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Graves Disease Is Associated With Endometriosis

A 3-Year Population-Based Cross-Sectional Study

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Abstract: The aim of this cross-sectional study was to compare the prevalence of thyroid diseases between women with and without endometriosis.

We established the endometriosis group according to diagnosis codes, surgery codes, and gonadotropin-releasing hormone agonist codes using the Korean Health Insurance Review and Assessment Service—National Inpatients Sample (HIRA-NIS) from 2009 to 2011. Four controls were randomly matched to each endometriosis case. Thyroid disease cases were selected using the thyroid disease diagnosis code (E0X).

Among the 1,843,451 women sampled, 5615 had endometriosis; 22,460 controls were matched to the endometriosis cases. After adjustment for age and sampling year, Graves disease was associated with endometriosis (odds ratio [OR]: 2.52; 95% CI: 1.30–4.88; $P < 0.01$), while hypothyroidism was not (OR: 1.17; 95% CI: 0.90–1.52; $P = 0.25$). Autoimmune hypothyroidism was also not associated with endometriosis (OR: 1.61; 95% CI: 0.88–2.94; $P = 0.12$).

This study revealed an association between Graves disease and endometriosis.

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Abbreviations: CI = confidence interval, ESR2 = estrogen receptor beta gene, GnRH = gonadotropin-releasing hormone, HIRA = the Health Insurance Review and Assessment Service, HIRA-NIS = the Korean Health Insurance Review and Assessment Service—National Inpatients Sample, KCD = the Korean Standard Classification of Diseases, OR = odds ratio, TRAbs = antibodies against the TSH receptor, TSHR = thyroid-stimulating hormone receptor.

INTRODUCTION

Endometriosis is a chronic inflammatory disease induced by the presence of endometrial tissues outside of the uterus.¹ Endometriosis is a common disease in obstetrics and

gynecology, affecting 10% of women of childbearing age.² The main clinical symptoms of endometriosis are chronic pelvic pain, dyspareunia, and infertility.³ The exact cause of endometriosis is not known. The leading hypothesis is the retrograde menstruation theory, which states that menstrual blood flowing into the abdominal cavity grows endometrial cells by regurgitation.⁴ However, because not all women with reflux menstruation also have endometriosis, the retrograde menstruation theory cannot explain all cases of endometriosis. One theory to complement the retrograde menstruation theory is the autoimmunity theory.^{4–6}

Endometriosis is associated with a chronic local inflammatory process and the presence of autoantibodies, and these are characteristics of other autoimmune diseases.^{4–6} In addition, the thyroid peroxidase antibody is more highly expressed in patients with endometriosis than in patients without endometriosis.⁷ These findings suggest that endometriosis and autoimmune thyroid diseases might be associated. Furthermore, a large cross-sectional study conducted in the United States concluded that the prevalence of autoimmune diseases, including hypothyroidism, was higher among patients with endometriosis than in the general population.⁸

The aim of this cross-sectional study was to use national claim sample data from 2009 to 2011 to compare the prevalence of thyroid diseases, including autoimmune thyroid diseases, between women with endometriosis and women without endometriosis. To our knowledge, this is the largest population-based study to assess the relationship between endometriosis and thyroid diseases.

METHODS

Sample

The Korean National Health Insurance Service is a single-payer social insurance system with compulsory enrollment.⁹ The raw claims dataset of the Health Insurance Review and Assessment Service (HIRA) includes approximately 46 million patients in South Korea annually.¹⁰ We analyzed the sample data of patients from 2009 to 2011, provided by the Korean Health Insurance Review and Assessment Service (HIRA-NIS) (extraction rates: 13% of the total inpatient population; 1% of the total outpatient population) (serial number: HIRA-NIS-2009-0066/2010-0084/2011-0063). This weighted sample (HIRA-NIS) used stratified sampling (sex, age) and a probabilistic sample extraction method (inpatient group, outpatient group). The inpatient population in this sample consisted of women who were hospitalized more than once in a year. Thus, the inpatient population in this sample had both admission records and visiting outpatient clinic records. The outpatient population in this sample had not been hospitalized in more than 1 year. The HIRA has no association with the results of the present study; it only provided data to the researchers. More

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information regarding HIRA-NIS data is available in the literature.^{10–12}

