosis and the controls are 21 239 without a diagnosis of endometriosis.

Identification of potential cases

The cohort of potential cases included all women with a code for endometriosis where the earliest date of diagnosis was after 1 January 1992 and who (a) were aged 15–55 years on the earliest date of diagnosis (index date), (b) had at least 3 years of data between the patient registration date (or practice up-to-standard date) and the index date, and (c) had at least 3 months between the index date and the date of last data collection.

Potential cases were defined as ‘definite’, ‘probable’, and ‘possible’ according to the reliability of the supporting evidence and this has been described in detail in the previous paper.2

Control selection

Four controls were sought from the GPRD female population for each case. Potential controls were all women without a code for endometriosis at any time. Cases were matched to controls by year of birth and practice, and each control was registered on the index date of the matched case. As for cases, controls had to have at least 3 years of data between the patient registration date (or practice up-to-standard date) and the index date, at least 3 months between the index date and the date of last data collection, and no current or recent pregnancy.

Identification of IBS and PID diagnoses

All coding of IBS and PID was performed ‘blind’ to case status. Cases and controls with a record of IBS before and/or after the index date were identified. Similarly, women with a record of PID before and/or after the index date were identified. Since both PID and IBS, when diagnosed within Primary Care are largely based on clinical symptoms, evidence to support these diagnoses was sought. An effort to qualify the diagnosis of IBS was made by identifying women diagnosed with IBS who were prescribed an IBS-specific treatment (antispasmodic, antimotility drug and laxative) on the same day. Although microbiological confirmation from endocervical swabs has the potential to provide additional supporting evidence of a PID diagnosis, it has been shown that this is only undertaken by 45% of GPs when PID is suspected. Since the RCOG4 recommend empirical treatment of PID where clinical signs are present, evidence to support the diagnosis of PID was sought from the prescription of an antibiotic on the same day.

Analysis

Unadjusted odds ratios and 95% CI were derived by conditional logistic regression to measure the association between endometriosis and IBS or PID. Subgroup analyses were performed limiting the analysis to ‘definite’ cases, ‘probable’ cases, or ‘possible’ cases.

Results

We identified 5540 women aged 15–55 years with a new diagnosis of endometriosis after 1 January 1992, giving an incidence rate of 0.97/1000 women/year. The cases were matched to 21 239 controls without endometriosis. The characteristics of the study population in terms of age, history, and/or subsequent diagnoses of IBS or PID and unadjusted odds ratios with 95% CI are given in Table 1.

Women with endometriosis were at a significantly increased risk of having received a prior diagnosis of PID (OR 6.4 [95% CI: 5.6–7.4]). The association between endometriosis and PID remained after the index date (OR 4.0 [95% CI: 3.4–4.9]) even when cases and controls with a history of PID were excluded (OR 4.0 [3.2–5.0]), although the strength of the association was reduced. The association described between PID and endometriosis remained of the same magnitude when PID was defined by a diagnosis of PID plus relevant prescribing.
Analyses stratified according to case status showed similar odds ratio for most associations, although when analysis was restricted to ‘possible’ cases, the odds ratio for PID after the index date was increased at 5.8 (95% CI: 3.3–10.2) The odds ratio remained largely unchanged in subgroup analysis by inclusion or exclusion of cases with adenomyosis.

There was a significant association between endometriosis and a history of IBS (OR 3.5 [95% CI: 3.1–3.9]). Although less strong, an association between endometriosis and a diagnosis of IBS remained after the index date (OR 2.6 [95% CI: 2.3–3.0]) even when cases and controls with a history of IBS before the index date were excluded (OR 2.5 [95% CI: 2.2–2.8]). When IBS was defined as a diagnosis of IBS plus a relevant treatment, the association with endometriosis was as strong after (OR 3.7 [95% CI: 3.2–4.1]) as before (OR 3.5 [95% CI: 3.0–4.2]) the index date. The associations between endometriosis and IBS remained in subgroup analyses stratifying cases according to the reliability of their case status; analysis among ‘possible’ cases showed slightly higher point estimates (e.g. the odds ratio associated with a diagnosis of IBS after the index date among ‘possible’ cases was 3.6 [95% CI: 2.8–4.8] compared with 2.5 [95% CI: 2.1–2.9] among ‘definite’ cases), although none of the differences between these subgroups of cases reached statistical significance. The ORs for the association between IBS and endometriosis were unchanged by inclusion or exclusion of cases with adenomyosis.

