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Original Article

Laparoscopic Myomectomy With Temporary Bilateral Uterine Artery Occlusion Compared With Traditional Surgery for Uterine Fibroids: Blood Loss and Recurrence

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Conflict of interest statement: The authors declare that there are no conflicts of interest.

Precis: Laparoscopic myomectomy with temporary bilateral uterine artery occlusion leads to less perioperative bleeding, shorter operative time, and may improve menorrhagia.

Summary :Bilateral uterine artery temporary occlusion in Laparoscopic myomectomy is an surgery to reduce blood loss, improve the symptom of menorrhagia ,and has no effect on fertility and recurrence rate.

Abstract

Study Objective: To compare the surgical technique of temporary bilateral uterine artery blockage with titanium clips in laparoscopic myomectomy with traditional surgery for uterine fibroids to determine efficacy, ability to control bleeding, and recurrence.

Design: Randomized, controlled, prospective study (Canadian Task Force classification I).

Setting: Obstetrics and gynecology department in Jinhua Municipal Central Hospital.

Patients: Women with symptomatic uterine myoma.

Interventions: 64 patients with symptomatic uterine fibroids were randomly divided into trial (Group A, n = 33) and control groups (Group B, n = 31). Temporary bilateral uterine artery occlusion and myomectomy were used in Group A, and laparoscopic myomectomy only was done in group B. Operative time, perioperative bleeding, follow-up relief of menorrhagia, and recurrence of fibroids were evaluated.

Measurements and Main Results: All the patients in this study underwent successful laparoscopic operation without intraoperative complications. Operative time between groups was not significantly different ($p = .255$ and $p = .811$ in single-myoma and multiple-myomas respectively), blood loss in Group A was notably lower than the

conventional surgery group ($p < .001$). At final follow-up (2 years), recurrence rate and menorrhagia symptom relief were not statistically significant ($p = .828$ and $p > .999$ respectively). The fertility index of anti-Mullerian hormone (AMH) showed no statistical difference between groups preoperatively, or at 2 days, 3 months, 6 months, and 1 year postoperatively ($p = .086$, $p = .247$, $p = .670$, $p = .753$, and $p = .857$, respectively).

Conclusion: Temporary bilateral uterine artery occlusion during laparoscopic myomectomy does not increase mean operative time, offers a possible option to reduce blood loss effectively, improves menorrhagia, and does not impact recurrence rate compared with conventional surgery.

Keywords: Anti-mullerian hormone; Fertility; Laparoscopy; Temporary blockage.

Introduction

Women with uterine fibroids are typically asymptomatic, and the majority are found in routine physical examinations. Hysterectomy is a long-established surgical protocol for women who do not need to preserve future reproductive capacity. For women who wish to preserve the uterus for fertility, myomectomy is an appropriate method. In conventional myomectomy [1,2], the use of oxytocin is insufficient to effectively control hemostasis, and blood pressure is negatively impacted owing to repeated doses of oxytocin. With the development of the minimally invasive technique, contraindications of the past such as multiple, large, intramural fibroids have been addressed to some extent. However, the high risk of blood loss and longer operative time still exists [3]. Recently, we introduced a surgical method to overcome these challenges using laparoscopic uterine artery occlusion (LUAO) during laparoscopic myomectomy [4, 5]. However, increased spontaneous abortion rates following treatment with LUAO limits the use of this method [6,7]. In view of these insufficiencies, we were determined to enhance the advantages of temporary bilateral uterine artery blockage by using titanium clips in laparoscopic myomectomy while trying to limit blood loss and recurrence. We describe our clinical experience and follow-up results herein.

