

# Increased risk of endometriosis in patients with endometritis — a nationwide cohort study involving 84,150 individuals

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## ABSTRACT

**Objectives:** To evaluate the incidence of endometriosis among endometritis patients and its association with confounding comorbidities.

**Material and methods:** A population-based, retrospective cohort study of women aged between 20 to 55 years, who were newly diagnosed with endometritis between 2000 to 2013. A total of 16,830 endometritis patients and 67,230 non-endometritis individuals were enrolled by accessing data from the National Health Insurance Research Database of Taiwan. The comorbidities accessed were uterine leiomyoma, rheumatoid arthritis, ovarian cancer, infertility and allergic diseases.

**Results:** The mean follow-up period was 9.15 years for the non-endometritis cohort and 9.13 years for the endometritis cohort. There were significantly higher percentages of uterine leiomyoma, rheumatoid arthritis, infertility, ovarian cancer and allergic diseases in the endometritis cohort than in the non-endometritis cohort. Patients with endometritis had a 1.5-fold increased risk of their condition advancing to endometriosis (HR 1.58, 95% CI 1.48–1.68).

**Conclusions:** Our results suggest that patients with endometritis exhibited a positive correlation in developing endometriosis.

**Key words:** endometritis; inflammation; microbial infection; endometriosis

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## INTRODUCTION

Endometriosis is defined by the presence of endometrial epithelial and stromal tissue outside the uterine cavity. It is not considered a malignant disease, but it can lead to common symptoms such as dysmenorrhea, dyspareunia, pelvic pain, and reduced fertility. About 10% of all menstruating women have endometriosis [1, 2].

The processes associated with the pathogenesis of endometriosis remain undetermined. Currently, the most agreed upon hypothesis is that of retrograde menstruation, through which endometrial tissues flow back through the fallopian tubes into the peritoneal cavity, where they attach and

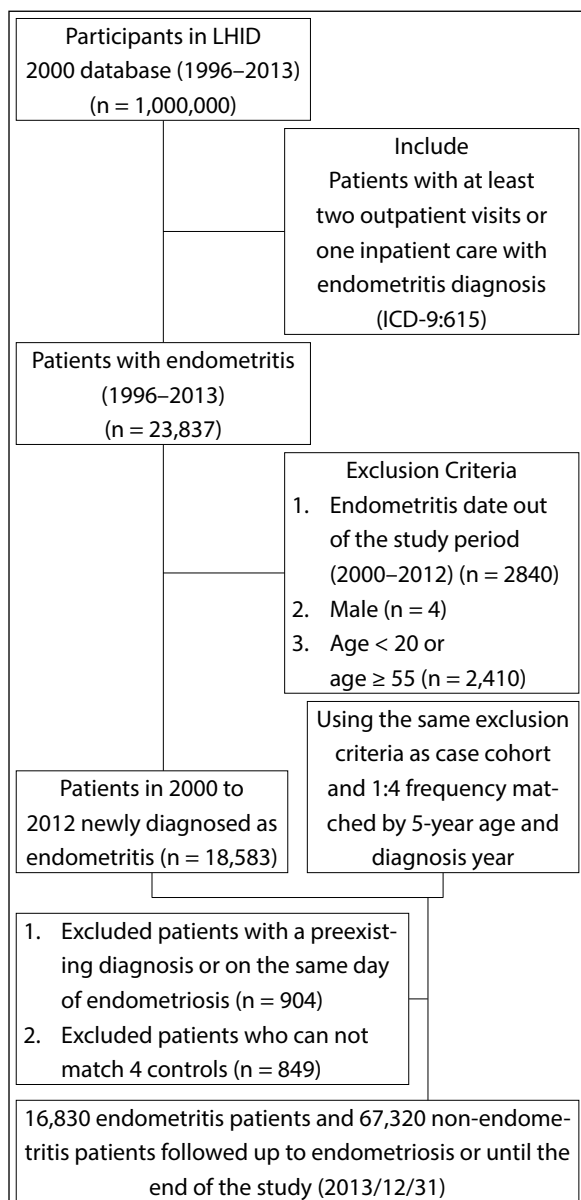
develop to form pelvic endometriosis [3]. It should be noted that about 90% of women exhibit retrograde menstruation; however, in only 6–10% of them is endometriosis established [1, 4]. Therefore, retrograde menstruation can only be considered as a risk factor, and not an exact pathogenic factor. Variations in the genetic, biochemical, and physiological properties of the ovaries, rectovaginal septum, and peritoneum mean that endometriosis may result from diverse circumstances.

