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Malignant risk of pelvic mass after hysterectomy for adenomyosis or endometriosis

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Abstract

Pelvic mass onset following a hysterectomy due to benign disease is not rarely seen. Appropriate diagnosis and treatment are of great importance.

This study aims to analyze the clinicopathological features of patients who have received surgery for pelvic mass following hysterectomy due to gynecological benign disease, especially endometriosis or adenomyosis.

This study retrospectively analyzed the patients undergone reoperation for pelvic mass subsequently to hysterectomy from January 2012 to December 2016 in a tertiary teaching hospital.

A total of 247 patients were enrolled in this study. There is a significant difference between the patients with or without a history of endometriosis/adenomyosis. Multivariate analysis showed that the pelvic mass had a higher risk of being ovarian endometrioid carcinoma, ovarian clear cell carcinoma, ovarian endometriosis, and ovarian physiological cysts in patients with a history of adenomyosis/endometriosis.

The pathology of the subsequent pelvic mass inclines to be benign, includes ovarian endometriosis, ovarian physiological cysts, and pelvic encapsulated effusion. Postoperative adjuvant therapy for those received hysterectomy due to endometriosis/adenomyosis, like gonadotropin releasing hormone agonists (GnRHa), may contribute to the prevention of benign pelvic mass. Patients with a history of hysterectomy due to endometrisos/adenomyosis tend to have a shorter time interval between hysterectomy and pelvic malignant tumors onset.

Abbreviations: CA125 = carbohydrate antigen-125, GnRHa = gonadotropin releasing hormone agonists, ROC = receiver operating characteristic.

Keywords: adenomyosis, clinicopathology, endometriosis, hysterectomy, pelvic mass

1. Introduction

It is common to find pelvic masses in need of surgical intervention after hysterectomy for benign diseases. It was reported that the incidence of pelvic mass after hysterectomy was as high as 50.7%, and the patients requiring reoperation accounted for 2.7% to 5.5%.[1,2] The diagnosis of pelvic mass after hysterectomy is more difficult, forcing the clinicians and patients to be more cautious for the risks associated with reoperation.[3] Therefore, it is of great importance and value to understand the clinicopathological characteristics of pelvic mass, thus facilitating to make appropriate diagnosis, treatment, and prevention strategies. However, there are few relevant research.[4,5] Thus, this study aims to provide a reference for the prevention, diagnosis, and treatment of such conditions by retrospectively

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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analyzing the clinicopathological features of pelvic mass in patients received hysterectomy for benign disease.

2. Material and methods

2.1. Ethical approval

This study was approved by the Ethics Committee of our hospital (No. S-K331, on August 24, 2017). The written informed consent was waived due to the retrospective nature of the study.

ICD-9 disease code was used to identify patients who underwent surgery in Peking Union Medical College Hospital for pelvic mass after hysterectomy due to benign disease from January 2012 to December 2016. Inclusion criteria: patients who have a clearly identified history of hysterectomy due to gynecological benign disease, and underwent reoperation due to pelvic mass were included. Exclusion criteria: Patients who underwent surgery for pelvic mass but had no history of hysterectomy, or those who had a uterine pathology of malignant tumors were excluded from the study.

Medical records of the patients were collected in detail, including the age of hysterectomy and the indications, the age of the pelvic mass onset, the time interval from the hysterectomy to the onset of pelvic mass, the oviduct or ovary being resected or remained in previous surgery, the main manifestations and imaging features at the time of pelvic mass onset, and the pathological type of the pelvic mass. According to the indications of hysterectomy, the patients were divided into endometriosis/adenomyosis group (Group A) and non-endometriosis/adenomyosis group (Group B). The clinicopathological characteristics of the two groups were compared and analyzed.

