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Review Article

Women with endometriosis have higher comorbidities: Analysis of domestic data in Taiwan

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Abstract

Endometriosis, defined by the presence of viable extrauterine endometrial glands and stroma, can grow or bleed cyclically, and possesses characteristics including a destructive, invasive, and metastatic nature. Since endometriosis may result in pelvic inflammation, adhesion, chronic pain, and infertility, and can progress to biologically malignant tumors, it is a long-term major health issue in women of reproductive age. In this review, we analyze the Taiwan domestic research addressing associations between endometriosis and other diseases. Concerning malignant tumors, we identified four studies on the links between endometriosis and ovarian cancer, one on breast cancer, two on endometrial cancer, one on colorectal cancer, and one on other malignancies, as well as one on associations between endometriosis and irritable bowel syndrome, one on links with migraine headache, three on links with pelvic inflammatory diseases, four on links with infertility, four on links with obesity, four on links with chronic liver disease, four on links with rheumatoid arthritis, four on links with chronic renal disease, five on links with diabetes mellitus, and five on links with cardiovascular diseases (hypertension, hyperlipidemia, etc.). The data available to date support that women with endometriosis might be at risk of some chronic illnesses and certain malignancies, although we consider the evidence for some comorbidities to be of low quality, for example, the association between colon cancer and adenomyosis/endometriosis. We still believe that the risk of comorbidity might be higher in women with endometriosis than that we supposed before. More research is needed to determine whether women with endometriosis are really at risk of these comorbidities.

Keywords: comorbidity; endometriosis; Taiwan

1. Introduction

Endometriosis, one of the most common gynecologic disorders, is found in 1−30% of women during their reproductive years, based on the different diagnostic criteria, and sometimes occurs in postmenopausal women. It is found in 70−90% of women with pelvic pain symptoms.[1−3] Endometriosis remains an enigmatic disease and cause of pain, and can subsequently result in pelvic inflammation, adhesion, chronic pain, and

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infertility, and occasionally in malignant transformation.[4,5] Since endometriosis-associated morbidity shows a significant negative impact on women's quality of life, it contributes to a long-term major health issue. This study report addresses the associations between endometriosis and other diseases from the domestic source in Taiwan. The majority of the data are obtained from a large-scale population-based study—the National Health Insurance Research Database (NHIRD).[6,7]

2. Epidemiology

Epidemiologic studies may be helpful in defining populations at a high risk of endometriosis[1,3−5]; however, it is not easy to estimate the real incidence or prevalence of endometriosis precisely even when the gold-standard method, laparoscopy, is used. Variations may be influenced by the wide range of visual appearance of endometriosis and pathological confirmation, resulting in an unknown true prevalence or the real incidence of endometriosis. Hopton and Redwine[8] noted that the visual appearance of endometriosis is important because therapy begins with a surgeon identifying the disease, and any inaccurate identification of endometriosis can introduce selection bias and confound all conclusions, leading to incorrect concepts of epidemiology, natural history, disease origin, and treatment. In 1995, Chu and colleagues'[9] pioneered study of the prevalence of endometriosis in Taiwan showed a wide variation (5−42%) on the basis of different indications for 752 consecutive laparoscopic procedures. The prevalence of endometriosis was 42%, 33%, 25%, and 12%, respectively, in women indicated for pelvic adhesion, infertility, myoma, and sterilization; the researchers concluded that the overall prevalence of endometriosis in asymptomatic patients was 24.7%. This study was one of the earliest to investigate the prevalence of endometriosis in Taiwan. However, this study might overestimate or underestimate the prevalence of endometriosis in Taiwan. Since surgery is always applied in a certain type of population, for example, women with needs and indications, surgery itself might be one of the most significant confounding factors, contributing to the high possibility of selection bias. In addition, the "illusory tale of occult microscopic endometriosis" might underestimate the prevalence of endometriosis.[8] Endometriosis is sometimes truly invisible to the surgeon because it is too small to see.[8] In previous studies from Taiwan,[1,3−5] the prevalence of endometriosis also varied markedly. With different criteria applied for enrollment of patients with endometriosis, the prevalence might be different. A recent report by Lee et al[3] might be one of the best representatives. Their results showed that the prevalence of endometriosis during reproductive years could be up to 30.8% and as low as 1.5%.[3] The dramatic difference in the prevalence could be well explained by the different criteria applied in the study. Yang et al[1] showed that the estimated prevalence of women with endometriosis was 8.9% based on the NHIRD of Taiwan. However, only two-fifths of these women with a clinical diagnosis of endometriosis had a surgicopathological confirmation of their endometriosis, contributing to 3.7% of the prevalence rate,[3] which was significantly lower than the 5−10% rate found in literature reviews.[10]

