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Practice Guideline

Evidence-Based Practice for Minimization of Blood Loss During Laparoscopic Myomectomy: An AAGL Practice Guideline

The Practice Guideline Committee of AAGL

ABSTRACT **Study Objective:** To provide evidence-based recommendations regarding the use of pre-operative medical adjuncts and intra-operative interventions for reducing blood loss during laparoscopic (conventional or robotic-assisted) myomectomy.
Design: A systematic review and meta-analyses of the relevant literature were performed to develop evidence-based guideline recommendations.
Setting: Published literature.
Patients: Patients undergoing laparoscopic myomectomy.
Interventions: Pre-operative medical adjuncts and intra-operative interventions for reducing blood loss.
Measurements and Main Results: The primary outcome was surgical blood loss. Secondary outcomes were change in hematocrit or hemoglobin and blood transfusion. Additional outcomes included length of procedure, intra- and post-operative complications, conversion to laparotomy, reoperation, readmission, and length of stay. A total of 75 studies fulfilled the eligibility criteria and formed the basis for this practice guideline. Evidence-based recommendations were developed regarding the use of pre-operative medical adjuncts including gonadotropin-releasing hormone agonist and progesterone), as well as intra-operative vasoconstrictors, uterine artery occlusion, electrosurgical devices and barbed suture.
Conclusions: Systematic review and multiple meta-analyses identified moderate evidence supporting the use of 3-month administration of leuprolide acetate prior to myomectomy and intra-operative use of misoprostol, epinephrine, vasopressin, oxytocin, and uterine artery occlusion for reducing blood loss during laparoscopic myomectomy. Journal of Minimally Invasive Gynecology (2025) 32, 113−132. © 2024 AAGL. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Keywords: Laparoscopy; Blood loss; Myomectomy

Uterine fibroids or leiomyomas are common benign tumors that occur in 70 - 80% of women by 50 years of age [1]. In younger asymptomatic individuals (aged 18−30), the prevalence using ultrasound screening was found to be 26% and 7% in Black and White women, respectively [2]. Affected individuals can present with heavy menstrual bleeding, pelvic pain, pressure symptoms and infertility [3]. Symptoms from fibroids can be debilitating and can contribute to workplace absenteeism and negative quality of life [4]. In the United States, the total direct and indirect costs among patients with fibroid tumors range from $11 717 to $25 023 per patient per year [5].

While medical treatment options have been found to be successful in symptomatic patients, surgical removal of fibroids remains a common procedure particularly in those who have failed medical therapy and those desiring fertility. In 2013, there were approximately 48 860 myoma-related surgeries in 13 states in the U.S. according to the Agency for Healthcare Research and Quality (AHRQ) [6]. While hysterectomy constituted most of the inpatient surgeries and hospital-based ambulatory surgery visits (76.5% and 66.8%, respectively) for benign uterine fibroids, myomectomy represented 22% of surgeries in both inpatient and ambulatory surgery settings. With increasing trends to delay pregnancy to later ages that coincide with the peak incidence of fibroid diagnosis [7], the number of myomectomy procedures is predicted to increase by 31% by 2050 [8].

Several surgical approaches including open, laparoscopic, and robotic-assisted laparoscopic myomectomy can

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be used to remove myomas not amenable to hysteroscopic resection. Compared to the open approach, laparoscopic (conventional and robotic-assisted) myomectomy incur fewer perioperative complications including less bleeding and shorter hospital stays [9]. Still, minimizing blood loss during laparoscopic myomectomy remains a consequential challenge. Although the average reported blood loss from prior studies of laparoscopic myomectomies was around 80 to 248 mL, some patients could experience blood loss up to 2000 mL and serious events including severe blood loss have been reported [9−11]. As yet, there is no consensus on the use of perioperative medical adjuncts or surgical methods to reduce blood loss during myomectomy despite the large volume of myomectomies performed each year.

The purpose of this clinical guideline is to provide evidence-based recommendations regarding preoperative medical adjuncts and intraoperative interventions that can be utilized to reduce blood loss during laparoscopic (including conventional and robotic-assisted) myomectomy. This has been accomplished via the conduct of a systematic review and meta-analyses of relevant literature to assess the efficacy of various preoperative medical adjuncts and intraoperative interventions while balancing considerations of potential benefits, risks/harms, and resource utilization.

Limitations of the Literature

The systematic review identified multiple limitations in published studies on the use of interventions to reduce blood loss during laparoscopic myomectomy. A major limitation was the lack of standardization in outcome measures for assessing surgical blood loss that limited the ability to perform a meta-analysis in many instances. Both direct and indirect measures were employed − such as estimated blood loss, change in hemoglobin/hematocrit, blood transfusion, and reoperation for hemorrhage. While many studies comparing similar interventions were identified, only studies with homogeneous outcome measures could be combined for meta-analysis. Furthermore, this review identified few randomized controlled trials (RCTs) and most evidence was based on retrospective observational studies of small samples. Patient cohorts also were inherently heterogeneous with variability in case complexity (fibroid size/number, comorbidities, prior surgical history, body habitus), provider team composition (surgeon experience and presence of trainees), and use of other medications or instruments. Routine perioperative practices such as use of energy devices or perioperative vasopressin were often involved as cointerventions that may confound the findings. In addition, there is heterogeneity within the studied interventions (e.g., dose and timing of administration, surgical technique) that makes it difficult to aggregate the findings. These limitations were considered when evaluating the quality of evidence and in subsequent development of this guideline document.

Materials and Methods

A complete description of the systematic review methodology, including search strategy, study selection, data extraction, quality assessment of included studies, synthesis of evidence, and formulation of recommendations, is provided in Appendix A.

Statistical versus Clinical Difference. Regarding surgical blood loss, it is recognized that a statistically significant difference in surgical blood loss may not translate to a clinically meaningful difference. This guideline document limited recommendations to interventions where a statistically significant surgical blood loss reduction of >50 mL is found.

Balancing Factors. Whenever available, evidence on balancing factors for the assessed intervention such as adverse effects, complications, operative time, and resource utilization were also reported.

Results

The flow diagram of study selection is shown in Fig. 1. Key characteristics of studies included in the systematic review are summarized in Table 1 (preoperative medical adjuncts) and Table 2 (intraoperative interventions). Results from risk of bias assessment of the included studies are reported in Fig. 2 (RCTs) and Fig. 3 (observational studies). A list of all recommendations is summarized in Table 3.

There is currently no evidence for additive effects of the interventions assessed in this guideline. As such, the use of all or combination (unless specifically reported) of the interventions noted on Table 3 is currently unknown.

Does Preoperative Use of Medical Adjuncts Reduce Blood Loss During Myomectomy?

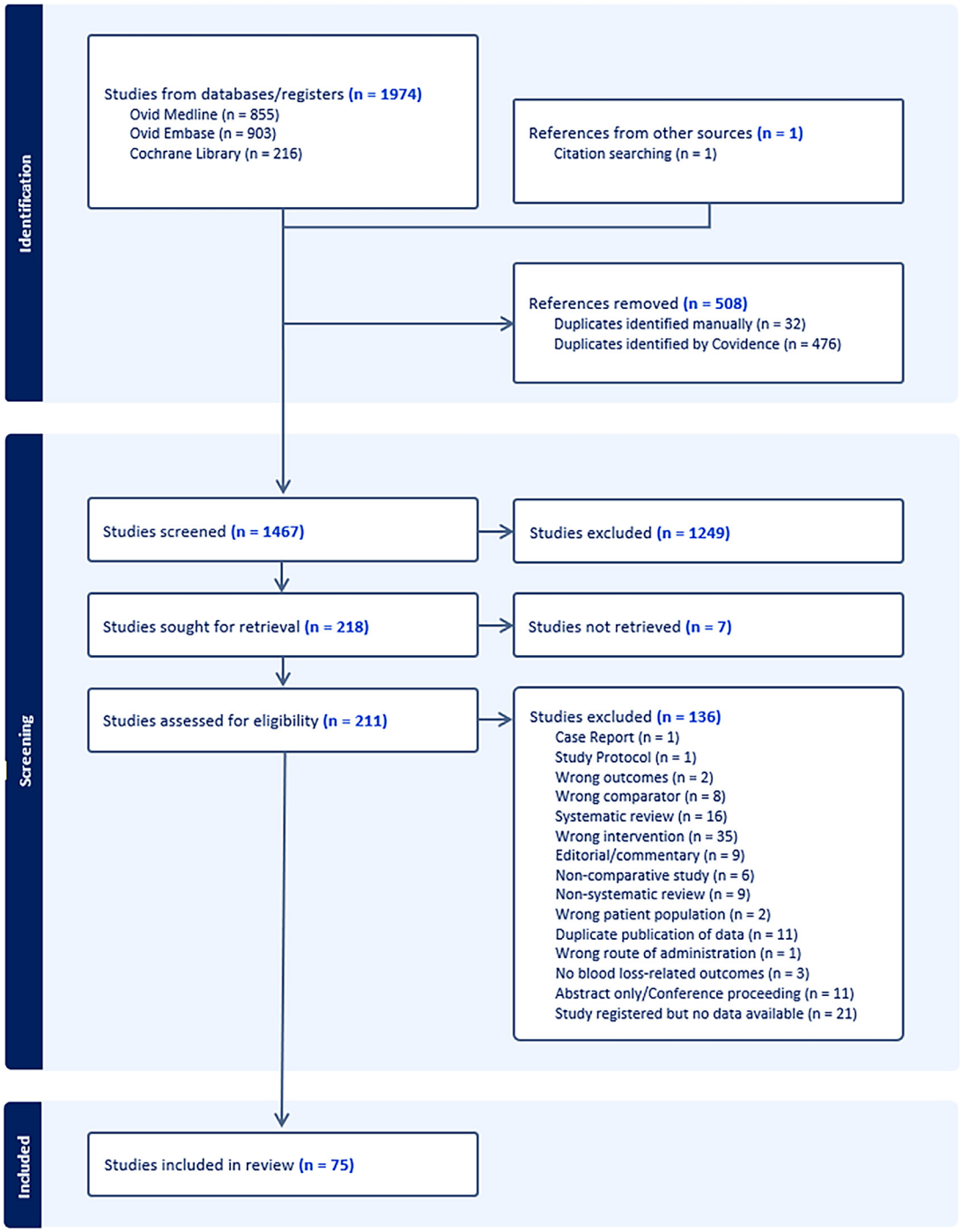
Many studies were identified that evaluated different medical adjuncts administered for up to 3 months prior to the surgery to minimize blood loss during laparoscopic myomectomy. Evidence on these studies are summarized below. Although studies on selective progesterone receptor modulators (SPRMs) were included in this review (see Appendix B), they are excluded from this practice guideline. Commercially available SPRMs used for treating uterine fibroids were removed from the global market. Also, the role of uterine artery embolization performed remotely before the myomectomy is outside the scope of this review and practice guideline.

