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ORIGINAL RESEARCH

Coexistence of Ovarian Mature Cystic Teratomas and Endometriosis: An Update

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Background: Mature cystic teratomas (MCTs) and endometriosis are the most common benign diseases in women of reproductive age. Their coexistence was traditionally considered rare. However, recent evidence suggests otherwise. This study aims to investigate the coexistence of MCTs and endometriosis and to analyze the clinical characteristics of this complex condition.

Materials and Methods: We retrospectively reviewed 285 women who underwent ovarian cystectomy for MCTs between January 2014 and December 2020. Serum anti-Müllerian hormone (AMH) levels were measured preoperatively and at 1 and 6 months postoperatively. Patients were followed for at least 6 months to assess recurrence.

Results: 57 (20%) patients had coexistence of MCTs and endometriosis (complex group); while 228 (80%) patients had MCTs alone (teratoma group). Endometrioma was found in 15 (26.79%) patients and peritoneal endometriosis in 41 (73.21%) patients. 39 (68.42%) patients had minimal/mild endometriosis, and 18 (31.58%) patients had severe endometriosis. Compared with the teratoma group, the complex group had a higher prevalence of dysmenorrhea (22.8% vs. 7.5%, p = 0.001) and higher serum CA125 levels (20.91 ± 16.93 vs. 14.00 ± 12.03 IU/mL, p = 0.01). Unclear cleavage planes between normal ovarian tissue and the cyst capsule were more frequent in the complex group (15.8% vs. 4.8%, p = 0.004). A greater decline in AMH at 1 month postoperatively was observed in the complex group (31.97% vs. 18.02%, p = 0.036), whereas no difference was noted at 6 months. Recurrence rates were similar between groups ($p = 0.484$).

Conclusion: Coexisting MCTs and endometriosis are not uncommon and is associated with more severe dysmenorrhea, elevated serum CA125 levels, and poorly defined cleavage planes between normal ovarian tissue and the cyst capsule. This complex condition may warrant consideration beyond the conventional management of either disease alone.

Keywords: coexistence, mature cystic teratomas, endometriosis

Introduction

Mature cystic teratomas (MCTs) and ovarian endometriosis (endometrioma) are common gynecologic diseases affecting reproductive age women. MCTs, also known as dermoid cysts, are the most common germ cell tumor, accounting for up to 70% of benign ovarian masses in women of childbearing age.[1,2] The actual prevalence is expected to be higher, as most MCTs are asymptomatic and are discovered incidentally during routine physical examinations or surgery for other pathologies.[3] Endometriosis is an estrogen-dependent chronic inflammatory condition defined as the presence of endometrial tissue outside the uterine cavity.[4] Endometriosis affects 3–43% women of reproductive age, and endometriomas are observed in 17–44% of women with endometriosis, accounting for up to 35% of benign ovarian cysts requiring surgery.[5] As such, these two diseases account for a large portion of the causes of benign ovarian cysts requiring surgery in women of childbearing age. MCTs and endometrioma are the most common and recurrent in women of childbearing age, and surgical treatment such as cyst removal shows negative results in terms of preserving ovarian reserve,[6] so management is changing from surgical removal to conservative treatment. Because

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MCTs generally show a gradual growth pattern with an average growth rate of about 1.8 mm per year, it has been suggested to approach them with expectant management in order to preserve ovarian function and reserve.[7] Early diagnosis and treatment have always been emphasized because delayed diagnosis of endometriosis can lead to detrimental consequences such as infertility caused by anatomical distortion of the reproductive and pelvic structures and a decrease in quality of life due to intractable pain such as dysmenorrhea and pelvic pain. In the case of endometrioma, laparoscopy has been known as the gold standard treatment.[8] However, as evidence has accumulated on a possible detrimental role of laparoscopic excision of endometrioma on ovarian function and reserve, the trend has recently shifted to trying medical therapy first rather than surgery.[9] Although treatment recommendations are provided for each disease, there is little recognition of the coexistence of these diseases. Our previous research indicated that the coexistence of MCTs and endometriosis is not uncommon, with a reported prevalence of approximately 22.54%.[3] As such, this complex condition may be frequently occurring, if not recognized. It is significant to investigate how MCTs and endometriosis affect each other and the clinical outcomes resulting from them, as the coexistence of these two diseases is not uncommon in women of reproductive age.