Endometritis is characterized as a microbial infectious and inflammatory disease. Bacteria commonly detected in patients with endometritis include streptococcus species, *Escherichia coli*, *Enterococcus faecalis*, staphylococcus

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**Figure 1.** Subject selection process

species, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, proteus species, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Gardnerella vaginalis*, and *Corynebacterium* [5]. Yeasts such as *Saccharomyces cerevisiae* and candida species are also present in the endometrium of patients with endometritis [5, 6]. Changes in the distribution of lactobacilli species in the female reproductive tract may represent another risk factor for endometritis [7, 8].

### Objectives

The aim of this study was to explore the possible association between endometritis and endometriosis. We analyzed data from the National Health Insurance Research Database (NHIRD) of Taiwan through a retrospective cohort

study to demonstrate whether patients with endometritis have a higher risk of endometriosis.

## MATERIAL AND METHODS

### Data source

We used the Longitudinal Health Insurance Database 2000 which randomly selected one million participants from the NHIRD of Taiwan and made sure that the age and sex distributions were comparable to those of the Taiwanese population. The identity of each participant was protected by encrypting the identification number before the data were released. All history diagnoses in the database were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115-R3).

### Study population

We enrolled 18,583 female patients who were aged between 20 and 55 years and newly diagnosed as having endometritis (ICD-9-CM 615) from 2000 to 2012; the diagnosis date was defined as the index date. The non-endometritis cohort was matched 1:4 by age (in 5-year bands) and index year. We excluded patients with a pre-existing diagnosis of endometriosis (ICD-9-CM 615.0–615.9) and those who could not match 4 controls. The same exclusion criteria were used in the non-endometritis cohort as in the endometritis cohort. A total of 16,830 endometritis patients and 67,320 non-endometritis patients were followed up to development of endometriosis, death, or until the end of the study (2013/12/31), whichever came first. We collected both demographic characteristics and endometriosis comorbidity history as potential confounders. The comorbidities included uterine leiomyoma (ICD-9-CM 218), rheumatoid arthritis (ICD-9-CM 714.0), ovarian cancer (ICD-9-CM 183.0), multiple sclerosis (ICD-9-CM 340), infertility (ICD-9-CM 628), cervical cancer (ICD-9-CM 180), breast cancer (ICD-9-CM 174), autoimmune diseases (ICD-9-CM 710.0), and allergic diseases (ICD-9-CM 477) (Fig. 1).

### Statistical analysis

Distribution of age, sex, and comorbidities between the endometritis cohort and non-endometritis cohort were described in terms of numbers and percentages and tested using the Chi-square test and T test. The hazard ratio (HR) and 95% confidence interval (95% CI) were estimated using the Cox proportional hazard model for evaluating the association between endometritis and endometriosis. The multivariate Cox proportional hazard model was used to estimate the HRs after adjustment for age, gender, and comorbidities, which were notably different in the univariate model or with/without comorbidity. Analysis of stratification by age and comorbidity was performed to explore the association between endometri-

