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Author(s)	Tsuzuki, Yoko; Hirata, Takumi; Tsuzuki, Shinya; Wada, Shinichiro; Tamakoshi, Akiko
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1	Risk Factors of Vaginal Cuff Infection in Women Undergoing Laparoscopic
2	Hysterectomy for Benign Gynecological Diseases
3	
4	Running Title: Vaginal cuff infection after TLH
5	
6	Yoko Tsuzuki, ^{1,2} Takumi Hirata, ² Shinya Tsuzuki, ³ Shinichiro Wada, ¹ Akiko
7	Tamakoshi ²
8	
9	¹ Department of Obstetrics and Gynecology, Teine Keijinkai Hospital, 1-40, 1-jou, 12-
10	choume, Maeda, Teine-ku, Sapporo city, Hokkaido, 006-8555, Japan
11	² Department of Public Health, Hokkaido University Faculty and Graduate School of
12	Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo city, Hokkaido, 060-8638, Japan
13	³ Disease Control and Prevention Center, National Center for Global Health and
14	Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo, 162-8655, Japan
15	
16	Corresponding author: Takumi Hirata, Department of Public Health, Hokkaido
17	University Faculty and Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku,
18	Sapporo city, Hokkaido, 060-8638, Japan

- 19 E-mail address: <u>t-hirata@med.hokudai.ac.jp</u>
- TEL: +81-11-706-5068
- FAX: +81-11-706-7805

23 Abstract

24	Aim: This study aimed to identify the risk factors for vaginal cuff infection after
25	laparoscopic hysterectomy for benign gynecological diseases.
26	Methods: We conducted a retrospective cohort study among 1559 Japanese women
27	who underwent total laparoscopic hysterectomy (TLH) for benign indications between
28	2014 and 2018 at Teine Keijinkai Hospital in Sapporo, Japan. All patients received
29	preoperative antibiotics based on appropriate timing, choice, and weight-based dosing.
30	We assessed the risk factors of vaginal cuff infection after TLH, including demographic
31	and clinical variables, and patient- and surgery-related factors, using univariable and
32	multivariable logistic regression analyses.
33	Results: Among all the patients who underwent TLH, 71 cases of vaginal cuff
34	infections (4.6%) were recorded. Univariate analyses showed that current smoking,
35	pathological result of adenomyosis, use of Seprafilm as an antiadhesive material, white
36	blood cell counts on postoperative day (POD) 2, C-reactive protein (CRP) level on
37	POD2, and postoperative vaginal cuff hematoma were significantly associated with an
38	increased risk of vaginal cuff infection. In multivariate analysis, current smoking, use of
39	Seprafilm, CRP level on POD2, and vaginal cuff hematoma were significantly
40	associated with an increased risk of vaginal cuff infection.

41	Conclusions: Current smoking, use of Seprafilm, CRP level on POD2, and vaginal cuff
42	hematoma were identified as significant risk factors of vaginal cuff infection in the 30
43	days after surgery in Japanese women who underwent TLH for benign indications.
44	
45	Keywords: Gynecological diseases, Hysterectomy, Laparoscopy, Risk factors, Surgical
46	site infection
47	

48 Introduction

49	Surgical site infection (SSI) is generally defined as an infection that occurs
50	after surgery in the same part of the body where the surgery took place ⁽¹⁾ , and it is
51	considered to be a common complication after hysterectomy ⁽²⁾ . Many infections can
52	occur after hospital discharge ⁽³⁾ . Some of the most common complications in patients
53	requiring readmission after hysterectomy are SSI ⁽⁴⁾ . These infections can often lead to
54	significant social and economic costs for both the patient and the healthcare system ^(5–7) .
55	Hysterectomy has been considered to be one of the most common surgical
56	procedures in women, and the majority of hysterectomies are performed for benign
57	indications ⁽⁸⁾ . Laparoscopy has widely replaced laparotomy for gynecological surgery in
58	the past two decades ⁽⁹⁾ . The number of laparoscopic hysterectomies performed has
59	increased, whereas fewer abdominal hysterectomies are performed ⁽¹⁰⁾ . It has been
60	reported that the rate of all SSIs after total laparoscopic hysterectomy (TLH) was lower
61	than that after abdominal hysterectomy $(2\% \text{ vs } 4\%)^{(11)}$. Despite these lower rates, SSIs
62	are not uncommon after laparoscopic hysterectomy ⁽²⁾ . In our experience, we have found
63	that vaginal cuff infection after TLH often requires rehospitalization and treatment with
64	antibiotics. In addition, vaginal cuff infection after TLH may decrease the subsequent
65	quality of life (QOL) outcomes including post-traumatic stress in patients undergoing

66	TLH ⁽¹²⁾ . In other words, the prevention of vaginal cuff infection may improve QOL
67	outcomes after TLH. Thus, identifying the risk factors of vaginal cuff infection is
68	clinically vital to reduce the rates of morbidity and rehospitalization and to lighten the
69	burden for both patients and the healthcare system.
70	Therefore, in this present study, we aimed to determine the risk factors of
71	vaginal cuff infection after TLH, which were identified before, during, and after
72	operation, in Japanese patients with benign gynecological diseases.
73	
74	Methods
75	Study Design and Population
76	We conducted a retrospective cohort study among 1559 women who
77	underwent TLH for benign indications between January 1, 2014 and December 31,
78	2018 at Teine Keijinkai Hospital in Sapporo, Japan. All patients have received
79	antibiotics within 60 min of incision in the operating room. Intraoperative redosing was
80	conducted every 3 h. All patients were admitted to the hospital 1 day before their
81	surgery and had a blood test on postoperative day (POD) 2, according to our
82	department's clinical protocol (Table S1). This study has been approved by the research
83	ethics committee of Teine Keijinkai Hospital (Approval number: 2018121).