3. Comorbidity of endometriosis

Previous research suggests that a comorbidity relationship exists between endometriosis and many functional and/or pathological diseases,[1,11,12] although the results of some studies were not consistent. For example, endometriosis was not associated with diabetes mellitus in one cross-sectional study,[13] and reports showed that women with endometriosis might have a lower body mass index and be less frequently obese[14,15]; however, domestic nationwide population-based studies showed that women with endometriosis seemed to have a tendency of being obese and a higher rate of diabetes mellitus.[4,5,11,12] One report showed 7.5% of women with diabetes mellitus in the endometriosis group compared with 5.8% in the nonendometriosis (control) group.[4] Another report found diabetes mellitus in 16% of women with endometriosis compared with that in 13% of women without endometriosis.[12] Besides a higher rate of diabetes mellitus in women with endometriosis, domestic data showed that Taiwanese women with endometriosis seemed to have a higher tendency to be obese.[11,12] This finding was different from those of previous reports from Western countries[14,15]—a discrepancy that needs further investigation. Of course, different criteria might have resulted in the different prevalence estimations, suggesting that sampling differences might have contributed to this finding.

A domestic study also found that a higher proportion of women with endometriosis had pelvic inflammatory disease (76.0% vs. 38.4%, endometriosis vs. controls, $p < 0.0001$), infertility (10.2% vs. 2.0%, $p < 0.0001$), cardiovascular diseases (4.9% vs. 3.5%, $p < 0.0001$), chronic liver disease (2.2% vs. 1.5%, $p = 0.0002$), and rheumatic disease (4.0% vs. 2.4%, $p < 0.0001$).[4] Similar findings were also reported from another domestic population-based study.[12] Wu et al[12] showed that women with endometriosis frequently had hypertension (24.0% vs. 20.6%, $p < 0.001$) and hyperlipidemia (28.7% vs. 23.0%, $p < 0.001$). Both hypertension and hyperlipidemia might be considered among the important components of cardiovascular diseases, suggesting that women with endometriosis are frequently associated with metabolic and cardiovascular problems. By contrast, a recent domestic study showed that women with endometriosis had a lower rate of hypertension than women without endometriosis. Although this study did not support a higher incidence of hypertension in women with endometriosis, the finding could be discarded, mainly because Yu et al's[11] study showed an unusually higher proportion of hypertension in their study population. More than one-half of their studied patients had hypertension status; this occurred in both cohort groups (50.7% of women with endometriosis and 55.7% of women without endometriosis, $p < 0.001$), suggesting that the study population might not really be representative of the general population. In addition, Yu et al[11] also showed an unusually higher proportion of study population with hyperlipidemia (53.9% and 44.9% in women with and without endometriosis, respectively; $p < 0.001$) and

diabetes mellitus (31.6% and 26.8% in women with and without endometriosis, respectively; $p < 0.001$) than that of the general population.

In addition to the higher comorbidity, women with endometriosis might also have a higher risk of other medical illnesses. For example, Wu et al[12] showed that women with endometriosis had a higher rate of depression (1.0% vs. 0.5%, $p < 0.001$) than those without it. Taken together, women with endometriosis should be given much attention for medical care, since they not only have endometriosis-related health problems, such as dysmenorrhea, menorrhagia, and chronic pelvic pain,[16–18] but also have many other medical illnesses.[10]

4. Risks for functional illnesses

As shown above, women with endometriosis often have other functional and/or pathological illnesses, which might worsen the established endometriosis-related diseases. A recent study showed that women with endometriosis had a higher risk of an attack of irritable bowel syndrome, with a hazard ratio (HR) of 1.79 and 95% confidence interval (CI) of 1.55–2.07 ($p < 0.001$).[12] It is interesting that the new onset of irritable bowel syndrome was especially higher within the 1st year of follow-up (HR 1.90, 95% CI 1.42–2.55, $p < 0.001$) in women with endometriosis.[12] In addition, the increased risk of irritable bowel syndrome could persist over 5 years.[12] Wu and colleagues[12] tried to explain the association between endometriosis and irritable bowel syndrome, and raised the hypothesis that both diseases might share similar risk and pathogenic factors, such as visceral hypersensitivity, similar inflammatory processes in the peritoneal cavity and gastrointestinal mucosa, and mast cell activation.

