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Research report

Risk of developing major depression and anxiety disorders among women with endometriosis: A longitudinal follow-up study



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ABSTRACT

Backgrounds: Several cross-sectional studies suggested a link between endometriosis and mood disorders. However, the temporal association between endometriosis and mood disorders (depression and anxiety disorders) is still unclear.

Methods: Using the Taiwan National Health Insurance Research Database, 10,439 women with endometriosis and 10,439 (1:1) age-/sex-matched controls between 1998 and 2009 were enrolled, and followed up to the end of 2011. Those who developed depression or anxiety disorders during the follow-up were identified.

Results: Women with endometriosis had an increased risk of developing major depression (hazard ratio [HR]: 1.56, 95% confidence interval [CI]:1.24–1.97), any depressive disorder (HR: 1.44, 95% CI: 1.25–1.65), and anxiety disorders (HR: 1.44, 95% CI: 1.22–1.70) in later life compared to those without endometriosis. Stratified by age group, women with endometriosis aged < 40 years and those aged ≥40 years were both prone to developing major depression (HR: 1.52, 95% CI: 1.15–1.99; HR: 1.69, 95% CI: 1.09–2.62), any depressive disorder (HR: 1.43, 95% CI: 1.21–1.69; HR: 1.45, 95% CI: 1.13–1.56), and anxiety disorders (HR: 1.39, 95% CI: 1.14–1.71; HR: 1.53, 95% CI: 1.15–2.04).

Limitation: the incidence of depression and anxiety disorders may be underestimated since only those who sought medical consultation and help would be enrolled in our study.

Conclusion: Endometriosis was associated with an elevated likelihood of developing depression and anxiety disorders. Further studies may be required to investigate the underlying pathophysiology between endometriosis and both depression and anxiety disorders.

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1. Introduction

Several previous studies have reported on the relationship between endometriosis and depression, as well as anxiety disorders, but the findings were inconsistent (Low, Edelmann et al., 1993; Waller and Shaw, 1995; Siedentopf, Tariverdian et al., 2008). In 1993, Low et al. reported that women with endometriosis had a higher rate of neuroticism and anxiety symptoms, but not depressive symptoms compared to healthy women (Low et al., 1993). In 1995, Waller et al. determined that there was an elevated level

of depressive symptoms among women with endometriosis, but no significant difference in anxiety symptoms between women with or without endometriosis (Waller and Shaw, 1995). In addition, those previous studies were cross-sectional in design, and did not investigate the temporal association between endometriosis and depression and anxiety disorders.

In our study, using the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal study design, we investigated the temporal association between endometriosis and depression or anxiety disorders.

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Table 1Demographic data of the women with endometriosis and the control group.

| | Women with endometriosis ($n = 10,439$) | Controls (n=10,439) | <i>p</i> -Value |
|---|---|---------------------|-----------------|
| Age at enrollment (years, SD, n, %) | 35.88 (8.82) | 35.88 (8.82) | |
| < 40 years | 6798 (65.1) | 6798 (65.1) | |
| ≧40 years | 3641 (34.9) | 3641 (34.9) | |
| Sex (F, %) | 10439 (100) | 10439 (100) | |
| Major depression (n, 1000 person-years) | 185 (2.17) | 118 (1.38) | < 0.001 |
| Age at diagnosis (years, SD) | 40.16 (9.46) | 39.05 (8.90) | 0.309 |
| Duration between enrollment and diagnosis (years, SD) | 4.92 (3.45) | 4.97 (3.01) | 0.913 |
| Any depressive disorder (n, 1000 person-years) | 495 (5.94) | 343 (4.07) | < 0.001 |
| Age at diagnosis (years, SD) | 40.26 (9.49) | 39.82 (9.41) | 0.506 |
| Duration between enrollment and diagnosis (years, SD) | 4.71 (3.19) | 5.31 (3.20) | 0.008 |
| Anxiety disorder (n, 1000 person-years) | 347 (4.12) | 239 (2.82) | < 0.001 |
| Age at diagnosis (years, SD) | 41.63 (9.08) | 40.69 (9.47) | 0.228 |
| Duration between enrollment and diagnosis (years, SD) | 5.13 (3.45) | 5.52 (3.32) | 0.167 |
| Medical comorbidities $(n, \%)$ | , , | , , | |
| Hypertension | 927 (8.9) | 607 (5.8) | < 0.001 |
| Dyslipidemia | 696 (6.7) | 535 (5.1) | < 0.001 |
| Diabetes mellitus | 396 (3.8) | 310 (3.0) | 0.001 |
| Obesity | 58 (0.6) | 41 (0.4) | 0.107 |
| Cerebrovascular diseases | 108 (1.0) | 55 (0.5) | < 0.001 |
| Pelvic inflammatory disease | 7621 (73.0) | 7372 (70.6) | < 0.001 |
| Level of urbanization (n, %) | , | ` , | 0.002 |
| 1 (most urbanized) | 3959 (37.9) | 3826 (36.7) | |
| 2 | 3363 (32.2) | 3292 (31.5) | |
| 3 | 1550 (14.8) | 1595 (15.3) | |
| 4 | 1077 (10.3) | 1122 (10.7) | |
| 5 (most rural) | 490 (4.7) | 604 (5.8) | |
| Income-related insured amount | • , | . , | 0.143 |
| ≤ 15,840 NTD/month | 2395 (22.9) | 2361 (22.6) | |
| 15,841-25,000 NTD/month | 3756 (36.0) | 3892 (37.3) | |
| ≥ 25,001 NTD/month | 4288 (41.1) | 4186 (40.1) | |