### Discussion

To our knowledge, this is first and largest study of its kind to investigate the association between endometriosis and an increased risk of being diagnosed with IBS or PID. Women with endometriosis were six times more likely to have received a diagnosis of PID and 3.5 times more likely to have received a diagnosis of IBS than women without endometriosis, even when those diagnoses were defined as a diagnosis plus relevant treatment. We analysed the data to see whether the association between endometriosis and PID or IBS could be explained by either (a) a previous failure to diagnose endometriosis or (b) a co-morbidity between endometriosis and IBS or PID. If the association was due to co-morbidity, we would not expect to see an increased risk of being newly diagnosed with PID or IBS among women with endometriosis once the diagnosis of endometriosis had been made. Although the association between endometriosis and PID was less strong after a diagnosis of endometriosis had been reached, cases remained four times more likely to have subsequent diagnoses of PID than controls. Similarly, an association between endometriosis and IBS remained but was less strong after the index date. These findings did not change materially when the analysis was restricted to ‘definite’ cases of endometriosis only. This suggests some misdiagnosis among women with endometriosis, while posing the possibility of co-morbidity between endometriosis and PID or IBS.

### Table 1. Characteristics of cases and controls: age and diagnoses of irritable bowel syndrome and pelvic inflammatory disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls n (%)</th>
<th>Cases n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–25</td>
<td>2760 (13.0)</td>
<td>730 (13.2)</td>
<td>—</td>
</tr>
<tr>
<td>26–35</td>
<td>8547 (40.2)</td>
<td>2290 (41.3)</td>
<td>—</td>
</tr>
<tr>
<td>36–45</td>
<td>7784 (36.7)</td>
<td>1983 (35.8)</td>
<td>—</td>
</tr>
<tr>
<td>46–55</td>
<td>2148 (10.1)</td>
<td>537 (9.7)</td>
<td>—</td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History* of IBS diagnosis**</td>
<td>702 (3.3)</td>
<td>587 (10.6)</td>
<td>3.5 (3.1–3.9)</td>
</tr>
<tr>
<td>History* of IBS diagnosis + treatment (on the same day)</td>
<td>635 (3.0)</td>
<td>555 (10.0)</td>
<td>3.7 (3.2–4.1)</td>
</tr>
<tr>
<td>IBS diagnosis** after the index date</td>
<td>828 (3.9)</td>
<td>529 (9.5)</td>
<td>2.6 (2.3–3.0)</td>
</tr>
<tr>
<td>IBS diagnosis** after the index date and no history* of IBS diagnosis**</td>
<td>671 (3.3)</td>
<td>380 (7.7)</td>
<td>2.5 (2.2–2.8)</td>
</tr>
<tr>
<td>IBS diagnosis + treatment (on the same day) after the index date</td>
<td>341 (1.6)</td>
<td>295 (5.3)</td>
<td>3.5 (3.0–4.2)</td>
</tr>
<tr>
<td>IBS diagnosis + treatment (on the same day) after the index date and no history* of treated IBS</td>
<td>18 (0.1)</td>
<td>7 (0.1)</td>
<td>2.0 (0.8–4.9)</td>
</tr>
<tr>
<td>PID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History* of PID diagnosis**</td>
<td>391 (1.8)</td>
<td>569 (10.3)</td>
<td>6.4 (5.6–7.4)</td>
</tr>
<tr>
<td>History* of PID diagnosis + treatment (on the same day)</td>
<td>341 (1.6)</td>
<td>464 (8.4)</td>
<td>5.9 (5.1–6.9)</td>
</tr>
<tr>
<td>PID diagnosis** after the index date</td>
<td>251 (1.2)</td>
<td>245 (4.4)</td>
<td>4.0 (3.4–4.9)</td>
</tr>
<tr>
<td>PID diagnosis** after the index date and no history* of PID diagnosis**</td>
<td>213 (1.0)</td>
<td>170 (3.4)</td>
<td>4.0 (3.2–5.0)</td>
</tr>
<tr>
<td>PID diagnosis + treatment (on the same day) after the index date</td>
<td>203 (1.0)</td>
<td>187 (3.4)</td>
<td>3.8 (3.1–4.6)</td>
</tr>
<tr>
<td>PID diagnosis + treatment (on the same day) after the index date and no history* of treated PID</td>
<td>170 (0.8)</td>
<td>131 (2.60)</td>
<td>4.0 (3.1–5.1)</td>
</tr>
</tbody>
</table>