Selection of Subjects

Study subjects were extracted using the Korean Standard Classification of Diseases (KCD), 6th Revision, which was modified from the 10th Revision of the International Classification of Diseases, and uses procedure codes and drug codes created by the Ministry of Korea Health and Welfare. To increase diagnostic accuracy, endometriosis patients were defined by surgery codes (benign extirpation of adnexal tumor [R4421], bilateral adnexectomy [R4332], foreign body removal [R4166], fulguration [R4165], incision and drainage of ovarian cyst [R4435], Kustner operation [R4181], laparotomy [R4345], ligation of fallopian tubes [R4341], manual reduction [R4182], metroplasty of uterine anomaly [R4170], myomectomy [R4122], ovarian wedge resection [R4430], pelvic adhesiolysis [R4160], surgical fulguration of oviduct [R4342], total hysterectomy [R4183], unilateral adnexectomy [R4331]) with an endometriosis diagnosis code (N80) in the primary or secondary diagnosis field between January 1, 2009 and December 31, 2011. Additionally, endometriosis patients were defined using a gonadotropin-releasing hormone (GnRH) agonist codes (182602BIJ [leuprolide acetate], 182604BIJ [leuprolide acetate], 244902BIJ [triptorelin acetate], 167202BIJ [goserelin acetate], 167201BIJ [goserelin acetate], 198501CSI [nafarelin]) or a danazol code (140301ACH, 140302ACH) with an endometriosis diagnosis code (N80) in the primary or secondary diagnosis field between January 1, 2009 and December 31, 2011. All of the surgery codes included both laparoscopy and laparotomy. Each endometriosis case was randomly matched to 4 controls (1:4 matching) with respect to the case's 5-year age group, sampling year, and sampling weight (Figure 1). Using KCD-6 diagnostic codes, we selected patients with thyroid disease from the endometriosis and control groups; these subjects had at least 1 claim record with a thyroid disease diagnosis code (E0X) (iodine deficiency disease [E01], subclinical iodine-deficiency hypothyroidism [E02], hypothyroidism [E03], nontoxic goiter [E04], hyperthyroidism [E05], Graves disease [E05.0], other thyrotoxicosis [E05.8], unspecified thyrotoxicosis [E05.9], thyroiditis [E06], autoimmune thyroiditis

[E06.3]) between January 1, 2009 and December 31, 2011 (Figure 1). All thyroid diseases were selected independently before or after endometriosis were diagnosed. All subjects were selected without distinguishing whether they were members of the inpatient group or outpatient group.

Statistics

All statistical analyses were conducted using R statistical software (version 3.0.3; Vienna, Austria). All *P* values <0.05 were considered statistically significant. All statistical analyses were performed using 2-tailed tests. The Chi-squared test and Fisher exact test were used to compare the differences between 2 groups. After adjustments for age and sampling year, a weighted logistic multivariate analysis was performed to evaluate the effects of thyroid diseases on endometriosis.

Ethics Statement

The Institutional Review Board of MizMedi Hospital approved our research. All patients in the HIRA-NPS dataset have an anonymous identification code for information protection.

RESULTS

A total of 1,843,451 women were extracted from the HIRA-NIS database, which comprises approximately 3 million individuals from 2009 to 2011. Among the 1,843,451 women sampled, 5615 had endometriosis; 22,460 controls were matched to endometriosis cases according to 5-year age groups, sampling year, and sampling weights, with a case:control match ratio of 1:4 (Figure 1; Table 1). All endometriosis cases were selected from inpatients sample; 3774 (67.2%) of endometriosis group were selected using surgery code and 1841 (32.8%) were selected using drug (GnRH agonist or danazol) code. After adjustment for age and sampling year, we observed that Graves disease was associated with endometriosis (odds ratio [OR]: 2.52; 95% confidence interval [CI]: 1.30, 4.88; *P* < 0.01). After adjustment for age and sampling year, hypothyroidism (diagnosis code E03) was not associated with endometriosis (OR: 1.17; 95% CI: 0.90–1.52; *P* = 0.25). Additionally, after adjustment for covariates, autoimmune hypothyroidism was not associated with endometriosis (OR: 1.61; 95% CI: 0.88–2.94; *P* = 0.12; Table 2).

DISCUSSION

Graves disease is an autoimmune disease characterized by hyperthyroidism, goiter, ophthalmopathy, and dermopathy.¹³ In individuals with Graves disease, an IgG antibody binds to the thyroid-stimulating hormone receptor (TSHR). This binding causes hypersecretion of thyroid hormone (hyperthyroidism), hyperplasia, hypertrophy of the thyroid follicles (goiter), and ophthalmopathy.¹⁴

This study found a higher prevalence of Graves disease among women with endometriosis than among the control group. The prevalences of other thyroid diseases did not differ significantly different between the 2 groups. Characteristics that distinguish Graves disease from other thyroid diseases may be a link between Graves disease and endometriosis.