Patient selection

This study was a single-center, controlled, single-blinded trial with randomization to two groups. From August 2012 to August 2013, 64 patients were diagnosed with hysteromyoma and dominant fibroids from 3 cm to 12 cm in diameter. The study was approved by the Ethics Committee of Jinhua Municipal Central Hospital and written

informed consent was signed by all patients before enrollment. The indications for surgery in these patients included menorrhagia, anemia, frequent urination or symptoms of rectosigmoid compression. Preoperatively, all patients underwent a diagnostic examination to exclude other diseases as well as intramural myomas. Inclusion criteria were symptoms attributed to myomas, and the inability to undergo hysterectomy. The exclusion criteria included patients with a history of ovarian surgery, hormonal treatment within 3 months before surgery, or any other endocrine disorders. All patients were informed of the possibility of immediate laparotomy in case of massive bleeding perioperatively. Patients were assigned to two groups randomly (Fig.1). Group A consisted of 33 patients with hysteromyoma: 16 with single-myoma,17 with multiple-myoma. Group B consisted of 31 patients: 15 with single-myoma ,16 with multiple-myoma. Patient characteristics and related follow up data are described in Tables 1 and 2.

Methods

Surgical Technique

In the control group (Group B), unipolar electrode was used to make an incision over the myometrium covering the myoma, until the fibroids were exposed visually. Then catch pliers were used to remove the fibroids from the uterus, hemostasis was achieved by bipolar forceps, and the wound was closed with 2-0 absorbable vicryl sutures. Finally, the large myomas were electrically morcellated in vitro. In the trial group (Group A), the anterior leaf of the broad ligament was separated by blunt dissection with monopolar electrode. After dissection, the uterine artery could be seen

originating from the internal iliac artery and crossing over the ureter. After the uterine artery was separated, it was moved upward in the lateral direction. Titanium clips were used to occlude the bilateral uterine arteries in place under direct vision (Figs. 2–4). The titanium clip was easy to apply and remove and seemed to cause less damage to vessels compared with other clips. Reflow of both uterine arteries was accomplished by removing the titanium clip. Then the remainder of the procedure was carried out just like the control group. Finally, both titanium clips were removed safely (Figs. 5–6), the excised tumor was removed using an electric morcellator, and the peritoneum was closed with 3-0 absorbable sutures (Fig. 7).

Follow-up

Follow-up was 24 months. Perioperative blood loss was evaluated by calculating the blood volume in the suction bottles during the operation, and operative time was calculated. Relief of menorrhagia and pregnancy rate were determined by ultrasound examination during the follow-up evaluation for recurrence at 24 months postoperatively. Recurrence was defined as fibroids with a minimum diameter of 0.5 cm found in patients without residual fibroids at the end of the operation. In addition, anti-Mullerian hormone (AMH) was measured preoperatively and 2 days, 3 months, 6 months, and 1 year postoperatively.

Statistical Analysis

The Statistical Package for Social Science software (SPSS, Inc., IBM, Chicago, IL) was used for statistical analysis. Data are presented as mean ± standard deviation (SD), absolute number (%), or median (range). The difference in means between

groups was tested by using an analysis of variance (ANOVA) test. If the variable was not normally distributed, the rank sum test was used. Categorical variables are presented as percentages and were compared using χ^2 tests or Fisher's exact tests ($p < .05$ was considered statistically significant).

Results

Sixty-four patients underwent successful laparoscopic myomectomy with no cases converted to open operation and no clinical complications. There was no difference in age, body mass index, myoma diameter, and number of myomas between groups. Table 1 presents patient characteristics, including myoma diameter, operative time, blood loss, and relief of symptoms. In group A, the mean blood loss was 36.3 mL (SD 8.7 mL), which was significantly less than group B (126.7 ± 26.3; $p < .001$). Table 2 presents the level of AMH, follicular-stimulating hormone (FSH), and luteinizing hormone (LH) between groups preoperatively and 2 days, 3 months, 6 months, and 12 months postoperatively. The AMH in both groups showed a small but significant decrease 2 days postoperatively ($p < .001$).

Discussion

Uterine fibroids are the most common benign tumors in women of childbearing age [8]. Following the use of hysterectomy as treatment, ovarian function declines as does pelvic floor dysfunction [9,10]. Myomectomy has become the standard protocol for patients who wish to preserve their uterus.

In this study, one endpoint was to decrease perioperative blood loss. Currently, different methods have been employed to decrease perioperative blood loss,

including preoperative administration of gonadotropin releasing hormone (GnRH) agonist, the use of tourniquet, and injection of diluted oxytocin around the tumor during operation. However, there are challenges with these measures. To facilitate the GnRH agonist protocol is costly and involves waiting for 3 to 6 months for surgery. Placing a tourniquet to decrease blood loss is time-consuming and difficult to perform and release during laparoscopic surgery. Oxytocin is a posterior hormone with a strong vasoconstrictive effect on smooth muscle that increases the risk of blood loss. With the development of endoscopic technique and minimally invasive surgery, laparoscopic myomectomy is a preferred technique. However, sometimes it is difficult to maintain hemostasis during laparoscopy, especially for patients with large fibroids.

