Hum. Reprod. Advance Access published May 21, 2013
Human Reproduction, Vol.0, No.0 pp. 1–5, 2013
doi:10.1093/humrep/det231

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Reproductive prognosis in daughters of women with and without endometriosis

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Submitted on August 10, 2012; resubmitted on March 30, 2013; accepted on April 22, 2013

STUDY QUESTION: Do daughters of women with endometriosis exhibit an increased risk of endometriosis and impaired long-term reproductive prognosis when compared with daughters of women without endometriosis?

SUMMARY ANSWER: Daughters of women with endometriosis have over a 2-fold higher risk of endometriosis but no difference in long-term reproductive prognosis compared with controls.

WHAT IS KNOWN ALREADY: Several studies have found an increased prevalence of endometriosis in sisters and mothers of women with endometriosis, but none have examined the long-term reproductive prognosis in daughters of these patients.

STUDY DESIGN, SIZE, DURATION: A controlled historical cohort study with a 33-year follow-up.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Among women 15–49 years old during the period 1977–1982, 24 691 were diagnosed with endometriosis during the study period. These women were age matched to 98 764 women without endometriosis. Daughters of these two groups were followed until 31 December 2009 for an endometriosis diagnosis and reproductive outcomes. Women were excluded from the study at death or if they emigrated.

MAIN RESULTS AND THE ROLE OF CHANCE: Except for 4–6% of emigrated women, the follow-up rate of the study was almost 100%. Daughters of women with endometriosis ($n = 12\,389$) had a 2.12-fold (95% confidence interval 1.89–2.37, $P < 0.0001$) increased risk of being diagnosed with endometriosis, compared with daughters of women without endometriosis ($n = 52\,371$). Delivery rate, risk of spontaneous abortions and ectopic pregnancies were similar for the two cohorts, whereas induced abortions were slightly more frequent in the exposed cohort.

LIMITATIONS, REASONS FOR CAUTION: The most important limitation of the study was the lack of data concerning the attempt to become pregnant. Also, some women with endometriosis might never be diagnosed with the condition. This applies to both the control mothers and the control daughters, but also the daughters of mothers with endometriosis. Other limitations are lack of accounting for potential confounders and the lack of data on preterm birth. However, the influence of most confounding factors was expected to be minimal because of the close matching by age of controls.

WIDER IMPLICATIONS OF THE FINDINGS: The external validity of the study is expected to be high owing to the unselected inclusion criteria. The encouraging finding was that despite the increased risk of being diagnosed with endometriosis, daughters of women with endometriosis have a reproductive prognosis comparable with that of daughters of women without endometriosis.

STUDY FUNDING/COMPETING INTEREST(S): The Department of Gynaecology at Rigshospitalet University Hospital, Copenhagen, covered all expenses of the study. Ø.L. has, within the last 3 years, received honoraria for speeches in pharmacoepidemiological issues and has been expert witness in a legal US case in 2011–2012. None of the other authors have any conflicts of interest.

Key words: endometriosis / reproduction / delivery / ectopic pregnancy / spontaneous abortion

Introduction

Endometriosis is a chronic, benign gynaecological disorder, characterized by the presence of tissue resembling endometrium in extra-uterine sites, which induces a chronic inflammatory reaction. Evidence suggests that hormonal, immunological, environmental and genetic factors play a role in disease aetiology (Guo, 2009). Common symptoms are pelvic pain, dysmenorrhoea and impaired fertility (Giudice, 2010), but the

clinical presentation of the disease varies. Endometriosis can be asymptomatic, and the presence of endometrial tissue in the pelvic cavity of asymptomatic women does not necessarily constitute a pathological condition (Treloar et al., 1999), whereas in other women endometriosis cysts (endometriomas) and deep infiltrating endometriosis in many ways behave like a tumour (Kennedy et al., 2001). It is not known whether these subphenotypes represent the natural history of one disorder or are in fact different subentities (Montgomery et al., 2008).