**Table 1. Baseline characteristics of patients**

	Endometritis				p-value*
	No		Yes		
	(n = 67,320)		(n = 16,830)		
	n	%	n	%	
<b>Age</b>					> 0.99
20–25	12736	18.92	3184	18.92	
25–30	13392	19.89	3348	19.89	
30–35	11728	17.42	2932	17.42	
35–40	10448	15.52	2612	15.52	
40–45	9028	13.41	2257	13.41	
45–50	6532	9.7	1633	9.7	
50–55	3456	5.13	864	5.13	
Mean (SD)	34.2 (9.1)		34.1 (9.0)		0.467a
<b>Childbirth</b>					< 0.001
No	51747	76.87	11289	67.08	
Yes	15573	23.13	5541	32.92	
<b>Comorbidity</b>					
Uterine leiomyoma	2544	3.78	1104	6.56	< 0.001
Rheumatoid arthritis	416	0.62	140	0.83	0.002
Ovarian cancer	40	0.06	2	0.01	0.014
Multiple sclerosis	20	0.03	7	0.04	0.441
Infertility	1539	2.29	698	4.15	< 0.001
Cervical cancer	130	0.19	33	0.2	0.938
Breast cancer	202	0.3	52	0.31	0.85
Autoimmune	263	0.39	72	0.43	0.494
Allergic disease	10138	15.06	2978	17.69	< 0.001

\*Chi-square test; at-test

tis and endometriosis among specific populations. Cumulative incidence curves for endometriosis were computed using the Kaplan–Meier method, and differences between the endometritis cohort and the non-endometritis cohort were tested using a log-rank test. All statistical analyses were performed using Stata Statistical Software version 14 (StataCorp, College Station, TX, USA). Statistical significance was determined using two-tailed tests ( $p < 0.05$ ).

### RESULTS

The mean ages were 34.2 years and 34.1 years in the non-endometritis cohort and endometritis cohort, respectively. There were significantly higher percentages of uterine leiomyoma, rheumatoid arthritis, infertility, and allergic diseases in the endometritis cohort than in the non-endometritis cohort. The endometritis cohort also had a considerably lower percentage of ovarian cancer patients than the non-endometritis cohort (Tab. 1).

The mean follow-up period was 9.15 years for the non-endometritis cohort and 9.13 years for the endome-

tritis cohort ( $p = 0.479$ ). Associations of endometritis and other risk factors with endometriosis are shown in Table 2. Compared to non-endometritis patients, patients with endometritis had a 1.58-fold adjusted HR of development of endometriosis after adjustment for age and with/without comorbidity (model 1). Compared to patients aged 20–25 years, there were a 1.38-, 1.58-, 1.91-, and 1.59-fold risks of development of endometriosis in patients aged 25–30, 30–35, 35–40, and 40–45 years, respectively. However, patients aged 45–50 and 50–55 years had a significantly lower risk, with adjusted HRs of 0.79 and 0.14, respectively.

Compared to patients without comorbidity, patients with any one of the comorbidities had a 1.59-fold risk of developing endometriosis. After adjustment for age and the comorbidities of uterine leiomyoma, rheumatoid arthritis, infertility, and allergic diseases (model 2), patients with endometritis had a notably higher risk of endometriosis than non-endometritis patients [adjusted HR (95% CI) 1.55 (1.45–1.65)]. The association between age and endometriosis in model 2 was similar to that in model 1. Compared to