In the current study, temporary bilateral uterine artery occlusion is shown to decrease blood loss (36.3 ± 8.7 mL versus 126.7 ± 26.3 mL; $p < .001$). Mean operative time in the simple-myoma patients is 55.1 ± 10.61 minutes and 59.7 ± 11.38 minutes ($p = .255$), and in the multiple-myoma patients is 120 ± 20.18 minutes and 121.3 ± 15.77 minutes ($p = .811$). There was no statistical difference between groups on regarding operative time. Moreover, in group A, the peritoneum was incised via the anterior leaf of the broad ligament, which could reduce risk of formation of ovary adhesions while the risk for ovarian adhesions increases when incised via the posterior leaf of the broad ligament.

Laparoscopic myomectomy uterine artery occlusion with clips is not frequently used possibly because of concern about possible ischemic damage to the function of the ovary, mechanical damage to the uterine artery. Studies [6,11] have shown that

temporary clips placed in the uterine artery does not influence blood supply and function of the ovary. The use of titanium clips was based on the application of the conventional uterine tourniquet but made easier to perform and remove. Shao et al [12] first used titanium clips during laparoscopy for ectopic pregnancies located in the Caesarean scar, and reported effective control of perioperative blood loss. Compared with other surgical procedures [13], this technology is simpler and the clips are common. In the current study, we found no uterine artery injury related to the use of the titanium clips. Kwon et al [12–15] did not report any uterine artery injury by clips.

The high recurrence rate after laparoscopic myomectomy has been challenging [16]. Combined LUAO and myomectomy has been shown to be more effective than traditional surgery to minimize recurrence rate [4]. A recent study showed that the primary mechanism of apoptosis results in shrinking of myomas after LUAO [6]. However, in the current study, with 2 years follow-up, no difference in recurrence was found between groups ($p = .828$). Perhaps the time of occlusion was so short that the mechanism mentioned above did not play a role in reducing recurrence. Ninety percent of patients in group A and 85% in group B had relief of menorrhagia.

There are many ways to evaluate ovary function, however, inhibin B, LH, and FSH fluctuate during the menstrual cycle, making it difficult to accurately assess. Siefer et al have showed that serum AMH is the most reliable marker to evaluate ovarian reserve, and it can maintain a stable level throughout the menstrual cycle [17]. In the current study, the AMH was also found to be more sensitive to variable ovarian function during the menstrual cycle.

Also in the current study, 12 patients in group A and 14 patients in group B desired pregnancy after myomectomy. During the 24-month follow-up, pregnancy outcomes were compared. One patient had an ectopic pregnancy in group A and one patient in group B had a miscarriage during the 8th week of gestation. In the remaining patients, 27.27% (3 of 11) and 30.77% (4 of 13) had spontaneous pregnancies in groups A and B, respectively and of these, 3 patients (2 patients in group A and 1 patient in group B) had a live birth via Caesarean section. However, pregnancy rate was not considered during protocol initiation and the result cannot be evaluated as a true endpoint. Pregnancy needs to be further evaluated in a randomized controlled study with more patients.

Conclusion

Laparoscopic myomectomy with temporary bilateral uterine artery occlusion with titanium clips has the advantages of less intraoperative bleeding, no increase in operative time compared with routine myomectomy, and appears to benefit patients with large, multiple, and intrauterine wall myomas. However, owing to the limited number of patients recruited in this study, a large, long-term study is warranted to evaluate this approach and determine its efficacy and safety.

