Is there an association between endometriosis and the risk of pre-eclampsia? A population-based study

Ruth M. Hadfield, Samantha J. Lain, Camille H. Raynes-Greenow, Jonathan M. Morris, and Christine L. Roberts

1Perinatal Research, Kolling Institute, University of Sydney, B52, Level 2, Royal North Shore Hospital, St Leonard’s, NSW 2065, Sydney, Australia 2Department of Obstetrics & Gynaecology, Royal North Shore Hospital, St Leonard’s, Sydney, Australia

3Correspondence address. E-mail: rhadfield@med.usyd.edu.au

BACKGROUND: An association between endometriosis and reduced risk of pre-eclampsia has recently been reported. Longitudinally-linked electronic hospital records are a valuable resource for investigating such findings in a large, population-based sample. Our aim was to determine whether women with a history of endometriosis were at modified risk for pregnancy hypertension or pre-eclampsia.

METHODS: A population-based, longitudinal study of all women in the Australian state of New South Wales, aged from 15 to 45 years of age with a singleton birth during the period 2000–2005. Endometriosis was identified using ICD-10 codes. Endometriosis subgroups were analysed based on: (i) site of endometriosis (ovary or peritoneum), (ii) multiple (i.e. two or more) sites affected and (iii) infertility. To investigate the association between pregnancy hypertension and endometriosis, number of weeks gestation at birth and maternal age, we used logistic regression.

RESULTS: In the 3239 (1.6%) women with endometriosis diagnosed before their first birth, 352 (10.9%) had a diagnosis of pregnancy hypertension compared with 23,186/205,640 (11.3%) in women with no endometriosis diagnosis (OR 0.96; 95% CI 0.9–1.3). The frequency of pregnancy hypertension and pre-eclampsia was not significantly different in women with more severe endometriosis or endometriosis in conjunction with infertility when compared with those with no endometriosis. After adjusting for maternal age and weeks gestation there was still no altered risk.

CONCLUSIONS: We have found no evidence for an association between endometriosis and subsequent risk of either pregnancy hypertension or pre-eclampsia in this large population-based dataset.

Key words: endometriosis / pregnancy hypertension / pre-eclampsia / epidemiology / population-based research

Introduction

Recently an association between endometriosis and reduced risk of pre-eclampsia has been reported (Brosens et al., 2007) with a finding that pre-eclampsia was significantly less common in a group of 245 women with a previous history of endometriosis when compared with a control group of 274 women without endometriosis. The incidence of pre-eclampsia in the case group was 0.8% compared with 5.8% in the controls, giving an odds ratio (OR) of 7.5 (95% CI 1.7–33.3). One other study has reported a similar, albeit nonsignificant, observation with reduced risk of pre-eclampsia in women with endometriosis compared with controls and an OR of 1.8 (Kortelahahti et al., 1993).

These studies were small and therefore investigation in a larger population is warranted. In this study, we present our findings using longitudinal population-based health data in which records have been linked across sequential episodes of hospital care. Our aim was to determine, in a population of pregnant women, whether women with a history of endometriosis were at modified risk for pre-eclampsia.

Materials and Methods

Routinely collected population health data such as hospital discharge data are a potentially valuable source of data to study the aetiology of endometriosis. In the Australian state of New South Wales (NSW), data from all...
hospital admissions are electronically recorded with diagnosis codes according to the International Classification of Diseases version 10 (ICD-10). Probabilistic data record linkage enables the bringing together of multiple records, from a variety of sources, for one individual over time. For example, hospital admissions prior to pregnancy, such as for endometriosis, and subsequent pregnancy and childbirth data can be linked together.

Study design and population
A longitudinal, population-based study including all women in NSW, aged from 15 to 45 years of age with a singleton birth during the period 2000–2005 was conducted. A schematic diagram of the criteria for inclusion is shown in Fig. 1.