**Table 2. Incidence and hazard ratio of endometriosis for endometritis patients compared to controls**

				Crude Model 1 <sup>a</sup>		Adjusted			
	Event	PY	IR	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Endometritis									
No	3345	615940	5.43	Reference		Reference		Reference	
Yes	1348	153604	8.78	1.62 (1.52–1.72)	< 0.001	1.60 (1.50–1.70)	< 0.001	1.57 (1.47–1.67)	< 0.001
Age									
20–25	663	146805	4.52	Reference		Reference		Reference	
25–30	938	147361	6.37	1.41 (1.27–1.55)	< 0.001	1.42 (1.29–1.57)	< 0.001	1.41 (1.28–1.56)	< 0.001
30–35	960	132994	7.22	1.60 (1.45–1.77)	< 0.001	1.65 (1.49–1.83)	< 0.001	1.60 (1.45–1.78)	< 0.001
35–40	1056	120746	8.75	1.94 (1.76–2.14)	< 0.001	1.96 (1.78–2.16)	< 0.001	1.85 (1.68–2.04)	< 0.001
40–45	774	106683	7.26	1.61 (1.45–1.79)	< 0.001	1.58 (1.43–1.75)	< 0.001	1.43 (1.29–1.59)	< 0.001
45–50	277	76673	3.61	0.80 (0.70–0.92)	0.002	0.77 (0.67–0.89)	< 0.001	0.69 (0.60–0.80)	< 0.001
50–55	25	38282	0.65	0.14 (0.10–0.22)	< 0.001	0.14 (0.09–0.20)	< 0.001	0.12 (0.08–0.18)	< 0.001
Childbirth									
No	3458	584540	5.92	Reference		Reference		Reference	
Yes	1235	185003	6.68	1.12 (1.05–1.20)	0.001	0.87 (0.81–0.93)	< 0.001	0.87 (0.81–0.93)	< 0.001
Comorbidity									
No	3444	630892	5.46	Reference		Reference			
Yes <sup>c</sup>	1249	138652	9.01	1.63 (1.52–1.73)	< 0.001	1.60 (1.50–1.71)	< 0.001		
Uterine leiomyoma									
No	4267	740818	5.76	Reference				Reference	
Yes	426	28726	14.83	2.55 (2.31–2.81)	< 0.001			2.67 (2.40–2.96)	< 0.001
Rheumatoid arthritis									
No	4661	765068	6.09	Reference				Reference	
Yes	32	4476	7.15	1.16 (0.82–1.64)	0.403			1.13 (0.79–1.59)	0.507
Ovarian cancer									
No	4692	769246	6.10	Reference				Reference	
Yes	1	298	3.36	0.54 (0.08–3.84)	0.539			0.43 (0.06–3.09)	0.405
Infertility									
No	4500	752153	5.98	Reference				Reference	
Yes	193	17391	11.10	1.83 (1.59–2.11)	< 0.001			1.44 (1.24–1.66)	< 0.001
Allergic disease									
No	3930	670894	5.86	Reference				Reference	
Yes	763	98650	7.73	1.30 (1.20–1.40)	< 0.001			1.24 (1.15–1.35)	< 0.001

Event: No, patients with endometriosis; PY — person-years; IR — incidence rate, per 1,000-person years; HR — hazard ratio; CI — confidence interval

<sup>a</sup>Adjusted for age and with/without comorbidity

<sup>b</sup>Adjusted for age, uterine leiomyoma, rheumatoid arthritis, ovarian cancer, infertility, and allergic disease

<sup>c</sup>Patients with any one of the comorbidities were classified as the comorbidity group

patients without rheumatoid arthritis, infertility and allergic diseases, patients with these diseases exhibited positive association with the development of endometriosis.

Analysis of stratification by age and comorbidity are shown in Table 3. Except for patients older than 50 years, there were significantly higher risks of endometriosis in patients with endometriosis than in non-endometriosis patients in every age stratification (adjusted HR 1.33–2.16). Among

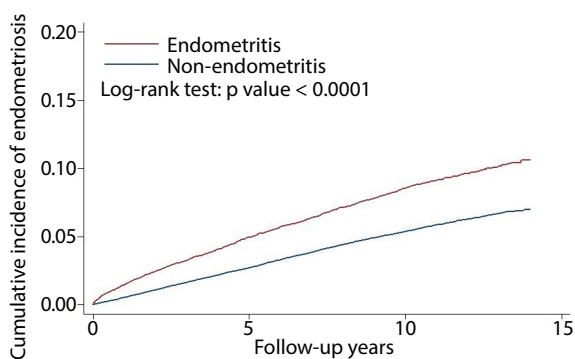
patients without any one of the comorbidities, patients with endometriosis had a 1.55-fold risk of endometriosis compared to non-endometriosis patients. Among patients with any one of the comorbidities, patients with endometriosis had a 1.64-fold risk of endometriosis compared to non-endometriosis patients. Endometriosis was significantly associated with endometriosis among patients with uterine leiomyoma [adjusted HR (95% CI) 1.63 (1.34–1.98)], infertility [adjusted

