# Factors for cecal intubation time during colonoscopy in women: Impact of surgical history

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Abstract Bac

**Background/Aim:** Cecal intubation during colonoscopy is prone to be prolonged in women, which may be related to frequent exposure to pelvic/abdominal surgery. We evaluated the association between Cecal Intubation Time (CIT) and prior episodes of pelvic/abdominal surgery in women.

**Patients and Methods:** A cross-sectional study was conducted on screening participants who underwent colonoscopy. Multivariate regression with parameter estimates ( $\beta$ ) was performed to determine the factors affecting CIT, including age, body mass index (BMI), bowel preparation, sedation, diverticulosis, experience of colonoscopists, and a surgical history. Also, subgroup analyses according to type of surgery were performed. **Results:** A total of 835 women were enrolled. The mean CIT was  $5.82 \pm 3.40 \text{ min}$ . 323 females (38.7%) had episodes of surgery. The CIT was prolonged in cases performed by non-experienced trainees ( $\beta = 3.61, P < 0.001$ ) and with a history of gynecological surgery ( $\beta = 0.97, P = 0.001$ ). In the subgroup of non-experienced trainees, lower BMI, poor preparation, and a history of cesarean section significantly prolonged the CIT. Also, the risk for difficult colonoscopy (CIT  $\geq 15 \text{ min}$ ) was increased with a history of cesarean section (odds ratio = 4.43, P = 0.024).

**Conclusion:** A prior episode of gynecological surgery prolonged CIT. Also, cesarean section history was associated with difficult colonoscopy in the examination by non-experienced trainees.

Keywords: Cecal intubation time, cesarean section, colonoscopy, gynecological surgery, women

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#### **INTRODUCTION**

As the incidence of colorectal cancer has continued to rise in Asia, including South Korea,<sup>[1]</sup> there has been an increased interest in screening colonoscopy – which allows immediate diagnosis for cancer as well as treatment of adenoma. As colonoscopy is performed more actively, naturally, the need for qualitative examination also

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increases. The cecal intubation rate is one of the quality indicators for colonoscopy along with the degree of bowel preparation and the adenoma detection rate.<sup>[2,3]</sup> Cecal intubation rate >95% is usually required in qualified screening colonoscopy, which can be reached usually with improvement in endoscopic equipment and techniques.<sup>[3]</sup> In this situation, efforts are being made to shorten Cecal

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Intubation Time (CIT) beyond successful insertion. With shortened CIT, patient satisfaction can be improved and the labor of colonoscopists be reduced as well, in addition to the effective operation of endoscopy room. Failed cecal intubation or prolonged CIT is reportedly related with old age, female gender, low body mass index (BMI), a small waist circumference, poor bowel preparation, and lack of colonoscopists' expertise.<sup>[4-7]</sup> Besides, there were studies which showed an association between prolonged CITs or difficult colonoscopic examinations with prior episodes of pelvic or abdominal surgery, which induce bowel adhesion frequently,<sup>[5,8-10]</sup> although some studies reported controversial results.<sup>[4,7,11]</sup> Since the degree and location of post-operative adhesion may vary depending on the type of surgery, it seems unreasonable to regard surgical history per se as a factor affecting prolonged CIT.

The female gender is considered as a risk factor for prolonged CIT.<sup>[12]</sup> Colonoscopy can be technically more challenging for females than males due to reasons such as higher sensitivity to pain, more frequent bowel angulation and anthropometric factor related to central obesity. In addition, females are prone to have more experiences with pelvic or abdominal surgery.<sup>[8]</sup> Representatively, the rate of cesarean delivery has increased remarkably.<sup>[13]</sup> The aim of this study was to evaluate the association between CIT and prior episodes of pelvic or abdominal surgery, according to the type of surgery, in women.