This purpose of this study was to investigate and analyze the clinical features of the coexistence of MCTs and endometriosis to help classify it from existing disorders and standardize its treatment.

Materials and Methods

Patients

From January 1, 2014 through December 31, 2020, we retrospectively enrolled women who had underwent cystectomy for MCTs. Patient data were obtained from medical records using the keyword "ovarian mature teratoma" or "dermoid cyst". This study was approved by the Institutional Review Board of Jeonbuk National University Hospital (File No.2021-07-003-011). The inclusion criteria were as follows: (1) under 45 years old; (2) MCTs confirmed by pathology; (3) Underwent surgical treatment including laparotomy, laparoscopy or the robot-assisted laparoscopy; (4) endometriosis confirmed by pathology and/or a visual confirmation of endometriosis lesions. Exclusion criteria were as follows: (1) a history of previous adnexal surgery; (2) any hormonal treatment within 6 months; (3) other surgeries, such as myomectomy, are performed at the same time as cyst removal.

Data Collection

Data regarding patient's age, body mass index (BMI), cyst size, location of cyst, number of cyst, serum cancer antigen (CA) 125 levels, serum carbohydrate antigen (CA)19–9 levels, the patient's clinical symptoms, and pathologic reports were retrieved from medical records. Cyst size was defined as the largest diameter measured by ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). Hemoglobin (Hb) level was measured before surgery and the day after surgery. Serum anti-Müllerian hormone (AMH) concentration was measured before surgery, 1 month after surgery, and six months after surgery. The serum AMH level was determined using a commercial kit (AMH Gen II assay; Beckman Coulter Inc., USA). Reduction rate of Hb level was calculated using the formula: 100 x (preoperative Hb - postoperative Hb)/ preoperative Hb. Reduction rate of AMH level was calculated using the formula: 100 x (preoperative AMH - postoperative AMH)/preoperative AMH. Endometriosis was classified according to the revised American Society for Reproductive Medicine classification.[10] Cystectomy was performed using a stripping technique, and hemostasis was achieved by suturing the entire ovary multiple times. In the case of laparoscopy, to reduce the risk of ovarian damage due to cauterization, the bleeding site after cystectomy was minimally cauterized and the ovary was sutured multiple. In the case of robotic surgery, hemostasis was achieved by suturing only the ovarian stroma. Outpatient follow-up examination were performed by ultrasound 1 month and 6 months after surgery, and recurrence was diagnosed when teratoma lesions that were not visible 1 month after surgery were suspected to be present in an ultrasound examination 6 months after surgery.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and were compared using an independent samples *t*-test. Categorical variables were expressed sample number and % and compared using Pearson's chi-squared test. P<0.05 was considered statistically significant.

Results

This study included 285 women with underwent ovarian cystectomy for MCTs, of whom 228 (80%) were in the teratoma group (pure MCTs only) and 57 (20%) were in the complex group with both MCTs and endometriosis. Table 1 summarized the baseline characteristics, clinical characteristics, preoperative and postoperative AMH levels, reduction rate of AMH levels, conversion to laparotomy, conversion to adnexectomy, and postoperative recurrence in the teratoma and the complex group (Table 1). Except for CA125 level, there was no significant difference in other parameters concerning age, BMI, parity, cyst size, location of cyst, number of cyst, CRP, and CA19-9 level. The serum CA125 levels in the complex group were significantly higher than in the teratoma group ($p = 0.01$). The clinical presentations that led to hospital visits were abdominal pain, dysmenorrhea (getting worse), irregular vaginal bleeding, or incidental finding. Although there was no difference in other clinical presentations between the two groups, the frequency of complaints of dysmenorrhea was significantly higher in the complex group than in the teratoma group ($p = 0.001$) (Figure 1).