References

1. Wang CJ, Lee CL, Yuen LT, Kay N, Han CM, Soong YK. Oxytocin infusion in laparoscopic myomectomy may decrease operative blood loss. *J Minim Invasive Gynecol.* 2007;14:184–188.
2. Neilson JP. Interventions to reduce haemorrhage during myomectomy for fibroids. *Obstet Gynecol*. 2007;109:1197–1198.
3. Wang CJ, Yuen LT, Lee CL, Kay N, Soong YK. Laparoscopic myomectomy for large uterine fibroids. A comparative study. *Surg Endosc*. 2006;20:1427–1430.
4. Liu WM, Wang PH, Chou CS, Tang WL, Wang IT, Tzeng IT. Efficacy of combined laparoscopic uterine artery occlusion and myomectomy via minilaparotomy in the treatment of recurrent uterine myomas. *Fertil Steril*. 2007;87:356–361.
5. Liang Z, Xu H, Chen Y, Li Y, Zhang Q. Laparoscopic blockage of uterine artery and myomectomy: a new method of treating symptomatic uterine leiomyomas. *Surg Endosc*. 2006;20:983–986.
6. Liu L, Li Y, Xu H, Chen Y, Zhang G, Liang Z. Laparoscopic transient uterine artery occlusion and myomectomy for symptomatic uterine myoma. *Fertil Steril*. 2011;95:254–258.
7. Holub Z, Mara M, Kuzel D, Jabor A, Maskova J, Eim J. Pregnancy outcomes after uterine artery occlusion: prospective multicentric study. *Fertil Steril*. 2008;90:1886–1891.
8. Duhan N, Sirohiwal D. Uterine myomas revisited. *Eur J Obstet Gynecol Reprod Biol*. 2010;152:119–125.

9. Moorman PG, Myers ER, Schildkraut JM, Iversen ES, Wang F, Warren N. Effect of hysterectomy with ovarian preservation on ovarian function. *Obstet Gynecol*. 2011;118:1271–1279.
10. Rivera CM, Grossardt BR, Rhodes DJ, Rocca WA. Increased mortality for neurological and mental diseases following early bilateral oophorectomy. *Neuroepidemiology*. 2009;33:32–40.
11. Chang KM, Chen MJ, Lee MH, Huang YD, Chen CS. Fertility and pregnancy outcomes after uterine artery occlusion with or without myomectomy. *Taiwan J Obstet Gynecol*. 2012;51:331–335.
12. Shao MJ, Hu MX, Hu M. Temporary bilateral uterine artery occlusion combined with vasopressin in control of hemorrhage during laparoscopic management of cesarean scar pregnancies. *J Minim Invasive Gynecol*. 2013;20:205–208.
13. Vercellino G, Erdemoglu E, Joe A, et al. Laparoscopic temporary clipping of uterine artery during laparoscopic myomectomy. *Arch Gynecol Obstet*. 2012;286:1181–1186.
14. Kwon YS, Roh HJ, Ahn JW, Lee SH, Im KS. Transient occlusion of uterine arteries in laparoscopic uterine surgery. *JSLS*. 2015;19:e2014.00189.
15. Wang CJ, Yuen LT, Han CM, Kay N, Lee CL, Soong YK. A transient occlusion uterine perfusion procedure to decrease operative blood loss in laparoscopic myomectomy. *Chang Gung Med J*. 2008;31:463–468.

16. Rossetti A, Sizzi O, Soranna L, Cucinelli F, Mancuso S, Lanzone A. Long-term results of laparoscopic myomectomy: recurrence rate in comparison with abdominal myomectomy. *Hum Reprod*. 2001;16:770–774.

17. Seifer DB, Maclaughlin DT. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. *Fertil Steril.* 2007;88:539–546.

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Fig. 1 Consort flow diagram.

Fig. 2 Transient occlusion of uterine arteries with a titanium clip (left side).

Fig. 3 Transient occlusion of uterine arteries with a titanium clip (left side).

Fig. 4 Transient occlusion of uterine arteries with a titanium clip (left side).

Fig. 5 Removal of the clip from the left side of the uterine artery.

Fig. 6 Removal of the clip from the left side of the uterine artery.

Fig. 7 The peritoneum being closed with 3-0 absorbable sutures.