Measurements of Exposures

86	Data were collected from 40 variables (Table S2), which included preoperative
87	(i.e., demographic data, comorbidities, and laboratory values within the 90 days before
88	surgery), intraoperative (i.e., surgical data, retrieval method of specimens, surgical
89	techniques in addition to TLH, type of antiadhesive material used, and intraoperative
90	complications), and postoperative variables (laboratory values on POD2, pathological
91	results, and 30-day postoperative complications before the onset of vaginal cuff
92	infection like vaginal bleeding requiring reoperation and vaginal cuff hematoma found
93	after TLH). We defined an experienced operator as a surgeon certified by the Skill
94	Qualification Committee of the Japan Society of Gynecologic and Obstetric Endoscopy
95	and Minimally Invasive Therapy or a surgeon with equivalent surgical skills.
96	
97	Measurements of Outcomes
98	Symptoms of vaginal cuff infection often manifest as fever, purulent vaginal
99	discharge, and pelvic, abdominal, or low back $pain^{(10)}$. We defined vaginal cuff
100	infection after TLH within 30 days of surgery, as per the Centers for Disease Control
101	and Prevention criteria ^(1,13) (Table S3). Vaginal cuff infection corresponds to deep and

102	organ/space infection, as these two categories are difficult to distinguish when
103	considering hysterectomy as the primary procedure ⁽¹⁴⁾ . Attending physicians diagnosed
104	vaginal cuff infection based on vital signs, physical findings, blood test, gynecological
105	examination findings, transvaginal ultrasound, and computed tomography in some
106	cases.
107	
108	Statistical Analysis
109	Data were reported as median (interquartile range [IQR]) for continuous
110	variables. Categorical variables were presented as proportions and were reported as
111	number (%). In order to identify the risk factors associated with vaginal cuff infection
112	during the 30 days after TLH, univariate analyses and multivariable logistic regression
113	were performed, and we also estimated odds ratios (OR) and 95% confidence intervals
114	(CI). In comparing each variable between the two groups, we have used the chi-square
115	test or Fisher's exact test for categorical variables and the Mann–Whitney U test for
116	continuous variables, because all variables were nonparametric distributions. For
117	selection of independent variables in multivariable logistic regression, significant

118 variables in univariate analysis as well as clinical variables of interest in backward

119	stepwise regression were included. All tests of significance were two-sided, with p set at
120	less than 0.05. We used statistical software R 3.6.1 for the statistical analyses ^{(15)} .
121	
122	Results
123	The clinical characteristics of patients are shown in Table 1. The median
124	patient age was 46.0 years (IQR, 43.0-49.0 years), and the median body mass index was
125	22.4 (IQR, 20.4–25.4) kg/m ² . Of the 1559 patients, 71 patients (4.6%) have developed
126	vaginal cuff infection during the 30 days after TLH. The median onset of vaginal cuff
127	infection was POD 7 (IQR, POD 5-9). Of the infected patients, the majority (35%) was
128	polymicrobial, with mixed aerobes and anaerobes or mixed aerobes flora in vaginal
129	cultures (Table S4).
130	Associations between various factors in the pre-, intra-, and postoperative
131	periods and the development of vaginal cuff infection during the 30 days after TLH are
132	all presented in Table 2. On univariate analysis, current smoking (OR, 2.5; 95% CI,
133	1.5–4.1), pathological result of adenomyosis (OR, 1.7; 95% CI, 1.1–2.9), use of
134	Seprafilm (OR, 7.8; 95% CI, 1.4–36.3), white blood cell count on POD2 (OR, 1.2; 95%
135	CI, 1.1–1.3), C-reactive protein (CRP) level on POD2 (OR, 1.1; 95% CI, 1.1–1.2), and
136	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⁾ .