Data sources and data linkage
NSW is the most populous state of Australia with a current population of ~6.82 million and around 86,000 births per annum. Data from births between 2000 and 2005 were obtained via the NSW Midwives Data Collection (referred to as ‘birth data’), a legislated population-based surveillance system that includes information on all babies born at ≥20 weeks gestation or weighing at least 400 g. Data from hospital admissions between 1st July 2000 and 30th June 2006 were obtained from the NSW Department of Health Admitted Patient Data Collection, an administrative dataset of all hospitalizations and day surgeries in NSW (referred to as ‘hospital data’).

Internal linkage of the hospital data, internal linkage of the birth data and external linkage between the hospital data and the birth data was carried out at the Centre for Health Record Linkage (CHeReL) in NSW, Australia. The CHeReL has been established to provide a means of data linkage while maintaining complete separation of personal identifiers required for linkage and the data records which are subsequently provided to researchers.

Explanatory and outcome variables
In the hospital data a maximum of 55 separate fields for principal diagnosis and co-morbidities were recorded for each patient discharge record and coded according to the International Classification of Diseases and Related Health Problems 10th revision—Australian Modification. Endometriosis cases were identified from those hospital records with any ICD-10 code for endometriosis (Table I). Patients with a diagnosis of adenomyosis alone (N80.1) were excluded. There is evidence that mild (revised American Fertility Society [rAFS] stage I–II) and severe endometriosis (rAFS stage III–IV) may be separate disease entities (Nisolle and Donnez, 1997). Although disease severity is not available from the hospital data, we were able to analyse the data on the basis of the number of sites affected and/or the type of site affected by endometriosis.

Pregnancy hypertension (PH) is hypertension arising after 20 weeks gestation and includes gestational hypertension, pre-eclampsia and eclampsia and was classified as any record of these conditions either in the hospital data (see Table I) or in the birth data. Pre-eclampsia was classified as PH with proteinuria. The broad category of PH was the primary outcome variable as it is more accurately reported in large population health datasets than the more specific category of pre-eclampsia (Roberts et al., 2008), which was included as a secondary outcome variable.

There is evidence that pre-eclampsia is more common among nulliparous women (Luo et al., 2007) and varies with maternal age (Duckitt and Harrington, 2005). Therefore, only births to nulliparous women, i.e.
those with no previous births, were included in this study (referred to as ‘first births’). Maternal age was included as a possible covariate, defined as the age at the first birth in the period 2000–2005 and grouped into three broad categories (<25, 25–35, >35 years). PH may influence the risk of preterm birth and therefore gestational age was also included as a possible covariate in three categories (<34, 34–36, >36 weeks gestation).

Because Brosens et al. (2007) found a relationship between endometriosis and reduced risk of pre-eclampsia in a group of women with infertility, we felt it was also important to attempt to form a suitable comparison group from our data-set. Any records with procedure codes related to in vitro fertilization (IVF)/assisted reproduction were therefore used to identify a subgroup with infertility.

Analysis

Contingency tables and Fisher’s Exact Test were used to analyse the occurrence of endometriosis and PH or pre-eclampsia. Subgroups were analysed based on: (i) site of endometriosis (i.e. ovary or peritoneum), (ii) multiple (i.e. two or more) sites affected and (iii) infertility. Endometriosis involving the ovary or multiple sites was included as a proxy for more severe disease.

We used logistic regression to investigate the association between PH, endometriosis, number of weeks gestation at birth and maternal age. Crude ORs with 95% confidence intervals were estimated for the explanatory variables. Adjusted ORs were calculated by entering the proposed explanatory variables into the logistic regression model and retaining variables that were significant at \( P < 0.01 \), apart from maternal age which was included \textit{a priori}.

Results

A total of 378 283 individuals were identified with one or more births, of whom 208 879 had a singleton, first birth, in the period 2000–2005 (Fig. 1). Of those with a first birth 3239 (1.6%) had a previously recorded diagnosis of endometriosis.

Of the 3239 women identified with endometriosis and a subsequent singleton, first birth in the study period, 846 (26%) had ovarian disease and 2386 (74%) had pelvic endometriosis. For 514 (16%) women more than one site was recorded as being involved.

The average age at first birth in women diagnosed with endometriosis was 31.4 years, and was significantly higher than for those with no diagnosis (Table II).

