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Risk Factors of Vaginal Cuff Infection in Women Undergoing Laparoscopic Hysterectomy for Benign Gynecological Diseases

Running Title: Vaginal cuff infection after TLH

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Abstract

Aim: This study aimed to identify the risk factors for vaginal cuff infection after laparoscopic hysterectomy for benign gynecological diseases.

Methods: We conducted a retrospective cohort study among 1559 Japanese women who underwent total laparoscopic hysterectomy (TLH) for benign indications between 2014 and 2018 at Teine Keijinkai Hospital in Sapporo, Japan. All patients received preoperative antibiotics based on appropriate timing, choice, and weight-based dosing. We assessed the risk factors of vaginal cuff infection after TLH, including demographic and clinical variables, and patient- and surgery-related factors, using univariable and multivariable logistic regression analyses.

Results: Among all the patients who underwent TLH, 71 cases of vaginal cuff infections (4.6%) were recorded. Univariate analyses showed that current smoking, pathological result of adenomyosis, use of Seprafilm as an antiadhesive material, white blood cell counts on postoperative day (POD) 2, C-reactive protein (CRP) level on POD2, and postoperative vaginal cuff hematoma were significantly associated with an increased risk of vaginal cuff infection. In multivariate analysis, current smoking, use of Seprafilm, CRP level on POD2, and vaginal cuff hematoma were significantly associated with an increased risk of vaginal cuff infection.

Conclusions: Current smoking, use of Seprafilm, CRP level on POD2, and vaginal cuff hematoma were identified as significant risk factors of vaginal cuff infection in the 30 days after surgery in Japanese women who underwent TLH for benign indications.

Keywords: Gynecological diseases, Hysterectomy, Laparoscopy, Risk factors, Surgical site infection

Introduction

Surgical site infection (SSI) is generally defined as an infection that occurs after surgery in the same part of the body where the surgery took place[1], and it is considered to be a common complication after hysterectomy[2]. Many infections can occur after hospital discharge[3]. Some of the most common complications in patients requiring readmission after hysterectomy are SSI[4]. These infections can often lead to significant social and economic costs for both the patient and the healthcare system[5–7].

Hysterectomy has been considered to be one of the most common surgical procedures in women, and the majority of hysterectomies are performed for benign indications[8]. Laparoscopy has widely replaced laparotomy for gynecological surgery in the past two decades[9]. The number of laparoscopic hysterectomies performed has increased, whereas fewer abdominal hysterectomies are performed[10]. It has been reported that the rate of all SSIs after total laparoscopic hysterectomy (TLH) was lower than that after abdominal hysterectomy (2% vs 4%)[11]. Despite these lower rates, SSIs are not uncommon after laparoscopic hysterectomy[2]. In our experience, we have found that vaginal cuff infection after TLH often requires rehospitalization and treatment with antibiotics. In addition, vaginal cuff infection after TLH may decrease the subsequent quality of life (QOL) outcomes including post-traumatic stress in patients undergoing

TLH[12]. In other words, the prevention of vaginal cuff infection may improve QOL outcomes after TLH. Thus, identifying the risk factors of vaginal cuff infection is clinically vital to reduce the rates of morbidity and rehospitalization and to lighten the burden for both patients and the healthcare system.

Therefore, in this present study, we aimed to determine the risk factors of vaginal cuff infection after TLH, which were identified before, during, and after operation, in Japanese patients with benign gynecological diseases.

Methods

Study Design and Population

We conducted a retrospective cohort study among 1559 women who underwent TLH for benign indications between January 1, 2014 and December 31, 2018 at Teine Keijinkai Hospital in Sapporo, Japan. All patients have received antibiotics within 60 min of incision in the operating room. Intraoperative redosing was conducted every 3 h. All patients were admitted to the hospital 1 day before their surgery and had a blood test on postoperative day (POD) 2, according to our department's clinical protocol (Table S1). This study has been approved by the research ethics committee of Teine Keijinkai Hospital (Approval number: 2018121).

Measurements of Exposures

Data were collected from 40 variables (Table S2), which included preoperative (i.e., demographic data, comorbidities, and laboratory values within the 90 days before surgery), intraoperative (i.e., surgical data, retrieval method of specimens, surgical techniques in addition to TLH, type of antiadhesive material used, and intraoperative complications), and postoperative variables (laboratory values on POD2, pathological results, and 30-day postoperative complications before the onset of vaginal cuff infection like vaginal bleeding requiring reoperation and vaginal cuff hematoma found after TLH). We defined an experienced operator as a surgeon certified by the Skill Qualification Committee of the Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Therapy or a surgeon with equivalent surgical skills.