There was no significant difference between the two groups in the type of surgical methods, such as laparotomy, laparoscopy, or robot-assisted laparoscopy (p = 0.886). Looking at the operative findings, the type of endometriosis in the complex group was peritoneal endometriosis in 41 (73.21%) patients and endometrioma in 15 (26.79%). The stage of endometriosis was mild stage (stage I and II) in 39 (68.42%) and moderate or severe stage (stage III and IV) in 18 (31.58%). Conversion to laparotomy and conversion from cystectomy to oophorectomy did not differ between the two

Table 1 Clinical Characteristics of the Patients

Variables	Subgroup	N	N (%)	Teratoma	Complex	P-value
Sample no (%)		285	100	228(80)	57(20)	
Age (years)		285	100	26.69±7.32	28.23±5.64	0.087
BMI (kg/m^2)		285	100	23.54±4.08	22.46±3.78	0.7
Parity (n)						0.568
	Multiparous	222	77.9	176(77.2)	46(80.7)	
	Nulliparous	63	22.1	52(22.8)	11(19.3)	
Clinical presentation (n)						
	Abdominal pain	79	27.7	64(28.1)	15(26.3)	0.791
	Dysmenorrhea	30	10.5	17(7.5)	13(22.8)	0.001**
	Irregular vaginal bleeding	73	25.6	63(27.6)	10(17.5)	0.119
	Incidental finding	101	35.4	82(36.0)	19(33.3)	0.71
Type of surgery (n)		285	100			0.886
	Laparotomy	34	11.9	28(12.3)	6(10.5)	
	Laparoscopy	218	76.5	173(75.9)	45(78.9)	
	Robot-assisted laparoscopy	33	11.6	27(11.8)	6(10.5)	
Cyst size (cm)		282	100	7.25±4.07	8.34±4.50	0.074
CRP (mg/L)		87	100	0.81±1.50	4.36±14.96	0.328
CA125 (U/mL)		253	100	14.00±12.03	20.91±16.93	0.01*
CA19-9 (U/mL)		252	100	113.30±347.85	70.02±111.85	0.396
Location of cyst (n)						0.358
	Lt	119	41.8	94(41.2)	25(43.9)	
	Rt	106	37.2	89(39.0)	17(29.8)	
	Both	60	21.1	45(19.7)	15(26.3)	

(*Continued*)

Table 1 (Continued).

Variables	Subgroup	N	N (%)	Teratoma	Complex	P-value
Number of cyst (n)						0.44
	Unilocular	133	46.7	109(47.8)	24(42.1)	
	Multilocular	152	53.3	119(52.2)	33(57.9)	
Type of endometriosis (n)						N/A
	Peritoneal endometriosis	41	73.21			
	Endometrioma	15	26.79			
Endometriosis stage (n, %)		57	100			N/A
	I and II	39	68.42			
	III and IV	18	31.58			
Uncertain cleavage plane (n)						0.004*
	0	265	93	217(95.2)	45(84.2)	
	1	20	7	11(4.8)	9(15.8)	
Preop Hb level (g/dl)		284	100	12.99±1.04	13.07±0.97	0.596
Postop Hb level (g/dl)		284	100	11.53±1.07	11.37±1.05	0.301
Decrease rate of Hb level (%)		284	100	11.10±6.12	13.03±4.83	0.27
Preop AMH level (ng/mL)		113	100	5.34±3.41	4.05±3.23	0.088
AMH level one month after surgery (ng/mL)		98	100	4.14±2.47	2.63±2.43	0.011*
AMH level 6 months after surgery (ng/mL)		54	100	5.39±3.71	4.41±3.94	0.388
Decrease rate of AMH level (1month) (%)		90	100	18.02±24.90	31.97±29.11	0.036*
Decrease rate of AMH level (6month) (%)		49	100	−5.08±30.95	−14.92±66.20	0.614
Laparotomy conversion (n)		2	0.7	1(0.4)	1(1.8)	0.361
Oophorectomy conversion (n)		3	1.1	1(0.4)	2(3.5)	0.103
Recurrence (n)		151	100			0.484
	0	136	90.1	102(91.1)	34(87.2)	
	1	15	9.9	10(8.9)	5(12.8)	