Endometriosis might be also associated with other painful diseases. For example, Dr Yang and colleagues[1] found that women with endometriosis were more likely to be diagnosed with migraine headache during the follow-up (HR 1.70, 95% CI 1.59–1.82, $p < 0.001$) than controls, and the diagnosis of migraine headache was often made after the diagnosis of endometriosis. Although the cause of comorbidity of endometriosis and migraine headache is unknown, a number of aspects of the pathophysiological pathways may explain the apparent relationship, including the activation of sensory nerve fibers within the endometriosis leading to central nervous system hypersensitivity, and activation and degranulation of mast cells within the endometriosis inducing the release of proinflammatory and allergic mediators, which sensitize primary afferent meningeal nociceptive neurons and cause hypersensitivity and hyperalgesia.[1]

5. Increased risk of malignant tumors in women with endometriosis

Women with endometriosis not only have the above-mentioned benign diseases or health problems, but also might be associated with much more severe health problems, for example, development of malignancy. As early as 1925, Sampson found a possible correlation between endometriosis and epithelial ovarian cancer (EOC), and soon after, many epidemiologic studies, systematic reviews, and meta-analyses indicated that women with endometriosis were at a risk of the development of EOC.[3] At least five domestic studies focusing on the correlation between endometriosis and EOC have been reported.[3–5,19,20]

The first study investigated the microenvironmental biomarkers of different types of ovarian cancers arising from endometriosis and found that these EOC displayed the following characteristics and appeared frequently: 56% for cyclooxygenase-2, 47% for AT-rich interactive domain 1A mutation (expressed by the loss of the corresponding protein BAF250a), 43% for estrogen receptor, 38% for hepatocyte nuclear factor-1 beta, 37% for loss of phosphatase and tensin homolog, and 13% for p53 mutation.[19] Furthermore, studying endometriosis-associated EOCs, such as clear cell carcinoma and endometrioid cell carcinoma, Lai et al[19] showed significantly high positive rates of estrogen receptor in endometrioid cell carcinoma (91%) and hepatocyte nuclear factor-1 beta in clear cell carcinoma (65%). In addition, they found that the staining results were similar between atypical endometriosis glandular epithelium and contiguous malignant portions, suggesting that endometriosis-associated EOCs may share common molecular and genetic features between precursors and cancers.[19]

The remaining four reports were epidemiologic studies.[3–5,20] The first attempt to evaluate a possible correlation between endometriosis and an increased risk of EOC in Taiwan appeared in 2014.[5] This study was performed using data from the NHIRD of Taiwan and showed that the EOC incidence rates of women with and without endometriosis were 3.31 per 10,000 person-years and 0.99 per 10,000 person-years, respectively, contributing to an adjusted HR of 3.28 (95% CI 1.37–7.85, $p < 0.01$).[5] This estimated three-fold increase of the risk of EOC in women with endometriosis was neither influenced by exposure time nor biased by surveillance.[5] Another study investigated the correlation between endometriosis and EOC.[4] Results showed that women with a new surgically confirmed endometriosis had a higher risk of EOC than those without.[4] The EOC incidence rate of women with endometriosis consistently increased with increasing age, with 4.99 per 10,000 person-years in women aged <30 years and 35.81 per 10,000 person-years in those aged more than 50 years, contributing to a risk of EOC constantly increasing with age.[4] The final study used data from the NHIRD to explain why the risk of EOC in women with endometriosis varied greatly; results showed that the risk of EOC in women with endometriosis might be more apparent than that previously estimated by either systematic reviews or meta-analyses, because data enrolled for analysis are often based on recalled endometriosis, which resulted in only a two-fold increase.[3]

Besides the well-known correlation between endometriosis and EOC, a correlation between endometriosis and other malignancies, especially gynecologic cancers,[11,20] has also been evaluated in Taiwan. One study showed that women with endometriosis had a significantly higher risk of endometrial cancer than those without during a 10-year follow-up, with an

adjusted HR of 2.83 (95% CI 1.49–5.35, $p < 0.01$).[11] The results of Yu et al's[11] study also showed that age at diagnosis of endometriosis might play an important role, since women with endometriosis who were younger than 40 years did not have an apparent increased risk of endometrial cancer compared with those without endometriosis, but the risk for the development of endometrial cancer was significantly increased in women with endometriosis when they were older than 40 years, with an adjusted HR of 7.08 (95% CI 2.33–21.55, $p = 0.007$).