SD: standard deviation; NTD: New Taiwan Dollar.

2. Methods

2.1. Data source

The Taiwan National Health Insurance (NHI) program was implemented in 1995 and offers comprehensive medical coverage for all residents of Taiwan. The National Health Research Institute (NHRI) is in charge of the entire insurance claims database, namely, the NHIRD, which consists of healthcare data from > 97% of the entire Taiwan population (http://www.nhi.gov.tw/). The NHRI audits and releases the NHIRD for use in health service studies. Now, only data before the end of 2011 are released. The diagnostic codes used in NHIRD were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Li et al., 2012; Chen et al., 2013a, 2013b; Shen et al., 2013; Chen et al., 2015).

2.2. Inclusion criteria for women with endometriosis and the control group

Women who were identified as having endometriosis (ICD-9-CM code: 617) diagnosed by gynecologists after an evaluation of the gynecological ultrasonography between January 1, 1998 and December 31, 2009, and who had no history of any psychiatric disorder (ICD-9-CM codes: 290–319) before enrollment, were included as the endometriosis cohort. The controls were randomly selected from the same database after eliminating the endometriosis cohort, those who had been given a diagnosis of endometriosis at any time, and those with any psychiatric disorder before enrollment. Each woman in the endometriosis cohort was matched on the basis of age, sex, and time of enrollment with an individual without endometriosis in a comparison cohort. Both the endometriosis and comparison cohorts were followed up to

December 31st, 2011 to determine if there had been any diagnoses of major depression (ICD-9-CM codes: 296.2X and 296.3X), any depressive disorder (ICD-9-CM codes: 296.2X, 296.3X, 300.4 and 311), or anxiety disorders (ICD-9-CM codes: 300.X except 300.3 and 300.4) given by board-certificated psychiatrists. We also assessed medical comorbidities at the enrollment and during the whole follow-up, including hypertension, dyslipidemia, diabetes mellitus, obesity, cerebrovascular diseases, and pelvic inflammatory disease in our study as confounding factors.

2.3. Statistical analysis

For between-group comparisons, the independent *t*-test was used for continuous variables and the Chi-square test for nominal variables, where appropriate. Multivariate Cox regression analyses were performed to investigate the hazard ratios (HR) with 95% confidence intervals (CI) of major depression, any depressive disorder, and anxiety disorders after adjusting for demographic data and medical comorbidities. A two-tailed *p*-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 21 software (SPSS Inc.) and Statistical Analysis Software (SAS) version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

In all, 10,439 women with endometriosis and 10,439 age-/sexmatched controls without endometriosis, with a mean age of 35.88 ± 8.82 years, were enrolled in our study (Table 1). Women with endometriosis had a higher incidence of developing major depression (2.17 vs. 1.38, 1000 person-years, p < 0.001), any depressive disorder (5.94 vs. 4.07, 1000 person-years, p < 0.001), and anxiety disorders (4.12 vs. 2.82, 1000 person-years, p < 0.001)

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