Endometriosis is diagnosed by laparoscopy and histology. However, it is well known that in practice endometriosis is often treated (and therefore diagnosed) empirically based on symptoms rather than on laparoscopic and histological diagnosis (Jacobson, 2011). The best estimates suggest that endometriosis (all stages from minimal to severe) affects 6–10% of all fertile women, 50–60% of women and adolescents with pelvic pain, and up to 50% of infertile women (Giudice, 2010). The prevalence of moderate-to-severe endometriosis has been estimated to be up to 2% (Montgomery et al., 2008). Research has suggested that environmental factors, including fetal exposure to hormone-like substances, may have an effect on the prevalence of disease (Treloar et al., 1999). In addition, several studies have suggested a genetic component (Kennedy et al., 2001), and more recently a possible role of epigenetics has been proposed (Guo, 2009). Consequently, endometriosis is today commonly being regarded as a complex trait caused by the interplay between multiple genetic and environmental factors (Montgomery et al., 2008).

Besides twin studies, several studies have examined the risk of endometriosis in sisters and/or mothers of patients with endometriosis in different ways (Simpson et al., 1980; Lamb et al., 1986; Coxhead and Thomas, 1993; Moen and Magnus, 1993; Kennedy et al., 1998; dos Reis et al., 1999; Stefansson et al., 2002; Kashima et al., 2004; Matalliotakis et al., 2008), indicating a 2.5 to 9.5-fold increased prevalence compared with the general population (summarized in Table I). However, until now, no studies have estimated the risk of endometriosis and reproductive prognosis in daughters of women with endometriosis.

The aim of this study was to compare the prevalence of diagnosed endometriosis and the reproductive prognosis in daughters of women with endometriosis (exposed daughters) with the same outcomes in daughters of women without endometriosis (non-exposed daughters).

Materials and Methods

Data collection

The study was designed as a historical controlled cohort study and was approved by the Danish Data Protection Agency (J. no. 2009–41–3867). Data for the study population were extracted from four registries. The Danish National Registry of Citizens includes all Danish citizens and their unique personal identification number. Since 1977, by law, all discharge diagnoses from any hospital in Denmark have been registered in the Danish National Registry of Patients, from which disease diagnoses were obtained. Since 1973, all women in Denmark have had a right to opt for an induced abortion within the first 12 weeks of their pregnancy, and records of these events are available in the Danish National Registry of Induced Abortions. Finally, information about births was obtained from the Danish National Birth Registry. All Danish women who were between 15 and 49 years old at any time during the time period from 1 January 1977 to 31 December 2009 were included. The exclusion criteria were emigration or death.

Methods

Using the Registry of Citizens and the National Registry of Patients, first, all women 15–49 years old (of reproductive age) during the period 1977–1982, and with at least one diagnosis of endometriosis (ICD8: 625.30–37 and ICD10: DN800–808) during the study period from 1 January 1977 to 31 December 2009, were identified. These women were termed exposed mothers. Next, all daughters of these women were identified (exposed daughters). We then established an age-matched (within 1 year) cohort of four non-exposed women for each exposed mother, who had never been registered with a diagnosis of endometriosis or polycystic ovary syndrome. Daughters of this non-exposed cohort of women constituted the control cohort (non-exposed daughters). Using the National Registry of Patients, the Registry of Induced Abortions and the Birth Registry, all registered pregnancy outcomes among the exposed and non-exposed daughters until the end of 2009 were identified, including spontaneous abortions (spontaneous abortion, missed abortion and pregnancy without fetus; ICD-8: 643 + 645·1, ICD-10: DO020, DO021 and DO030–DO039), induced abortions (ICD-8: 640–642, ICD-10: DO040–DO059), ectopic pregnancies (ICD-8: 631·09–99, ICD-10: DO000–009), hydatidiform mole (ICD-8: 634·29, ICD-10: DO010–DO019 and DO020B/C) and deliveries (ICD-8: 650–666, ICD-10: DO600–DO849). The obstetric codes were used to identify

Table I Prevalence of endometriosis in first-degree relatives of women with endometriosis and in controls reported in previous studies.