One of these potential links between Graves disease and endometriosis is autoimmunity. Endometriosis shares many characteristics with autoimmune diseases, including polyclonal B cell activation, abnormal functions of T and B cells, and inflammatory tissue damage.¹⁵ Regarding humoral immunity,

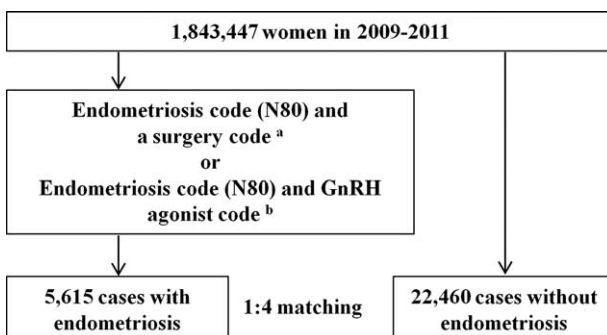


FIGURE 1. Flow chart representing the selection procedure based on the HIRA sample from 2009 to 2011. ^aSurgery codes: R4122, R4160, R4165, R4166, R4170, R4181, R4182, R4183, R4331, R4332, R4341, R4342, R4345, R4421, R4430, and R4435. ^bGnRH agonist codes: 182602BIJ, 182604BIJ, 244902BIJ, 167202BIJ, 167201BIJ, 198501CSI, 140301ACH, and 140302ACH. GnRH = gonadotropin-releasing hormone, HIRA = Health Insurance Review and Assessment Service.

TABLE 1. Characteristics of Patients in the Endometriosis Group and the Control Group, 2009 to 2011

	Endometriosis Group	Control Group	Total	P
Number of patients	5615	22,460	28,075	
Mean age at endometriosis diagnosis, y	36.01 ± 0.16	36.06 ± 0.09	36.10 ± 0.08	0.81
Year				1.00
2009	1564 (27.2%)	6256 (27.2%)	7820	
2010	2115 (37.7%)	8460 (37.7%)	10,575	
2011	1936 (35.1%)	7744 (35.1%)	9680	
Iodine deficiency-related thyroid disease status				1.00 [†]
Present	0 (0.0%)	3 (0.0%)	3	
Not present	5515 (100.0%)	22,457 (100.0%)	28,072	
Subclinical iodine-deficiency hypothyroidism status				0.56 [†]
Present	5 (0.1%)	14 (0.1%)	19	
Not present	5610 (99.9%)	22,446 (99.9%)	28,056	
Hypothyroidism				0.13
Present	189 (3.4%)	668 (3.0%)	857	
Not present	5426 (96.6%)	21,792 (97.0%)	27,218	
Nontoxic goiter				0.69
Present	159 (2.8%)	614 (2.7%)	773	
Not present	5456 (97.2%)	21,846 (97.3%)	27,302	
Thyrotoxicosis status*				0.28
Present	120 (2.1%)	430 (1.9%)	550	
Not present	5495 (97.9%)	22,030 (98.1%)	27,525	
Graves disease status				<0.01
Present	33 (0.6%)	72 (0.3%)	105	
Not present	5582 (99.4%)	22,388 (99.7%)	27,970	
Other thyrotoxicosis				0.51 [†]
Present	8 (0.1%)	25 (0.1%)	33	
Not present	5607 (99.9%)	22,435 (99.9%)	28,042	
Unspecified thyrotoxicosis				0.33
Present	64 (1.1%)	223 (1.0%)	287	
Not present	5551 (98.9%)	22,237 (99.0%)	27,788	
Thyroiditis [‡]				0.80
Present	89 (1.6%)	367 (1.6%)	456	
Not present	5526 (98.4%)	22,093 (98.4%)	27,619	
Autoimmune hypothyroidism				0.30
Present	37 (0.7%)	122 (0.5%)	159	
Not present	5578 (99.3%)	22,338 (99.5%)	27,916	

Data are presented as numbers (percentages) or means ± standard deviations.

*Includes Graves disease, other thyrotoxicosis, and unspecified thyrotoxicosis.

[†] Fisher exact test.