Gonadotropin-Releasing Hormone Agonist

Gonadotropin-releasing hormone (GnRH) agonists bind to GnRH receptors and stimulate the pituitary to release more luteinizing hormone (LH) and follicle stimulating hormone (FSH) during the first 10 days of treatment. Thereafter, prolonged receptor binding causes a reduction of pituitary secretion of LH and FSH that ultimately results in low levels of circulating estradiol and progesterone [12].

Fig. 1

Flow diagram of study selection



Lowered estrogen and progesterone levels, leading to endometrial atrophy and reduced fibroid volume, have been found to have therapeutic effects in the treatment of patients with fibroids [13].

Three studies [14–16] that compared 3-month preoperative use of leuprolide acetate (a GnRH agonist) to a control group reported on surgical blood loss and were included in a meta-analysis. Two [14,15] of these studies were RCTs and were found to have low risk of bias and the third [16] had serious risk of bias (mainly due to lack of collecting data or reporting on patient demographics and study design). Meta-analysis showed significantly less blood loss associated with 3-month use of preoperative leuprolide acetate (mean difference [MD] -75.35 mL; 95% CI

Table 1

Characteristics of included studies that examined preoperative medical adjuncts

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Campo et al. 1999 [15]	1993-1996	Italy	RCT	60	Preoperative GnRH agonist	1. IM administration of 3 monthly cycles of leuprolide acetate (3.75 mg) prior to laparoscopic myomectomy; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Chang et al. 2015 [16]	2011-2014	Taiwan	Observational	91	Preoperative GnRH agonist	1. IM administration of 3 monthly cycles of leuprolide acetate (3.75 mg) prior to laparoscopic myomectomy 4-6 weeks after the third injection; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Hudecek et al. 2012 [77]	NR	Czech Republic	RCT	90	Preoperative GnRH agonist	1. SQ administration of 3 monthly cycles of goserelin (3.6 mg) prior to laparoscopic myomectomy within a cohort of women undergoing both laparoscopic and abdominal myomectomy; vs 2. Control group without preoperative medical therapy
Palomba et al. 2001 [78]	NR	Italy	RCT	61	Preoperative GnRH antagonist	1. IM administration of monthly leuprolide acetate (3.75 mg + iron tablets (2 oral tablets daily)) + oral tibolone 2.5 mg/day (started on the 15th day after the first vial of leuprolide acetate was given) for 2 months prior to laparoscopic myomectomy; vs 2. IM leuprolide acetate (3.75 mg every 28 days + iron tablets (2 oral tablets daily) + oral placebo tablets (1 tablet per day started on the 15th day after the first vial of leuprolide acetate was given) for 2 months prior to laparoscopic myomectomy; vs 3. Iron tablets only (2 oral tablets daily) for 2 months prior to laparoscopic myomectomy
Zullo et al. 1997 [14]	1994-1996	Italy	RCT	77	Preoperative GnRH agonist	1. IM administration of monthly leuprolide acetate (3.75 mg) for 2 months prior to laparoscopic myomectomy 2-5 weeks after second injection; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Demura et al. 2017[79]	NR	Russia	Observational	75	Preoperative SPRMs	1. Oral ulipristal acetate (5 mg) for 3 months prior to laparoscopic myomectomy; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Ferrero et al. 2016 [80]	2013-2016	Italy	Observational	77	Preoperative SPRMs	1. Oral ulipristal acetate (5 mg/day) for 3 months prior to laparoscopic myomectomy; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Luketic et al. 2017 [81]	2012-2015	Canada	Observational	25	Preoperative SPRMs	1. Oral ulipristal acetate (5 mg/day) for at least 3 months prior to laparoscopic myomectomy; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Mallick et al. 2019 [82]	2016-2017	United Kingdom	Observational	62	Preoperative SPRMs	1. Oral ulipristal acetate (dose not specified) for 3 months prior to laparoscopic myomectomy; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Mara et al. 2021 [83]	2014-2017	Czech Republic	Observational	108	Preoperative SPRMs	1. Oral ulipristal acetate (5 mg/day) for 3 months prior to laparoscopic myomectomy; vs 2. Laparoscopic myomectomy without preoperative medical therapy
Goldman et al. 2012 [84]	2004-2010	United States	Observational	26	Preoperative uterine artery embolization	1. Preoperative uterine artery embolization (UAE); vs 2. Laparoscopic myomectomy alone
Lee et al. 2016 [85]	2013-2014	Korea	RCT	50	Preoperative ascorbic acid	1. Preoperative ascorbic acid. Starting 30 minutes before anesthesia, 2 g of ascorbic acid with 500 mL 0.9% sodium chloride (normal saline) or 500 mL 0.9% sodium chloride were administered to the study and control groups, respectively, for 2 hours intraoperatively; vs 2. Saline placebo
Leone Roberti Maggiore et al. 2014 [86]	NR	Italy	Observational	80	Preoperative aromatase inhibitors	1. Oral letrozole (2.5 mg/day), norethindrone acetate (2.5 mg/day), elemental calcium (1000 mg/day) and vitamin D3 (880 IU/day) continuously in the 3 mo prior to surgery; vs 2. Laparoscopic myomectomy without preoperative medical therapy

GnRH = gonadotropin-releasing hormone; NR = not reported; RCT = randomized controlled trial; SPRM = selective progesterone receptor modulators.

Table 2

Characteristics of included studies that examined intraoperative interventions

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Alborzi et al. 2009 [56]	2003-2005	Iran	Observational	152	Uterine Artery Occlusion	1. Laparoscopic uterine artery ligation with silk suture and myomectomy; vs 2. Laparoscopic myomectomy alone
Blagovest et al. 2015 [57]	2013-2015	Bulgaria	Observational	119	Uterine Artery Occlusion	1. Laparoscopic uterine artery clipping + myomectomy; vs 2. Laparoscopic myomectomy alone
Chang et al. 2009 [58]	2005-2007	Taiwan	Observational	105	Uterine Artery Occlusion	1. Laparoscopic uterine artery ligation + myomectomy; vs 2. Laparoscopic myomectomy alone
Ciavattini et al. 2017 [59]	2014-2017	Italy	Observational	66	Uterine Artery Occlusion	1. Laparoscopic uterine artery coagulation with bipolar forceps (RoBI® grasping forceps—Karl Storz, Tuttlingen, Germany) + myomectomy; vs 2. Laparoscopic myomectomy alone
Dubuisson et al. 2004 [60]	2001-2003	France	Observational	106	Uterine Artery Occlusion	1. Laparoscopic uterine artery clipping (with titanium ligaclip or polymer hemolok clip) + myomectomy (32 patients had bilateral clips; 21 patients had unilateral clips); vs 2. Laparoscopic myomectomy alone
Holub et al. 2005 [55]	2001-2004	Czech Republic	Observational	81	Uterine Artery Occlusion	1. Laparoscopic uterine artery occlusion and transection with ultrasonic energy before myomectomy; vs 2. Laparoscopic myomectomy alone
Ji et al. 2018 [61]	2012-2013	China	RCT	64	Uterine Artery Occlusion	1. Temporary titanium vascular clips placed on uterine arteries followed by laparoscopic myomectomy; vs 2. Laparoscopic myomectomy alone
Kwon et al. 2015 [54]	2011-2013	South Korea	Observational	110	Uterine Artery Occlusion	1. Transient clipping of the uterine arteries with endoscopic vascular clip (Temporary Atraumatic Endo-Vessel-Clips; B. Braun Korea Co., Ltd., Seoul, Korea) followed by laparoscopic myomectomy; vs 2. Laparoscopic myomectomy alone
Liu et al. 2011 [52]	2006-2008	China	Observational	167	Uterine Artery Occlusion	1. Temporary occlusion of uterine arteries with silk suture material tied as a slipknot, then laparoscopic myomectomy; vs 2. Laparoscopic myomectomy alone
Podzolkova et al. 2020 [53]	NR	Russia	Observational	145	Uterine Artery Occlusion	1. Temporary vascular clips placed on uterine arteries followed by laparoscopic myomectomy; vs 2. Laparoscopic myomectomy alone
Song et al. 2019 [49]	2017-2019	South Korea	Observational	64	Uterine Artery Occlusion	1. Temporary vascular bulldog clamps placed on uterine arteries followed by robotic myomectomy; vs 2. Robotic myomectomy alone
Vercellino et al. 2012 [48]	2007-2009	Germany	RCT	166	Uterine Artery Occlusion	1. Laparoscopic temporary clipping of uterine arteries by Yasargil vascular clips followed by laparoscopic myomectomy; vs 2. Laparoscopic myomectomy alone
Yang et al. 2016 [47]	2011-2012	China	Observational	504	Uterine Artery Occlusion	1. Laparoscopic uterine artery occlusion with bipolar energy + myomectomy; vs 2. Laparoscopic myomectomy alone