2.2. Statistical analyses

The statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL). It was taken as a reference whether the indication of hysterectomy was endometriosis/adenomyosis, and receiver operating characteristic (ROC) curve was used to group the patients by their ages of hysterectomy ($<$44 years vs $\geq$44 years), their ages of the operation for pelvic mass ($<$51 years vs $\geq$51 years), and the time interval from the hysterectomy to the onset of pelvic mass ($<$5 years vs $\geq$ 5 years). Continuous variables were summarized with medians and interquartile ranges. The two groups were analyzed by independent *t* test. The categorical variables were summarized with a rate, and chi-square test or Fisher exact test was adopted to perform the analysis. Pathologic variables with $P < .05$ by univariate analysis were included in multivariate analysis, and a logistic regression model was used for fitting with $P < .05$ being considered significant. All analyses were two-sided, and significance was set at a $P < .05$.

3. Results

3.1. Demographics data of study population

Our study included 247 patients and the details are shown in Supporting Information Table 1, http://links.lww.com/MD/E27. The median age was 43 (22–59) years old with 4 postmenopausal women. 85.43% (n=211) of the patients underwent total hysterectomy and 14.57% (n=36) subtotal hysterectomy. The 80.16% (n=198) of the patients received simple hysterectomy, 5.67% (n=14) hysterectomy and bilateral salpingectomy, 12.96% (n=32) hysterectomy and unilateral salpingo-oophorectomy and 1.21% (n=3) hysterectomy and bilateral salpingo-oophorectomy. Pathological diagnosis after hysterectomy showed that 23.08% (n=57) of the patients had adenomyosis, and 12.55% (n=31) had endometriosis. Some patients had more than one type of pathological diagnosis.

The median age of the surgery for pelvic mass was 50 (30–79) years old, and the median time interval from hysterectomy to the onset of pelvic mass was 5 years. More than half (52.63%) of the patients found the pelvic mass incidentally by physical examination, while the common manifestations were abdominal pain (23.08%) and abdominal distension and anorexia (16.59%). The 55.47% (n=137) of the patients found the pelvic mass in the format of cystic mass, 13.77% (n=34) were solid, and 26.32% (n=65) were mixed cystic solid mass. Referring to the tumor marker, 28.74% of the patients had elevated serum Carbohydrate antigen-125 (CA 125).

3.2. Postoperative pathology data

Of the total 247 patients, 34.01% (n=84) were diagnosed with malignant tumors confirmed by pathology (Supporting Information Table 2, http://links.lww.com/MD/E28), of which ovarian derived malignant tumors accounted for 76.19% (n=64). Among the 64 patients, ovarian epithelial carcinoma patients accounted for 82.81% (n=53). 65.99% (n=163) out of the total 247 patients were diagnosed with benign tumors confirmed by pathology (Supporting Information Table 3, http://links.lww.com/MD/E29), of which 67.48% of the patients' tumor arose from ovary, 19.02% from fallopian tube, and inflammation accounted for 12.27%. It is worth emphasizing that 16 patients with benign tumors had more than one kind of pathological types. All of the inflammatory masses were encapsulated effusions.

3.3. Comparison of clinicopathological characteristics between the two groups

This study compared the clinicopathological characteristics of the patients from 2 groups. The univariate analysis was shown in Table 1. Patients in group A were younger than those in group B [median(IQR), 42.0 (37.5, 45.0) vs 44. 0 (40.0, 48.0), $P = .003$] when the hysterectomy was performed, as well as when the pelvic mass was resected [median (IQR), 48.0 (45.0, 50.5) vs 52.0 (48.0, 58.0), $P < .001$]. The time interval between the hysterectomy and the pelvic mass onset was also shorter in group A [median(IQR), 3.0 (1.0, 7.0) vs 6.0 (2.0, 11.0), $P = .002$]. The time interval between the hysterectomy and the pelvic malignant mass confirmed was also shorter in group A [median(IQR), 5.0 (1.0, 8.5) vs 8.0 (3.0, 14.0), $P = .047$].

Pathological diagnosis after pelvic mass surgery showed that the pelvic mass tended to be ovarian endometriosis, ovarian physiological cysts, and pelvic encapsulated effusion in group A [32.4 vs 6.7%, $P < .001$; 22.1 vs 10.1%, $P = .013$; 16.2 vs 7.3%, $P = .035$]. However, the incidence of ovarian serous cystadenoma was lower in group A (2.9 vs 11.2%, $P = .043$). Among ovarian malignant tumors, group A had a higher risk of ovarian endometrioid carcinoma and ovarian clear cell carcinoma than group B (5.9 vs 1.7%, $P = .095$; 4.4 vs 0.6%, $P = .065$), while the rate of ovarian serous carcinoma was lower than group B (7.4 vs 14.5%, $P = .129$), but there was no significant difference. Other benign and malignant mass of ovarian and extraovarian origin did not show significant difference between the two groups.