Another study by Kok and colleagues[20] examined the correlation between endometriosis and other malignancies, including endometrial, breast, colorectal, and other cancers. Overall, this study found that women with endometriosis and adenomyosis had a higher risk of malignancy, with adjusted HRs of 1.8 (95% CI 1.4–2.4, $p < 0.05$) and 1.8 (95% CI 1.3–2.7, $p < 0.05$), respectively.[20] In terms of the localization of endometriosis, women with ovarian endometriosis associated with/without endometriosis variants (endometriosis at another site) had a higher risk of EOC and endometrial cancer, with adjusted HRs of 4.56 (95% CI 1.72–12.11, $p < 0.05$) and 4.05 (95% CI 1.20–13.66, $p < 0.05$), respectively.[20] By contrast, women with main endometriosis within the uterus accompanied with/without other areas of endometriosis also had a higher risk of EOC and endometrial cancer, with adjusted HRs of 5.50 (95% CI 1.95–15.50, $p < 0.05$) and 4.38 (95% CI 1.22–15.72, $p < 0.05$), respectively. With regard to the risk of endometrial cancer, women with pure adenomyosis without endometriosis in other sites had an unusually higher risk of endometrial cancer (adjusted HR 5.13, 95% CI 1.36–19.40, $p < 0.05$).[20] However, it is interesting to find that women with uterine endometriosis (adenomyosis) mixing with other sites of endometriosis had much higher risks of ovarian and colorectal cancers, with adjusted HRs of 10.35 (95% CI 3.07–34.91, $p < 0.05$) and 13.04 (95% CI 2.21–77.04, $p < 0.05$), respectively.[20] Although colon and rectum are reported as the second most common extragonadal sites for malignant transformation of endometriosis,[21] it is not clear why women with adenomyosis mixing with other sites of endometriosis are at a risk of colorectal cancer. It is relatively confusing that estrogen promotes endometriosis growth,[22] but estrogen might be beneficial for protection from the development of colorectal cancer, based on the findings from a previous scientific review[23] and a recent prospective study.[24] In addition, if the theory of estrogen is acceptable for the pathogenesis of endometriosis, EOC, and endometrial cancer, it can be further supposed that there is a possible correlation between endometriosis and breast cancer. However, domestic data did not show any correlation between endometriosis and breast cancer,[20] and from literature reviews, the available published evidence is inconclusive.[25]

6. Study limitation

This review was mainly based on the results from domestic data published between 2012 and 2015, and the data used for these published articles were all obtained from the NHIRD. The major issue with respect to the NHIRD is the accuracy of the diagnosis; therefore, without further validation, the results should be read more carefully and the conclusion should avoid a hasty generalization. Lee et al[3] also confirmed this, since they found that the incidence of endometriosis varied greatly. In fact, to report the incidence of endometriosis, so far, nobody could demonstrate the reality of the incidence.[2] However, as reported by Lee et al,[3] women with endometriosis really had a higher risk of ovarian cancer than those without, regardless of which criteria were used, suggesting that the association between endometriosis and comorbidity is somewhat present. In addition, numerous excellent articles are available in the literature, including many in the top journals, such as *Lancet Oncology, Annals of Internal Medicine, JAMA Internal Medicine, Medicine*, etc.,[26–30] which report on studies based on the data from the NHIRD, suggesting that information from the NHIRD in Taiwan is valuable for clinical reference. Although evidence from molecular or genetic studies might partly explain the possibly similar pathogenesis or genetic background between endometriosis and some of these comorbidities, for example, ovarian cancers,[31–33] we note that the evidence is still not strong enough to establish a bridge between the two.

In conclusion, evidence from nationwide large-scale population-based studies using domestic data suggests that women with endometriosis might be at a higher risk of several chronic diseases, including diabetes mellitus, cardiovascular disease, chronic liver disease, and rheumatoid arthritis, as well as fertility and pelvic inflammatory diseases, but possibly at a lower risk of chronic renal disease,[34] although we considered the evidence for some comorbidities to be of low quality. In addition to the abovementioned benign medical illnesses, these women might have higher risks of many kinds of malignancies, such as ovarian cancer and uterine cancers. The risk of comorbidity might be higher in women with endometriosis than was previously supposed, and these comorbidities might be harmful to long-term health in such women. More research is needed to determine whether women with endometriosis are really at a risk of these comorbidities.

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Appendix 1

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