# PATIENTS AND METHODS

#### Study design and population

This cross-sectional study was conducted on consecutive participants in a voluntary health screening program of Dongguk University Ilsan Hospital, between January 2017 and May 2018. Among the women who underwent colonoscopy, the following were excluded: insufficient baseline information, 80 years or older, non-Koreans, previous history of colonic resection, incomplete study due to inadequate preparation or other clinical conditions such as excessive pain or paradoxical reaction to midazolam, and unconfirmed CIT. Information regarding surgical history of pelvis or abdomen was obtained via established questionnaires. The surgical history was classified as gynecological surgery, cesarean section, appendectomy, and other abdominal operation. Gynecological surgery included hysterectomy, operation of ovary or fallopian tubes, and uterine myomectomy. Operations for liver, gallbladder, pancreas, kidney, urinary bladder, spleen, stomach, and peritoneum were classified as other abdominal surgery. BMI was calculated as weight divided by height in meters squared  $(kg/m^2)$ , and divided into three groups ( $\leq 22.9, 23.0-24.9, \geq 25.0$ ). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by the institution's human research committee. This study was approved by the Institutional Review Board (DUIH 2018-04-009).

#### Procedure

All participants were examined using a video colonoscope (Olympus CF-H260 or CF-Q260, Olympus Optical Co., Ltd, Tokyo, Japan) by six expert colonoscopists or five training fellows. All the experts had performed at least 1000 colonoscopic examinations. All of the training fellows had less than one year of endoscopic training and less than 300 colonoscopy experiences. Trainees performed colonoscopy independently or sometimes under minor supervision.

All the subjects received 2L doses of a polyethylene glycol and electrolyte solution (CoolPrep powder, Taejoon Pharm, Seoul, Korea) before the examinations for bowel cleansing. The degree of bowel preparation was assessed using Aronchick scale (excellent, good, fair, poor, or inadequate).<sup>[14]</sup> Subjects with inadequate preparation were excluded from this study due to incomplete examination. Intravenous midazolam was administered to those who sought sedative endoscopy. The dose was determined according to a unified protocol based on a subject's age and weight. Meperidine was routinely applied as analgesia. CIT was defined as the time interval from the start of an examination until the cecum was reached. The examination was defined as difficult colonoscopy when the CIT was longer than 15 minutes. Abnormal colonoscopic findings such as diverticulosis, and colorectal neoplasms were recorded.

#### Statistical analyses

Descriptive statistics for CIT were presented as continuous variables (mean  $\pm$  standard deviation). Episodes of pelvic or abdominal surgery and other covariates were analyzed as categorical variables. Independent sample *t*-tests or one-way analyses of variances (ANOVA) were used for categorical variables to analyze their relationships with CIT. To determine the factors that affect CIT, multivariate regression analyses for parameter estimates, and beta-coefficients ( $\beta$ ), was performed. The regression model included variables with *P* values <0.2 in the univariate analyses. Finally, the risk of difficult colonoscopy was evaluated using multivariate logistic regression for odds ratios (OR) and 95% confidence intervals (CI). All two-sided *P* values <0.05 were considered significant. SPSS Statistics 19.0 (IBM, Armonk, NY, USA) was used to perform the statistical analyses.

#### RESULTS

# Population and clinical characteristics

A total of 931 from 3,219 women who participated in the screening program underwent colonoscopy during the study period. After exclusion of 96 ineligible participants, 835 women were included in the final analyses [Figure 1]. The mean age of the study population was 47.4  $\pm$  11.2 years (range, 22-79). The mean level of CIT was 5.82  $\pm$  3.40 min (range, 1.42-19.92). Colorectal polyps were observed in 167 (20.0%) patients and the adenoma detection rate was 13.9% (116/835). Among the participants, 803 patients (96.2%) chose sedation during colonoscopy, and the mean dose of intravenous midazolam was 5.1  $\pm$  1.1 mg (range, 2-10 mg). The mean CIT did not differ according to sedation (P = 0.532) [Table 1].



Figure 1: Study population.

Table 1: Comparison of cecal intubation time based on clinical characteristics

In terms of the BMI category, the mean CIT level was shortened when the BMI increased (P < 0.001) [Table 1]. The number of examinations performed by non-experienced trainees was 172 (20.6%). The mean level of CIT was different between the experts and the training fellows (5.05 min. vs. 8.81 min., P < 0.001), and it was also different by the degree of bowel preparation (P = 0.009) and colonic diverticulosis (P = 0.021). Any Prior episode of pelvic or abdominal surgery was reported in 323 (38.7%) of the 835 participants. The most common was cesarean section (n = 184, 22.0%) followed by gynecological surgery (n = 113, 13.5%). There was no difference in the mean level of CIT by the episode of pelvic or abdominal surgery in general (P = 0.203), whereas gynecological surgery and appendectomy were associated with prolonged CIT in univariate analyses (P = 0.001 and P = 0.003, respectively).