**Table 3.** Incidence and hazard ratio of endometriosis for endometritis patients compared to controls stratified by age, childbirth, and comorbidities

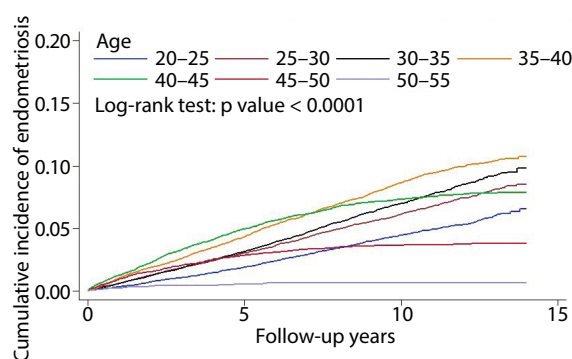
	Crude		Adjusted	
	HR (95% CI)	p-value	HR (95% CI) <sup>a</sup>	p-value
Overall				
Age				
20–25	1.35 (1.13–1.60)	0.001	1.38 (1.15–1.65)	< 0.001
25–30	1.57 (1.36–1.81)	< 0.001	1.57 (1.36–1.81)	< 0.001
30–35	1.58 (1.37–1.82)	< 0.001	1.56 (1.35–1.79)	< 0.001
35–40	1.51 (1.32–1.73)	< 0.001	1.44 (1.26–1.66)	< 0.001
40–45	1.87 (1.61–2.18)	< 0.001	1.77 (1.52–2.06)	< 0.001
45–50	2.37 (1.86–3.03)	< 0.001	2.16 (1.69–2.76)	< 0.001
50–55	1.88 (0.81–4.36)	0.14	1.77 (0.76–4.12)	0.188
Childbirth				
No	1.72 (1.59–1.85)	< 0.001	1.64 (1.52–1.77) <sup>a</sup>	< 0.001
Yes	1.36 (1.21–1.54)	< 0.001	1.42 (1.26–1.60) <sup>a</sup>	< 0.001
Uterine leiomyoma				
No	1.55 (1.45–1.66)	< 0.001	1.56 (1.45–1.66)	< 0.001
Yes	1.69 (1.39–2.04)	< 0.001	1.63 (1.34–1.98)	< 0.001
Rheumatoid arthritis				
No	1.62 (1.52–1.73)	< 0.001	1.57 (1.47–1.68)	< 0.001
Yes	1.04 (0.47–2.32)	0.919	1.12 (0.49–2.55)	0.783
Ovarian cancer				
No	1.62 (1.52–1.72)	< 0.001	1.57 (1.47–1.67)	< 0.001
Yes	–	–	–	–
Infertility				
No	1.60 (1.50–1.71)	< 0.001	1.56 (1.46–1.67)	< 0.001
Yes	1.62 (1.22–2.16)	0.001	1.56 (1.17–2.08)	0.003
Allergic disease				
No	1.62 (1.51–1.74)	< 0.001	1.57 (1.47–1.69)	< 0.001
Yes	1.55 (1.33–1.81)	< 0.001	1.55 (1.33–1.81)	< 0.001

HR — hazard ratio; CI — confidence interval; <sup>a</sup>Adjusted for other covariates

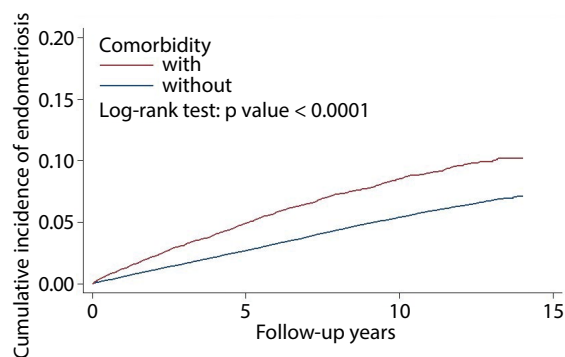
HR (95% CI) 1.58 (1.18–2.11)], and allergic diseases [adjusted HR (95% CI) 1.50 (1.29–1.75)].