Table 1

Comparison of clinicopathological characteristics between endometriosis/adenomyosis group and non-endometriosis/adenomyosis group.

	Value assigned	Non-endometriosis/adenomyosis group N (%)	Endometriosis/adenomyosis group N (%)	*P* value
Numbers		179	68	
Age of hysterectomy (median[IQR], years)		44 [40.0, 48.0]	42 [37.5, 45.0]	.003
Age group for hysterectomy	<44	67 (37.4)	44 (64.7)	<.001
	≥44	112 (62.6)	24 (35.3)	
Age of resection of pelvic mass (median[IQR], years)		52 [48.0, 58.0]	48 [45.0, 50.5]	<.001
Age group for surgery of pelvic mass	<51	87 (48.6)	56 (82.4)	<.001
	≥51	92 (51.4)	12 (17.7)	
Time interval between hysterectomy and pelvic mass onset (median[IQR], years)		6 [2,11]	3 [1, 7]	.002
Time interval between hysterectomy and malignant mass confirmed (median[IQR], years)		8 [3, 14]	5 [1, 8.5]	.047
Benign or malignant	0	116 (64.8)	47 (69.1)	.523
	1	63 (35.2)	21 (30.9)	
Serous carcinoma	0	153 (85.5)	63 (92.6)	.129
	1	26 (14.5)	5 (7.4)	
Mucinous carcinoma	0	173 (96.6)	66 (97.1)	.869
	1	6 (3.4)	2 (2.9)	
Endometrioid carcinoma	0	176 (98.3)	64 (94.1)	.095
	1	3 (1.7)	4 (5.9)	
Clear cell carcinoma	0	178 (99.4)	65 (95.6)	.065
	1	1 (0.6)	3 (4.4)	
Sarcoma	0	177 (98.9)	67 (98.5)	.9999
	1	2 (1.1)	1 (1.5)	
Undifferentiated carcinoma	0	178 (99.4)	67 (98.5)	.475
	1	1 (0.6)	1 (1.5)	
Primary PNET	0	178 (99.4)	67 (100.0)	.9999
	1	1 (0.6)	0 (0)	
Unknown classification	0	172 (96.1)	67 (98.5)	.297
	1	7 (3.9)	1 (1.5)	
Cervical leiomyoma	0	175 (97.8)	68 (100.0)	.578
	1	4 (2.2)	0 (0)	
Cervical intraepithelial neoplasia	0	178 (99.4)	68 (100.0)	.9999
	1	1 (0.6)	0 (0)	
Hydrosalpinx	0	162 (90.5)	65 (95.6)	.191
	1	17 (9.5)	3 (4.4)	
Mesenchymal cyst of oviduct	0	170 (95.0)	64 (94.1)	.791
	1	9 (5.0)	4 (5.9)	
Ovarian abscess	0	177 (98.9)	68 (100.0)	.9999
	1	2 (1.1)	0 (0)	
Ovarian endometriosis	0	167 (93.3)	46 (67.7)	<.001
	1	12 (6.7)	22 (32.4)	
Ovarian physiological cysts	0	161 (89.9)	53 (77.9)	.013
	1	18 (10.1)	15 (22.1)	
Mucinous cystadenoma	0	164 (91.6)	65 (95.6)	.261
	1	15 (8.4)	3 (4.4)	
Serous cystadenoma	0	159 (88.8)	66 (97.1)	.043
	1	20 (11.2)	2 (2.9)	
Ovarian fibroma	0	177 (98.9)	65 (95.6)	.130
	1	2 (1.1)	3 (4.4)	
Ovarian teratoma	0	176 (98.3)	68 (100).0	.563
	1	3 (1.7)	0 (0)	
Oviduct abscess	0	177 (98.9)	68 (100.0)	.9999
	1	2 (1.1)	0 (0)	
Ovarian epidermoid cyst	0	177 (98.9)	68 (100.0)	.9999
	1	2 (1.1)	0 (0)	
Ovarian Sertoli cell tumors	0	178 (99.4)	68 (100.0)	.9999
	1	1 (0.6)	0 (0)	
Ovarian granulocytoma	0	178 (99.4)	68 (100).0	.9999
	1	1 (0.6)	0 (0)	
Encapsulated effusion	0	166 (92.7)	57 (83.8)	.035