Notes: Continuous variables are expressed as mean ± SD; Categorical variables are expressed as sample number and %; *$p < 0.05$; **$p < 0.01$.
Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; CRP, C-reactive protein; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; EMS, endometriosis; Hb, hemoglobin; r-AFS, revised American Fertility Society; r-asrm, revised American Society for Reproductive Medicine; NA, not available.

groups ($p = 0.361$ and $p = 0.103$, respectively). In most cases of MCTs, the cleavage plane between the capsule of the cyst and the normal ovarian tissue is clear during cystectomy, making separation easy. However, in some cases, the capsule shows adhesion to normal tissue, making the cleavage plane unclear and making separation difficult. Figure 2 shows the above situation. In the complex group, cases with uncertain cleavage plane were significantly more common than in the teratoma group ($p = 0.004$). There was no difference in preoperative and postoperative Hb level in the two groups ($p = 0.596$ and $p = 0.301$, respectively).

There was no statistically significant difference in preoperative AMH level between the complex group and the teratoma group ($p = 0.388$). One month after surgery, the serum AMH level and reduction rate of AMH level were significantly lower in the complex group than in the teratoma group ($p = 0.011$ and $p = 0.036$, respectively). However, the serum AMH level and reduction rate of AMH level showed no significant difference between the two groups after 6 months after surgery ($p = 0.388$ and $p = 0.614$, respectively). There were no cases of reoperation in either patient group, and no postoperative complications such as chemical peritonitis occurred. Conversion from laparoscopy to laparotomy occurred in one patient in each group. In the teratoma group, it was due to large cyst size, and in the complex group, it was due to severe adhesions; there was no difference between the two groups ($p = 0.361$). There was no difference in conversion from cystectomy to oophorectomy between the two groups ($p = 0.103$). Moreover, 6 months after surgery, 10 (8.9%) patients in the teratoma group and 5 (12.8%) patients in the complicated group had recurrences, with no significant difference between the two groups ($p = 0.484$).

