HHS Public Access

Author manuscript

Lupus. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Lupus. 2016 August ; 25(9): 1045–1049. doi:10.1177/0961203316631635.

Endometriosis and systemic lupus erythematosus: a population-based case-control study

Holly R. Harris[1,2], **Julia F. Simard**[3,4,5], and **Elizabeth V. Arkema**[3]

[1]Division of Nutritional Epidemiology, The National Institute for Environmental Medicine, Karolinska Institute, Stockholm, Sweden

[2]Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Boston, Massachusetts, USA

[3]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institute, Stockholm Sweden

[4]Division of Epidemiology, Department of Health Research and Policy, Stanford School of Medicine, Stanford, CA, USA

[5]Division of Immunology & Rheumatology, Department of Medicine, Stanford School of Medicine, Stanford, CA, USA

Abstract

Objective—To investigate the association between endometriosis and systemic lupus erythematosus (SLE) in prospectively collected population-based data.

Methods—We conducted a case-control study using Swedish registers, identifying female SLE cases from the National Patient Register (NPR) and female controls sampled from the general population matched on birth year, sex, and county during 1964–2011. We identified endometriosis diagnoses from the NPR using ICD codes. We estimated odds ratios (OR) and 95% confidence intervals (CIs) using conditional logistic regression models.

Results—We identified 2834 cases of SLE and 14164 controls. 78 cases were diagnosed with endometriosis prior to their SLE diagnosis and 288 controls were diagnosed prior to the index date. We observed a significant association between endometriosis and subsequent SLE with an OR of 1.39 (95% CI=1.09–1.78). The association was similar when requiring a laparoscopy/laparotomy within 6 months of the endometriosis diagnosis (OR=1.33; 95% CI=0.84–2.12) while the association was stronger when restricted to endometriosis diagnosed at the same time as hysterectomy (OR=2.26; 95% CI=1.47–3.64).

Conclusions—Our findings suggest an association between endometriosis and SLE. Future prospective studies with extended follow-up will be necessary to clarify whether this association is influenced by the timing and severity of endometriosis diagnosis.

To whom correspondence and reprint requests should be addressed: Dr. Holly Harris, Unit of Nutritional Epidemiology, Institute for Environmental Medicine, Karolinska Institutet, P.O. Box 210, SE-171 77 Stockholm, Sweden, Telephone: 46-8-524-86460, Fax: 46-8-304571, holly.harris@ki.se.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with a heterogeneous presentation that can affect multiple systems including skin, joints, and kidneys. SLE is observed primarily in women consequently female hormones likely play a role in its etiology.[1] In Sweden, prevalence estimates for SLE in females range from approximately 79 to 144 per 100,000[2] but may vary among other populations depending on multiple factors including racial and geographic differences as well as differing clinical definitions.[3]

Endometriosis is a hormone-dependent disorder characterized by the presence of endometrial tissue outside the uterine cavity and affects approximately 10% of reproductive aged women.[4] The etiology of endometriosis is not fully understood but there is evidence that an aberrant immunologic response contributes to its pathogenesis.[5] Heightened immune surveillance has been observed in both endometriosis and SLE, conditions that not only share clinical features but also immunologic characteristics such as the presence of antinuclear antibodies (ANA).[6–8]

Results from a survey of the U.S. Endometriosis Association female membership suggested that women with endometriosis had a higher than expected prevalence of autoimmune diseases, including a prevalence odds ratio for SLE of over 20 compared to the general U.S female population.[9] A handful of studies have further examined this association finding mixed results. One hospital-based case-control study found no difference in SLE prevalence between women with and without endometriosis[10] while two cohort studies found a significant positive association between endometriosis and SLE,[11, 12] however their definitions and restrictions differed with respect to laparascopy and hysterectomy. Furthermore, because SLE is not a common disease and can be difficult to accurately characterize in epidemiologic investigations, these studies may have been underpowered.

Using population-based registers in Sweden we designed a case-control study to investigate the association between endometriosis and SLE with over 2,800 cases of SLE. In addition, we examined whether the association differed when the endometriosis definition was limited to those who had undergone laparoscopy/laparotomy within six months of their initial endometriosis diagnosis or when endometriosis was diagnosed at the same time as a hysterectomy.