Authors (year)	Country	*n*	Sisters (%)	Mothers (%)	Mothers or sisters (%)	Controls (%)
Simpson et al. (1980)	USA	123	5.8	8.1	6.9	1.0
Lamb et al. (1986)	USA	43	3.8[a]	6.2[a]	4.9[a]	1.9[a]
Moen and Magnus (1993)	Norway	515	4.8	3.9	4.3 (OR: 7.2)	0.7
Coxhead and Thomas (1993)	UK	64	—	—	9.4	1.6
Kennedy et al. (1998)	UK	29	—	—	14.3	—
dos Reis et al. (1999)	Brazil	81	—	—	8.6	0
Stefansson et al. (2002)	Iceland	750	(RR: 5.2)	—	—	—
Kashima et al. (2004)	Japan	339	8.8 (RR: 5.7)	—	—	1.5
Matalliotakis et al. (2008)	USA	485	5.6[b]	3.9[b]	9.5[b] (OR: 10.2)[b]	1.0[b]

[a]Calculated by extrapolation to a general population.
[b]Calculated as a percentage of the exposed cohort.
OR, odds ratio; RR, rate ratio. All RR and OR refer to comparison with controls.

if a birth had taken place and then it was cross-checked to determine whether there was a simultaneous code for a birthweight, ensuring that each child was only counted once. ICD-8 was in use from 1977 to 1993, ICD-10 from 1994.

Data analysis

The average age of delivery among the exposed mothers and among the closely age-matched non-exposed mothers was assessed to ensure a similar age of the two daughter cohorts. After ensuring that the proportion of censored women due to emigration or death was similar in the two daughter cohorts, the reproductive outcomes were calculated as incidence rates of each pregnancy outcome during the follow-up period. In addition, rate ratios (RR) with 95% confidence intervals (CI) were calculated for each reproductive outcome and with the non-exposed daughters as the comparison group. The same calculations were performed for the prevalence of endometriosis. Cox-regression analysis was not possible owing to the multiple long-term outcomes. The weight of women with a single versus more than one delivery was assessed for both the exposed and the control cohort to detect a possible differential reproductive pattern between the two groups. Furthermore, the rate of assisted reproduction technology (ART) for both groups of daughters was obtained from the National ART Registry. Data were analysed using SAS software statistical program version 9.1.3.

Differences were tested by the *z*-test, and *P*-values <0.05 were considered as statistically significant.

Results

A total of 24 691 mothers with endometriosis gave birth to 12 389 daughters, of which 455 (3.7%) were diagnosed with endometriosis during the follow-up period. Correspondingly, 98 764 age-matched control women without endometriosis gave birth to 52 371 daughters, of which 908 (1.7%) were diagnosed with endometriosis, resulting in an RR of 2.12 (95% CI: 1.89–2.37, $P < 0.0001$) (Table II). Thus, daughters of women with endometriosis had a well over doubled risk of being diagnosed with endometriosis when compared with daughters of women without endometriosis. The average age at first birth among mothers with endometriosis was 25.9 years and 26.2 years among the age-matched control mothers, ensuring approximately similar ages of the daughters. A total of 256 (2.1%) of the exposed daughters versus 1238 (2.4%) of the non-exposed daughters were excluded due to death during the study period, whereas 460 (3.7%) versus 3051 (5.8%) were excluded due to emigration.

Table II Prevalence of endometriosis in daughters of mothers with (exposed) and without (non-exposed) endometriosis.

Exposure	Daughters, *n*	Endometriosis *n* (%)	Rate ratio (95% CI)
Mother with endometriosis ($n = 24\,691$)	12 389	455 (3.7)	2.12 (1.89–2.37)
Mother without endometriosis ($n = 98\,764$)	52 371	908 (1.7)	

Follow-up 1977–2009.
CI, confidence interval.