(*continued*)

Table 1

(continued).

	Value assigned	Non-endometriosis/adenomyosis group N (%)	Endometriosis/adenomyosis group N (%)	*P* value
	1	13 (7.3)	11 (16.2)	
Intravascular leiomyomatosis	0	175 (97.8)	68 (100.0)	.578
	1	4 (2.2)	0 (0)	
Pelvic leiomyoma	0	177 (98.9)	67 (98.5)	.9999
	1	2 (1.1)	1 (1.5)	

The 0 s in the table refer that the matter didn't happen, while the 1s is defined as the occurrence of the event.
PNET = primitive neuroectodermal tumor.

Table 2

Multivariate analysis of clinicopathological characteristics between endometriosis/adenomyosis group and non-endometriosis/adenomyosis group.

Parameter	β	S.E.	*P*	OR (95%CI)
Intercept	−1.6844	0.2534	<.005	
Ovarian serous carcinoma	−0.15	0.6	.803	0.86 (0.27–2.77)
Ovarian endometrioid carcinoma	1.97	0.8	.014	7.19 (1.48–34.79)
Clear cell carcinoma	2.78	1.18	.019	16.17 (1.59–164.03)
Ovarian endometriosis	2.04	0.43	<.001	7.67 (3.33–17.65)
Ovarian physiological cysts	1.09	0.43	.012	2.98 (1.27–6.97)
Serous cystadenoma	−0.8	0.8	.313	0.45 (0.09–2.13)
Pelvic encapsulated effusion	1.11	0.49	.023	3.04 (1.17–7.92)

In the multivariate analysis, the equation is of significance when the *P* value of the whole test is less than .05.

However, multivariate analysis showed that the indication for the hysterectomy being adenomyosis/endometriosis had independent correlation with the subsequent pelvic masses confirmed to be ovarian endometrioid carcinoma [OR (95% CI), 7.19 (1.48 -34.79); $P=.014$], ovarian clear cell carcinoma [OR (95% CI), 16.17 (1.59–164.03); $P=.019$], ovarian endometriosis [OR (95% CI), 7.67 (3.33–17.65); $P<.001$], ovarian physiological cysts [OR (95% CI), 2.98 (1.27–6.97); $P=.012$] and pelvic encapsulated effusion [OR (95% CI), 3.04 (1.17–7.92)); $P=.023$] (Table 2).

In addition, there was no significant difference for the malignant pelvic mass in patients who received simple resection of the uterus with or without unilateral salpingo oophorectomy between the 2 groups (27.1 vs 33.8%, $P=.479$; 30% vs 38.09%, $P=.999$). However, the risk of malignant pelvic mass was higher in group A than group B for those receiving hysterectomy with bilateral salpingectomy (50% vs 25%), but the data was not suitable for statistical analysis due to small sample size.

4. Discussion

It is believed that hysterectomy is a "radical" surgery, and patients will not receive a second surgery for gynecological diseases. However, our single arm retrospective study showed that in the past 5 years, a total of 247 patients have undergone reoperation for pelvic mass following a hysterectomy. For the pelvic mass that occurs after hysterectomy, is it necessary to perform exploratory surgery actively? Is it possible to judge the nature of the pelvic mass through clinical features, and can the malignant tumor be screened early through clinical high risk factors? Studies with large samples are not available for reference at present.[5–7] The risk assessment of pelvic mass after hysterectomy may help to make a preliminary judgment on the nature and derivation, reducing unnecessary surgical treatment and the possibility of delay in the diagnosis of malignant tumors.