Table 2

Continued

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Yin et al. 2014 [51]	2008-2009	China	Observational	48	Uterine Artery Occlusion	1. Laparoscopic uterine artery occlusion with ultrasonic energy before myomectomy; vs 2. Laparoscopic myomectomy alone
Bae et al. 2011 [62]	2006-2007	South Korea	Observational	90	Uterine Artery Occlusion + Vasopressin	1. Laparoscopic uterine artery ligation with bipolar energy + vasopressin before myomectomy; vs 2. Laparoscopic myomectomy + vasopressin
Chang et al. 2012 [65]	2007-2009	Taiwan	Observational	144	Uterine Artery Occlusion + Vasopressin	1. Laparoscopic uterine artery ligation with extracorporeal ties via a knot pusher + vasopressin before in situ morcellation and myomectomy; vs 2. Laparoscopic myomectomy + vasopressin before in situ morcellation
Jin et al. 2019 [87]	2012-2015	China	RCT	200	Uterine Artery Occlusion + Vasopressin Uterine Artery & Utero-ovarian Pedicle Occlusion + Vasopressin	1. Temporary titanium vascular clips placed on uterine arteries followed by vasopressin & laparoscopic myomectomy; vs 2. Temporary titanium vascular clips placed on uterine arteries & temporary vascular bulldog clamps placed on uteroovarian pedicles, followed by vasopressin & laparoscopic myomectomy; vs 3. Laparoscopic myomectomy + vasopressin
Noh et al. 2021 [63]	2016	South Korea	Observational	56	Uterine Artery Occlusion + Vasopressin	1. Single port laparoscopic uterine artery occlusion with bipolar energy + vasopressin before myomectomy; vs 2. Single port laparoscopic myomectomy + vasopressin
Peng et al. 2021 [64]	2015-2017	China	Observational	122	Uterine Artery Occlusion + Vasopressin	1. Laparoscopic uterine artery occlusion with bipolar energy + vasopressin before myomectomy; vs 2. Laparoscopic myomectomy + vasopressin
Yu et al. 2012 [50]	2007-2008	China	Observational	65	Uterine Artery Occlusion + Vasopressin	1. Laparoscopic permanent clipping with titanium clips of uterine arteries followed by laparoscopic myomectomy + pituitrin 2 U/8 mL; vs 2. Laparoscopic myomectomy + pituitrin 2 U/8 mL
Kim et al. 2019 [88]	2016-2018	South Korea	RCT	62	Uterine Artery & Utero-ovarian Pedicle Occlusion	1. Transient placement of laparoscopic bulldog clamps on uterine arteries & utero-ovarian pedicles, then laparoscopic myomectomy; vs 2. Laparoscopic myomectomy alone
Alessandri et al. 2010 [74]	2010	Italy	RCT	44	Suture type − barbed	1. Continuous V-loc 180 barbed suture (Covidien, Tyco Healthcare Group, Norwalk, CT); vs 2. Continuous absorbable suture (Vicryl, Ethicon Inc, Sommerville, NJ) with intracorporeal knots
Angioli et al. 2012 [73]	2010-2011	Italy	Observational	39	Suture type − barbed	1. Continuous g 2−0 V-Loc barbed suture; vs 2. Continuous 0-polyglactin using intracorporeal knots
Aoki et al. 2014 [72]	2011-2013	Japan	Observational	83	Suture type − barbed	1. Continuous 0-V-Loc 180 barbed suture; vs 2. 0-Polysorb suture (Covidien, Mansfield, MA, USA)
Chan et al. 2016 [70]	2010-2012	Taiwan	RCT	62	Suture type − barbed	1. Absorbable 2-0 PDS barbed suture; vs 2. Interrupted 2-0 Vicryl suture
Einarsson et al. 2011 [71]	2007-2010	USA	Observational	138	Suture type − barbed	1. Quill bidirectional barbed suture (Angiotech Pharmaceuticals, Inc., Vancouver, BC, Canada); vs 2. 2-0 polydioxanone suture using intracorporeal knots

Table 2

Continued

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Giampaolino et al. 2015 [69]	2013-2014	Italy	RCT	50	Suture type – barbed	1. 0 PDO Stratafix barbed suture (Ethicon Inc., Somerville, NJ); vs 2. Continous1 Vicryl suture (Ethicon Inc., Somerville, NJ, USA) with intracorporeal knots
Nakayama et al. 2020 [68]	2015-2020	Japan	Observational	44	Suture type – barbed	1. Stratafix (Ethicon Inc., USA) barbed suture; vs 2. Vicryl (Ethicon Inc., USA) conventional suture
Ota Y et al. 2021 [76]	2020	Japan	Observational	26	Suture type – barbed	1. 0 Stratafix PDS barbed suture (Ethicon Endo-Surgery, Tokyo, Japan); vs 2. Continuous and interrupted 0 Vicryl suture (Ethicon Endo-Surgery, Tokyo, Japan)
Song et al. 2015 [24]	2012-2013	Korea	Observational	60	Suture type – barbed	1. 1-0 V-Loc 180 barbed suture; vs 2. Continuous 1-0 Vicryl (Ethicon, Somerville, NJ, USA), with intracorporeal knots
Tinelli et al. 2016 [66]	2009-2015	Italy	Observational	720	Suture type – barbed	1. Continuous V-Loc barbed suture; vs 2. Interrupted Polysorb 0 GS-21 (Polysorb, USSC, Norwalk, CT) using extracorporeal knots
Zhang et al. 2022 [75]	2019-2020	China	Observational	48	Suture type – barbed	1. Continuous 1-0 V-loc barbed suture vs sutures (Covidien); vs 2. Vicryl 1-0 suture (Ethicon, NJ)
Angioli et al. 2012 [73]	2009-2011	Italy	Observational	30	Hemostatic agent – fibrin	1. Interrupted 2-layer intracorporeal uterine suture (0-polyglactin) with bipolar forceps coagulation for hemostasis on uterine suture bleeding sites; vs 2. Interrupted 2-layer intracorporeal uterine suture (0-polyglactin) with Tisseel applied over uterine sutures by Duploject Spray Set
Baldoni et al. 1995 [35]	1992-1994	Italy	Observational	168	Intraoperative prostaglandin; Intraoperative oxytocin and methylergonovine	1. IV sulprostone infused at 4-12 ug / minute; vs 2. Intraoperative methylergonovine and oxytocin (dosage not specified for retrospective control group)
Kalogiannidis et al. 2011 [21]	2007-2009	Greece	RCT	64	Intraoperative misoprostol	1. Single intravaginal dose of misoprostol 400 mcg (Cytotec 200 mcg pills, Pfizer); vs 2. Single intravaginal dose of placebo (similar appearance to the active drug)
Niroomand et al. 2015 [22]	2012-2013	Iran	RCT	90	Intraoperative misoprostol	1. 200 ug vaginal misoprostol 3 hours before surgery; vs 2. Vaginal vitamin B6 placebo 3 hours before surgery
Srivastava et al. 2018 [19]	2014-2015	India	RCT	60	Intraoperative misoprostol	1. Rectal misoprostol 600 ug with extensive use of lubricant placed 30 minutes prior to surgery plus intramyometrial vasopressin (20 U in 100 mL normal saline); vs 2. Rectal exam with lubricant 30 minutes prior to surgery plus intramyometrial vasopressin (20 U in 100 mL normal saline)
Cohen et al. 2017 [30]	2011-2015	USA	RCT	152	Intraoperative vasopressin	1. 20 U of vasopressin diluted in 400 mL (0.05 U/mL) of normal saline, with 200 mL injected at time of myomectomy; vs 2. 20 U of vasopressin diluted in 60 mL (0.33 U/mL) of normal saline, with 30 mL total injected at time of myomectomy
Guo et al. 2021 [32]	2018	China	RCT	118	Intraoperative vasopressin	1. 2 U of vasopressin; vs 2. 4 U of vasopressin; vs 3. 6 U of vasopressin; vs 4. 0 U of vasopressin. Vasopressin (Pituitrin, batch number: 1171102; Xinbai Manufacturing Industry, Nanjing, China) was diluted with 0.9% normal saline to a total volume of 20 mL, and "study solution" was marked on the syringe. Entire volume injected into myoma capsule