Measurements of Outcomes

Symptoms of vaginal cuff infection often manifest as fever, purulent vaginal discharge, and pelvic, abdominal, or low back pain[10]. We defined vaginal cuff infection after TLH within 30 days of surgery, as per the Centers for Disease Control and Prevention criteria[1,13] (Table S3). Vaginal cuff infection corresponds to deep and

organ/space infection, as these two categories are difficult to distinguish when considering hysterectomy as the primary procedure[14]. Attending physicians diagnosed vaginal cuff infection based on vital signs, physical findings, blood test, gynecological examination findings, transvaginal ultrasound, and computed tomography in some cases.

Statistical Analysis

Data were reported as median (interquartile range [IQR]) for continuous variables. Categorical variables were presented as proportions and were reported as number (%). In order to identify the risk factors associated with vaginal cuff infection during the 30 days after TLH, univariate analyses and multivariable logistic regression were performed, and we also estimated odds ratios (OR) and 95% confidence intervals (CI). In comparing each variable between the two groups, we have used the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables, because all variables were nonparametric distributions. For selection of independent variables in multivariable logistic regression, significant variables in univariate analysis as well as clinical variables of interest in backward

stepwise regression were included. All tests of significance were two-sided, with *p* set at less than 0.05. We used statistical software R 3.6.1 for the statistical analyses[15].

Results

The clinical characteristics of patients are shown in Table 1. The median patient age was 46.0 years (IQR, 43.0–49.0 years), and the median body mass index was 22.4 (IQR, 20.4–25.4) kg/m^2. Of the 1559 patients, 71 patients (4.6%) have developed vaginal cuff infection during the 30 days after TLH. The median onset of vaginal cuff infection was POD 7 (IQR, POD 5–9). Of the infected patients, the majority (35%) was polymicrobial, with mixed aerobes and anaerobes or mixed aerobes flora in vaginal cultures (Table S4).

Associations between various factors in the pre-, intra-, and postoperative periods and the development of vaginal cuff infection during the 30 days after TLH are all presented in Table 2. On univariate analysis, current smoking (OR, 2.5; 95% CI, 1.5–4.1), pathological result of adenomyosis (OR, 1.7; 95% CI, 1.1–2.9), use of Seprafilm (OR, 7.8; 95% CI, 1.4–36.3), white blood cell count on POD2 (OR, 1.2; 95% CI, 1.1–1.3), C-reactive protein (CRP) level on POD2 (OR, 1.1; 95% CI, 1.1–1.2), and postoperative vaginal cuff hematoma (OR, 8.8; 95% CI, 2.7–28.9) were all determined

137 to be associated with vaginal cuff infection. Independent risk factors for vaginal cuff
138 infection in the multivariate model were current smoking (OR, 2.2; 95% CI, 1.3–3.7),
139 use of Seprafilm (OR, 8.6; 95% CI, 2.3–32.9), CRP level on POD2 (OR, 1.1; 95% CI,
140 1.0–1.2), and postoperative vaginal cuff hematoma (OR, 8.2; 95% CI, 2.4–28.1).
141

142 **Discussion**

143 The rate of deep and organ/space SSI after TLH has been reported to range
144 between 0.5% and 1.2%[14,16]. Neiboer et al., after reviewing previous studies, have
145 reported that the rate of vaginal cuff infection was 3.48%[17]. In the present study, the
146 rate of 30-day vaginal cuff infection was found to be at 4.6%, which is higher than that
147 reported in previous studies. Our study identified four risk factors associated with
148 increased odds of vaginal cuff infection after TLH.

149 Regarding preoperative risk factors, current smoking has been related to
150 increased deep and organ/space SSI after hysterectomy in previous studies[14,18].
151 Smoking can cause ischemia and delayed wound healing, which in turn can lead to
152 increased rates of SSI[19]. Patients should be advised to stop smoking at least 30 days
153 before an elective surgery[20].