Methods

Study Population

SLE cases were identified from the Swedish National Patient Register (NPR), which contains data on hospitalizations (1964–2011, nationwide since 1987), day surgery (1997–2000), and outpatient specialist visits including day surgery (2001–2011). Coverage of the inpatient portion of the NPR is approximately 100%[13] while the outpatient portion has been estimated to cover approximately 87% of visits, with missing visits primarily from private caregivers.[13, 14] Cases were required to have at least two discharge diagnoses with ICD codes specifying SLE from either inpatient or outpatient care (ICD-8 734.1, ICD-9 710.0, ICD-10 M32) including at least one discharge from a department or specialist typically

known to diagnose, treat, or manage SLE (rheumatology, dermatology, nephology, internal medicine, and pediatrics). Drug-induced lupus was excluded. Cases were restricted to those who received their first SLE ICD code Jan 2002 or later as a proxy for incident SLE. Controls were identified from the Total Population Register and matched to cases (5 to 1) on birth year, sex, and county of residence the year that the case was first observed as a case (index date). Cases and controls were restricted to females aged 16 or older at SLE diagnosis or index date. Ethical approval was obtained by the Ethical Review Board of Karolinska Institute.

Identification of endometriosis

Information about endometriosis diagnosis was obtained from the NPR. Women were considered to have endometriosis if they had a discharge diagnosis (main or contributory) between 1964 and 2011 using the following ICD codes: ICD8: 625.30–625.33, 625.38, 625.39, ICD9: 617A-G, 617X, and ICD10: N80.0–N80.9. Procedure codes were used to identify women who had undergone a laparoscopy/laparotomy within 6 months of their initial endometriosis report or hysterectomy at the first recording of endometriosis. Diagnosis of endometriosis has previously been validated in the inpatient portion of the NPR with a positive predictive value of 98%.[13, 15]

Statistical analysis

We calculated the prevalence odds ratio for SLE comparing those with to those without a history of endometriosis among women alive and living in Sweden as of December 31, 2011. This cross-sectional assessment did not account for whether endometriosis was identified before or after SLE.

We examined whether the median age of endometriosis diagnosis differed across time periods corresponding to potential changes in inpatient and outpatient surgical procedures. We then used conditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between endometriosis and SLE. In this primary analysis, only first-time endometriosis diagnoses occurring prior to SLE diagnosis were included. Age was dichotomized at age 50 as a proxy for menopausal status. Effect modification by age at SLE diagnosis was assessed with a likelihood ratio test comparing a model with the cross-product term between endometriosis and age with main effects only.

To account for potential misclassification and other concerns about how endometriosis was defined, we performed several sensitivity analyses. First, because outpatient visit data only became available in 2001, we restricted to inpatient diagnoses of endometriosis for the entire study period. We then also modified our definition of endometriosis: 1) limited to those who had undergone laparoscopy/laparotomy within six months of their initial endometriosis report and 2) among those diagnosed with endometriosis at the same time as a reported hysterectomy.

Results

In the cross-sectional analysis, 427 individuals had at least one discharge diagnosis of endometriosis recorded in the NPR during the study period (1964–2011), of whom 95 of

who were also diagnosed with SLE. As of December 31, 2011, the age-adjusted prevalence odds ratio was 1.49 (95% CI=1.18–1.89).

In the case-control analysis examining endometriosis prior to SLE diagnosis, 2834 cases of SLE and 14164 controls were identified. Eighty-one cases had a diagnosis of endometriosis prior to their SLE diagnosis and 290 controls were diagnosed prior to the index date (Table 1). The median age of cases at first observation with SLE was 48.7 years and median age of at first observation with endometriosis was 40.8 years. When examined by time periods corresponding to potential changes in inpatient and outpatient surgical procedures for endometriosis[15] the median age at endometriosis diagnosis was 39.5 prior to 1994, 43.9 between 1994 and 2000, and 42.1 from 2001 to 2011. The median time between endometriosis and SLE diagnosis was 14.2 years (range 43 days – 34.7 years), while among the controls the median time between endometriosis diagnosis and index date was 13.0 years (range 3 days – 37.1 years).

We observed a significant association between endometriosis diagnosis and subsequent SLE (OR=1.39; 95% CI=1.09–1.78) (Table 2). The association was similar when the endometriosis diagnosis was from inpatient care only (OR=1.37; 95% CI=1.06–1.76). The association was similar with wider confidence intervals when requiring a laparoscopy or laparotomy procedure code within six months of the endometriosis diagnosis (OR=1.33; 95% CI=0.84–2.12) (Table 2). The median age of endometriosis diagnosis among those with a laparoscopic surgery at the time of initial diagnosis was 32.8 years. The association increased when restricted to endometriosis diagnosed at the same time as hysterectomy (OR=2.26; 95% CI 1.47–3.46) (Table 2) where the median age at endometriosis diagnosis was 48.0 years.