Table 2

Continued

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Lin et al. 2008 [29]	2004-2006	China	Quasi-randomized controlled trial	280	Intraoperative vasopressin; Intraoperative oxytocin; Other	1. Group A: Pedicle ligation (intraoperative ligation of the fibroid pedicle with bipolar ligation); vs 2. Group B: Vasopressin (12 U vasopressin diluted with 20 mL of saline and injected into the muscle layer around the fibroid); vs 3. Group C: Oxytocin (20 U of oxytocin in 20 mL saline injected into the muscle layer around the fibroid) + pedicle ligation; vs 4. Group D: Vasopressin (12 U vasopressin diluted with 20 mL of saline and injected into the muscle layer around the fibroid) + pedicle ligation
Matasariu DR et al. 2021 [89]	2013-2019	Romania	Observational	188	Intraoperative vasopressin analogue	1. Terlipressin 0.2 mg/mL (5 mL solution) injected into the myometrium and the subcapsular space around each myoma; vs 2. No intervention
Protopapas et al. 2020 [20]	2011-2019	Greece	Observational	200	Intraoperative vasopressin; Intraoperative misoprostol	1. Misoprostol 400 mcg (2 tablets 200 mcg each dampened with normal saline) placed at the posterior vaginal fornix 1 hour prior to induction of anesthesia; vs 2. Intraoperative dilute vasopressin (20 U/100 mL normal saline); vs 3. Laparoscopic myomectomy alone
Soliman R et al. 2021 [31]	2015-2019	Egypt	RCT	194	Intraoperative vasopressin	1. 15 mL vasopressin (0.1 unit/mL) per myoma injected into myoma pseudocapsule; vs 2. 15 mL normal saline per myoma injected into myoma pseudocapsule
Song et al. 2015 [24]	2013-2014	South Korea	RCT	60	Intraoperative vasopressin; Intraoperative epinephrine	1. Vasopressin (5 U in 50 mL saline) up to 20 mL injected into serosa or myometrium before uterine incision; vs 2. Epinephrine (0.5 mg in 50 mL saline) up to 20 mL injected into serosa or myometrium before uterine incision
Zhang et al. 2015 [28]	2012-2014	China	RCT	90	Intraoperative vasopressin; Intraoperative carboprost; Intraoperative carboprost plus oxytocin	1. 12 U intramyometrial vasopressin (Xinbai Pharmaceutical Co. Ltd., Nanjing, China) diluted with 40 mL saline solution; vs 2. 250 μg deep intramuscular carboprost tromethamine (Changzhou Siyao Pharmaceutical Co. Ltd., Changzhou, China) injection 30 minutes prior to myomectomy; vs 3. 250 μg deep intramuscular carboprost tromethamine injection 30 minutes prior to myomectomy, followed by intravenous infusion of 20 U oxytocin (Xinbai Pharmaceutical Co. Ltd.) in 250 mL of 5% glucose solution at a rate of 120 mU/min during myomectomy
Zhao et al. 2011 [27]	2006-2008	China	RCT	105	Intraoperative vasopressin	1. 6 U vasopressin diluted with 20 mL saline solution injected between the myometrium and myoma. Vertical incision made with monopolar electrode. When 2/3 of the myoma was enucleated, the pseudocapsule, which was still attached to the myoma, was ligated with a loop at the basal part of the myoma by Roeder knot; vs 2. 6 U vasopressin diluted with 20 mL saline solution injected between the myometrium and myoma. Vertical incision made with monopolar electrode; vs 3. No vasopressin injection or Roeder knot used
Hudecek et al. 2016 [25]	2008-2014	Czech Republic	RCT	190	Intraoperative epinephrine	1. Intramyometrial epinephrine (12 μg epinephrine hydrochloride diluted in 20 mL of NaCl solution) applied to the capsular space of the fibroids, followed by sagittal incision of the fibroid surface by a monopolar needle; vs 2. Intramyometrial NaCl applied to the capsular space of the fibroids, followed by sagittal incision of the fibroid surface by a monopolar needle.

Table 2

Continued

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Nickol et al. 2018 [90]	2001-2017	Germany	Observational	185	Intraoperative epinephrine	1. 1 μg epinephrine/mL sodium chloride in 16 participants and 2 μg epinephrine/mL sodium chloride in 70 patients (amount administered not specified); vs 2. No intervention
Zullo et al. 2004 [23]	2002	Italy	RCT	60	Intraoperative epinephrine	1. 50 mL bupivacaine cloridrate 0.25% (Bupicain; Monico SpA., Mestre, Venice, Italy) and 0.5 mL of epinephrine (1/2 vial of 1 mg/mL) infiltrated to serosa and myometrium overlying myoma; vs 2. Saline solution
Opoku-Anane et al. 2020 [37]	2015-2018	USA	RCT	60	Intraoperative medical adjunct − TXA	1. Single bolus IV injection of TXA 15 mg/kg infused at 1 mL/min; vs 2. Single bolus IV injection of normal saline infused at 1 mL/min
Wang et al. 2007 [34]	2002	Taiwan	RCT	60	Intraoperative oxytocin	1. 2 ampules of oxytocin (10u /mL/ amp) in 1 L normal saline, run with intravenous infusion at a rate of 120 mL/h; vs 2. Normal saline solution intravenous infusion at 120 mL/h
Choussein et al. 2015 [45]	2011-2014	USA	Observational	236	Energy − laser; Energy − ultrasonic	1. Fexible, fully-articulated CO2 laser delivery system (BeamPath Robotic Fiber and its dedicated armored guidance system FlexGuide ULTRA, OmniGuide, Inc, Cambridge, MA) producing divergent beam that cuts at 3-10 mm and coagulates at greater distances. robotic approach; vs 2. Ultrasonic shears (Harmonic ACE Curved Shears, Intuitive Surgical, Sunnyvale, CA), robotic approach
Huang et al. 2018 [42]	1997-2015	Taiwan	Observational	817	Energy − bipolar electrosurgery; Energy − ultrasonic; Energy − advanced vessel sealing device	Unipolar electrode to dissect to pseudocapsule plus further dissection/enucleation/hemostatsis with: 1. Bipolar forceps; vs 2. Harmonic scalpel (5 mm), Ethicon Endosurgery, Cincinnati, OH; vs 3. LigaSure (5 mm), Valleylab, Boulder, CO
Su et al. 2011 [43]	2002-2008	Taiwan	Observational	194	Energy − advanced vessel sealing device; Energy − bipolar electrosurgery	1. PlasmaKinetic biopolar cutting forceps (Gyrus 2. Medical, Maple Grove, MN, USA); vs 3. Unipolar electrosurgical enucleation plus bipolar coagulation
Kuo et al. 2017 [41]	2010-2014	Taiwan	Observational	591	Energy − ultrasonic; Energy − bipolar electrosurgery	1. Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) for transverse elliptical incision over myoma pseudocapsule, myoma enucleation and hemostasis; vs 2. Unipolar electrode for transverse elliptical incision over myoma pseudocapsule and myoma enucleation, with bipolar diathermy for hemostasis.
Litta et al. 2005 [40]	1996-2002	Italy	Observational	186	Energy − ultrasonic; Energy − monopolar electrosurgery	1. Perimyometrial epinephrine (10 mL 1:100,000 solution) plus harmonic scalpel 10mm for myoma enucleation; vs 2. Perimyometrial epinephrine plus monopolar scalpel and laparoscopic shears for myoma enucleation
Li et al. 2018 [44]	2010-2014	Taiwan	Observational	374	Energy − advanced vessel sealing device; Energy − bipolar electrosurgery	1. Ligasure (not routinely used, only in select cases with menometrorrhagia, abdominal-pelvic pain, pelvic pressure, and infertility); vs 2. Bipolar electrosurgery

Table 2

Continued

Study	Data Year	Country	Study Design	Overall Sample Size	Category of Interventions Studied	Description of Interventions Studied
Litta et al. 2010 [39]	2006-2008	Italy	RCT	182	Energy – monopolar electrosurgery; Energy – ultrasonic	1. Electrosurgery plus perimyometrial infiltration of 50 mL NS with 0.5 mL of epinephrine before uterine incision; vs 2. Harmonic Scalpel Ultracision (Ethicon Endosurgery, Cincinnati, OH) without epinephrine/NS infiltration
Morita et al. 2004 [91]	2004	Japan	RCT	50	Other	1. Vertical hysterotomy incision; vs 2. Transverse hysterotomy incision
Xie et al. 2018 [92]	2014-2015	China	Observational	40	Other	1. Running baseball suture with 2-0 absorbable suture; vs 2. Interrupted suturing of the myometrium using 2-0 absorbable suture, followed by continuous suturing of the seromuscular layer
Yuen et al. 2007 [93]	2001-2002	Taiwan	RCT	62	Other	1. Extracorporeal knots through the suprapubic port site tied with continuous non-running-lock suture at 1-cm increments; vs 2. Intracorporeal knots tied through 5mm port with similar uterine repair
Zeng et al. 2022 [94]	2020-2021	China	Observational	124	Other	1. Parallel mattress suturing with 2–0 absorbable barbed suture; vs 2. Simple continuous suturing with 2–0 absorbable barbed suture

NR = not reported; RCT = randomized controlled trial.