In addition, Shiber et al[5] and Yanaranop et al[7] reported that the main risk factors of malignant pelvic mass include mixed cystic solid pelvic mass, an elevated level of serum CA 125, and longer time intervals from hysterectomy to pelvic mass onset. The results of our study showed that the proportion of malignant pelvic mass following a hysterectomy was as high as 34%, which was higher than that reported in previous study.[5] 76.19% of malignant pelvic masses aroused form ovary, of which serous carcinoma, mucinous carcinoma, endometrioid carcinoma and clear cell carcinoma accounted for 38.10%, 10.71%, 7.14%, and 4.76%, respectively. In benign pelvic masses, ovarian derived cases accounted for 67.48%, and inflammation accounted for 12.27%. Among the ovarian-derived benign diseases, endometriosis is most common.

Our study focused on the clinicopathological characteristics between the patients with a history of hysterectomy for endometriosis/adenomyosis. The results showed that the occurrence of pelvic mass was closely related to the histopathological type of hysterectomy. The pelvic mass in group A had a significantly higher risk of being ovarian endometriosis (32.4 vs 6.7%, $P<.001$), pelvic encapsulated effusion (16.2 vs 7.3%, $P=.035$), and ovarian physiological cysts (22.1 vs 10.1, $P=.013$) than group B. Multivariate analysis of this study showed that the risk of ovarian endometriosis for group A was 7.67 times higher than group B [$P<.001$, OR (95% CI): 7.67 (3.33–17.65)], and the risk of pelvic encapsulated effusion and ovarian physiological cysts was 3.04 times and 2.98 times higher than group B [$P=.023$, OR (95% CI): 3.04 (1.17–7.92); $P=.012$, OR (95%

CI): 2.98 (1.27–6.97)]. It is suggested that pelvic masses tend to be the recurrence of endometriosis, encapsulated cyst or ovarian physiological cyst in the patients from group A. The rate of serous cystadenoma was higher in the patients from group B (11.2 vs 2.9%, $P=.043$). For patients diagnosed with endometriosis, hysterectomy with ovaries preserved has been a risk factor for disease recurrence and reoperation.[8] It is reported that the outcomes of postoperative adjuvant treatment, like GnRHa, is significantly better for those patients than the referential group.[9] Therefore, for patients receiving hysterectomy for endometriosis/adenomyosis with ovaries preserved, GnRHa and long-term oral contraceptive treatment may be beneficial to reduce the risk of recurrence of endometriosis. However, there is a lack of evidence whether it can also reduce the occurrence of pelvic encapsulated cysts and ovarian physiological cysts.

Univariate analysis of clinicopathological characteristics of the 2 groups showed that patients in group A were younger than B when the uterus was resected [median (IQR), 42.0 (37.5, 45.0) vs 44.0 (40.0, 48.0), $P=.003$], as well as when the pelvic mass was resected [median(IQR), 48.0 (45.0, 50.5) vs 52.0 (48.0, 58.0), $P<.001$]. The time interval between the hysterectomy and the pelvic mass onset was also shorter in group A [median(IQR), 3.0 (1.0, 7.0) vs 6.0 (2.0, 11.0), $P<.002$]. Adjuvant therapy after hysterectomy (such as GnRHa) in group A may be beneficial to decrease the incidence of pelvic mass in the short term and reduce the probability of reoperation for pelvic mass. The efficacy of the adjuvant treatment requires to be validated by prospective cohort studies.

In addition, there is a consensus that the risk of ovarian cancer increases in patients with endometriosis, ovarian clear cell carcinoma and endometrioid carcinoma being the main pathological types.[10–12] A number of large clinical retrospective analyses have shown that the overall risk of ovarian cancer in patients with endometriosis is 1.3 to 1.9 times.[13] The relative risk of ovarian cancer is 2.7 times in endometriosis-related infertility patients, the relative risk rises to 4.2 times in the case with a history of endometriosis more than 10 years, and the proportion increased by 13% in endometriosis patients older than 50 years.[14] The results of Peter et al. showed that patients with a history of endometriosis had a three-fold increased risk of developing ovarian clear cell carcinoma and a two-fold increased risk of developing ovarian endometrioid cancer.[15]

