The co-occurrence of endometriosis with multiple sclerosis, systemic lupus erythematosus and Sjögren syndrome

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Introduction

Endometriosis is an estrogen-dependent inflammatory disorder affecting ~5–10% of women during reproductive years (Bulun, 2009). The disorder is caused by the implantation of endometrial tissue outside the uterus, a phenomenon believed to be the result of retrograde menstruation in combination with a defect in immune surveillance, which would otherwise have eliminated the ectopic endometrium (Giudice and Kao, 2004). In light of the postulated underlying immune mechanisms, endometriosis might be associated with other immune-mediated disorders, as suggested by others (Sinaii et al., 2002), or the condition might be an early marker of underlying immune dysregulation in a pre-disease phase of a not yet clinically diagnosed autoimmune disease.

A possible association between endometriosis and autoimmune diseases has been suggested by clinical case series (Thomson and Redwine, 2005; Alviggi et al., 2006) and, most notably, by findings in a cross-sectional survey conducted by the US Endometriosis Association and the US National Institutes of Health (Sinaii et al., 2002). Specifically, in 1998, approximately 10 000 members of the US Endometriosis Association received questionnaires concerning symptoms of endometriosis and general health. Overall, 3680 women with surgically diagnosed endometriosis, predominantly in the age interval 25–44 years, participated in the survey. Unexpectedly, high proportions of participants reported having MS (0.5%, n = 19), SLE (0.8%, n = 31) or SS (0.6%, n = 23), resulting in prevalence odds ratios of 7 for MS, 21 for SLE and 24 for SS, using prevalence estimates for the general female US population for comparison. However, the study had several methodological shortcomings, such as the use of self-reports of autoimmune diseases, a selected group of study participants and the use of inappropriate background rates for comparison. Findings in a few other studies did not support these remarkable findings (Villard-Mackintosh and Vessey, 1993;
using ICD8 codes 62530-62539 and ICD10 code group N80. Women with endometriosis were identified to its 10th revision (ICD10) since January 1994 (the 9th revision of ICD national Classification of Diseases (ICD8) from 1977 to 1993 and accord-linked to the patient’s unique 10-digit personal identification number. Diagnoses were coded according to the 8th revision of the WHO International Classification of Diseases (ICD8) from 1977 to 1993 and according to its 10th revision (ICD10) since January 1994 (the 9th revision of ICD was not used in Denmark). Women with endometriosis were identified using ICD8 codes 62530-62539 and ICD10 code group N80.

Materials and Methods

Patients with endometriosis

Information about all women with a hospital contact for endometriosis in Denmark in the period 1977–2007 was drawn from the nationwide Danish Hospital Discharge Register (Andersen et al., 1999). This register contains information about all non-psychiatric hospital admissions in Denmark since January 1977. Outpatient hospital contacts have been included since 1995. Information concerning dates of admission and discharge, diagnoses and surgical procedures is kept for every hospitalization linked to the patient’s unique 10-digit personal identification number. Diagnoses were recorded hospital contact in the Danish Hospital Discharge Register.

Autoimmune diseases outcomes

Cases of MS, SLE and SS were identified in the Danish Hospital Discharge Register from 1977 to 2007, using the following ICD8 codes and ICD10 code groups; MS (ICD8:340, ICD10:G35), SLE (ICD8:73419, ICD10:M32) and SS (ICD8:73490, ICD10: M350).