[‡] Includes autoimmune hypothyroidism, acute thyroiditis, subacute thyroiditis, chronic thyroiditis with transient thyrotoxicosis, drug-induced thyroiditis, other chronic thyroiditis, and unspecified thyroiditis.

the incidence of positive antinuclear antibodies (ANAs) is higher among patients with endometriosis than among control patients; this is also the case in Graves disease.¹⁵ In addition to ANAs, the reactivity of some autoantibodies (particularly thyroid peroxidase antibody) is higher in both Graves disease and endometriosis patients.^{7,16}

The second possible link between Graves disease and endometriosis is estrogen. Endometriosis is an established estrogen-dependent disease. Estrogen also plays a role in the pathogenesis of Graves disease by modulating the autoimmune response.¹³ Graves disease is 5-fold more prevalent among women than men, reflecting the possible effect of estrogen.¹⁴ Differential expression of the estrogen receptor beta gene

(ESR2) was confirmed recently by microarray and immunohistochemistry in patients with endometriosis.¹⁷ In addition, polymorphism of the ESR2 is associated with susceptibility to Graves disease.¹⁸ Thus, changes in ESR2 function might be a common link between Graves disease and endometriosis.

Our findings differ from those of a previous study. Petta et al¹⁹ reported that the prevalence of Graves disease was similar among women with endometriosis and women without endometriosis. However, group size in that study (approximately 150 subjects per group) was too small to evaluate the prevalence of Graves disease. The 12-month prevalence of Graves disease is 0.2 to 5.0 per 1000 person-years.²⁰ The diagnostic criteria used by Petta et al regarding Graves disease

TABLE 2. Multivariate Analysis of Endometriosis and Thyroid Disease Status Using a Weighted Analysis

Adjustment	Crude OR		Adjusted OR*	
	OR (95% CI)	P	OR (95% CI)	P
Subclinical iodine deficiency hypothyroidism	0.77 (0.20–2.95)	0.70	0.77 (0.20–2.95)	0.70
Hypothyroidism	1.17 (0.90–1.52)	0.25	1.17 (0.90–1.52)	0.25
Nontoxic goiter	1.11 (0.85–1.45)	0.45	1.11 (0.85–1.45)	0.44
Thyrotoxicosis†	1.42 (0.99–2.03)	0.06	1.42 (0.99–2.03)	0.06
Graves disease	2.51 (1.30–4.86)	<0.01	2.52 (1.30–4.88)	<0.01
Other thyrotoxicosis	1.28 (0.58–2.84)	0.54	1.28 (0.58–2.85)	0.54
Unspecified thyrotoxicosis	1.55 (0.93–2.59)	0.09	1.56 (0.93–2.60)	0.09
Thyroiditis‡	1.09 (0.74–1.61)	0.66	1.09 (0.74–1.61)	0.66
Autoimmune hypothyroidism	1.61 (0.88–2.94)	0.12	1.61 (0.88–2.94)	0.12

CI = confidence interval, OR = odds ratio.

* Covariates: age, sample data per year.

† Includes Graves disease, other thyrotoxicosis, and unspecified thyrotoxicosis.

‡ Includes autoimmune hypothyroidism. The odds ratio of iodine deficiency disease could not be properly calculated owing to insufficient observations.

constitute another limitation of the study. The thyroid peroxidase antibody test and thyroglobulin antibody test used in that study are not specific for the diagnosis of Graves disease. Although these antibodies are detectable in the majority of individuals with Graves disease, measurement of these antibodies is generally not useful for Graves disease diagnosis. In contrast, antibodies against the TSH receptor (TRAbs) are pathognomonic for Graves disease. They are detectable in the serum of more than 98% of individuals with untreated Graves disease using a third-generation assay.²¹

Although the OR of Graves disease was 2.52 (95% CI: 1.30–4.88; $P < 0.01$), the relationship between Graves disease and endometriosis might be clinically weak because only 0.6% of the endometriosis patients had Graves disease. However, this study was not a long-term longitudinal study, but a cross-sectional study. If a patient was diagnosed with Graves disease beginning in 2008, but did not visit a clinic for Graves disease during 2009 to 2012, that patient was considered to be without Graves disease in our study. The same standard was used for endometriosis. Therefore, additional studies, such as longitudinal case–control studies and cohort studies, are necessary to verify the clinical importance of the association. In addition, the present study did not analyze causality; therefore, it is not possible to establish a causal relationship between endometriosis and Graves disease. However, the age ranges of patients with both diseases may be important for predicting the causal relationship between the 2 diseases. The mean age at the time of initial diagnosis of EMS is 25 to 35 years.^{22,23} This mean age is similar to the average age of the EMS group in this study (36.01 ± 0.16 years). In contrast, the mean age of patients with Graves disease is 48 years.²⁰ Consequently, EMS is likely to precede Graves disease. However, because the results of this study indicate that EMS is associated with Graves disease, further research may be required to determine the causal relationship between these 2 diseases.