#### Factors for prolonged CIT

With multivariate analyses using variables with *P* values <0.2 in the univariate analyses, the CIT was shortened as BMI increased [Table 2]. Compared to the examinations performed by experienced colonoscopists, those performed by the non-experienced trainees showed increased CIT ( $\beta = 3.61$ , P < 0.001). Gynecological surgery was a significant factor for prolonged CIT ( $\beta = 0.97$ , P = 0.001), but a history of appendectomy was not a significant factor. The degree of bowel preparation and diverticulosis also showed no significance in the multivariate analyses.

Variable		n (%)	CIT (Mean±SD)	Р
Age, year	≤59	715 (85.6)	5.78±3.37	0.364
	≥60	120 (14.4)	6.08±3.58	
BMI, kg/m <sup>2</sup>	≤22.9	496 (59.4)	6.18±3.57	< 0.001
-	23.0-24.9	154 (18.4)	5.67±3.33	
	≥25.0	185 (22.2)	4.97±2.81	
Bowel preparation	Excellent or good	654 (78.3)	5.64±3.23	0.009
	Fair or poor	181 (21.7)	6.47±3.90	
Sedation	No	32 (3.8)	6.19±3.46	0.532
	Yes	803 (96.2)	5.81±3.40	
Colonoscopists	Experienced	663 (79.4)	5.05±2.79	< 0.001
	Non-experienced	172 (20.6)	8.81±3.86	
Colonic diverticulosis	No	793 (95.0)	5.86±3.45	0.021
	Yes	42 (5.0)	5.02±2.16	
Previous abdominal or pelvic surgery, any	No	512 (61.3)	5.70±3.27	0.203
	Yes	323 (38.7)	6.01±3.61	
Gynecologic surgery <sup>a</sup>	No	722 (86.5)	5.65±3.30	0.001
	Yes	113 (13.5)	6.92±3.36	
Cesarean section	No	651 (78.0)	5.65±3.55	0.451
	Yes	184 (22.0)	5.52±3.40	
Appendectomy	No	791 (94.7)	5.88±3.45	0.003
	Yes	44 (5.3)	4.76±2.25	
Other abdominal surgery <sup>b</sup>	No	810 (97.0)	5.83±3.41	0.791
	Yes	25 (3.0)	5.64±3.35	

BMI:Body Mass Index; CIT:Cecal Intubation Time, SD:Standard Deviation. <sup>a</sup>Includes hysterectomy, operation of ovary or fallopian tubes, and uterine myomectomy. <sup>b</sup>Indicates abdominal surgeries except gynecological surgery, cesarean section, and appendectomy

#### Subgroup analyses

Table 3 represents stratified analyses by BMI and the colonoscopists' experience – along with the type of surgery performed. In the subgroups of experienced colonoscopists, gynecological surgery prolonged the CIT, while cesarean section did not affect the CIT. In the subgroup of non-experienced examiners, however, a history of cesarean section prolonged CIT ( $\beta = 1.67$ , P = 0.028), while gynecological surgery did not ( $\beta = 0.60$ , P = 0.411). Appendectomy and other abdominal surgery were not related with prolonged CIT regardless of the BMI category or the experience of colonoscopists.

# Factors for prolonged CIT in non-experienced examiners

Table 4 shows univariate analyses in the subgroup of non-experienced trainees. With multivariate analyses using variables with P value <0.2 in the univariate analyses, BMI, poor or fair bowel preparation, and a history of cesarean section were associated with prolonged CIT [Table 5]. When the CIT was analyzed as a categorical variable, OR of cesarean section for difficult

Table 2: Multivariate analyse	s of factors affecting cecal
intubation time	

Variable		Coef. (β)	SE	95% CI	Р
BMI, kg/m <sup>2</sup>	≤22.9	ref			
	23.0-24.9	-0.63	0.27	-1.16, -0.09	0.022
	≥25.0	-1.24	0.26	-1.75, -0.74	< 0.001
Bowel preparation	Excellent or good	ref			
	Fair or poor	0.46	0.25	-0.03, 0.95	0.065
Colonoscopists	Experienced	ref			
	Non-experienced	3.61	0.26	3.10, 4.11	< 0.001
Colonic diverticulosis	No	ref			
	Yes	-0.73	0.47	-1.66, 0.19	0.119
Gynecologic surgeryª	No	ref			
	Yes	0.97	0.30	0.37, 1.56	0.001
Appendectomy	No	ref		,	
	Yes	-0.76	0.46	-1.67, 0.15	0.100