Table 1. Patient characteristics

Characteristics	Group A	Group B	p value
Age, year	31 (20–46)	32 (21–48)	.529
Number of patients, n	33	31	
Body mass index, kg/m^2	23.76 (18.6–27.2)	22.55 (17.6–27.8)	.065
Myomas diameter, cm			
Single-myoma	7.8 (5–12)	7.6 (6–10)	.770
Multiple-myomas	5.6 (3–11)	6.2 (4–11)	.398
Single-myoma, n	16	15	
Multiple-myomas, n	17	16	
Operative time, minutes			
Single-myoma	55.1 ± 10.61	59.7 ± 11.38	.255
Multiple-myomas	120 ± 20.18	121.3 ± 15.77	.811
Blood loss, mL	36.3 ± 8.7	126.7 ± 26.3	< .001
Menorrhagia relief rate, %	19/21 (90.48)	17/20 (85)	> .999
Greatly reduced	12/21 (57.14)	11/20 (55)	
Generally reduced	7/21 (33.33)	6/20 (30)	
No reduction	2/21 (9.52)	3/20 (15)	
Recurrence rate, %	6/33 (18.18)	5/31 (16.13)	.828
Pregnancy rate, %	3/11 (27.27)	4/13 (30.77)	

P value < .05. Values given as mean ± standard deviation (range) or number (%).

Table 2. Preoperative and follow-up AMH, FSH, and LH

Group	Time	AMH (ul/L)	FSH (U/L)	LH (U/L)
A	**T1**	1.49 ± 0.44	8.35 ± 2.09	8.13 ± 3.23
	T2	1.19 ± 0.40	8.78 ± 3.31	8.75 ± 3.87
	T3	1.46 ± 0.31	8.53 ± 2.33	6.99 ± 2.33
	T4	1.48 ± 0.28	8.26 ± 1.93	8.29 ± 2.73
	T5	1.50 ± 0.26	8.64 ± 2.71	8.56 ± 3.77
B	**T1**	1.48 ± 0.37	8.39 ± 2.11	7.47 ± 2.21
	T2	1.20 ± 0.32	9.04 ± 2.99	8.29 ± 2.11
	T3	1.47 ± 0.29	8.62 ± 3.34	7.33 ± 3.09
	T4	1.46 ± 0.31	8.79 ± 2.17	8.59 ± 3.23
	T5	1.49 ± 0.29	8.64 ± 2.44	8.62 ± 2.77

AMH = anti-Mullerian hormone; FSH = follicular-stimulating hormone; LH = luteinizing hormone; T1 = preoperation; T2 = 2 days after operation; T3 = 3 months after operation; T4 = 6 months after operation; T5 = 1 year after operation). P value < .05 compared with preoperation.

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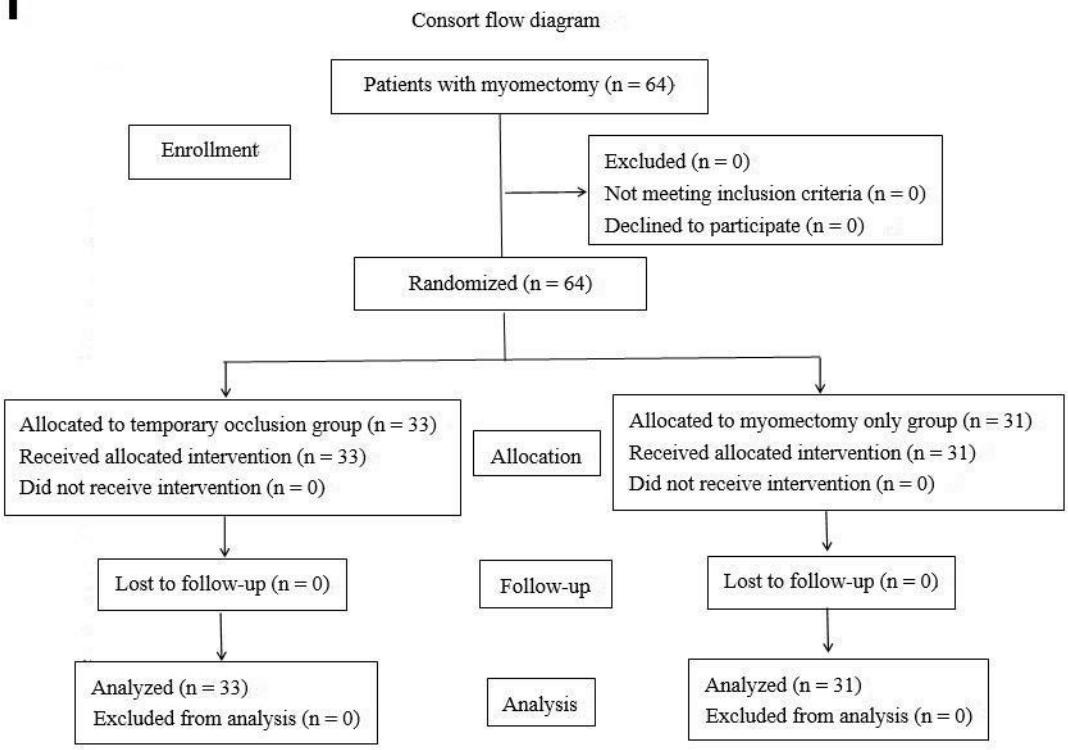