Statistics

In outcome-specific analyses, patients with endometriosis were followed for the occurrence of the autoimmune disease in question (MS, SLE or SS) from 1 year after the date of first hospital contact with endometriosis until diagnosis of the autoimmune disease in question, death, emigration, disappearance or 31 December 2007, whichever came first. Information about deaths and emigrations was obtained in the Danish Civil Registration System, a continually updated demographic database covering the entire Danish population (Pedersen et al., 2006). For each studied autoimmune disease the standardized incidence ratio (SIR), i.e. the ratio of observed to expected numbers of autoimmune disease outcomes in the cohort, served as our measure of relative risk. Expected numbers of MS, SLE and SS were calculated as the sum of age- and period-specific person-years at risk in the endometriosis cohort multiplied by corresponding national age- and period-specific incidence rates for MS, SLE and SS among Danish women, respectively. Women who were diagnosed with one of the three studied autoimmune diseases before endometriosis did not contribute person-years at risk in the outcome-specific analysis as they were not at risk of developing the autoimmune disease in question. Incidence rates of MS, SLE and SS were calculated by using demographic data from Statistics Denmark (Statistic Denmark, Statbank Denmark, 2010) and by defining the time of MS, SLE and SS as the date of first recorded hospital contact in the Danish Hospital Discharge Register. We estimated 95% confidence intervals (CIs) for the SIRs from Wald’s test assuming a Poisson distribution of the observed cases. We also calculated SIRs of endometriosis among women with MS, SLE or SS, excluding women recorded with endometriosis before the autoimmune disease in question. In these calculations, we compared observed and expected numbers of women with endometriosis in each of the three autoimmune disease cohorts, using age and period-specific first hospitalization rates for endometriosis in Danish women to calculate expected numbers.

Robustness analyses

In the main analyses, we included both inpatients and outpatients with endometriosis. However, as outpatients were only recorded in the Danish Hospital Discharge Register since 1995, we conducted a robustness analysis in which we restricted the endometriosis cohort to individuals treated as inpatients. While a clinical diagnosis of endometriosis can often be reliably established from the patient’s description of her symptoms, a definitive diagnosis can only be made by means of laparoscopy. In a second robustness analysis, therefore, we used information in the Danish Hospital Discharge Register about surgical procedures to establish a subcohort of women with endometriosis who had undergone laparoscopy or laparatomy (national surgery codes 402.40 or 402.20 or ICD10 procedural codes KJAH01 or KJAH00) at the time of diagnosis. For each of the three autoimmune disease outcomes, SIR calculations were repeated in this cohort of surgically confirmed endometriosis patients. In a third robustness analysis, we wanted to evaluate the possible impact of misclassification of the autoimmune disease outcomes studied. To do so, we restricted counts of observed and expected cases of MS, SLE or SS in the SIR analyses to patients recorded in the Danish Hospital Discharge Register with at least two distinct hospital contacts with the same autoimmune disease, defining the time of diagnosis as the date of the second hospital contact.

Results

Overall, a total of 37 661 women were clinically diagnosed with endometriosis in Danish hospitals between 1977 and 2007, of whom 4789 (13%) were only treated in outpatient hospital settings. Most women (65%) were between 25 and 44 years of age, with a mean age of 38.6 ± 10.5 years (SD) at the time of endometriosis diagnosis. SIRs for endometriosis were marginally or not significantly elevated among women with MS, SLE or SS in the SIR analyses to patients recorded in the Danish Hospital Discharge Register with at least two distinct hospital contacts with the same autoimmune disease, defining the time of diagnosis as the date of the second hospital contact.

Robustness analyses

Among the 32 872 endometriosis patients who had been hospitalized and diagnosed as inpatients, overall SIRs of MS (SIR = 1.2; 1.02–1.5, n = 119), SLE (SIR = 1.6; 1.3–2.1, n = 53) and SS (SIR = 1.7; 1.4–2.1, n = 86) were similar to those observed among all endometriosis patients. The subcohort of 9191 women who were diagnosed surgically with endometriosis was younger at the time of endometriosis with a mean age at diagnosis of 33.7 ± 8.6 years (SD) (Table I).
During slightly more than 117 000 person–years of follow-up, a total of 43, 10 and 15 cases of MS, SLE and SS, respectively, were observed; SIR = 1.4 (1.04–1.9) for MS, SIR = 1.1 (0.6–2.1) for SLE and SIR = 1.4 (0.9–2.3) for SS (Table II). In the third robustness analysis, restricting the numbers of observed and expected cases of MS, SLE or SS in the cohort to patients recorded on at least two distinct hospital contacts for the same autoimmune disease produced virtually unchanged results for MS (SIR = 1.2; 1.03–1.5, n = 105), SLE (SIR = 1.5; 1.01–2.1, n = 29) and SS (SIR = 1.6; 1.2–2.3, n = 32).