**Figure 2.** Cumulative incidence curve of endometriosis between endometritis patients and non-endometritis patients

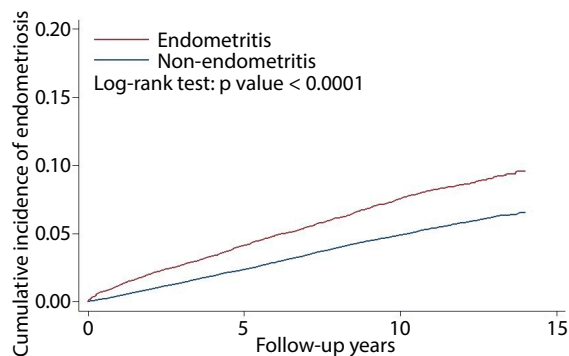


**Figure 3.** Cumulative incidence curve of endometriosis in each age group

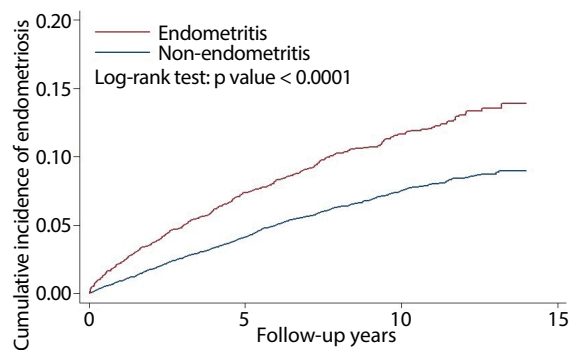


**Figure 4.** Cumulative incidence curve of endometriosis in patients with comorbidity and without comorbidity

During the whole follow-up period there was a significantly higher cumulative incidence of endometriosis for patients with endometritis than patients without endometritis (log-rank  $p < 0.0001$ ) (Fig. 2). There was a considerably different cumulative incidence of endometriosis in the different age stratifications (log-rank  $p < 0.0001$ ) (Fig. 3). Patients with comorbidity had significantly higher cumulative incidences of endometriosis than patients without comorbidity (log-rank  $p < 0.0001$ ) (Fig. 4). Among patients with any one of the comorbidities, patients with endometritis had



**Figure 5.** Cumulative incidence curve of endometriitis between patients with endometriitis and non-endometriitis, among patients without any of the comorbidities listed in Table 2



**Figure 6.** Cumulative incidence curve of endometriitis between patients with endometriitis and non-endometriitis, among patients with any one of the comorbidities listed in Table 2

particularly higher cumulative incidences of endometriitis than non-endometriitis patients (log-rank  $p < 0.0001$ ) (Fig. 5). Among patients without comorbidity, those with endometriitis also had considerably higher cumulative incidences of endometriitis than non-endometriitis patients (log-rank  $p < 0.0001$ ) (Fig. 6).

## DISCUSSION

This nationwide retrospective cohort study revealed that patients with endometriitis had a 1.5-fold increase in the risk of developing endometriitis, compared with women without endometriitis. Uterine leiomyoma, infertility, rheumatoid arthritis, and allergic diseases exhibit higher incidences in women with endometriitis. It is not known why the frequency of ovarian cancer was lower in patients with endometriitis. Although we found a significant association of endometriitis with endometriitis, this association should be viewed with caution: the association between endometriitis and the incidence of endometriitis may result from a causal connection, which may indicate that endometriitis might incline women to the development of endometriitis. In addition, there might be a third confounding variable, which implies that there is an overlapping risk factor or pathological process which alters the development of endometriitis and endometriitis.