-138.06 mL to -12.64 mL, p = 0.02). When only the RCTs [14−16] were considered in a sensitivity analysis, the difference in effect remained significant.

Other surgical outcomes were reported by the 3 studies [14−16]. There were no complications resulting in conversion to laparotomy or reoperation. Two studies [15,16] that evaluated on the rate of perioperative transfusion showed a significant reduction only in one study [16]. Lastly, operative time was reported as shorter in the treatment arm in 2 studies [14,16], but longer in the other study [15].

More detailed description of the included studies on GnRH agonists, meta-analysis results, and appraisal of balancing factors are available in Appendix C.

Summary Statement. There is moderate evidence that 3-month administration of GnRH agonist before laparoscopic myomectomy results in a statistically significant reduction in surgical blood loss. Reduction in uterine/fibroid volume following leuprolide acetate administration is likely a contributing factor to reduction in surgical blood loss, but other mechanisms may further contribute to this finding. While statistically significant, the mean difference in surgical blood loss found in the meta-analysis was small in magnitude (75.35 mL). Meanwhile, only one [14] of the 2 RCTs included in the meta-analysis found a statistically significant reduction in blood loss, whereas the other RCT [15] did not show a statistically significant reduction in blood loss.

Recommendation. The use of GnRH agonist, leuprolide acetate, administered for 3 months before laparoscopic myomectomy may reduce surgical blood loss. *Strength of Evidence: Grade B; Strength of Recommendation: Moderate).*

Prostaglandin

Prostaglandins induce uterine smooth muscle contraction [17] that reduce blood flow to the uterus [18]. Four studies [19−22] investigated preoperative use of misoprostol, of which 3 [19,21,22] were RCTs. Two RCTs [21,22] and 1 nonrandomized study [20] compared preoperative rectal (200 μg, 3 hours before surgery) [22] or vaginal (400 μg, 1 hour before surgery) [20,21] misoprostol against placebo. Included RCTs [19,21,22] were deemed at low risk of bias, while the one nonrandomized study [20] was deemed at critical risk of bias due to confounding factors.

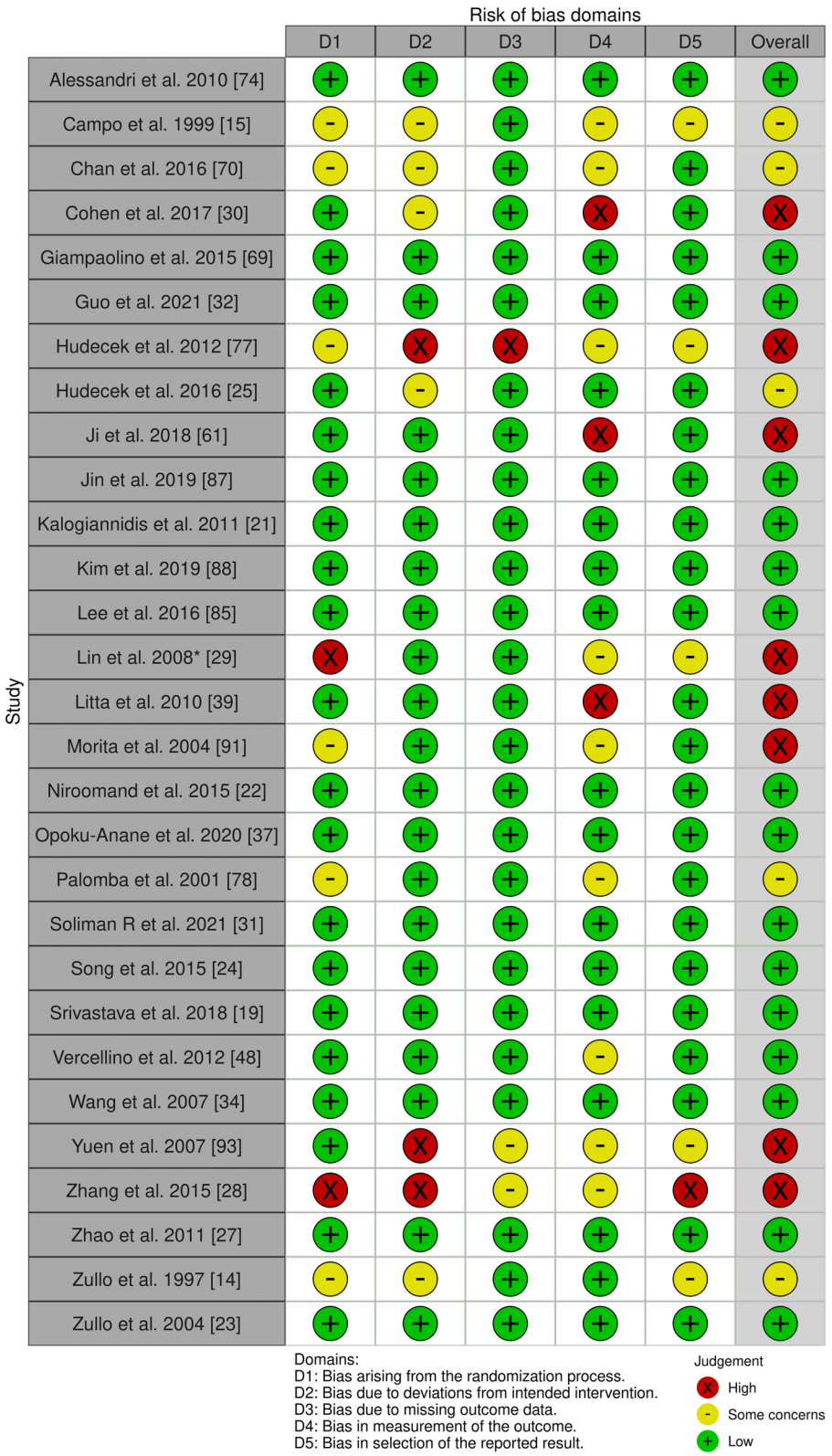
Meta-analysis of 3 studies comparing preoperative misoprostol with control [20−22] showed decreased blood loss (MD in blood loss -127.50 mL, 95% CI -194.73 mL to -60.28 mL, p<0.01). The findings remained significant in sensitivity analysis restricted to the 2 RCTs [21,22].

Two studies [21,22] reported a lower postoperative reduction in hemoglobin in the misoprostol group compared with control, one of which [22] also reported a lower transfusion rate (0/40 (0%) vs 9/40 (22.5%)) as well as shorter surgical duration in the misoprostol group. Complications and adverse events were limited in both groups and were clinically comparable. The lack of reported typical side

Fig. 2

Risk of bias assessment for included randomized controlled trials.