Regarding intraoperative factors, we found a significant association between the use of Seprafilm and postoperative vaginal cuff infection. Seprafilm is composed of two anionic polysaccharides, sodium hyaluronate and carboxymethylcellulose, which have been reported to be chemically modified. This barrier transforms into a gel after being placed in the peritoneum; it is reabsorbed in approximately 7 days, after normal tissue repair has taken place and the inflammatory cascade has subsided[21]. Seprafilm thus reduces the incidence of postoperative adhesions[22–25]. Despite its advantages, it has also been reported to carry an increased risk of intraabdominal abscess formation, anastomotic leaks[25], fluid collection, and sterile peritonitis[21,26,27]. However, only 15 patients in whom Seprafilm was used in our study were included. Further research is needed to confirm the correlation between the use of Seprafilm and the occurrence of vaginal cuff infection after TLH.

Lastly, regarding postoperative factors, we identified CRP level on POD2 and postoperative hematomas as risk factors for vaginal cuff infection. We perform a blood test on POD2 for all patients undergoing TLH. A normal CRP range on POD2 after TLH was reported as between to be 6.19 and 7.83 mg/dL[28,29]. The median CRP value on POD2 in patients with postoperative vaginal cuff infection in our study was 3.3 (IQR, 1.6–5.9) mg/dL, which is lower than the values reported in previous studies. A

172 significant difference was recognized between the vaginal cuff infection group and the
173 non-vaginal cuff infection group in our study, but the median CRP value on POD2 in
174 patients without vaginal cuff infection was 2.1 (IQR, 1.1–3.6) mg/dL, and the
175 differences were found to be small. Anticipating postoperative vaginal cuff infection at
176 POD2 might be difficult.

177 It has been reported that postoperative hematomas after hysterectomy
178 predispose to the development of infection. Maintaining hemostasis, gentle handling of
179 tissue, and eradicating hematoma are important intraoperative steps in preventing
180 infection[2,30–32]. Five patients (35.7%) took prophylactic antibiotics prescribed by
181 attending physicians among 14 patients with postoperative vaginal cuff hematoma.
182 Among five patients who took prophylactic antibiotics, no patients developed vaginal
183 cuff infection. On the other hand, among nine patients who did not take prophylactic
184 antibiotics, four patients (44.4 %) developed vaginal cuff infection. Therefore, taking
185 prophylactic antibiotics were important to prevent the incidence of vaginal cuff
186 infection in patients with postoperative vaginal cuff hematoma. In the case of vaginal
187 cuff hematoma after TLH, prophylactic antibiotic medication to prevent subsequent
188 vaginal cuff infection should be implemented.

In our study, we surveyed patients undergoing TLH for only benign indications. Katherine et al. have reported there were no differences seen between benign and malignant surgical indications in rates of deep and organ space SSI after TLH[33]. Although operative time was not independent risk factor of vaginal cuff infection after TLH in our study, longer operative time has been identified as a risk factor of SSI included deep and organ space SSI in previous many studies[11,18,34,35]. The study of Yüksel et al. showed that the operative time of TLH was predisposed to be longer for malignant gynecologic indication than benign gynecologic indication[36], and thus, the morbidity of vaginal cuff infection after TLH for malignant diseases might increase seemingly compared with benign diseases. Further research is warranted to examine the risk factors for SSI in patients with malignant diseases undergoing TLH.

We found that vaginal cuff infection was caused mainly by polymicrobial in this study. When the vagina is opened during surgery, as in the procedure of hysterectomy, endogenous polymicrobial flora of aerobes and anaerobes in the vagina may ascend from the breached vagina and endocervix to the operative site, in addition to the microorganisms from the skin, which are the flora of predominantly aerobic Gram-positive cocci. Therefore, the source of pathogens for vaginal cuff infection is usually polymicrobial[2,16,37,38].

The strength of this study is the inclusion of detailed perioperative information from our database. Moreover, all patients received standardized and homogenized management in our hospital. On the other hand, this study also has several limitations, and the results should be interpreted with caution. First, this study has the inherent bias associated with its retrospective design. Second, we could not consider an association between vaginal cuff infection and TLH for pelvic organ prolapse among benign indications[39] because the patients with pelvic organ prolapse was too low in the present study. Thus, further studies are needed to clarify the impact of vaginal cuff suspension after TLH in patients with apical pelvic organ prolapse. Finally, our study reflected the experience of a single hospital, and this might not be generalizable to other institutions and settings.