Similar to the results mentioned above, the univariate analysis of our study showed that it was comparable in the recurrence of malignant pelvic mass of the patients whether with a history of hysterectomy for endometriosis/adenomyosis (30.88 vs 35.2%, $P=.523$). However, the probability of ovarian endometrioid carcinoma and clear cell carcinoma was higher in the former without significant difference (5.9 vs 1.7%, $P=.095$; 4.4 vs 0.6%, $P=.065$), while the probability of ovarian serous carcinoma was lower (7.4 vs 14.5%, $P=.129$). Multivariate analysis showed different results that patients with a history of endometriosis/adenomyosis had a significantly increased risk of developing ovarian endometrioid carcinoma [$P=.014$, OR (95% CI): 7.19 (1.48~34.79)] and ovarian clear cell carcinoma [$P=.019$, OR (95% CI): 16.17 (1.59~164.03)] than those without endometriosis/adenomyosis disease. In addition, the results of our study showed that the median time interval between hysterectomy and pelvic malignant tumors onset was shorter in group A [median (IQR), 5 years (1, 8.5) vs 8y (3, 14), $P=.047$]. According to the results mentioned above, when pelvic mass appears within a short time (5–8 years) after hysterectomy, special attention should be paid to detect ovarian endometrioid carcinoma and ovarian clear cell carcinoma in patients from group A.

The data of our study also showed that referring to the hysterectomy with or without unilateral salpingo-oophorectomy, there was no significant difference in the probability of subsequent malignant tumors between the two groups (27.1 vs 33.8%, $P=.479$; 30 vs 38.09%, $P=.999$). However, for patients with a history of hysterectomy with bilateral salpingectomy, those in group A had a higher probability of developing malignant tumors than the latter one (50% vs 25%). In 2015, ACOG recommended hysterectomy with bilateral salpingectomy as a method to prevent ovarian cancer, especially serous ovarian cancer.[16] The results of our previous study suggest that hysterectomy with bilateral salpingectomy may be less efficacy in preventing the following ovarian cancer,[17] and the possible reason may be that the ovarian epithelium cancer of these patients are mainly endometrioid and clear cell carcinoma instead of serous cancer.

There are also some limitations in this study. When the patients included in our study underwent a hysterectomy, prophylactic bilateral salpingectomy was yet to be adopted as a medical practice. Therefore, the related data in this study are limited. A prospective study will be launched to investigate the value of simultaneously prophylactic bilateral salpingectomy at the time of hysterectomy in preventing ovarian cancer in patients with endometriosis/adenomyosis. Besides, this study was performed in a tertiary teaching hospital, thus there may be bias for the patients enrollment. Multicenter research should be implemented in the future. At last, the surgical approach on the subsequent pelvic mass was not analyzed for the large span of the time interval between 2 surgeries.

5. Conclusion

In summary, the pathology of the subsequent pelvic mass inclines to be benign, and there was no significant difference referring to the occurrence rate of subsequent malignant tumors between the 2 groups. But the incidence of ovarian endometrioid carcinoma and ovarian clear cell carcinoma was higher in those with a history of hysterectomy due to endometriosis/adenomyosis. Postoperative adjuvant therapy for those received hysterectomy due to endometriosis/adenomyosis may contribute to prevention the occurrence of benign pelvic mass. However, this study is a retrospective one, while there have been great changes in the recent surgical approaches (such as changes in the ratio of laparoscopic and open laparotomy) and the scope of surgery (such as the resection of the uterus and the simultaneous salpingectomy). Therefore, we will launch a prospective cohort study in the future to explore the clinicopathological characteristics of pelvic mass following hysterectomy for endometriosis or adenomyosis.

Author contributions

SW and HS conceived of the original idea for the study and edited the manuscript. XC and YL obtained ethical approval, contributed to the data collection and analysis, and contributed to drafts of the paper. MJ, QF and JL contributed to the study design, interpretation of results and commented on drafts of the

paper. All authors have approved the final version of the manuscript.

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