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Original Research

The association of body mass index with incidence, stage and recurrence of endometriosis: case-control study in Korean women

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Summary

Purpose: The aim of this study is to evaluate the association between body mass index (BMI) and endometriosis in Korean women. *Materials and Methods:* In a hospital-based case-control study, 134 endometriosis cases and 282 ovarian teratoma cases as controls were selected. All cases were histologically confirmed after laparotomy or laparoscopic surgery, and they were categorized by BMI, as < 18.5, 18.5-22.9, 23-24.9, and > 25 kg/m^2, respectively, according to the World Health Organization (WHO) guidelines for Asia-Pacific populations. Diagnosis for recurrences evaluated mainly by ultrasound or surgery. The authors collected requisite patient information from medical records of seven years. *Results:* Development of endometriosis was not significantly related to varying BMI. However, when comparing overall median BMI values in endometriosis [21.43 (19.59, 23.61)] and teratoma [22.19 (20.41, 24.61)], BMI was significantly lower in endometriosis cases than in teratoma cases ($p = 0.014$). There was no significant relation between the BMI groups and American Fertility Society (AFS) stages (Spearman's $r = 0.06584$, $p = 0.4498$). In both of endometriosis and ovarian teratoma patients, the patients with higher BMI than 23 kg/m^2 showed elevated recurrence rates ($p = 0.024$, HR = 2.104 and $p = 0.026$, HR = 4.417, respectively). Yet, considering varying BMI groups and recurrence rates, recurrence rate had no association among 46 recurrent endometriosis and teratoma cases ($p = 0.338$). *Conclusion:* In this study, lower BMI was observed to be possibly associated with endometriosis in comparison to that of other benign disease. BMI did not affect disease severity, whereas obesity was related to the recurrence of endometriosis.

Key words: Endometriosis; Body mass index (BMI); Stage; Incidence; Recurrence.

Introduction

Endometriosis is a common gynecological disease, defined by external uterine implantation of endometrial tissue, usually to the pelvic peritoneum, ovaries, and rectovaginal septum. As widely known, the frequency of endometriosis is different for Caucasian and Asian; Asian women are more likely to have endometriosis [1, 2]. Regarding the staging of endometriosis, the most commonly used staging system is the revised American Fertility Society (AFS) classification. Physicians score the disease extends by the inspection during the laparotomy or laparoscopic surgery, followed by pathologic confirmation. Stages are categorized into four main groups explaining severity of disease [3].

Diverse hypotheses such as nutritional, hormonal, environmental. and genetics have been presented to explain the factors affecting occurrence and recurrence of endometriosis (4), and some researchers have found that body mass index (BMI) is not only related to the high risk of metabolic diseases, but also have possible correlation with endometriosis [5]. However, such studies on the association between BMI and endometriosis have inconsistent results. Shah *et al.* showed that BMI at age 18 years and current BMI were inversely associated with endometriosis [6]. Through their meta-analysis of 11 studies comparing endometriosis patients with normal weight, Liu and Zhang recently suggested that higher BMI could have been associated with lower risk of endometriosis [7]. On the other hand, in a German case-control study, BMI, along with parity, age at menarche and use of oral contraceptives, was not predictive of endometriosis; other studies on different ethnicities have also failed to observe relevant association between endometriosis and BMI [8-10]. With regards to disease severity, a case-control study reported by Lafay Pillet *et al.* reported that patients with the lowest BMI (< 18.5 kg/m^2) are at high risk of deep infiltrating endometriosis (4). Furthermore, concerning BMI in recurrence of endometriosis, Ianieri *et al.* suggested that higher BMI could be a risk factor of deep infiltrating endometriosis recurrence, but the number of studies in such topic is limited [11]. Comprehensively, regarding BMI in evaluating endometriosis, controversies are still on-going. Current reports on the association between BMI and endometriosis are inconsistent world-wide. Thus, the purpose of this study

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is to evaluate the incidence, stage, and recurrence of endometriosis according to varying BMI in Korean women through a case-control study, while possibly adding to further clarification of the role of BMI in endometriosis in Korean ethnicity.

Materials and Methods

This analysis was A hospital-based case-control study of 134 endometriosis cases and 282 ovarian teratoma cases as controls from January 2009 to December 2015. The patients were further followed up until March 2018. Requisite patient information was collected from the medical records at Pusan National University Hospital. All patients were diagnosed by histological confirmation after initial laparotomy or laparoscopic surgeries, including ovarian cystectomy, salpingectomy, and/or oophorectomy. Patients with other coexisting benign gynecological diseases such as myoma uteri and endometrial polyps were included in both groups. Patients with both ovarian teratoma and endometriosis were excluded, as well as the patients with gynecologic cancers.