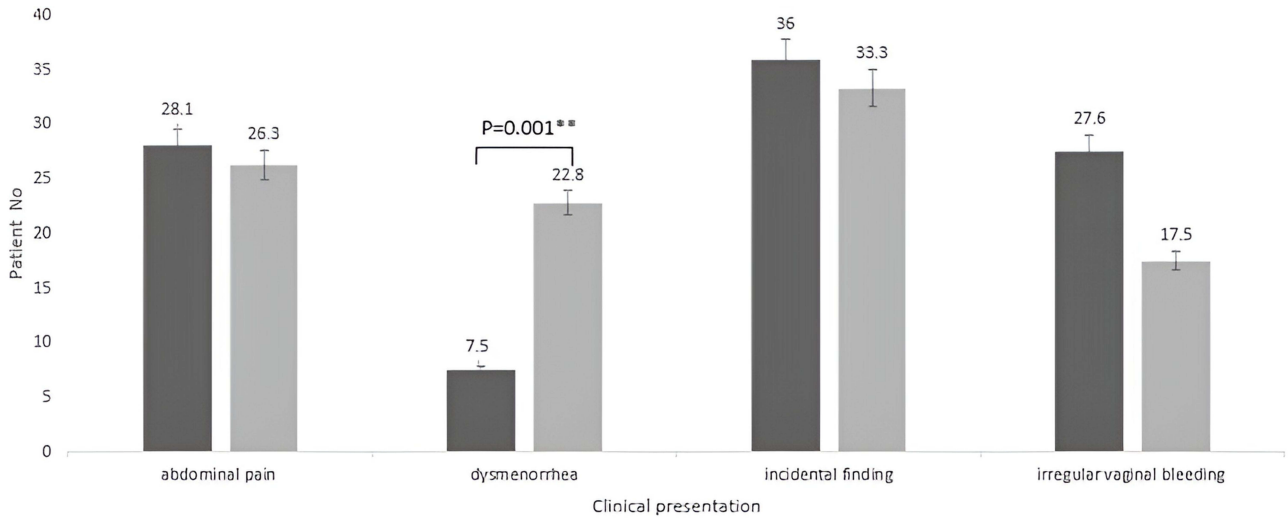

Figure 1 Distribution of clinical presentation between the teratoma group and the complex group. Y axis expressed as the number of patients. Patients percentage (%) of each clinical presentation was displayed on each bar (**$p < 0.01$).

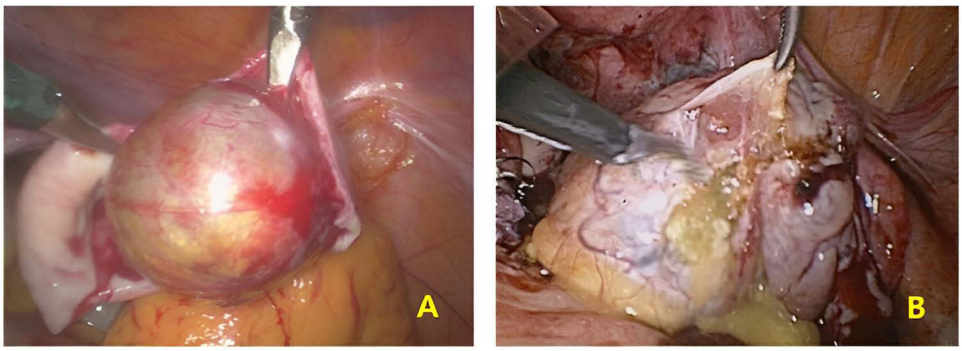

Figure 2 Surgical findings showing the cleavage plane between cyst and normal ovarian tissue during cyst removal. (**A**) is a case where the cleavage plane between cyst and normal ovarian tissue is clear. (**B**) is a case where the cleavage plane between cyst and normal ovarian tissue is unclear.

Discussion

In the present study, we explored the clinical characteristics of patients with coexistence of MCTs and endometriosis. Although previous reports suggested that such co-occurrence was uncommon,[11] our findings indicate that 20% of women undergoing cystectomy for MCTs also had pathologically and/or visually confirmed endometriosis. This high prevalence challenges the traditional view that coexistence is rare and underscores the importance of greater clinical awareness.

Two notable clinical differences emerged between women with MCTs alone and those in the complex group (MCTs plus endometriosis). First, patients in the complex group had statistically significantly more complaints of dysmenorrhea than those in the teratoma group. Second, patients in the complex group exhibited statistically significantly higher CA125 level, a noninvasive biomarker commonly elevated in the chronic inflammatory conditions such as endometriosis.[12]