BMI:Body Mass Index; CI:Confidence Interval; SE:Standard Error. <sup>a</sup>Includes hysterectomy, operation of ovary or fallopian tubes, and uterine myomectomy colonoscopy was 4.43 (95% CI, 1.22 to 16.16, P = 0.024) in the subgroup of non-experienced trainees [Table 6]. Meanwhile, there was no association between difficult colonoscopy and BMI, bowel preparation, or a history of gynecological surgery.

# DISCUSSION

This study confirmed that lower BMI, examinations by non-experienced examiners and a history of gynecological surgery were associated with prolonged CIT in women. This study has strengths in that it provides detailed analysis based on the type of surgical history. Interestingly, the influence of prior cesarean section on the CIT was different between experienced and non-experienced examiners. A history of cesarean section was a meaningful factor for difficult colonoscopy in non-experienced examiners.

As mentioned previously, it is generally thought that prior episodes of pelvic or abdominal surgery would prolong CIT. Pelvic or abdominal surgery include various types according to techniques, sites, and extent, which determine the degree of adhesion. For example, minor operations such as appendectomy may be less likely to cause post-operative adhesion than major operations. The impact of intra-abdominal surgeries, such as gastrectomy or hepatic lobectomy, on colonoscopy, may be different from that of intra-pelvic surgeries like hysterectomy. A recent study reported that pelvic surgery was associated with incomplete insertion of sigmoidoscopy while abdominal surgery was not.<sup>[10]</sup> After all, pelvic or abdominal surgery encompasses a variety of heterogeneous operations and needs to be classified according to specific types, so as to investigate the association with CIT.

According to our data, gynecological surgery prolonged the CIT significantly. Prolonged CIT in women compared to men is partially associated with the large intra-pelvic volume in women. Furthermore, hysterectomy may increase free space in the pelvic area, which causes more frequent sigmoid looping.<sup>[5]</sup> Hysterectomy and other gynecological operation may also cause post-operative adhesion, and

#### Table 3: The effect of abdominal or pelvic surgery on CIT; multivariate analyses in the subgroups

Subgroups	G	ynecol	ogical	surgery <sup>a</sup>		Cesarean section			Appendectomy				Other abdominal surgery <sup>b</sup>			
	n	β	SE	95% CI	n	β	SE	95% CI	n	β	SE	95% CI	n	ß	SE	95% CI
BMI ≤22.9	59	0.79*	0.44	-0.06, 1.65	112	-0.09	0.34	-0.76, 0.57	31	-0.89	0.58	-2.03, 0.26	12	- 1.17	0.92	-2.98, 0.64
BMI, 23.0-24.9	23	2.32‡	0.64	1.06, 3.58	33	0.53	0.56	-0.57, 1.63	6	-0.94	1.17	-3.24, 1.35	4	-0.58	1.41	-3.35, 2.19
BMI ≥25.0	31	0.47	0.51	-0.54, 1.47	39	0.10	0.46	-0.79, 1.00	7	-0.25	0.98	-2.18, 1.68	9	0.87	0.87	-0.84, 2.57
Experienced	79	1.18‡	0.33	0.54, 1.82	155	-0.30	0.25	-0.79, 0.19	40	-0.68	0.45	-1.56,0.19	18	-0.19	0.65	-1.47, 1.10
Non-experienced	34	0.60	0.72	-1.82, 2.02	29	1.67†	0.76	0.18, 3.15	4	-1.73	1.86	-5.37, 1.91	7	-0.70	1.42	-3.48, 2.08

BMI:Body Mass Index; CI:Confidence Interval; CIT:Cecal Intubation Time; SE:Standard Error.  $\beta$  indicates a mean change in CIT of subjects with each surgical history compared to subjects without the surgical history in the subgroups. All regression models were adjusted by body mass index, bowel preparation, expertize of examiners, diverticulosis and each surgical history. <sup>a</sup>Includes hysterectomy, operation of ovary or fallopian tubes and uterine myomectomy. <sup>b</sup>Indicates abdominal surgeries except gynecological surgery, cesarean section and appendectomy. \*P<0.1, †P<0.05, †P<0.01

this may affect the CIT as well. In addition, some patients who experienced pelvic surgery due to ovarian neoplasm