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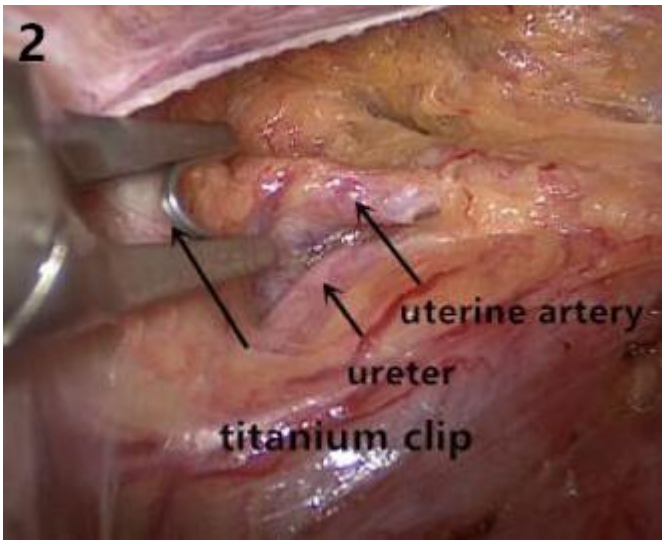

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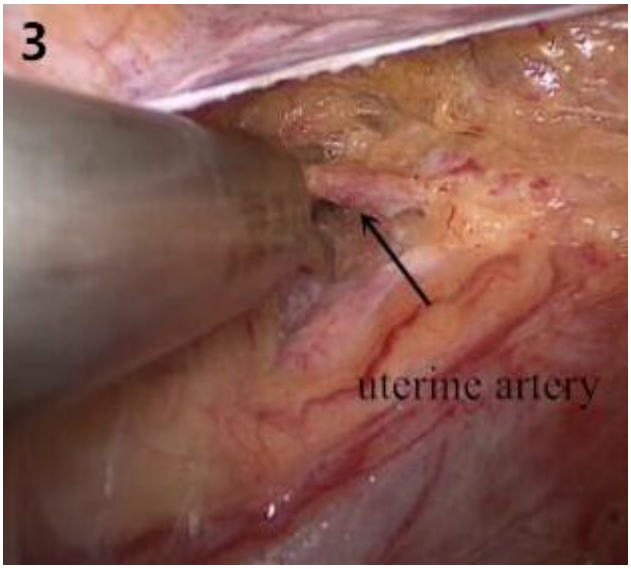

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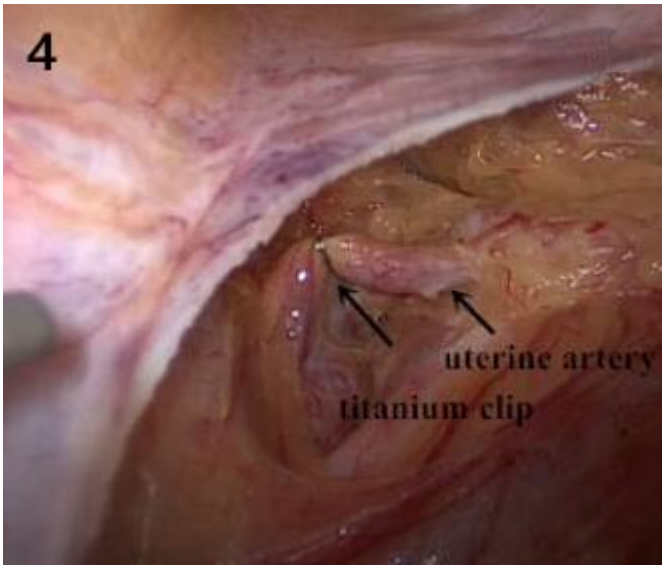