When we stratified by age at SLE diagnosis, the association between endometriosis and SLE was similar comparing older age at SLE diagnosis to younger age (p interaction=0.72). Those diagnosed with SLE at 50 years or older had an OR=1.44 (95% CI=1.06–1.96), compared to those diagnosed at younger than 50 years (OR=1.33; 95% CI=0.88–2.01).

Discussion

In this large population-based case-control study, we observed a significant association between endometriosis and incident SLE. The association was similar in magnitude among women who had a laparoscopy or laparotomy at the time of endometriosis diagnosis and did not differ by age at SLE diagnosis. The association was strongest among women who had a hysterectomy at the time of endometriosis, which may represent more severe endometriosis.

SLE and endometriosis share overall general dysregulation of the immune response indicated by altered immune surveillance, heightened humoral immune response and elevated levels of inflammatory cytokines.[6, 8] Endometriosis may be caused by an abnormal immune response that influences a woman’s susceptibility to the extra-uterine growth of endometrial tissue. This underlying immune dysfunction may also put individuals at risk for systemic autoimmune inflammatory disease later in life or endometriosis itself may trigger an immunologic response that is relevant to SLE development.

To our knowledge, only one retrospective case-control study and two prospective cohort studies have examined the association between endometriosis and SLE risk. In a relatively small hospital based case-control study, Matorras et al. observed no association in SLE prevalence among cases with histologically-confirmed endometriosis compared to controls without endometriosis, but these estimates were based on only three individuals with SLE.[10] Nielsen, et al. identified women with endometriosis using the Danish Hospital Discharge Register (1977–2007), which included outpatient data from 1995, and followed them for diagnosis with SLE. They reported a standardized incidence ratio (SIR) of 1.6 (95% CI=1.2–2.1) for the association between a discharge diagnosis code for endometriosis and a subsequent discharge diagnosis code for SLE.[12] Similar to our results, when they restricted to laparoscopy or laparotomy confirmed endometriosis, the association was considerably attenuated and no longer significant (SIR=1.1; CI=0.6–2.1), however, the attenuation we observed in our study was less extreme. Most recently, the Nurses' Health Study II (NHS II) reported a two-fold increased risk of SLE in women with laparoscopically-confirmed endometriosis (HR=2.03; 95% CI=1.17–3.51). The NHS II differed from our study in that endometriosis and laparoscopic confirmation were self-reported and if women reported endometriosis at the same time as reporting a hysterectomy they were excluded.[16]

The identification and classification of endometriosis was a challenge in the present study. The majority of the study period relied on the inpatient register, spanning more than 40 years, during which clinical and diagnostic procedures have evolved. Day surgeries have only been included in the NPR since 1997 therefore laparoscopic surgery not requiring an inpatient stay prior to 1997 would be missed in this study. Endometriosis identified through the inpatient portion of the NPR during the time when the outpatient surgery was becoming more common may therefore represent more severe endometriosis and older patients.[15] We observed some evidence of this as median age at endometriosis diagnosis increased after 1994 among our study population, potentially due to incomplete coverage of the outpatient and day surgery registers during the later time period. Furthermore, hysterectomy is considered a treatment for severe endometriosis, which may explain the stronger association observed when requiring endometriosis be diagnosed concurrent with hysterectomy. While misclassification of endometriosis may have affected our study it is likely non-differential. Using ICD codes to identify endometriosis has been validated[13, 15] and results were similar when using a stricter definition requiring a laparoscopy, although with lower power.

Both endometriosis and SLE are diseases that tend to onset months to years before their clinical diagnosis. Thus a limitation of any study examining the association between them will be the inability to confirm the temporal relationship. In this study we calculated the prevalence odds ratio, which makes no temporal assumptions. Our results are similar to the NHS II study where regardless of whether endometriosis was examined as the exposure or outcome, a positive association was noted with SLE.[11] In addition, similar to the NHS II, our study population was primarily Caucasian. If the association between endometriosis and SLE differs by race/ethnicity our results would not be generalizable to non-Caucasian populations.

Strengths of our study include a population-based design with substantial follow-up time, prospectively collected data, validated endometriosis diagnostic codes,[13, 15] and an SLE definition based on more than one clinical visit reducing the likelihood of misclassification.[2]

In conclusion, our findings suggest an association between endometriosis and SLE. Endometriosis may be a risk factor for, or share a common cause with, SLE development. Future prospective studies with extended follow-up that address both the timing and severity of endometriosis diagnosis will be necessary to clarify this association.