All the endometriosis cases were staged by AFS classification with pathologic confirmation and visual inspection during the surgery. BMI was calculated as the weight in kilograms divided by height in meters squared (kg/m^2) and categorized into underweight, normal weight, overweight and obesity by < 18.5, 18.5-22.9, 23-24.9 and > 25 kg/m^2, respectively, according to the WHO guidelines for Asia-Pacific populations [12].

Diagnosis of endometriosis recurrence was decided either by surgery or ultrasound examination. After reoperation, recurrence was confirmed histologically. On ultrasound examination, the following criteria were used to diagnose recurrent endometriosis – a round-shaped ovarian cystic mass, with a minimum diameter of 20 mm, irregular margins, and homogenous low echogenic fluid content with scattered internal echoes [13]. Recurrence of ovarian teratoma was diagnosed by histological findings after reoperation.

Data analysis was performed using SPSS statistics 22 and R 3.3.2 programs. The p value < 0.05 was considered statistically significant. Comparisons between the two groups were made using the Fisher's exact test in categorical variables. The Kaplan-Meier method was used for the recurrence rate, and the log-rank test and the Cox proportional hazards model was used to compare the recurrence rates. The association between the patient's BMI and AFS was assessed using Spearman's correlation analysis.

Results

Comparing the endometriosis and ovarian teratoma groups, no statistical difference was found in the patient's age, parity, and age at menarche (p = 0.489) (Table 1). Endometriosis incidence also showed no statistical relationship to varying BMI. However, when evaluating overall median BMI values of the endometriosis and ovarian teratoma groups, significantly lower BMI was observed in endometriosis cases than in ovarian teratoma cases (p = 0.014) (Table 1). Table 2 shows the association between BMI and AFS stages. Data revealed no significant relationship between two variables (p = 0.605).

Table 1. — *Patients characteristics of endometriosis and teratoma groups.*

	Endometriosis (n=134)	Teratoma (n=282)	p-value
Age (years)	34.23 ± 8.08	32.44 ± 13.91	0.990
Parity	0.43 ± 0.81	0.61 ± 1.11	0.550
Age at menarche (years)	14.05 ± 1.45	13.91 ± 1.83	0.489
BMI*	21.43 [19.59, 23.61]	22.19 [20.41, 24.61]	0.014
BMI group**			0.203
<18.5	18 (13.4)	24 (8.5)	
18.5 – 22.9	76 (56.7)	148 (52.5)	
23 – 24.9	16 (11.9)	47 (16.7)	
>25	24 (17.9)	63 (22.3)	

*Values are mean ± standard deviation; *median(min-max); **number (%). BMI: body mass index.*

Table 2. — *AFS stages of endometriosis in relation to BMI.*

AFS stage	BMI category				p-value
	<18.5 (n=18)	18.5 – 22.9 (n=76)	23 – 24.9 (n=16)	>25 (n=24)	
1	1 (5.6)	5 (6.6)	0 (0.0)	0 (0.0)	0.605
2	1 (5.6)	1 (1.3)	1 (6.2)	2 (8.3)	
3	6 (33.3)	29 (38.2)	5 (31.2)	7 (29.2)	
4	10 (55.6)	41 (53.9)	10 (62.5)	15 (62.5)	

Values are number (%). BMI: body mass index; AFS: American Fertility Society.

Both endometriosis and ovarian teratoma patients with BMI higher than 23 kg/m^2 showed elevated recurrence rate (p = 0.024, HR = 2.104 and p = 0.026, HR =4 .417, respectively) (Table 3), while the patients with BMI lower than 23 in both groups did not show relevant recurrence. Although not shown in the table, when evaluating varying BMI and the overall recurrence rate in 46 recurrent endometriosis and teratoma cases, no significant association was found (p = 0.338).

Discussion

Endometriosis is one of the commonly known pelvic inflammatory disease. Despite of a large number of studies, complete understanding of pathogenesis or related factors of the disease has still not been achieved. One of the widely accepted theory regarding development of endometriosis states that the risk of the disease might be increased by recurrent exposure to menstruation (i.e., shorter cycle length, longer duration of flow or reduced parity), and others report that it might also be related to altered estrogen levels [2]. Moreover, more recent studies have shown the relationship between endometriosis development and BMI, but these studies still contain inconsistent results and require further research to explain the practical influence of BMI [4, 6, 9, 10, 14]. Studies supporting the association between BMI and endometriosis suppose that it is due to estrogen-dependent aspect of the disease [15, 16]. Unlike endometrio-

Table 3. — *Comparison of recurrence rate by BMI groups in endometriosis and ovarian teratoma.*