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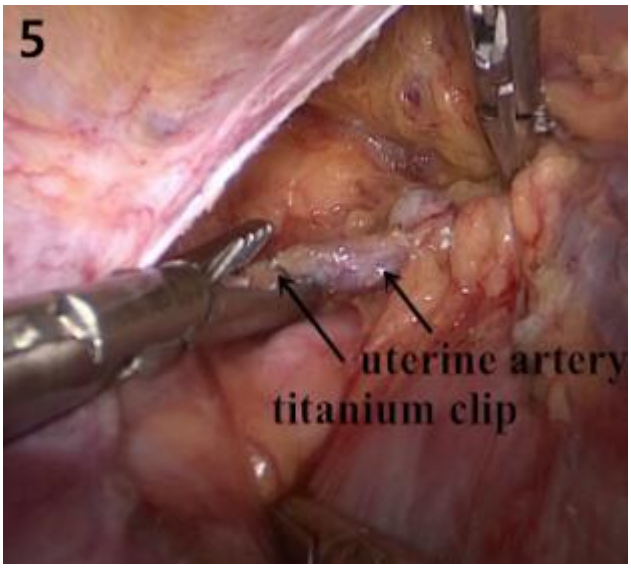

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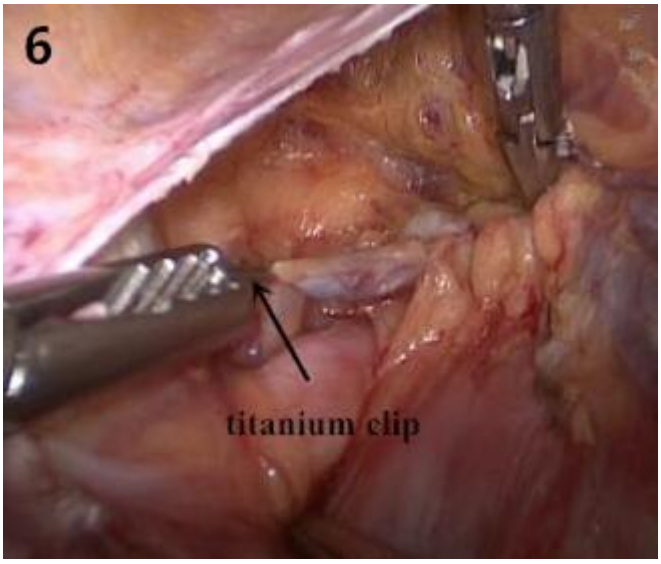

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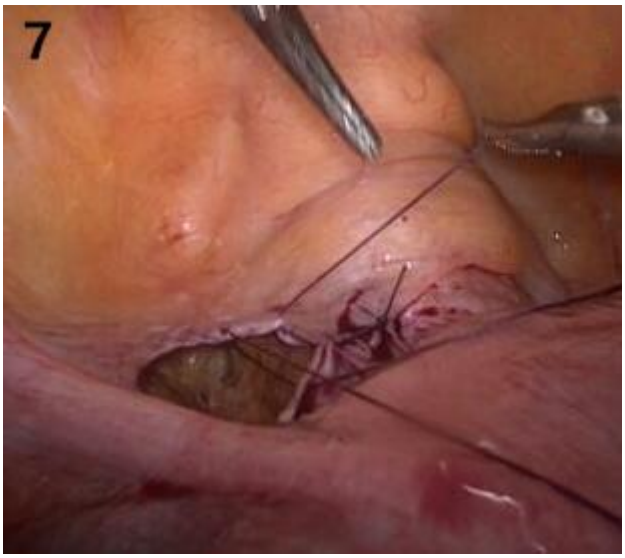

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