*History refers to the period before the index date.

**Diagnosis with or without treatment.
Although there is controversy about bowel involvement in endometriosis, the majority of sites for endometriosis deposits are areas of the posterior pelvic compartment peritoneum in close proximity to the terminal large bowel. The inflammatory nature of the lesions and local prostaglandin release may explain any altered bowel function. There is no agreement among investigators about the extent to which the gastrointestinal (GI) tract may be involved in endometriosis. Some suggest the GI tract may be involved in up to one-third of cases, whereas others suggest endometriosis is seldom associated with GI symptoms.

There is evidence to suggest that endometriosis is associated with some co-morbidity such as autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome, atopic diseases, and migraine. A few studies report on diagnoses of IBS and PID being associated with endometriosis. However, this is usually reported in the context of diagnostic difficulty when women present with CPP without investigating further any potential for coexisting disease. For instance, Zondervan et al. reported that 41% of women with CPP who have IBS and genitourinary symptoms receive more than one diagnosis, although they also reported that it is unusual for endometriosis to precede other diagnoses associated with CPP. In their comparison of people with IBS, PID and endometriosis, Lea et al. attempted to exclude women with coexisting disease although even in their population of women with endometriosis, a proportion with possible PID or IBS remained. Given the overlapping symptomatology, reaching a diagnosis of endometriosis is complicated and the possibility of disorders such as PID and IBS being present when women present with CPP needs to be considered. Our study suggests diagnosis may be further complicated because, as has been suggested elsewhere, PID, IBS, and endometriosis can coexist.

Our study reiterates the potential for diagnostic confusion in women with endometriosis. About 10% of women with endometriosis had been treated for IBS during the period before diagnosis and more than 8% had been treated for PID. The observation that these proportions were significantly reduced after a diagnosis of endometriosis had been reached indicates a considerable problem of misdiagnosis among women with endometriosis. Misdiagnosis inevitably contributes to diagnostic delay and an increased economic burden on the health service through inappropriate management regimens.

Nonetheless, it appears that for some women with endometriosis, these conditions coexist and probably add to the burden of co-morbidity among women with endometriosis reported by others. If there is coexisting PID, then this needs rigorous treatment to reduce the risk of even greater subfertility and appropriate management of IBS may reduce endometriosis-related bowel symptoms. This study, therefore, supports the need for a multidisciplinary approach to the diagnosis and treatment of endometriosis. Further research comparing cohorts of women diagnosed with PID, IBS, endometriosis, or a combination of these using a database such as the GPRD might provide more insight into differences in symptom patterns between these diseases. This in turn should result in a decrease in the diagnostic delay currently seen in endometriosis, and the institution of appropriate treatment regimens.

Disclosure of interest
None of the authors have any conflicting financial interests.

Contribution to authorship
K.D.B. and J.T.W. are responsible for the idea for the study and securing funding. All authors contributed towards the data analysis and preparation of the manuscript.

Details of ethics approval
Multicentre research ethics committee approval (06/MREC 04/72) and scientific approval from the Independent Scientific Advisory Committee (ISAC 06-004) was obtained.

Funding
Funding was obtained from a project grant from the BUPA Foundation.

Acknowledgements
We are grateful to the BUPA Foundation for providing a grant to fund the research that was the basis for this study.

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