In conclusion, in a population of women who underwent TLH for benign indications at Teine Keijinkai Hospital, we found that current smoking, use of Seprafilm, CRP level on POD2, and postoperative vaginal cuff hematoma were significant SSI risk factors of vaginal cuff infection. To reduce the morbidity rate of vaginal cuff infection after TLH, patients are advised to stop smoking before the operation. Furthermore, in the case of vaginal cuff hematoma after TLH, we should

consider prophylactic antibiotic medication to prevent subsequent vaginal cuff infection.

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Disclosure

The authors declare no conflicts of interest directly relevant to the content of this article.

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356 Table 1. Demographic, preoperative, intraoperative, and postoperative characteristics of
357 patients who underwent laparoscopic hysterectomy for benign indication
358

Variable	Infected patients	Uninfected patients	*P*-value
Number of patients	71	1488	
Preoperative factors			
Age (y)	45.0 (42.0–48.0)	46.0 (43.0–49.0)	.151
BMI (kg/m^2)	23.2 (21.0–25.7)	22.4 (20.4–25.3)	.466
Parity			
Para 0	21 (30)	497 (34)	.551
Para 1	17 (24)	304 (20)	
Para 2	23 (32)	530 (36)	
Para 3	8 (11)	140 (9)	
Para 4–7	2 (3)	17 (1)	
History of vaginal delivery	43 (61)	885 (59)	.950
History of cesarean section	12 (17)	208 (14)	.605
Current diabetes mellitus	0 (0)	24 (2)	.623
Current smoking	26 (37)	281 (19)	**<.001**
ASA classification			
ASA class 1	49 (69)	934 (63)	.280
ASA classes 2–3	22 (31)	554 (37)	
Hb before operation, g/dl	12.8 (11.5–13.7)	12.8 (11.9–13.7)	.818
PLT before operation, $10^4/\mu L$	26.4 (22.6–31.7)	26.1 (22.2–30.6)	.608
Past history of abdominal surgery	25 (35)	561 (38)	.766
Intraoperative factors			
Intraperitoneal adhesion	30 (42)	457 (31)	.055
Uterine retrieval through vagina	68 (96)	1381 (93)	.474
Uterine morcellation	3 (4)	118 (8)	.167
Specimen weight, g	287.4 (169.4–427.5)	283.0 (178.2–460.8)	.778
Intraoperative bleeding, g	80.0 (20.0–200.0)	50.0 (20.0–100.0)	.054
An experienced operator	48 (68)	879 (59)	.191
Operative time, min	147.0 (103.5–189.5)	132.0 (105.0–168.0)	.123
Transfusion	0 (0.0)	7 (0.5)	1.00
Additional operative technique			

(included multiple responses)			
Salpingo-oophorectomy	7 (10)	252 (17)	.161
Oophorocystectomy	5 (7)	83 (6)	.594
Salpingectomy	35 (49)	614 (41)	.223
Antiadhesive material			
Beriplast P	13 (18)	291 (20)	.916
Bolheal	5 (7)	170 (11)	.336
Interceed	47 (66)	893 (60)	.360
Seprafilm	3 (4)	12 (1)	**.028**
AdSpray	2 (3)	77 (5)	.578
Urinary tract injury	0 (0.0)	4 (0.3)	1.00
Bladder injury	0 (0.0)	5 (0.3)	1.00
Intestinal injury	0 (0.0)	3 (0.2)	1.00
Intestinal resection	0 (0.0)	6 (0.4)	1.00
Postoperative factors			
WBC count on POD2, mm^3	6830 (5580–8495)	6360 (5390–6703)	**.029**
Hb count on POD2, g/dl	11.4 (9.9–12.4)	11.6 (10.6–12.5)	.079
PLT count on POD2, $10^4/\mu L$	23.1 (18.3–26.6)	22.3 (18.9–23.1)	.975
CRP level on POD2, mg/dL	3.3 (1.6–5.9)	2.1 (1.1–3.6)	**<.001**
Pathological result (included multiple responses)			
Leiomyoma	57 (80)	1275 (86)	.067
Adenomyosis	25 (35)	353 (24)	**.039**
Endometriosis	18 (25)	303 (20)	.387
Postoperative vaginal bleeding	1 (1)	1 (0.1)	.089
Postoperative vaginal cuff hematoma	4 (6)	10 (1)	**.003**