Subgroup analysis of the population with endometriosis diagnosed before their first birth is presented in Table III. In all of the subgroups analysed, women with endometriosis were at no significantly altered risk for PH or pre-eclampsia leading up to their first birth.

When the relationship between PH and endometriosis was modelled, taking into account maternal age group and weeks gestation at birth, the adjusted ORs did not change markedly in comparison to the crude ORs (Table IV). Similar models were established for both pre-eclampsia and endometriosis and PH, IVF and endometriosis, with no significant associations observed.

Furthermore, in second or higher pregnancies following endometriosis diagnosis there was no significant difference in the occurrence of PH compared with those with no endometriosis diagnosis (4.3% compared with 4.5%, respectively, OR 0.96, 95% CI 0.7–1.3).

Table I The ICD-10 codes used to define variables for analysis

<table>
<thead>
<tr>
<th>Description</th>
<th>Variable name</th>
<th>ICD-10 code</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>N80.1</td>
<td>Endometriosis of ovary</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.2</td>
<td>Endometriosis of fallopian tube</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.3</td>
<td>Endometriosis of pelvic peritoneum</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.4</td>
<td>Endometriosis of rectovaginal septum and vagina</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.5</td>
<td>Endometriosis of intestine</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.6</td>
<td>Endometriosis in cutaneous scar</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.8</td>
<td>Other endometriosis</td>
<td></td>
</tr>
<tr>
<td>Endometriosis</td>
<td>N80.9</td>
<td>Endometriosis, unspecified</td>
<td></td>
</tr>
<tr>
<td>All PH</td>
<td>Pre-eclampsia</td>
<td>O11</td>
<td>Pre-existing hypertensive disorder with superimposed proteinuria</td>
</tr>
<tr>
<td>All PH</td>
<td>O14</td>
<td>Gestational [pregnancy-induced] hypertension with significant proteinuria</td>
<td></td>
</tr>
<tr>
<td>All PH</td>
<td>O14.0</td>
<td>Moderate pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>All PH</td>
<td>O14.1</td>
<td>Severe pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>All PH</td>
<td>O14.9</td>
<td>Pre-eclampsia, unspecified</td>
<td></td>
</tr>
<tr>
<td>All PH</td>
<td>O15</td>
<td>Eclampsia</td>
<td></td>
</tr>
<tr>
<td>Other PH</td>
<td>O13</td>
<td>Gestational [pregnancy-induced] hypertension without significant proteinuria</td>
<td></td>
</tr>
<tr>
<td>Other PH</td>
<td>O16</td>
<td>Unspecified maternal hypertension</td>
<td></td>
</tr>
</tbody>
</table>

Table II Characteristics of women with singleton, first births 2000–2005

<table>
<thead>
<tr>
<th>Description</th>
<th>N</th>
<th>Mean age* (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women with a singleton, first birth (2000–2005)</td>
<td>208 879</td>
<td>28.3 (5.7)</td>
</tr>
<tr>
<td>All women with no endometriosis</td>
<td>205 640</td>
<td>28.3 (5.7)</td>
</tr>
<tr>
<td>All women with endometriosis</td>
<td>3239</td>
<td>31.4 (5.1)</td>
</tr>
<tr>
<td>PH</td>
<td>23 538</td>
<td>28.4 (5.7)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>6667</td>
<td>28.7 (5.8)</td>
</tr>
</tbody>
</table>


**Significantly different to all women with no endometriosis (\( P < 0.0001 \)).
Discussion

Given that both endometriosis and pre-eclampsia may involve the uterus in their pathology, it is surprising that more investigations of the inter-relationship of these two diseases have not been conducted. There is biological plausibility for the hypothesis that similar mechanistic pathways may be responsible for both conditions and these were discussed in detail by Brosens et al. (2007). The finding of a relationship between endometriosis and reduced risk of pre-eclampsia has generated considerable interest (Fernando et al., 2009).