154	Regarding intraoperative factors, we found a significant association between
155	the use of Seprafilm and postoperative vaginal cuff infection. Seprafilm is composed of
156	two anionic polysaccharides, sodium hyaluronate and carboxymethylcellulose, which
157	have been reported to be chemically modified. This barrier transforms into a gel after
158	being placed in the peritoneum; it is reabsorbed in approximately 7 days, after normal
159	tissue repair has taken place and the inflammatory cascade has subsided ⁽²¹⁾ . Seprafilm
160	thus reduces the incidence of postoperative adhesions ⁽²²⁻²⁵⁾ . Despite its advantages, it
161	has also been reported to carry an increased risk of intraabdominal abscess formation,
162	anastomotic leaks ⁽²⁵⁾ , fluid collection, and sterile peritonitis ^(21,26,27) . However, only 15
163	patients in whom Seprafilm was used in our study were included. Further research is
164	needed to confirm the correlation between the use of Seprafilm and the occurrence of
165	vaginal cuff infection after TLH.
166	Lastly, regarding postoperative factors, we identified CRP level on POD2 and
167	postoperative hematomas as risk factors for vaginal cuff infection. We perform a blood
168	test on POD2 for all patients undergoing TLH. A normal CRP range on POD2 after
169	TLH was reported as between to be 6.19 and 7.83 mg/dL ^{$(28,29)$} . The median CRP value
170	on POD2 in patients with postoperative vaginal cuff infection in our study was 3.3
171	(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.

189	In our study, we surveyed patients undergoing TLH for only benign
190	indications. Katherine et al. have reported there were no differences seen between
191	benign and malignant surgical indications in rates of deep and organ space SSI after
192	TLH ⁽³³⁾ . Although operative time was not independent risk factor of vaginal cuff
193	infection after TLH in our study, longer operative time has been identified as a risk
194	factor of SSI included deep and organ space SSI in previous many studies ^(11,18,34,35) . The
195	study of Yüksel et al. showed that the operative time of TLH was predisposed to be
196	longer for malignant gynecologic indication than benign gynecologic indication ⁽³⁶⁾ , and
197	thus, the morbidity of vaginal cuff infection after TLH for malignant diseases might
198	increase seemingly compared with benign diseases. Further research is warranted to
199	examine the risk factors for SSI in patients with malignant diseases undergoing TLH.
200	We found that vaginal cuff infection was caused mainly by polymicrobial in
201	this study. When the vagina is opened during surgery, as in the procedure of
202	hysterectomy, endogenous polymicrobial flora of aerobes and anaerobes in the vagina
203	may ascend from the breached vagina and endocervix to the operative site, in addition
204	to the microorganisms from the skin, which are the flora of predominantly aerobic
205	Gram-positive cocci. Therefore, the source of pathogens for vaginal cuff infection is
206	usually polymicrobial ^(2,16,37,38) .

207	The strength of this study is the inclusion of detailed perioperative
208	information from our database. Moreover, all patients received standardized and
209	homogenized management in our hospital. On the other hand, this study also has several
210	limitations, and the results should be interpreted with caution. First, this study has the
211	inherent bias associated with its retrospective design. Second, we could not consider an
212	association between vaginal cuff infection and TLH for pelvic organ prolapse among
213	benign indications ⁽³⁹⁾ because the patients with pelvic organ prolapse was too low in the
214	present study. Thus, further studies are needed to clarify the impact of vaginal cuff
215	suspension after TLH in patients with apical pelvic organ prolapse. Finally, our study
216	reflected the experience of a single hospital, and this might not be generalizable to other
217	institutions and settings.
218	In conclusion, in a population of women who underwent TLH for benign
219	indications at Teine Keijinkai Hospital, we found that current smoking, use of
220	Seprafilm, CRP level on POD2, and postoperative vaginal cuff hematoma were
221	significant SSI risk factors of vaginal cuff infection. To reduce the morbidity rate of
222	vaginal cuff infection after TLH, patients are advised to stop smoking before the
223	operation. Furthermore, in the case of vaginal cuff hematoma after TLH, we should

224 consider prophylactic antibiotic medication to prevent subsequent vaginal cuff

- 225 infection.
- 226

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236 Disclosure

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

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353	Laparos	copic duplication of the uterosacral ligaments following hysterectomy for stage
354	III-IV a	pical pelvic organ prolapse. Updat Surg. 2020 Mar;72(1):199–204.

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)		
Para 1	17 (24)	304 (20)	551	
Para 2	23 (32)	530 (36)	.551	
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

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

361 Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index;

CRP, *C*-reactive protein; ; *Hb*, hemoglobin; PLT, platelet; *POD*, postoperative day;

WBC, white blood cell.

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

Characteristic	Univariate analysis				Multivariate analysis			
	OR	95% CI	95% CI	<i>p</i> -value	Adjusted	95% CI 9	95% CI	
		lower	upper		OR	lower	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, $10^4/\mu L$	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	13	1.0	1.8	074				
Transfusion	1.0	0.1	24.4	1.00				
Additional operative technique	1.4	0.1	<u>∠</u> 7.7	1.00				
(included multiple responses)								
Salpingo-oophorectomy	04	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 <i>antiadhesive</i>								
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	88	27	28.0	003	87	24	28 1	~ 001
hematoma	0.0	<i>4.1</i>	20.7	.005	0.4	2.4	20.1	\.001

368 For selection of independent variables in multivariable logistic regression, we included

369 significant variables in univariate analysis and clinical variables of interest in backward

370 stepwise regression.

371 Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index;

372 CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; OR, odds ratio; PLT,

373 platelet; POD, postoperative day; WBC, white blood cell.