MCTs are asymptomatic in 21.1% of cases, and is mostly discovered incidentally when undergoing physical examination or surgery for other causes.[13] Large MCTs may cause abdominal pain, such as chronic abdominal discomfort, due to increased pelvic pressure. The most common cause of acute abdominal pain in MCTs is ovarian torsion, which occurs in about 5–10% of cases and may be accompanied by symptoms such as nausea, vomiting, abnormal bleeding, and fever.[14] In addition, tumor rupture occurs in 1.2–3.8% of cases, which may cause acute abdominal pain.[15] In this study, asymptomatic cases accounted for 35.4% of all patients with MCTs, cases without

endometriosis accounted for 36%, and cases with coexisting endometriosis accounted for 33.3%, showing the most common clinical symptom of MCTs regardless of endometriosis. In addition, abdominal pain was reported in 27.7% of the total, 28.1% in patients with only MCTs, and 26.3% in patients with coexisting endometriosis, showing that endometriosis did not significantly affect abdominal pain. In this study, 25.6% of all patients with MCTs experienced irregular vaginal bleeding, but the presence of coexisting endometriosis did not affect this. The hallmark symptom of endometriosis is pelvic pain, usually dysmenorrhea, which is typically worsening around menstruation. Endometriosis is the main cause of secondary dysmenorrhea in young women, with a high prevalence of up to 71–87% of women with pelvic pain and 40–60% of those with dysmenorrhea.[16] In the present study, dysmenorrhea is observed in 10.5% of all patients with MCTs, which is a significant difference from the 7.5% in cases with only MCTs (22.8%) when endometriosis is present.

When comparing ovarian tumor markers between patients with MCTs and those with concurrent MCTs and endometriosis, serum CA125 level was significantly elevated in patients with concurrent endometriosis. Serum CA125 levels are elevated not only in endometriosis but also in many other gynecological diseases, such as uterine fibroids, adenomyosis, and pelvic inflammatory disease. In particular, serum CA 125 is currently the most widely used biomarker for the diagnosis and treatment of endometriosis, despite its low sensitivity and specificity and its elevation in many physiological and benign conditions making it far from a reliable biomarker.[17] In MCTs, CA19-9 elevation is more frequent and CA125 elevation is rare, but CA125 elevation can occur due to torsion and inflammatory process.[18] Some studies have also reported the possibility of malignant neoplasms in patients with MCTs when CA19-9 and CA125 levels were simultaneously elevated.[19]

In the present study, patients in the complex group (MCTs and plus endometriosis) had more complaints of dysmenorrhea and exhibited higher CA125 levels. These findings align with previous research showing that CA125 is commonly increased in endometriosis. Our data thereby highlight that in patients presenting with MCTs who also report significant dysmenorrhea and elevated CA125 levels, clinicians should have a heightened index of suspicion for concurrent endometriosis.

Since the primary target of MCTs and endometriosis is women of childbearing age, the possibility of damage to ovarian function and reserve due to surgery is a very important issue. In the case of endometrioma, which is an ovarian endometriosis, many studies have already revealed that ovarian function decline occurs after surgery.[6,20] In the case of MCTs, a retrospective cohort study investigated that the impact of MCTs or MCTs surgery on ovarian reserve in patients undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). The study showed that ovarian reserve was significantly reduced after MCTs excision.[21] Laparoscopic stripping technique for cystectomy have been shown to have destructive effects on ovarian function and reserve in both MCTs and endometrioma, with laparoscopic excision of endometrioma having a greater destructive effect on ovarian reserve than MCTs.[22] This difference may be because endometriomas may be closer to and more adherent to the ovary than MCTs, and thus more ovarian stroma and follicles are inadvertently removed during laparoscopic cystectomy. During cystectomy, the cleavage plane between normal ovarian tissue and the cyst was more frequently obscured in the complex group. This finding suggests that the chronic inflammatory changes and fibrotic processes associated with endometriosis may lead to more adhesions and make surgical dissection more challenging.[23] From a surgical perspective, this has two clinical implications. First, the uncertain cleavage planes can increase the risk of unintentional removal of normal ovarian tissue, which may adversely affect ovarian reserve.