Reproductive outcomes in daughter cohorts

The 12 389 exposed daughters had 18 276 deliveries, whereas the 52 371 non-exposed daughters had 77 166 deliveries (RR: 1.00; 95% CI: 0.99–1.02) (Table III). The proportion of single children was similar in the exposed cohort; 2409/18 645 or 13%, versus 9356/78 535 or 12% in the control cohort. The average age at the first birth was 24.6 years in the exposed daughters and 24.8 years in the non-exposed control daughters. Compared with the non-exposed daughters, the exposed daughters had the same rate of spontaneous abortions (Table III). The exposed daughters had 10% more induced abortions when compared with the control cohort ($P < 0.0001$). A 10% higher incidence rate of ectopic pregnancy and a 19% higher incidence rate of hydatidiform mole among the exposed daughters both just failed to reach statistical significance, compared with the incidence rate in the non-exposed cohort. The rate of ART for all pregnancies was 518/29 232 or 1.8% ART pregnancies among the exposed daughters, compared with 1747/109 362 or 1.6% in the non-exposed daughters.

Discussion

In summary, we found that daughters of women with endometriosis showed a 2.12-fold increased risk of being diagnosed with endometriosis compared with daughters of women without endometriosis. Despite this increased risk, daughters of women with endometriosis exhibited the same pregnancy outcomes as daughters of women without endometriosis.

To our knowledge, this is the first study using a down-line approach, identifying first women with endometriosis and subsequently their daughters. Other studies have used an up-line or side-line approach, identifying women with endometriosis with a subsequent follow-up of their ancestors or sisters. The study is also larger than previous studies, taking advantage of the Danish National Health registers all going back to at least 1977.

Table III Pregnancy outcomes in daughters of mothers with (exposed) and without (non-exposed) endometriosis.

	n	Delivery	Spontaneous abortion	Induced abortion	Ectopic pregnancy	Hydatidiform mole
Exposed	12 389	18 276	2497	5243	334	33
Non-exposed	52 371	77 166	10 616	20 180	1279	117
RR (95% CI)		1.00 (0.99–1.02)	0.99 (0.95–1.04)	1.10 (1.07–1.13)	1.10 (0.98–1.25)	1.19 (0.81–1.75)

Follow-up 1977–2009.

Compared with other studies of endometriosis in first-degree relatives of women with endometriosis (Table I), we found a similar prevalence rate of 1.7% in the general population. Our finding of a prevalence rate in the exposed cohort of 3.7% is comparable with a few of the studies but lower than most of the earlier reported values ranging from 3.8 to 14.3%. One reason for a lower prevalence in our study could be that a majority of women with endometriosis were never hospitalised, and, therefore, never recorded in the National Registry of Patients. Furthermore, in the beginning of the study period, especially during the primary diagnostic time period for the mothers (1977–1982), the clinical and phenotypic criteria for defining endometriosis differed from today, most likely towards mainly diagnosing more severe cases. To reduce this bias, we included all diagnoses of endometriosis throughout the full observation period from 1977 to 2009, also for the mothers. Yet, expecting that the primary diagnostic time period would be during or immediately after reproductive age, this could tend to bias the data for the mothers towards underestimating the prevalence of endometriosis. Diagnosing fewer mothers with endometriosis would additionally tend to bias the data towards underestimating the heritability of endometriosis. The majority of the other studies included all types and stages of endometriosis, some, however, excluded women with minimal endometriosis (dos Reis *et al*., 1999) or included in first instance only moderate-to-severe endometriosis (Kennedy *et al*., 1998; Kashima *et al*., 2004). The recruitment of relatives of women with endometriosis also varies from interviewing the patients about their relatives (Moen and Magnus, 1993), to interview and a subsequent follow-up of the relatives' medical records (Coxhead and Thomas, 1993), to inviting all relatives with a history suggestive of endometriosis to an interview and a diagnostic laparoscopy (dos Reis *et al*., 1999), and the proportion of relatives assessed with endometriosis not surprisingly increased successively. Also recruitment protocols for the control cohort differed. Some studies used a random group matched to the exposed cohort, others used a group of patients from the same time period who had undergone laparoscopy or laparotomy without any visible signs of endometriosis. Simpson *et al*. used the sisters and mothers of the husbands of the women with endometriosis (Simpson *et al*., 1980) whereas Lamb *et al*. used their best female friend and found RRs of endometriosis between sisters and friends similar to ours (Lamb *et al*., 1986). In accordance with our results, an Australian sample of twin pair families with endometriosis reported a 2.34 times increased risk of self-reported endometriosis in sisters of women with endometriosis compared with sisters of women without endometriosis (Treloar *et al*., 1999).