Values are presented as n (%) or median (interquartile range).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; *CRP, C-reactive protein; ; Hb, h*emoglobin; PLT, p*latelet; POD, postoperative day; WBC, white blood cell.*

366 Table 2. Univariate and multivariate analysis for factors associated with SSI

367

Characteristic	Univariate analysis				Multivariate analysis			
	OR	95% CI lower	95% CI upper	*p*-value	Adjusted OR	95% CI lower	95% CI upper	*P* value
Preoperative factors								
Age, y	1.0	0.9	1.0	.151				
BMI, kg/m^2	1.0	1.0	1.1	.466				
Parity (ref = Para 0)								
Para 1	1.3	0.7	2.6	.389				
Para 2	1.0	0.6	1.9	.936				
Para 3	1.4	0.6	3.1	.451				
Para 4-7	3.0	0.4	11.3	.166				
History of vaginal delivery	1.0	0.6	1.7	.950				
History of cesarean section	1.3	0.7	2.4	.605				
Current diabetes mellitus	0.4	0.03	6.9	.623				
Current smoking	**2.5**	**1.5**	**4.1**	**<.001**	**2.2**	**1.3**	**3.7**	**.002**
ASA classification (ref = ASA 1)								
ASA class 2-3	0.8	0.4	1.2	.283				
Hb before operation, g/dl	1.0	0.8	1.1	.818				
PLT before operation, 10^4/μL	1.0	1.0	1.0	.608				
Past history of abdominal surgery	0.9	0.5	1.5	.766				
Intraoperative factors								
Intraperitoneal adhesion	1.7	1.0	2.7	.055				
Uterine retrieval through vagina	1.8	0.5	5.7	.474				
Uterine morcellation	0.5	0.2	1.7	.167				
Specimen weight, g/100	1.0	0.9	1.1	.767				
Intraoperative bleeding, g	1.0	1.0	1.0	.054				
An experienced operator	1.4	0.9	2.4	.191				
Operative time, min/100	1.3	1.0	1.8	.074				
Transfusion	1.4	0.1	24.4	1.00				
Additional operative technique (included multiple responses)								
Salpingo-oophorectomy	0.4	0.2	0.9	.161				

Oophorocystectomy	1.0	0.4	2.5	.594				
Salpingectomy	1.4	0.9	2.2	.223				
Antiadhesive material (ref = no use of *antiadhesive material*)								
Beriplast P	1.2	0.5	3.4	.661				
Bolheal	0.8	0.2	2.9	.779				
Interceed	1.5	0.6	4.1	.406				
Seprafilm	**7.8**	**1.4**	**36.3**	**.011**	**8.6**	**2.3**	**32.9**	**.002**
AdSpray	0.7	0.1	2.9	.665				
Urinary tract injury	2.3	0.1	43.3	1.00				
Bladder injury	1.9	0.1	34.4	1.00				
Intestinal injury	3.0	0.2	58.0	1.00				
Intestinal resection	1.6	0.1	28.6	1.00				
Postoperative factors								
WBC count on POD2, mm^3/1000	**1.2**	**1.1**	**1.3**	**<.001**	1.0	1.0	1.0	.135
Hb count on POD2, g/dl	0.8	0.7	1.0	.079				
PLT count on POD2, $10^4/\mu L$	1.0	1.0	1.0	.975				
CRP level on POD2, mg/dL	**1.1**	**1.1**	**1.2**	**<.001**	**1.1**	**1.0**	**1.2**	**.011**
Pathological result (included multiple responses)								
Leiomyoma	0.6	0.3	1.0	.067				
Adenomyosis	**1.7**	**1.1**	**2.9**	**.039**	1.6	1.0	2.8	.064
Endometriosis	1.3	0.8	2.3	.387				
Postoperative vaginal bleeding	21.2	1.3	343.1	.089				
Postoperative vaginal cuff hematoma	**8.8**	**2.7**	**28.9**	**.003**	**8.2**	**2.4**	**28.1**	**<.001**

For selection of independent variables in multivariable logistic regression, we included significant variables in univariate analysis and clinical variables of interest in backward stepwise regression.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; OR, odds ratio; PLT, platelet; POD, postoperative day; WBC, white blood cell.