			Log-rank test	Cox PH regression analysis	
	BMI category	n	*p*-value	HR [95% CI]	*p*-value
Endometriosis	< 18.5	2	0.151	0.652 [0.150, 2.836]	0.569
	18.5–22.9	18		1	
	23–24.9	3		2.035 [0.582, 7.110]	0.266
	> 25	12		1.983 [0.945, 4.159]	0.070
	< 23	20	0.024	1	
	> 23	15		2.104 [1.066, 4.154]	0.032
Teratoma	< 18.5	1	0.082	1.929 [0.168, 22.122]	0.597
	18.5–22.9	4		1	
	23–24.9	3		10.092 [1.323, 76.992]	0.026
	> 25	3		3.902 [0.627, 24.297]	0.145
	< 23	5	0.026	1	
	> 23	6		4.417 [1.030, 18.954]	0.046

BMI: body mass index.

sis, the origin of the ovarian teratoma is explained by the pathogenetic hypothesis, derived from germ cell or embryo development. As previously reported, etiology of the ovarian teratoma is independent with menstrual or reproductive factors, so pathologically diagnosed patients with ovarian teratoma were chosen as controls in this study [17, 18].

The study investigated the incidence of endometriosis according to groups of varying BMI (< 18.5, 18.5-22.9, 23-24.9, and > 25 kg/m^2), and no significant association was found. Similarly, analysis of endometriosis stages using AFS according to varying BMI groups did not show any significant relationship; since AFS staging represent the measurement of the disease severity, it could be interpreted that BMI was not observed to affect severity of endometriosis [3]. However, when comparing endometriosis cases with ovarian teratoma cases, overall mean BMI of ovarian teratoma cases were higher than that of endometriosis cases ($p = 0.014$). Such results could possibly raise multiple explanations; extending boundaries of previous knowledge, ovarian teratoma might have been associated with higher body weight, and/or endometriosis with lower BMI although the data was not significant ($p = 0.203$) [17]. As discussed earlier, the results are not completely consistent throughout the literature, but several studies reporting an inverse relationship between endometriosis and BMI still exist. In a prospective study of endometriosis incidence and comparative body sizes during childhood and early adulthood, an inverse relationship was observed, independent of adult BMI and menstrual cycle characteristics [15]. In another prospective study of a 20-year-long follow-up BMI, the patient's BMI at age 18 years and current BMI were each significantly inversely associated with endometriosis [6]. Therefore, the statistical insignificance of the present results that still suggest the similar inverse relationship between BMI and endometriosis cases to previous studies might have been merely due to the small number of the subjects included in this project.

The exact mechanism explaining the influence of BMI on endometriosis is yet obscure. However, some researchers have hypothesized polycystic ovarian syndrome (PCOS) to be inversely correlated with the development of endometriosis and BMI. PCOS is related to obesity, and its anovulatory condition can lead decreasing retrograde menstruation which is known to be a possible cause of the disease [19]. Furthermore, hyperandrogenic hormonal environment of these patients seemingly allow slow progression of endometrial lesion [6]. Additional hypothesis explains that the diagnosis of the disease itself may have been delayed, as obesity is mostly accompanied by chronic pain condition in general and consequently could lead to relative insensitivity to pain [20, 21]. Such delaying of diagnosis may draw diagnostic bias.

Lastly, endometriosis recurrence was analyzed in the current study. Several recent studies have stated higher BMI as a risk factor for the disease recurrence [18]. Results of the present study agreed with such results, but the control group also showed higher recurrence rate with increasing BMI. The present authors postulate that extreme obesity might have interfered with complete resection of the tumor. No definite knowledge has been accumulated regarding the effect of higher BMI on benign ovarian neoplasm – it could be hypothesized that higher BMI might be a novel risk factor for recurrent ovarian tumors. However, as the number of studies on the effect of BMI on the other benign ovarian neoplasm is limited, further investigations are warranted.

As one of the limitations, the current study showed rather different results from previous studies suggesting possible correlation of BMI and endometriosis incidence and severity, and racial difference could have played a role in such aspect [4, 7, 9, 14]. Relative frequency of endometriosis has been known to be different for Caucasians and Asians, as the prevalence is higher in Asians than in Caucasians [1, 22]. Namely, different BMI classifications and disease distributions for Asian populations could have been required. Other than in Asian ethnicity, WHO originally categorizes BMI into four main groups as > 30, 25-29.9, 18.5-24.9, and

< 18.5 kg/m^2. Due to the relatively narrow range of BMI applied to Asian ethnicity, statistical differences in results of the present study could have been veiled. Nevertheless, even when the BMI categories were changed according to the above criteria, similar results were obtained as the initial values. Despite of aforementioned limitations, this study has the advantage of reduced surgical-related variables, since only two individual operators performed the surgery in a single institution. In addition, the follow-up period for endometriosis recurrence in this study was more than two years with homogenous ethnicity of Korean, possibly adding to Korean-specific characteristics in investigating endometriosis recurrence and BMI.

In conclusion, endometriosis may be related to lower BMI compared to other benign ovarian tumor diseases. BMI was not found to affect disease severity, but obesity was associated with the recurrence of endometriosis. Further investigations to clarify inconsistent results of the present study are needed.

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