Acknowledgments

Funding: EVA and JFS are partly supported by the Strategic Research Program in Epidemiology at Karolinska Institutet. JFS is also supported by the NIH NIAMS K01-AR06687801. HRH is partly supported by the Swedish Cancer Foundation.

References

1. Masi A, Kaslow R. Sex effects in systemic lupus erythematosus: a clue to pathogenesis. Arthritis Rheum. 1978; 21:480–484. [PubMed: 656163]
2. Simard JF, Sjöwall C, Rönnblom L, Jönsen A, Svenungsson E. Systemic Lupus Erythematosus Prevalence in Sweden in 2010: What Do National Registers Say? Arthritis Care Res. 2014; 66:1710–1717.
3. Danchenko N, Satia J, Anthony M. Epidemiology of systemic lupus erythematosus: a comparision of worldwide disease burden. Lupus. 2006; 15:308–318. [PubMed: 16761508]
4. Missmer SA, Cramer DW. The epidemiology of endometriosis. Obstet Gynecol Clin North Am. 2003; 30:1–19. [PubMed: 12699255]
5. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. Fertil Steril. 2001; 75:1–10. [PubMed: 11163805]
6. Nothnick WB. Treating endometriosis as an autoimmune disease. Fertil Steril. 2001; 76:223–231. [PubMed: 11476764]
7. Pasoto SG, Abrao MS, Viana VST, Bueno C, Leon EP, Bonfa E. Endometriosis and Systemic Lupus Erythematosus: A Comparative Evaluation of Clinical Manifestations and Serological Autoimmune Phenomena. Am J Reprod Immunol. 2005; 53:85–93. [PubMed: 15790342]
8. Tedeschi SK, Bermas B, Costenbader KH. Sexual disparities in the incidence and course of SLE and RA. Clin Immunol. 2013; 149:211–218. [PubMed: 23578823]
9. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. Hum Reprod. 2002; 17:2715–2724. [PubMed: 12351553]
10. Matorras R, Ocerin I, Unamuno M, et al. Prevalence of endometriosis in women with systemic lupus erythematosus and Sjögren's syndrome. Lupus. 2007; 16:736–740. [PubMed: 17728368]
11. Harris H, Costenbader K, Mu F, et al. Endometriosis and the risks of systemic lupus erythematosus and rheumatoid arthritis in the Nurses' Health Study II. Ann Rheum Dis. 2015
12. Nielsen NM, Jørgensen KT, Pedersen BV, Rostgaard K, Frisch M. The co-occurrence of endometriosis with multiple sclerosis, systemic lupus erythematosus and Sjögren syndrome. Hum Reprod. 2011; 26:1555–1559. [PubMed: 21471158]
13. Ludvigsson J, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011; 11:450. [PubMed: 21658213]
14. Socialstyrelsen. , editor. Kodningskvalitet i patientregistret. 2013.
15. Melin A, Sparén P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. Hum Reprod. 2006; 21:1237–1242. [PubMed: 16431901]

16. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of Laparoscopically Confirmed Endometriosis by Demographic, Anthropometric, and Lifestyle Factors. Am J Epidemiol. 2004; 160:784–796. [PubMed: 15466501]

Table 1

Characteristics of systemic lupus erythematosus (SLE) cases and matched controls

	SLE cases	Controls
N	2834	14164
Age at SLE diagnosis/Index date (years), mean (std dev)	48.8 (17.6)	48.8 (17.6)
Year of SLE diagnosis, median	2005	n/a
History of endometriosis diagnosis, n	81	290
Age at endometriosis diagnosis (years), mean (std dev)	41.2 (10.3)	40.0 (10.1)
Time between endometriosis diagnosis and SLE diagnosis/index date, mean (std dev)	14.2 (8.6)	14.1 (8.9)

Table 2

Odds ratios and 95% confidence intervals of systemic lupus erythematosus (SLE) by endometriosis history among 2,834 SLE cases and 14,164 matched controls, Sweden, 1964–2011

Endometriosis definition	SLE cases with endometriosis	Controls with endometriosis	OR (95% CI)
Any first-time endometriosis diagnosis prior to SLE	81	290	1.39 (1.09–1.78)
Laparoscopy/laparotomy at time of endometriosis diagnosis	22	82	1.33 (0.84–2.12)
Hysterectomy at time of endometriosis diagnosis	28	59	2.26 (1.47–3.46)