Longitudinally linked population health data are a convenient tool for investigating such findings in a larger sample. Such data sets have been used in the past for endometriosis research. For example, the Oxford Record Linkage Study investigated subsequent hospitalizations for women with an initial diagnosis of pelvic inflammatory disease and showed that cases were six times more likely than controls to receive a future diagnosis of endometriosis (Buchan et al., 1993). Longitudinally linked data has also been successfully used in Canada to study patterns of readmission for women with a diagnosis of endometriosis in hospital discharge data (Weir et al., 2005). In both Sweden (Melin et al., 2006, 2007) and Japan (Kobayashi et al., 2007) linked data have been utilized to demonstrate the link between endometriosis and the risk of ovarian cancer.

In a large population-based dataset, we have found no evidence of an association between endometriosis and subsequent risk of pre-eclampsia or PH. This is in contrast to the findings of Brosen’s et al. (2007) in which a small matched case–control study from a single IVF centre gave evidence for a protective association between endometriosis and pre-eclampsia. Our analysis of the subpopulation of women with procedures relating to assisted reproduction, found no relationship between endometriosis and PH. Moreover, taking disease severity into account, maternal age and gestation at birth did not significantly alter the risk for PH or pre-eclampsia in women with endometriosis.

To the best of our knowledge this is the first time that the incidence of surgically diagnosed endometriosis in a population of fertile women of child-bearing age has been reported. We observed a frequency of 1.6% of surgically diagnosed endometriosis among women having their first birth between 2000 and 2005. This is comparable to findings from the United States

### Table III Incidence of PH and pre-eclampsia for women with no previous births

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>PH (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Pre-eclampsia (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No endometriosis</td>
<td>205 640</td>
<td>23 186 (11.3)</td>
<td>Referent</td>
<td></td>
<td>6564 (3.2)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Any endometriosis^</td>
<td>3239</td>
<td>352 (10.9)</td>
<td>0.96 (0.9–1.1)</td>
<td>0.48</td>
<td>103 (3.2)</td>
<td>1.00 (0.8–1.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Ovarian endometriosis</td>
<td>846</td>
<td>94 (11.1)</td>
<td>0.98 (0.8–1.2)</td>
<td>0.96</td>
<td>24 (2.8)</td>
<td>0.89 (0.6–1.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>Peritoneal endometriosis</td>
<td>2386</td>
<td>266 (11.2)</td>
<td>0.99 (0.9–1.1)</td>
<td>0.85</td>
<td>78 (3.3)</td>
<td>1.03 (0.8–1.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>Multiple sites affected</td>
<td>514</td>
<td>59 (11.5)</td>
<td>1.02 (0.8–1.3)</td>
<td>0.89</td>
<td>14 (2.7)</td>
<td>0.85 (0.5–1.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>No endometriosis plus IVF</td>
<td>4935</td>
<td>601 (12.2)</td>
<td>Referent</td>
<td></td>
<td>182 (3.7)</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Endometriosis^ plus IVF</td>
<td>841</td>
<td>84 (10.0)</td>
<td>0.80 (0.6–1.0)</td>
<td>0.07</td>
<td>21 (2.5)</td>
<td>0.67 (0.4–1.1)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

^Endometriosis diagnosed before first birth.

### Table IV Results of the logistic regression for PH and endometriosis, age group and weeks gestation at birth

<table>
<thead>
<tr>
<th>Endometriosis^</th>
<th>Number</th>
<th>PH (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>205 640</td>
<td>23 186 (11.3)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>3239</td>
<td>352 (10.9)</td>
<td>0.96 (0.9–1.1)</td>
<td>0.93 (0.8–1.0)</td>
</tr>
<tr>
<td>Maternal age§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>59 245</td>
<td>6679 (11.3)</td>
<td>1.02 (1.0–1.0)</td>
<td>1.01 (1.0–1.0)</td>
</tr>
<tr>
<td>25–35 years</td>
<td>124 603</td>
<td>13 843 (11.1)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>&gt;35 years</td>
<td>25 031</td>
<td>3016 (12.1)</td>
<td>1.10 (1.1–1.1)</td>
<td>1.08 (1.0–1.1)</td>
</tr>
<tr>
<td>Gestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;34 weeks</td>
<td>4244</td>
<td>968 (22.8)</td>
<td>2.49 (2.3–2.7)</td>
<td>2.49 (2.3–2.7)</td>
</tr>
<tr>
<td>34–36 weeks</td>
<td>8947</td>
<td>1829 (20.4)</td>
<td>2.17 (2.1–2.3)</td>
<td>2.16 (2.1–2.3)</td>
</tr>
<tr>
<td>&gt;36 weeks</td>
<td>195 688</td>
<td>20 741 (10.6)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
</tbody>
</table>