The present study also has several limitations. First, the data analyzed in this study did not include endometriosis histology. Therefore, the individuals that were considered endometriosis patients were limited to those who underwent surgery or received a GnRH agonist injection. Second, this

study could not be adjusted for other potential confounders (e.g., socioeconomic status, smoking, other gynecologic diseases, obstetric history, endometriosis stage, endometriosis location) except for age and sampling year.

In conclusion, we found that the prevalence of Graves disease was higher among women with endometriosis group than among the members of a matched control group. Additional studies, such as long-term longitudinal cohort studies, are needed to confirm our findings and their clinical importance.

REFERENCES

- Dunselman GAJ, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29:400–412.
- Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am*. 1997;24:235–258.
- Bulun SE. Endometriosis. *N Engl J Med*. 2009;360:268–279.
- Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004;364:1789–1799.
- Nothnick WB. Treating endometriosis as an autoimmune disease. *Fertil Steril*. 2001;76:223–231.
- Eisenberg VH, Zolti M, Soriano D. Is there an association between autoimmunity and endometriosis? *Autoimmun Rev*. 2012;11:806–814.
- Poppe K, Glinier D, Van Steirteghem A, et al. Thyroid dysfunction and autoimmunity in infertile women. *Thyroid*. 2002;12:997–1001.
- Sinaii N, Cleary SD, Ballweg ML, et al. 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.
- H-well NHIS. <http://www.nhis.or.kr/static/html/wbd/g/a/wbdga0302.html>. Accessed June 18, 2014
- Kim L, Kim J-A, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. *Epidemiol Health*. 2014;36:e2014008.
- Health Insurance Review & Assessment Service. Introduction to HIRA-NPS. HIRA. https://www.dropbox.com/sh/gj8quoh6w40gpl/1_jgCZzGVA. Accessed October 18, 2012.

12. Yuk J-S, Kim YJ, Hur J-Y, et al. Association between socioeconomic status and ectopic pregnancy rate in the Republic of Korea. *Int J Gynaecol Obstet.* 2013;122:104–107.
13. Weetman AP. Graves' disease. *N Engl J Med.* 2000;343:1236–1248.
14. Bahn RS. Autoimmunity and Graves' disease. *Clin Pharmacol Ther.* 2012;91:577–579.
15. Pasoto SG, Abrao MS, Viana VST, et al. Endometriosis and systemic lupus erythematosus: a comparative evaluation of clinical manifestations and serological autoimmune phenomena. *Am J Reprod Immunol.* 2005;53:85–93.
16. Taylor PV, Maloney MD, Campbell JM, et al. Autoreactivity in women with endometriosis. *Br J Obstet Gynaecol.* 1991;98:680–684.
17. Vouk K, Smuc T, Guggenberger C, et al. Novel estrogen-related genes and potential biomarkers of ovarian endometriosis identified by differential expression analysis. *J Steroid Biochem Mol Biol.* 2011;125:231–242.
18. Kisiel B, Bednarczuk T, Kostrzewa G, et al. Polymorphism of the oestrogen receptor beta gene (ESR2) is associated with susceptibility to Graves' disease. *Clin Endocrinol (Oxf).* 2008;68:429–434.
19. Petta CA, Arruda MS, Zantut-Wittmann DE, et al. Thyroid autoimmunity and thyroid dysfunction in women with endometriosis. *Hum Reprod.* 2007;22:2693–2697.
20. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev.* 2003;2:119–125.
21. Zöphel K, Roggenbuck D, Schott M. Clinical review about TRAb assay's history. *Autoimmun Rev.* 2010;9:695–700.
22. Hediger ML, Hartnett HJ, Louis GMB. Association of endometriosis with body size and figure. *Fertil Steril.* 2005;84:1366–1374.
23. Kuohung W, Jones GL, Vitonis AF, et al. Characteristics of patients with endometriosis in the United States and the United Kingdom. *Fertil Steril.* 2002;78:767–772.