## Discussion

In the present study, which is among the largest epidemiological studies on the possible association of endometriosis with autoimmune diseases, we fail to find support for claims of markedly increased risks of MS, SLE and SS in women with endometriosis. Our main analyses do suggest that Danish women with endometriosis may be slightly more likely to be diagnosed with MS, SLE and SS than women in the general population. However, findings, at least for SLE and SS, were not robust and lost statistical significance in analyses restricted to 9191 women whose endometriosis diagnosis was confirmed by laparoscopy or laparotomy.

Previously Sinaii et al. (2002) reported 7–24-fold increased risks of MS, SLE and SS among 3680 US women with surgically diagnosed endometriosis. However, findings were based on self-reports obtained in a questionnaire compared with literature-based prevalence estimates of autoimmune diseases in the general female population without appropriate controls for major confounding factors such as age and calendar period. Despite its methodological shortcomings, the study by Sinaii et al. has been cited frequently in the literature (Alviggi et al., 2006; Cavallà et al., 2006; Gao et al., 2006; Costa and Colia, 2008; Schulke et al., 2009; Bronner et al., 2010; Matalliotakis et al., 2010), and only few and relatively small studies have evaluated the postulated associations between endometriosis and autoimmune diseases in other settings (Lamb and Nichols, 1986; Matorras et al., 2007; Petta et al., 2007).

Our findings that women with endometriosis are either at a moderately increased risk (20–60%) or at no unusual risk of MS, SLE and SS is compatible with findings in prior case–control studies. In a case–control study nested in a cohort of 17 032 women, who from 1968 to 1974 annually were followed up to obtain information about pregnancy, hospital admission etc., Villard-Mackintosh and Vessey (1993) observed no association between endometriosis and MS; however, the numbers were small. Only 63 MS patients and 126 controls participated in the study. Matorras et al. observed no difference in the prevalence of SLE among 342 women with endometriosis and 501 population controls [odds ratio (OR) = 2.9; (0.3–32.6)]. Neither among women with endometriosis nor among controls were cases of SS observed. Likewise, no increased risk of endometriosis was observed when comparing controls with 120 patients with SLE or 22 patients with SS [OR = 0.4; (0.1–1.6)] for SLE and OR = 2.2; (0.5–9.9) for SS (Matorras et al., 2007).

Based on the present findings, we are not able to reject the hypotheses that altered immune surveillance might contribute to the aetiology of endometriosis or that other autoimmune diseases than the ones studied might co-occur with endometriosis. Of note, the objective of this article was to re-evaluate previously reported strong associations between endometriosis and MS, SLE and SS, which have led to the widespread belief that women with endometriosis might be at markedly elevated risk of these autoimmune diseases, a situation which finds little support in our study.

In the present study, all estimates were inherently adjusted for age and period by using age- and period-specific rates in the calculation of autoimmune diseases among patients with endometriosis. We used information from the nationwide Danish Hospital Discharge Register, which minimizes the risk of recall and selection bias. However, using the Danish Hospital Discharge Register to identify both exposure (endometriosis) and outcomes (MS, SLE and SS) does increase the risk of ascertainment bias. Being hospitalized and treated for endometriosis may increase the probability of being diagnosed and subsequently admitted to a hospital with an autoimmune disease. If so, our risk estimates may be slightly overestimated, and the marginally increased SIRs for the three studied autoimmune diseases that we observed among women with endometriosis should be viewed in this light.

Using hospital data also implies that only patients diagnosed or treated in hospitals are considered, while patients with mild diseases treated outside Danish hospitals by general practitioners or private specialists are not recorded. Accordingly, our study findings may not be relevant to that subset of women whose endometriosis is managed exclusively in ambulatory settings outside Danish hospitals, and the SIRs should be cautiously interpreted when considering
### Table II  Standardized incidence ratios of MS, SLE and SS in women previously diagnosed with endometriosis, Denmark 1977–2007.