OR= odds ratio.
^Endometriosis diagnosed before the first birth.
§Age at first birth.
†Adjusted for maternal age and weeks gestation.
aged 30–39 years in a study of private payer administrative claims (Mirkin et al., 2007).

The strength of this study is the large, longitudinally linked population data set that has been validated against the medical record for both PH and pre-eclampsia (Roberts et al., 2008). The reliability of these variables has been estimated in the hospital data with PH having a specificity of 99.6% and a positive predictive value of 94% and pre-eclampsia 67 and 99%, respectively. Moreover, by using PH recorded in either hospital or birth data, the sensitivity and specificity of identification of true cases increases further still, giving an increased sensitivity of 82% compared with either birth data (63%) or hospital data (68%) alone. Because of misclassification of gestational hypertension and pre-eclampsia, the broad category of PH is more accurately and reliably reported than either of the more specific diagnoses (Roberts et al., 2008).

Because the hospital data is a census of all hospital separations from public hospitals, private hospitals and day procedures, and because surgical procedures are generally well ascertained in such data (Quan et al., 2004), we can be confident that no surgical diagnosis has been received during the study period for those women with no endometriosis diagnosis. This is in contrast to many other studies where comparison groups of unknown endometriosis status are utilized. This has been identified as a common problem in endometriosis studies (Zondervan et al., 2002).

Although the recording of PH has been validated in the hospital data, the recording of endometriosis has not, and there is evidence that hospital discharge data may tend to under-estimate conditions. However, findings from an analysis of the hysterectomy rate in Western Australia showed that 12% had a principal or secondary ICD-10 code for endometriosis which is comparable to that hospital discharge data. Some support that endometriosis is reliably recorded in hospital data is provided by the fact that comparisons with either birth data (63%) or hospital data (68%) alone. Because of misclassification of gestational hypertension and pre-eclampsia, the broad category of PH is more accurately and reliably reported than either of the more specific diagnoses (Roberts et al., 2008).

In conclusion, we have found no relationship between endometriosis and subsequent risk of PH or pre-eclampsia in this large population-based data set. The frequency of pre-eclampsia was not significantly different amongst women with severe endometriosis or endometriosis in conjunction with infertility when compared with those with no endometriosis. After adjusting for maternal age and weeks gestation at birth, there was still no altered risk.

Ethics approval

Ethics approval was obtained for data linkage from the NSW Department of Health Population & Health Services Research Ethics Committee (No. DoHEC 2006-06-011) and for the project from the University of Sydney Human Research Ethics Committee (No. 02-2008/10713).

Acknowledgements

We acknowledge the efforts of the hospital staff that collect the data. We are indebted to Lee Taylor, Kim Lim and all the staff at the CHeReL for conducting the data linkage.

Funding

R.H. and C.H.R.G. are funded by National Health and Medical Research Council (NHMRC) Post-doctoral Training Research Fellowships and C.R. is supported by an NHMRC Senior Research Fellowship.

References


Splitsbury K, Semmens JB, Hammond I, Bolck A. Persistent high rates of hysterectomy in Western Australia: a population-based study of 83 000 procedures over 23 years. BJOG 2006;113:804–809.


Zondervan KT, Cardon LR, Kennedy SH. What makes a good case–control study? Design issues for complex traits such as endometriosis. Hum Reprod 2002;17:1415–1423.

Submitted on January 7, 2009; resubmitted on March 9, 2009; accepted on April 8, 2009.