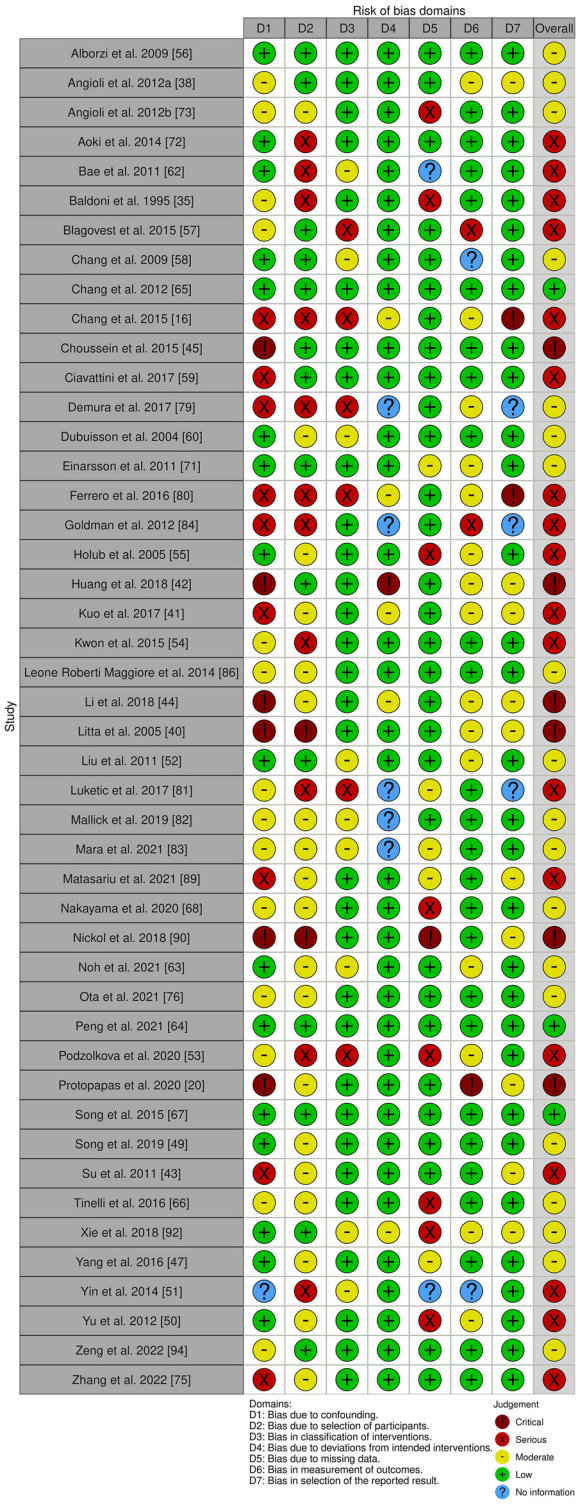
Lin et al. 2008* [29] was a quasi-randomized controlled trial. Version 2 Cochrane Risk of Bias Tool (RoB 2) was used to assess its risk of bias.



This figure was generated using the robvis tool (McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1-7. https://doi.org/10.1002/jrsm.1411).

Fig. 3

Risk of bias assessment for included observational studies.



This figure was generated using the robvis tool (McGuinness, LA, Higgins, JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1-7. https://doi.org/10.1002/jrsm.1411).

effects from misoprostol such as chills, uterine cramping or vomiting may be due to a masking effect of general anesthesia.

One high-quality RCT [19] excluded from meta-analysis compared intramyometrial vasopressin alone against preoperative 600 μg rectal misoprostol 30 minutes before surgery plus intramyometrial vasopressin. It reported a significant reduction in blood loss with the addition of misoprostol (MD in blood loss −67 mL, 95% CI -130.3 mL to -3.6 mL).

More detailed description of included studies on prostaglandin, meta-analysis results, and appraisal of balancing factors are available in Appendix D.

Summary Statement. Misoprostol administered preoperatively, either vaginally or rectally at 200 to 400 μg, reduces estimated blood loss at the time of laparoscopic myomectomy (−127.50 mL). This estimate is based on 2 heterogeneous RCTs at low risk of bias and one non-RCT with serious risk of bias.

Evidence from one RCT [19] suggests that addition of preoperative misoprostol to intramyometrial vasopressin reduces blood loss, though to a lesser extent (−67 mL).

Recommendation. There is moderate evidence supporting preoperative use of misoprostol to reduce blood loss at the time of laparoscopic myomectomy. (*Strength of Evidence: Grade B; Strength of Recommendation: Moderate).* The use of misoprostol should be considered based on its benefits, low cost, ready availability, and lack of reported serious side effects.

There is limited evidence to recommend that patients already receiving vasopressin benefit from the addition of misoprostol to reduce surgical blood loss at the time of laparoscopic myomectomy (*Strength of Evidence: Grade B. Strength of Recommendation: Weak).*

What Intraoperative Medical Interventions Reduce Blood Loss During Laparoscopic Myomectomy?

Epinephrine

Epinephrine is a potent vasoconstrictor, thereby motivating its use during laparoscopic myomectomy to reduce blood loss. Three studies [23−25], all RCTs, investigated the role of intramyometrial epinephrine in reducing blood loss during laparoscopic myomectomy. One [23] compared epinephrine plus bupivacaine (0.25% bupivacaine and 0.5 mL epinephrine solution) against placebo, another [24] compared epinephrine (0.5 mg epinephrine in 50 mL saline solution) against vasopressin, and the last [25] compared epinephrine (12 μg epinephrine diluted in 20 mL of NaCl solution) against placebo. Two studies [23,24] were rated to be at low risk of bias, while the third [25] was rated as having some concerns, largely due to its open randomization procedure and missing data.

Two studies comparing epinephrine +/- bupivacaine versus control [23,25] were included in a meta-analysis. The results suggested a significantly reduced blood loss with

Table 3

Recommendations for the use of preoperative medical adjuncts and intraoperative interventions to reduce surgical blood loss at the time of laparoscopic myomectomy

	Recommendations	Strength of evidence	Strength of recommendation
Preoperative medical adjuncts (class of agent)			
Leuprolide acetate (*GnRH agonist*)	1. The use of GnRH agonist, leuprolide acetate, administered for 3 months before laparoscopic myomectomy may reduce surgical blood loss.	B	Moderate
Misoprostol *(Prostaglandin)*	2. There is moderate evidence supporting preoperative use of misoprostol to reduce blood loss at the time of laparoscopic myomectomy. The use of misoprostol should be considered based on its benefits, low cost, ready availability, and lack of reported serious side effects.	B	Moderate
	3. There is limited evidence to recommend that patients already receiving vasopressin benefit from the addition of misoprostol to reduce surgical blood loss at the time of laparoscopic myomectomy	B	Weak
Intraoperative medical adjuncts (class of agent)			
Epinephrine *(Vasoconstrictors)*	4. There is moderate evidence supporting the use of intramyometrial epinephrine at the time of laparoscopic myomectomy to reduce surgical blood loss.	B	Moderate
Vasopressin *(Vasoconstrictors)*	5. There is moderate evidence that the use of vasopressin at the time of laparoscopic myomectomy reduces surgical blood loss.	B	Moderate
Oxytocin *(Vasoconstrictors)*	6. There is moderate evidence that oxytocin reduces blood loss at the time of laparoscopic myomectomy.	B	Moderate
Tranexamic acid *(Hemostatic agents)*	7. There is moderate evidence that tranexamic acid does not reduce blood loss during laparoscopic myomectomy.	B	Weak
Intraoperative surgical interventions			
Electrosurgical energy device	8. There is insufficient evidence to recommend one energy device over another to reduce blood loss at the time of laparoscopic myomectomy.	C	No Recommendation
Uterine artery occlusion	9. There is moderate evidence to support uterine artery occlusion, temporary or permanent, at the time of laparoscopic myomectomy to reduce surgical blood loss.	B	Moderate
	10. Uterine artery occlusion is not recommended to further reduce blood loss at the time of laparoscopic myomectomy when intramyometrial vasopressin is already used.	C	Weak
Barbed suture	11. There is insufficient evidence to recommend the use of barbed suture for hysterotomy closure at the time of laparoscopic myomectomy to reduce blood loss. Use of barbed suture may be considered at the discretion of the surgeon primarily for ease of suturing and shorter operative time.	C	Weak

the use of epinephrine (MD in blood loss -78.62 mL, 95% CI -95.26 mL to -61.98 mL, p<0.01).

One of the RCTs [23] also identified reduced surgical difficulty, smaller reduction in hemoglobin, faster myoma enucleation and reduced post-operative tramadol analgesic use in the epinephrine group. Although this study was confounded by the co-intervention of bupivacaine, blood loss reduction benefits are most likely attributable to epinephrine. The latter RCT [25] reported no significant related complications, though the epinephrine group had a shorter surgical duration and shorter length of stay.

More detailed description of the included studies on epinephrine, meta-analysis results, and appraisal of balancing factors are available in Appendix E.

Summary Statement. Intramyometrial epinephrine reduced blood loss at the time of laparoscopic myomectomy based on 2 RCTs, though overall effect size is modest (-78.62 mL). The side effect profile of epinephrine in laparoscopic myomectomy from clinical trials is favorable. Secondary outcomes such as myoma enucleation time also favor use of epinephrine.

Recommendation. There is moderate evidence supporting the use of intramyometrial epinephrine at the time of laparoscopic myomectomy to reduce surgical blood loss (*Strength of Evidence: Grade B; Strength of Recommendation: Moderate).*

Vasopressin

Vasopressin, a nonapeptide hormone with multiple systemic effects, is most notably used for its potent vasoconstrictive effects on vascular smooth muscle. In addition to

its autonomic effects, it also leads to fluid retention via antidiuretic action and potentiates a central stress response [26].

Seven studies [20,24,27−31] compared intramyometrial vasopressin to other interventions, including no intervention [20,27,29,31], concentrated vasopressin [30], intramuscular carboprost [28], intramuscular carboprost plus intravenous oxytocin [28], intramyometrial epinephrine [24], vaginal misoprostol [20] or intramyometrial oxytocin [29]. One additional study [32] compared varying doses of bovine posterior pituitary hormone extract (containing vasopressin plus oxytocin) injected intramyometrially against placebo.