The slightly higher frequency of induced abortions among exposed daughters might be explained by the fact that many of these women grew up with a mother diagnosed with endometriosis and perhaps impaired fertility, and hence the possible perception that the daughters themselves could also be affected, leading to a less cautious attitude towards avoiding unwanted pregnancies. This is, however, purely speculative.

The validity of the study results depends on the validity of the diagnosis codes. Some women with an endometriosis diagnosis may have obtained their diagnosis alone from symptoms suggestive of endometriosis, some of which, therefore, could be misclassified. It is also certain that some women without an endometriosis diagnosis could have endometriosis. This bias was reduced by classifying a woman as a woman with endometriosis, whenever during the 33-year study period she was diagnosed with the disease. Both of these potential biases tend to underestimate the difference in reproductive outcomes between exposed and non-exposed daughters. On the other hand, daughters of mothers diagnosed with endometriosis may be more aware of this condition, and could be more likely to seek medical help in case of the typical symptoms of endometriosis. This bias tends to overestimate the difference between exposed and non-exposed daughters, meaning that the differences we found could be even smaller. On the other hand, the proportion of daughters with endometriosis could be higher due to an increased awareness of the disease.

To increase the statistical power of the study, we chose four control women for each woman with endometriosis. Another strength was the close to 100% complete follow-up rate. The influence of most confounding factors was limited or eliminated by the close age matching, because the majority of potential confounders are correlated to age, although this attempt does not exclude residual confounding. Many factors which may influence fertility and the treatment of infertility have changed over the 33-year long study period, but the close age-matching between women with and without endometriosis helped to reduce any influence of these factors on the two mother and two daughter cohorts, even though the impact of specific potential confounders, such as body size, smoking and menstrual characteristics, was not accounted for. It is not possible to conclude in which direction such a theoretical residual confounding might have influenced the results. The proportion of children being a single child was equal in the exposed and control cohorts (13 versus 12%). In principle, the applied model assumed the independence of each woman or observation. The possible impact of the independence violation on the variance estimation is probably small due to the similar proportion of single children and siblings in the two cohorts. The most important limitation to this study is the missing information about the attempt of daughters to become pregnant. We only have two proxy measures to address this point. The first one is the rate of induced abortions, which was 10% higher in the exposed when compared with the non-exposed daughters. The other is the rate of ART, which was 1.8% among the exposed daughters and 1.6% in the non-exposed daughters. Thus, the first proxy variable points towards a slightly lower pregnancy attempt and the second proxy variable points towards a slightly higher pregnancy attempt in the exposed daughters, suggesting roughly similar attempt among exposed and non-exposed daughters. Another limitation of the study is that we did not have information on the gestational age at delivery and hence no data on preterm birth.

In conclusion, this study confirms that close relatives, in this case daughters, of women with endometriosis are at an increased risk of being diagnosed with endometriosis, but also provides the encouraging finding that, despite this pre-disposition, daughters of women with endometriosis have a reproductive prognosis comparable with that of daughters of women without endometriosis.

Authors' roles

All authors participated in the design of the study, acquisition, analysis and interpretation of data and critical discussion. T.D. wrote the manuscript, M.V.H.H., D.H. and Ø.L. revised the draft critically and all approved the final version.

Funding

The Department of Gynaecology at Rigshospitalet University Hospital, Copenhagen, covered all expenses of the study.

Conflict of interest

Ø.L. has within the last 3 years received honoraria for speeches in pharmacoepidemiological issues and has been expert witness in a legal US case in 2011–2012.

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