<table>
<thead>
<tr>
<th></th>
<th>Multiple sclerosis</th>
<th>Systemic lupus erythematosus</th>
<th>Sjögren syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pyrs.</td>
<td>Obs.</td>
<td>Exp.</td>
</tr>
<tr>
<td>All cases of endometriosis</td>
<td>456 367</td>
<td>130</td>
<td>104.7</td>
</tr>
<tr>
<td>Age at diagnosis of endometriosis (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>35 626</td>
<td>14</td>
<td>8.7</td>
</tr>
<tr>
<td>25–34</td>
<td>135 490</td>
<td>47</td>
<td>36.9</td>
</tr>
<tr>
<td>35–44</td>
<td>167 444</td>
<td>53</td>
<td>39.6</td>
</tr>
<tr>
<td>45+</td>
<td>117 608</td>
<td>16</td>
<td>19.4</td>
</tr>
<tr>
<td>Test for homogeneity</td>
<td>P = 0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at follow-up (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>57 680</td>
<td>21</td>
<td>12.6</td>
</tr>
<tr>
<td>35–44</td>
<td>114 527</td>
<td>49</td>
<td>32.4</td>
</tr>
<tr>
<td>45–54</td>
<td>147 256</td>
<td>36</td>
<td>39.9</td>
</tr>
<tr>
<td>55–64</td>
<td>96 660</td>
<td>19</td>
<td>16.1</td>
</tr>
<tr>
<td>65+</td>
<td>40 244</td>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>Test for homogeneity</td>
<td>P = 0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since diagnosis of endometriosis (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>127 106</td>
<td>42</td>
<td>30.0</td>
</tr>
<tr>
<td>5–9</td>
<td>121 207</td>
<td>34</td>
<td>29.0</td>
</tr>
<tr>
<td>10–14</td>
<td>90 374</td>
<td>24</td>
<td>21.7</td>
</tr>
<tr>
<td>15–19</td>
<td>64 363</td>
<td>22</td>
<td>14.6</td>
</tr>
<tr>
<td>20+</td>
<td>53 318</td>
<td>8</td>
<td>9.3</td>
</tr>
<tr>
<td>Test for homogeneity</td>
<td>P = 0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgically verified endometriosis cases</td>
<td>117 169</td>
<td>43</td>
<td>30.6</td>
</tr>
</tbody>
</table>

SIR, standardized incidence ratio; CI, confidence interval; Pyrs, person-years at risk; Obs, observed; Exp, expected.
milder cases of autoimmune diseases. However, while such reservations may have some relevance to SS, it should not be a major concern for MS and SLE, both of which are severe autoimmune diseases that often require hospital contact.

Our study cohort was followed for a considerable period of time (mean 12.1 years), during which 130 cases of MS, 54 cases of SLE and 86 cases of SS occurred. However, despite its high statistical power compared with (most) previous studies on the subject, follow-up may have been insufficient to capture all subsequent cases of autoimmune diseases in the cohort, notably for the youngest endometriosis patients. The median attained age of women with endometriosis who were alive at the end of follow-up on 1 January 2008 was 51.7 years. Consequently, because the median age at diagnosis among Danish women diagnosed with MS, SLE and SS between 1977 and 2007 was 43.6, 46.9 and 59.3 years, respectively, our ability to determine possible long-term increases in risk were most favourable for MS. Reassuringly, there was no indication in Table II of an excess risk for MS in the long-term follow-up interval 20 or more years after the endometriosis diagnosis (SIR = 0.9; 0.4–1.7). However, corresponding long-term risk estimates for SLE (SIR = 2.3; 1.1–4.5) and SS (SIR = 1.9; 1.2–2.9) were both higher than expected, thus deserving attention in future studies.

In conclusion, our population-based findings fail to support much debated claims of markedly elevated risks of MS, SLE and SS among women with endometriosis. However, further studies are needed to clarify if the modest (20–60%) increase in risk of MS, SLE and SS observed in our main analysis reflects a true association or if there is really no link between endometriosis and the studied autoimmune diseases, as suggested by the findings for SLE and SS in the robustness analysis restricted to women with surgically verified endometriosis. Additional cohort studies with extended periods of follow-up and the use of objective, high-quality information about both exposure (endometriosis) and outcomes (autoimmune diseases) are clearly warranted.

Authors’ roles

All authors contributed to the conception and design of the study, the interpretation of data, the drafting of the article and revised the manuscript critically for important intellectual content and finally approved the version to be published. N.M.N. and M.F. were responsible for the acquisition of data. N.M.N., K.R. and B.V.P. carried out the statistical analyses.

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