



Title	Risk factors of vaginal cuff infection in women undergoing laparoscopic hysterectomy for benign gynecological diseases
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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

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22

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% 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).

84

85 *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/m². 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 Septrafilm (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 Sefrafilm, 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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235

236 **Disclosure**

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

238

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- 355

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	<i>P</i> -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 /μL	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
<i>Antiadhesive material</i>			
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 /μL	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

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

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

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

363 WBC, white blood cell.

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366 Table 2. Univariate and multivariate analysis for factors associated with SSI
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Characteristic	Univariate analysis				Multivariate analysis			
	OR	95% CI lower	95% CI upper	<i>p</i> -value	Adjusted OR	95% CI lower	95% CI upper	<i>P</i> 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				

Oophorectomy	1.0	0.4	2.5	.594				
Salpingectomy	1.4	0.9	2.2	.223				
<i>Antiadhesive material</i>								
(ref = no use of <i>antiadhesive material</i>)								
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 /μL	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

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.