Table 4: Comparison of cecal intubation time in the non-experienced examiners (n=172)

Variable		n (%)	Mean±SD	Р
Age, year	≤59	144 (83.7)	8.95±3.90	0.280
	≥60	28 (16.3)	8.09±3.63	
BMI, kg/m <sup>2</sup>	≤22.9	101 (58.7)	9.43±4.16	0.019
-	23.0-24.9	35 (20.3)	8.47±3.62	
	≥25.0	36 (20.9)	7.39±2.72	
Bowel preparation	Excellent or	123 (71.5)	8.39±3.69	0.023
	good			
	Fair or poor	49 (28.5)	9.86±4.11	
Sedation	No	4 (2.3)	7.40±0.76	0.018
	Yes	168 (97.7)	8.84±3.90	
Colonic diverticulosis	No	165 (95.9)	8.85±3.91	0.455
	Yes	7 (4.1)	7.74±2.56	
Previous abdominal or	No	105 (61.0)	8.50±3.79	0.192
pelvic surgery, any				
	Yes	67 (39.0)	9.29±3.95	
Gynecologic surgery <sup>a</sup>	No	138 (80.2)	8.77±3.98	0.807
	Yes	34 (19.8)	8.95±3.39	
Cesarean section	No	143 (83.1)	8.57±3.54	0.163
	Yes	29 (16.9)	9.98±5.07	
Appendectomy	No	168 (97.7)	8.85±3.90	0.032
	Yes	4 (2.3)	7.15±1.02	
Other abdominal surgery <sup>b</sup>	No	165 (95.9)	8.86±3.89	0.403
	Yes	7 (4.1)	7.61±3.11	

BMI:Body Mass Index; SD:Standard Deviation. <sup>a</sup>Includes hysterectomy, operation of ovary or fallopian tubes, and uterine myomectomy. <sup>b</sup>Indicates abdominal surgeries except gynecological surgery, cesarean section, and appendectomy

#### Table 5: Multivariate analyses of factors affecting CIT in the non-experienced examiners

Variable		<b>Coef.</b> (β)	SE	95% CI	Ρ
BMI, kg/m <sup>2</sup>	≤22.9	ref			
	23.0-24.9	-0.81	0.72	-2.22, 0.61	0.264
	≥25.0	-2.04	0.72	-3.45, -0.63	0.005
Bowel	Excellent or	ref			
preparation	good				
	Fair or poor	1.36	0.62	0.14, 2.58	0.029
Sedation	No	ref			
	Yes	0.79	1.87	-2.88, 4.45	0.674
Cesarean section	No	ref			
	Yes	1.65	0.75	0.17, 3.13	0.029
Appendectomy	No	ref			
-	Yes	-1.78	1.86	-5.42, 1.86	0.338

BMI:Body Mass Index; CI:Confidence Interval; CIT:Cecal Intubation Time; SE:Standard Error

might have endometriosis, which already has the potential to cause adhesion in the pelvis.<sup>[15,16]</sup>

Previous studies found no influence of cesarean section on sigmoidoscopy.<sup>[10,17]</sup> Interestingly, our subgroup analyses with non-experienced examiners revealed that cesarean section prolonged CIT and was an independent risk factor for difficult colonoscopy. The performance of cesarean section has gradually increased in the countries belonging to the Organization for Economic Cooperation and Development (OECD) and it has reached up to 36% of all deliveries in South Korea.<sup>[13]</sup> Cesarean section may cause postoperative adhesions frequently, although the extent varies.<sup>[18]</sup> Recent studies found that pelvic adhesion was developed in 46 to 65% of women who delivered by cesarean section, and the risk of adhesion formation increased with repeated cesarean section.<sup>[19,20]</sup> Additionally, in a recent cohort study, a history of cesarean section was a factor with increased risk of complications during subsequent hysterectomy, which was only attributable to the presence of adhesion.<sup>[21]</sup> Since to pass through the sigmoid colon without looping is important for successful cecal intubation, caution should be used when performing colonoscopy in females with a history of cesarean section, especially for non-experienced examiners. There were objective differences in colonoscopy technique between trainee and expert colonoscopists,<sup>[22]</sup> which may support our results. A previous study has reported that the use of ancillary techniques such as postural change, abdominal hand pressure, and water flush can minimize pain during colonoscopy.<sup>[23]</sup> Training for appropriate use of the ancillary techniques may reduce sigmoid looping and colonic distension. Understanding of loop formation and resolution through magnetic devices or physical models can also be helpful for trainees.<sup>[24,25]</sup>