To evaluate the impact of laparoscopic cystectomy on ovarian reserve, we measured and compared serum AMH levels, a well-known ovarian reserve marker, before and after surgery.[24] Although the two groups did not differ significantly in their baseline AMH levels, the complex group experienced a greater immediate drop in AMH at one month postoperatively. This acute reduction likely reflects damage to the follicles secreting AMH after surgery and more extensive surgical manipulation. Reassuringly, by six months postoperatively, the AMH levels appeared to recover to a level similar to that of the teratoma group. The reason why AMH levels recovered is said to be because "rearrangement of follicle cohorts" occurs, in which the primordial follicles remaining after cystectomy are recruited and grow into follicles that secrete AMH.[25] At last, this partial "catch-up" suggests that the short-term impact on ovarian reserve need

not translate into long-term compromise, although close monitoring remains critical for these patients, especially those desiring future fertility.

Second, in cases such as the complex group with adhesive and ambiguous the cleavage planes, the risk of cyst rupture and spillage of cystic contents during excision of MCTs using stripping technique may be increased compared to the teratoma group. Because cyst rupture and spillage of cystic contents carries a high risk of postoperative complications such as chemical peritonitis, adhesion formation, or iatrogenic spills of malignant cells, prevention of cyst rupture and spillage of cystic contents is emphasized.[26] In our study, there were no cases of reoperation in either group, and there was no difference between the two groups in cases of conversion from laparoscopy to laparotomy or conversion from cystectomy to oophorectomy. Thus, obscured cleavage planes make it more challenging for clinicians to remove the cyst, but do not significantly increase the risk of conversion to laparotomy or postoperative complications.

Previous studies have reported that the recurrence rate of MCTs after cystectomy using laparoscopy or open surgery ranges from 3.4% to 11.2%.[27,28] Risk factors for recurrence of MCTs include younger age, large cyst, and bilaterality.[29] In our study, the overall recurrence rate was 9.9%. Our findings did not show any significant difference in the occurrence of recurrence between the two groups over a minimum follow-up of six months. Long-term studies will be important to determine whether these results apply to larger populations or over longer period of time, especially in the presence of coexisting endometriosis and obscured cleavage planes.

The findings in this important group of patients, representing 20% of the study population, highlight the need for a more meticulous approach to diagnosis and treatment. Women with suspected MCTs should continue to be cautious about the possibility of coexisting endometriosis, especially those with dysmenorrhea and elevated CA 125 levels. From a therapeutic perspective, early initiation of conservative medical treatment for endometriosis (eg, hormonal suppression) combined with close monitoring of MCTs may help minimize the risk of surgical complications and potential compromise of ovarian reserve.

Future research may include the following: First, prospective multicenter studies with larger sample sizes and longer follow-up periods should be conducted to verify our findings and clarify the long-term risk of recurrence. Second, studies on the molecular or genetic mechanisms underlying the co-occurrence of these conditions may provide new insights that may inform personalized management strategies.

This study has several limitations. First, this study was a retrospective, single-center study with a relatively limited sample size, which may have introduced selection and information bias and limited the generalizability of the findings. Second, the short follow-up period of 6 months may not fully reflect the natural course or recurrence rate of this disease. Third, the diagnosis of peritoneal endometriosis lesions by visual inspection rather than pathological confirmation may lead to overestimation or underestimation.

Conclusion

Our study suggests that the coexistence of MCTs and endometriosis is more common than previously recognized, occurring in approximately one fifth of cases. Patients with this complex condition tend to have more pronounced dysmenorrhea, higher CA 125 levels, and more challenging cystectomy due to obscured cleavage planes. Although decline in ovarian reserve was more pronounced immediately after surgery, fortunately this decline was transient, and recovery was comparable to women with MCTs alone. Recognizing this coexistence as a distinct clinical entity may improve diagnostic accuracy and guide more nuanced management strategies aimed at preserving ovarian function.

Data Sharing Statement

Data are available from the corresponding author Hee-Suk Chae upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Jeonbuk National University Hospital (File No. 2021-07-003-011). Written informed consent was obtained from all participants prior to study commencement.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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