Six studies were RCTs [24,27,28,30−32], one was a retrospective cohort study [20] and the last was a quasi-randomized controlled trial using alternation as the method of assignment [29]. Four were found at low risk of bias [24,27,31,32], while the others were at high risk of bias due to deviations from intended interventions and lack of appropriate randomization [28], lack of blinding [29], and non-quantitative methods used to estimate blood loss [30]. One was at critical risk of bias due to variability in measuring outcomes and uncontrolled differences in baseline characteristics between groups [20].

Meta-analysis of the 4 studies comparing intramyometrial vasopressin versus control [20,27,29,31] demonstrated significantly lower surgical blood loss with use of vasopressin (MD in blood loss -103.68 mL, 95% CI -150.74 mL to -56.62 mL, p<0.01). However, these studies were characterized by considerable heterogeneity ($I^2 = 78.39\%$), which remained significant when meta-analysis was restricted to the 2 RCTs [27,31] at low risk of bias ($I^2 = 70.40\%$).

One RCT [31] reported a lower rate of blood transfusion and slightly shorter surgical time with vasopressin compared with control. This study also reported increases in minor cardiovascular side effects, but there were no serious events of myocardial infarction, pulmonary edema, cardiac arrest, or mortality. Another RCT [27] also reported a shorter surgical time with use of vasopressin, while the transfusion rate and laparotomy conversion rates were comparable. The quasi-randomized controlled trial [29] reported reduced postoperative hemoglobin drop and shorter hospital stay with use of vasopressin compared with control. Lastly, one study [20] identified no significant differences in rates of intraoperative hypercapnia or subcutaneous emphysema with use of vasopressin, and a low rate of events that could be attributed to any study intervention. Overall, none of the studies identified significant complications attributable to vasopressin.

Six studies utilizing vasopressin [20,24,28−30,32] reported on unique comparator interventions that were not included in a meta-analysis. Only two of these studies [24,32] were judged to be at low risk of bias. Nonetheless, based on single studies, blood loss associated with intramyometrial vasopressin was reported to be comparable to that of concentrated vasopressin [30], intramuscular carboprost [28], intramyometrial epinephrine [24] or vaginal misoprostol [20]. In contrast, one study [29] reported significantly lower blood loss with vasopressin compared with oxytocin (106 ± 73 mL vs 184 ± 140 mL, p <0.01). The study using posterior pituitary extract [32] reported reduced blood loss in all treatment arms compared with control but did not identify greater benefits with higher doses of pituitary extract.

More detailed description of the included studies on vasopressin, meta-analysis results, and appraisal of balancing factors are available in Appendix F.

Summary statement. Intraoperative vasopressin at the time of laparoscopic myomectomy reduced surgical blood loss (-103.68 mL) based on 2 RCTs and 2 non-RCTs. Vasopressin was also found to be associated with a reduction in intraoperative transfusion rate, postoperative hemoglobin decline and surgical time. Some patients experienced transient systemic effects from vasopressin, including hypertension and bradycardia, but these were reliably managed intraoperatively, and serious adverse events were not reported in the included studies.

There is insufficient evidence to suggest that vasopressin is superior to alternative agents such as epinephrine, carboprost, misoprostol or oxytocin, or whether addition of vasopressin to other hemostatic agents reduces blood loss.

Recommendation. There is moderate evidence that the use of vasopressin at the time of laparoscopic myomectomy reduces surgical blood loss (*Strength of Evidence: Grade B; Strength of Recommendation: Moderate).*

Oxytocin

While oxytocin has a well-established effect in inducing uterine contractions in the pregnant uterus, its effect in non-pregnant human uteri remains controversial though biologically plausible [33]. This has prompted studies evaluating its role in minimizing blood loss during myomectomy.

Studies reporting on the effect of oxytocin in laparoscopic myomectomy were limited and highly heterogeneous, precluding any meta-analysis. One RCT of 60 total patients compared oxytocin started with induction of anesthesia against placebo [34]. This study was rated as low risk of bias and reported significantly lower blood loss with oxytocin compared with placebo (269.5 ± 225.8 mL vs 445 ± 268.6 mL, p <0.05). The study also reported a lower transfusion rate in the oxytocin arm (2/30 (6.7%) vs 11/30 (36.7%), p = 0.01) and no differences in other outcomes.

Another RCT [29] compared intraoperative oxytocin plus myoma pedicle ligation against placebo or vasopressin. This study was graded as at high risk of bias given quasi-randomization and lack of blinding, and no study arm investigated the effect of oxytocin alone. One study [28] compared oxytocin plus carboprost against carboprost alone. However, this study was at high risk of bias due to lack of appropriate randomization. Another retrospective cohort study [35] compared sulprostone against a historical cohort of patients receiving oxytocin and methylergonovine but was rated as at serious risk of bias in light of a poorly matched retrospective comparison group. Given their

serious limitations, the results of these other studies on oxytocin could not be aggregated.

More detailed description of the included studies on oxytocin and appraisal of balancing factors are available in Appendix G.

Summary statement. Evidence regarding oxytocin use during laparoscopic myomectomy is limited to one RCT of low risk of bias. This study found that oxytocin reduced blood loss and transfusion rate compared with placebo during laparoscopic myomectomy.

Recommendation. There is moderate evidence that oxytocin reduces blood loss at the time of laparoscopic myomectomy (*Strength of Evidence: Grade B; Strength of Recommendation: Moderate*).

Hemostatic Agents

Tranexamic acid blocks lysine binding sites on plasminogen molecules, thereby inhibiting the interaction between plasminogen and formed plasmin and fibrin. Its antihemorrhagic effects have been investigated extensively in various surgical procedures including myomectomy [36].

One study [37] investigated intraoperative intravenous tranexamic acid (15 mg/kg, 20 minutes before surgical incision) against placebo in an RCT. This small yet well-designed trial (30 patients per arm) at low risk of bias found no reduction in intraoperative blood loss with use of tranexamic acid.

One non-randomized study [38] compared intraoperative fibrin sealant (Tisseel, Baxter, IL) applied over uterine sutures against the use of bipolar coagulation of bleeding over suture sites without intraoperative fibrin. This study matched 15 patients receiving fibrin to a retrospective cohort of 15 patients and was rated as at moderate risk of bias due to an unclear process for selecting a matching control group and a small sample size. The study reported significantly reduced blood loss with use of fibrin sealant compared with coagulation (111.3 ± 77.3 vs 230 ± 75.6 mL, $p < 0.05$).

Summary statement. No reduction in blood loss was noted with the use of intraoperative tranexamic acid based on a single and small RCT. There is insufficient evidence that intraoperative fibrin reduces blood loss during laparoscopic myomectomy.

Recommendation. There is moderate evidence that tranexamic acid does not reduce blood loss during laparoscopic myomectomy (*Strength of Evidence: Grade B; Strength of Recommendation: Weak*).

What Intraoperative Surgical Interventions Reduce Blood Loss During Laparoscopic Myomectomy?

Intraoperative Energy Devices

Energy devices are commonly used in laparoscopic surgeries. We identified multiple studies that have evaluated various energy devices on surgical blood loss during laparoscopic myomectomy.

Ultrasonic Shears

One RCT [39] and 3 non-RCT studies [40−42] compared ultrasonic shears against unipolar/bipolar electrosurgery. These studies were rated as at high/serious/critical risk of bias due to multiple limitations such as co-interventions, inclusion of ineligible patients [39], inadequate account of group imbalances in surgeon experience, and case complexity [39−42], that precluded a meta-analysis. The single RCT [39] comparing ultrasonic shears against conventional electrosurgery reported a significantly lower blood loss with ultrasonic shears compared with electrosurgery plus epinephrine (135.2 ± 89.1 mL vs 182.8 ± 116.8 mL, $p = 0.004$). The other non-RCT studies [40−42] reported no significant differences in blood loss between the electrosurgery and ultrasonic shears groups.

Electrosurgical Vessel Sealing Devices

Three studies [42−44] compared electrosurgical vessel sealing devices (such as Ligasure [Medtronic, MN] or pulsed bipolar PK [Olympus, PA] Forceps) against conventional electrosurgical devices (unipolar electrode for dissection and bipolar instruments for coagulation). Risk of bias was rated as serious/critical due to an unclear/inadequate account of group imbalances in patient characteristics and co-interventions, as well as unclear protocol for measuring blood loss [42−44], precluding meta-analysis. One retrospective matched control study [43] reported lower blood loss with the PK device compared with conventional bipolar instruments (190.4 ± 178.5 mL versus 243.8 ± 150.4 mL, $p = 0.025$) and otherwise comparable surgical times, transfusion rates and hemoglobin decrease. Two retrospective cohort studies [42,44] reported comparable blood loss between study groups using electrosurgical vessel sealing device (Ligasure) vs conventional electrosurgery despite larger myoma or greater myoma weight in the Ligasure group. One study [44] suggested slightly shorter operative time in the Ligasure group.

CO2 Laser vs Ultrasonic Shears

One study [45] reported decreased blood loss with the use of a CO2 laser system compared with ultrasonic shears (mean blood loss ± standard deviation: 96.2 ± 115.0 mL vs 180.7 ± 218.3 mL, $p < 0.001$). However, this study was at critical risk of bias, as more complicated cases performed by potentially less experienced surgeons received the ultrasonic shears intervention.