Local chronic inflammation has been suggested as a risk factor for the development of endometriitis [9–11]. Increasing levels of monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-8, IL-6, IL-1 $\beta$ , and tumor necrosis factor (TNF)- $\alpha$  enhance the implantation of ectopic endometrial tissue [12–14]. In addition, the inflammatory cytokines and chemokines secreted by ectopic endometriotic tissues attract macrophages to the peritoneal cavity, which enhances inflammation [15]. The number of activated macrophages in the peritoneal cavity of patients with endometriitis is elevated [16]. It is possible that inflammation in the peritoneal cavity may be related to infections [17], with in-

creased production of inflammatory cytokines through bacterial infection further enhancing the development of endometriitis [18]. The induction of inflammation may be related to infections in the upper reproductive tract, lower reproductive tract, or pelvis [17, 19, 20]. Bacterial colonization increases the levels of inflammatory mediators, which promote development of endometriitis [18].

Imbalance and inflammatory reactions are two potential factors linked with endometriitis and endometriitis. In Rhesus monkeys with endometriitis, the levels of intestinal microflora were changed, with these monkeys showing lower amounts of lactobacilli but higher concentrations of gram-negative bacteria [21]. It was found that the number of *E. coli* in the menstrual blood of patients with endometriitis was elevated. The endotoxin levels in menstrual and peritoneal fluid were also elevated [22]. Bacterial endotoxins could promote inflammation by inducing the expression of inflammatory cytokines and chemokines [23]. The inflammatory cytokines and chemokines could attract macrophages, which can be activated by endotoxins through toll-like receptor 4 (TLR4). Activated macrophages would further sustain/amplify inflammatory reactions [23]. The bacteria present in the uterine cavity and peritoneal fluid might induce the TLR4-mediated growth of endometrial lesions [24]. In cystic fluid of patients with ovarian endometriitis, presence of the Streptococcaceae and Staphylococcaceae families is significantly elevated [25]. The imbalance of endometrial microbiota in the uterine cavity could influence the balance of immune responses which increase inflammation, thus promoting the pathogenesis of endometriitis [26].

The varied concentrations of estradiol and progesterone during the menstrual cycle have significant consequences for the balance of the microbiota, which may promote infections. Estradiol encourages the infiltration of macrophages into the endometrium to reduce the risk of bacterial infections [27, 28]. A high concentration of progesterone reduces uterus lymphocyte infiltration, which may increase the risk



of bacterial infections [27, 28]. The growth of eutopic and ectopic endometriotic tissues could be enhanced by treatment with bacterial endotoxins. In endometrial stromal cells and macrophages treated with bacterial endotoxins, levels of hepatocyte growth factor, vascular endothelial cell growth factor (VEGF), IL-6, IL-8, and TNF- $\alpha$  were elevated [29, 30]. The expression of VEGF is important to sustain the growth of eutopic and ectopic endometriotic tissues [31, 32]. Treating endometrial stromal cells with combined estradiol and lipopolysaccharide significantly increased the proliferation rate [33]. Moreover, the expression levels of IL-6 and TNF- $\alpha$  were higher in macrophages isolated from patients with endometriosis [34]. These findings suggest that estradiol and progesterone levels influence the risk of bacterial infection in the female reproductive tract and promote the expansion of ectopic and eutopic endometriotic tissues to encourage endometriosis.

There are various limitations of this study. First, this is a retrospective cohort study, which makes it hard to define the causation of the two associated diseases. Secondly, we used insurance claims data to select our study population by ICD coding, which could have resulted in misclassification bias. Thirdly, we could not ascertain reasons why participants were lost to follow-up. It should also be noted that patients with endometritis would probably have a higher chance of being diagnosed with endometriosis since they may receive more medical attention to the female reproductive tract than those without the disease. In addition to age and the comorbidities that were adjusted for, there are still some confounding variables. Body mass index (BMI), number of births, use of birth control pills or devices, and length and interval of menstrual cycle were not analyzed in this study. A more detailed prospective cohort study should be conducted to understand the correlation between endometritis and endometriosis better.

In conclusion, the results of this study indicate that patients with endometritis are at higher risk of developing endometriosis compared with patients without endometritis. This indicates that either endometritis predisposes to endometriosis or that some specific pathogenic factors influence the development of both conditions. Although the exact pathological factors are not yet known, these findings make a meaningful contribution to the diagnosis and management of patients with endometritis.

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