Most studies have found that low BMI was an affecting factor for difficult colonoscopy, although the relationship was not stratified by gender in these studies.<sup>[5,11,12,26]</sup> Our study showed inverse relationship between BMI and CIT

	Table 6: Odds ratios	for difficult colonoscopy	in the non-experienced examiners
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Variable		CIT <15 min	CIT ≥15 min	Crude OR	95% CI	Ρ	Adjusted OR	95% CI	Ρ
Age, year	≤59	133 (84.2)	11 (78.6)	ref			ref		
	≥60	25 (15.8)	3 (21.4)	1.45	0.38, 5.58	0.588	2.96	0.66, 13.42	0.159
BMI, kg/m²	≤22.9	90 (57.0)	11 (78.6)	ref			ref		
	>23.0	68 (43.0)	3 (21.4)	0.36	0.10, 1.34	0.129	0.30	0.08, 1.23	0.095
	Excellent or good	115 (72.8)	8 (57.1)	ref			ref		
	Fair or poor	43 (27.2)	6 (42.9)	2.01	0.66, 6.12	0.221	2.58	0.77, 8.59	0.124
Gynecologic surgery <sup>a</sup>	No	126 (79.7)	12 (85.7)	ref			ref		
	Yes	32 (20.3)	2 (14.3)	0.66	0.14, 3.08	0.593	0.65	0.13, 3.26	0.599
Cesarean section	No	134 (84.8)	9 (64.3)	ref			ref		
	Yes	24 (15.2)	5 (35.7)	3.10	0.96, 10.06	0.059	4.43	1.22, 16.16	0.024

BMI:Body Mass Index; CI:Confidence Interval; CIT:Cecal Intubation Time; OR:Odds Ratio. <sup>a</sup>Includes hysterectomy, operation of ovary or fallopian tubes, and uterine myomectomy

in women as well, which was consistent with the prior studies. There was a study which showed that BMI had a positive association with CIT for women, but had a negative association with CIT for men.<sup>[27]</sup> In this study, BMI was categorized by 25 and 30, while the categorization based on 23 and 25 was used in our study. It seems reasonable to conclude that an intermediate BMI may be more favorable for colonoscopy compared to being too thin or obese. This is supported by recent studies showing difficult colonoscopy was associated with low or high visceral adipose tissue (VAT) compared to intermediate VAT. <sup>[28,29]</sup> More difficult colonoscopy that is expected in obese patients may be related to the fact that abdominal pressure or repositioning might have less impact on such patients.

Our study has several limitations. First, we could not exclude selection bias, because this study was performed using check-up data of a single university hospital. Second, since the history of pelvic or abdominal surgery was collected via subjects' memory, recall bias was also possible. In addition, we could not evaluate the interval between the surgery and colonoscopy or whether the cesarean delivery was repeated. Third, the sample size was relatively small for analyses of the subgroups. Fourth, only female subjects were included in our study. Our results need to be verified for men in terms of age, obesity-related factors, and surgical histories. Finally, other factors such as degree of sedation, participants' anxiety or pain sensitivity, colonoscopists' skills, and colonic redundancy can influence the outcome of this study. In addition, we could not achieve a concordance among examiners for assessment of bowel preparation. However, this was unlikely to be a confounding factor since we used a verified scoring system.

#### CONCLUSION

Prior episodes of gynecological surgery prolonged CIT in women. Also, history of cesarean section was associated with difficult colonoscopy when performed by non-experienced trainees. This study found that cesarean section could make colonoscopy insertion difficult for non-experienced trainees. Therefore, it may be necessary to pay attention to the insertion of the distal colon such as overcoming the pelvic adhesion or minimizing sigmoid looping in women, for guiding trainees.

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# **Conflicts of interest**

There are no conflicts of interest.

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