More detailed description of the included studies on intraoperative energy devices and appraisal of balancing factors are available in Appendix H.

Summary statement. There is insufficient evidence favoring any particular energy device for laparoscopic myomectomy. All studies comparing such devices were either nonrandomized or were at high/serious/critical risk of bias, and most included very small sample sizes.

Recommendation. There is insufficient evidence to recommend one energy device over another to reduce blood loss at the time of laparoscopic myomectomy. *(Strength of Evidence: Grade C. Strength of Recommendation: No Recommendation).*

Uterine Artery Occlusion

Laparoscopic uterine artery occlusion prior to uterine incision has been reported as an approach to diminish blood loss during myomectomy [46]. Fifteen studies [47−61] assessed intraoperative uterine artery occlusion - temporary or permanent techniques - at the time of minimally invasive myomectomy. Fourteen studies assessed laparoscopic myomectomy and one assessed robotic-assisted laparoscopic myomectomy [49]. Two were RCTs [48,61] and 13 were observational studies.

Of the 2 RCTs [48,61], one was rated low risk of bias [48], while the other was high risk of bias due to concerns regarding randomization, allocation concealment and outcome measurement [61]. Six of 13 observational studies were rated as some/moderate risk of bias [47,49,52,56,58,60] and 7 were high/serious/critical risk of bias [50,51,53−55,57,59]. For studies scored as having moderate or high/serious/critical risk of bias, concerns for bias were related to selection of participants, classification/allocation of intervention, missing data, and outcome measurement.

A meta-analysis was conducted on thirteen studies that reported surgical blood loss comparing uterine artery occlusion to myomectomy alone [47,49−59,61]. This meta-analysis reported significantly lower surgical blood loss with use of uterine artery occlusion (MD in blood loss -126.84 mL, 95% CI -169.16 mL to -84.51 mL, $p < 0.01$). The statistically significant reduction of blood loss with uterine artery occlusion compared with control persisted in sensitivity analyses stratified by RCT vs observational study design, by low/moderate versus high/serious/critical risk of bias, and when limiting to studies without imputed mean/standard deviation of blood loss. However, considerable heterogeneity in estimated effects was identified across studies (e.g., $I^2 = 98.54\%$ in primary analysis). More detailed description of the included studies on uterine artery occlusion, meta-analysis results, and appraisal of balancing factors are available in Appendix I.

Summary Statement. All 13 studies included in the meta-analysis were consistent in finding a significant reduction in estimated surgical blood loss following uterine artery occlusion (either permanent or temporary) at the time of laparoscopic myomectomy. Although study heterogeneity was high, this finding remained significant throughout all sensitivity analyses. Studies did not report an increase in complications due to this additional surgical step, and uterine artery occlusion did not appear to vastly alter operative times.

Recommendation. There is moderate evidence to support uterine artery occlusion, temporary or permanent, at the time of laparoscopic myomectomy to reduce surgical blood loss. *(Strength of Evidence: Grade B; Strength of Recommendation: Moderate).*

Uterine Artery Occlusion and Intramyometrial Vasopressin

Four studies compared permanent uterine artery occlusion techniques and vasopressin at the time of laparoscopic myomectomy to a control group that also received vasopressin [62−65]. Three studies used bipolar occlusion [62−64] and 1 used suture ligation [65]. All 4 were observational studies. Three had low/moderate risk of bias [63−65] and 1 had serious risk of bias because of concerns regarding study design, patient allocation, and missing data [62].

Meta-analysis including all 4 studies did not find a significant difference in surgical blood loss between the two groups (MD in blood loss -30.74 mL, 95% CI -71.01 mL to 9.53 mL, $p = 0.13$). There was substantial heterogeneity in these studies ($I^2 = 80.30\%$). Similar findings were observed in sensitivity analyses stratified by risk of bias rating of the four studies or when excluding a study that involved some ineligible patients [63]. A contour-enhanced funnel plot revealed little concern for publication bias.

More detailed description of the included studies on uterine artery occlusion with vasopressin, meta-analysis results, and appraisal of balancing factors are available in Appendix I.

Summary Statement. Uterine artery occlusion does not result in significant reductions in estimated blood loss at the time of laparoscopic myomectomy when intramyometrial vasopressin is infiltrated. However, this finding is based on a meta-analysis of only 4 observational studies, only 2 of which were graded as low risk of bias, and with concerns related to high heterogeneity.

Recommendation. Uterine artery occlusion is not recommended to further reduce blood loss at the time of laparoscopic myomectomy when intramyometrial vasopressin is already used. *(Strength of Evidence: Grade C; Strength of Recommendation: Weak).*

Intraoperative Barbed Suture

Because use of barbed suture obviates the need to tie knots in laparoscopic surgery, its use in myomectomy was rapidly adapted. More rapid or efficient completion of surgery has theoretical potential to reduce intraoperative blood loss.

Eleven studies examining suture type for hysterotomy closure during laparoscopic myomectomy were included [66−76]. Of these eleven studies, 3 were RCTs [69,70,74] and the remaining were comparative observational studies [66−68,71−73,75,76]. Various brands/types of barbed suture were used, including Stratafix (Ethicon, NJ)

[68,69,76], Quill (Corza Medical, CA) [71], and V-Loc (Medtronic, MN) [66,67,72−75].

Only one observational study [67] was judged to be at low risk of bias as it was prospectively designed with clearly described measurements and outcomes. The remaining observational studies were judged to be moderate to high risk of bias due to varying degrees of concern about selection bias and the quality of the assessment of blood loss, and the retrospective nature of the studies. Of the randomized trials, two of the 3 studies [69,74] were low risk of bias, and one found to have some concerns [70] due to unclear randomization processes. All these studies demonstrated less intraoperative blood loss with the use of barbed suture.

Of the eleven studies, 8 studies (of which 7 were observational) compared barbed suture with conventional continuous suture and reported adequate data on blood loss [66,67,69,71−73,75,76]. In meta-analysis, barbed suture was associated with a statistically significant reduction in blood loss compared with conventional suture (MD in blood loss -36.46 mL, 95% CI -59.70 mL to -13.21 mL, $p<0.01$), although the reduction in blood loss may be clinically insignificant. There was considerable heterogeneity in estimated magnitude of the intervention effect across the 8 studies ($I^2 = 92.59\%$). However, reduced blood loss remained statistically significant in sensitivity analysis that excluded studies with high/serious/critical risk of bias.

Use of barbed suture during hysterotomy closure may be used for convenience and technical ease of suturing. Nine studies showed significant improvement in operating times when barbed suture was employed over conventional suture, with time savings ranging from 7 to 58 minutes for total operative time [66−69,71−73,75,76]. There was no difference in complication rates noted when barbed vs conventional continuous suture was employed. One RCT study [69] evaluated postoperative adhesions and found no difference when barbed vs conventional continuous suture was used. Two studies [67,74] evaluated technical difficulty and found barbed suture to be significantly easier to use than conventional suture.

More detailed description of the included studies on barbed suture, meta-analysis results, and appraisal of balancing factors are available in Appendix J.

Summary Statement. There is weak evidence showing a reduction in blood loss associated with the use of barbed suture during laparoscopic myomectomy. However, the magnitude of the reduction in blood loss (-36.46 mL) is not clinically significant. Use of barbed suture may be beneficial for other considerations such as reducing operative time or technical ease of closure and may be selected for these benefits.

Recommendation. There is insufficient evidence to recommend the use of barbed suture for hysterotomy closure at the time of laparoscopic myomectomy to reduce blood loss. Use of barbed suture may be considered at the discretion of the surgeon primarily for ease of suturing and shorter operative time. *(Strength of evidence: C; Grade of recommendation: Weak)*

Other Intraoperative Interventions

Several additional studies assessed other forms of intraoperative interventions to reduce blood loss at the time of laparoscopic myomectomy. There is insufficient evidence about their effectiveness in reducing surgical blood loss. These studies are summarized in Appendix K.

Conclusions

Despite an anticipated increase in fibroid-related procedures in the coming years, high-quality definitive studies regarding the use of medical adjuncts and surgical techniques to minimize blood loss during laparoscopic myomectomy are lacking. Given the current evidence, this systematic review with resulting meta-analyses supports the modest benefits of 3-month administration of leuprolide acetate prior to myomectomy, preoperative use of misoprostol, and intraoperative use of epinephrine, vasopressin, oxytocin, and uterine artery occlusion to reduce blood loss during laparoscopic myomectomy. The other interventions and adjuncts evaluated did not show benefit in reducing blood loss. Additionally, the benefits of these interventions used in combination have not been established.

There is a clear need for additional high-quality studies such as RCTs that evaluate single interventions and co-interventions to minimize blood loss using standardized measurement and reporting of outcomes, especially blood loss. More studies are also needed to assess the long-term effects of these interventions on fertility and pregnancy outcomes. In addition, rigorous cost analysis of the different interventions to minimize blood loss during laparoscopic myomectomy would be helpful.

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Supplementary materials

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