Uterine artery closure at the origin vs at the uterus level in total laparoscopic hysterectomy: A randomized controlled trial

Stefano Uccella[1,2] | Simone Garzon[2] | Gabriele Lanzo[1] | Davide Gallina[1] |
Mariachiara Bosco[2] | Irene Porcari[2] | Salvatore Gueli-Alletti[3] | Stefano Cianci[4] |
Massimo Franchi[2] | Pier Carlo Zorzato[1,2]

[1]Division of Obstetrics and Gynecology, Department of Maternal, Neonatal and Infant Health, ASL Biella, Biella, Italy

[2]Department of Obstetrics and Gynecology, AOUI Verona, University of Verona, Verona, Italy

[3]Division of Gynecologic Oncology, Department of Women and Children's Health, A. Gemelli University Hospital and Institute for Research and Care, Rome, Italy

[4]Unit of Gynecology, Department of Human Pathology of Adult and Childhood "G. Barresi", University of Messina, Messina, Italy

Correspondence
Stefano Uccella, Department of Obstetrics and Gynecology, AOUI Verona, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy.
Email: stefucc@libero.it

Abstract

Introduction: The transfusion rate in hysterectomies for benign pathology is almost 3%. However, despite the strong interest in reducing intraoperative bleeding, limited evidence is available regarding the technical aspects concerning uterine vessel management during a total laparoscopic hysterectomy (TLH). Uterine artery (UA) closure in TLH can be performed at the origin from the internal iliac artery or at the uterus level (UL). However, low-quality evidence is available regarding the superiority of one method over the other.

Material and methods: We performed a single-blind randomized (1:1) controlled trial (NCT04156932) between December 2019 and August 2020. One hundred and eighty women undergoing TLH for benign gynecological diseases were randomized to TLH with UA closure at the origin from the internal iliac artery ($n = 90$), performed at the beginning of the procedure by putting two clips per side at the origin, vs closure at the UL ($n = 90$). Intraoperative blood loss estimated from suction devices was the primary outcome. Secondary end points were perioperative outcomes, the conversion rate from one technique to the other, and complication rates with 4 months of follow up.

Results: Uterine artery closure at the origin was completed in all 90 patients (0%), whereas closure at the UL was converted to closure at the origin in 11 cases (12.2%; $p < 0.001$); failures were mainly associated with the presence of endometriosis (81.8% [9/11] vs 10.1% [8/79]; $p < 0.001$). In the intention-to-treat analysis, the intraoperative blood loss was higher in the group assigned to the closure at the UL (108.5 mL) than in the group with closure at the origin (69.3 mL); the mean difference was 39.2 mL (95% CI 13.47–64.93 mL; $p = 0.003$). Other perioperative outcomes and complications rates did not differ.

Conclusions: Uterine artery closure at the origin reduces intraoperative blood loss during a TLH and appears to be more reproducible than closure at the UL without

higher complication rates. However, the absent translation in clinical benefits impedes the support of a clinical superiority in all women. Closure at the origin may provide clinical advantages in the presence of severe preoperative anemia or pelvic anatomic distortion.

KEYWORDS
hysterectomy, laparoscopy, randomized controlled trial, surgical blood loss, uterine artery

1 | INTRODUCTION

Hysterectomy is the second most common gynecological surgical procedure.[1] Among minimally invasive options,[2] laparoscopic hysterectomy has gained increasing popularity for treating benign pathologies, becoming the most common approach with progressively fewer limitations and more comprehensive applications.[3–7] Nevertheless, despite the extensive use, evidence on the technique to perform the procedure is limited to only some steps.[8,9]

An efficient closure of uterine arteries (UAs) is crucial during a total laparoscopic hysterectomy (TLH). The two main options consist of closing UAs at the origin from the internal iliac artery or at the uterus level (UL). This latter approach is the most used for a TLH, commonly considered easier because it avoids opening the retroperitoneum. Nevertheless, this choice is based exclusively on the surgeon's opinion and preference.

Available evidence comparing the two techniques is limited, and the superiority of one method over the other is unclear. Three randomized controlled trials tried to answer this question.[10–12] However, they provided heterogeneous results and did not reach definitive conclusions. A recent meta-analysis focusing on strategies to minimize blood loss during hysterectomies stressed the presence of low-quality evidence on this specific issue and the need for further investigation.[13]

On that basis, we performed a randomized controlled trial to compare TLH for benign pathologies performed with UA closure at the origin from the internal iliac artery vs UA sealing at the UL. We compared the two techniques regarding perioperative outcomes, complications rate, and rate of conversion to the other approach.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

This study is a single-blind, parallel groups, two-arm, randomized controlled trial. The trial was conducted at the Division of Obstetrics and Gynecology, Department of Maternal, Neonatal and Infant Health, ASL Biella, Biella, Italy. Patient recruitment began on December 1, 2019 and ended on August 31, 2020. The institutional review board and the ethical committee of the ASL Biella/University of East Piedmont approved the study in June 2019 (Protocol: 440/

> **Key message**
>
> Uterine artery closure at the origin during a total laparoscopic hysterectomy is associated with a lower intraoperative blood loss and a higher success rate than closure at the uterus level, without different hemoglobin drop, hospital stay, or complications rate.

CA; Study number: CE40/19). The trial was registered on clini caltrials.gov before starting recruitment on November 8, 2019 (NCT04156932; https://clinicaltrials.gov/ct2/show/NCT04156932). The study was conducted and reported following the CONSORT statement.[14] Written informed consent was obtained from all patients at the time of preoperative evaluation and was reconfirmed on the day of surgery.

All consecutive women who were scheduled for elective TLH with or without adnexectomy were screened for eligibility. Inclusion criteria were age ≥18 years and benign condition as the indication. Exclusion criteria were preoperative evidence of malignant disease, previous vaginal or pelvic radiotherapy, and pre-randomization planned radical hysterectomy or uterine vessels approach.

2.2 | Randomization and concealment

Patients were randomly assigned to treatment groups by the creation of a password-protected randomization database. Block randomization was used, generated by computer with randomization blocks of 20 to ensure the balance between groups. Randomization was performed at the start of the hysterectomy, immediately after the access to the abdominal cavity. Patients were randomized with a 1:1 ratio to undergo either uterine vessel closure at the origin or at the UL. Single blinding was obtained as follows: patients were concealed to the allocation arm up to the study's completion but masking the surgeons was not possible. To reduce measure bias, the investigators performing postoperative follow up and analysis were blinded, and the primary outcome was assessed by the anesthesiologist.

2.3 | Intervention

The involved institution is a high-volume referral center with more than 300 major gynecologic procedures per year. Only open, vaginal, or total laparoscopic approaches for total hysterectomy are used at the center, with TLH representing more than 80% of hysterectomies for benign indications. Operations were performed by the same team of surgeons (SU, DG, PCZ, GL). All surgeons perform hysterectomy using the same laparoscopic technique, which is standardized at the center in terms of instruments, steps, colpotomy, and colporrhaphy.

Patients assigned to uterine vessels closure at the UL underwent hysterectomy with UA securing where it joins the uterus, without opening the retroperitoneum. Sealing of the UAs was performed in all cases by coagulation with bipolar laparoscopic forceps and section with laparoscopic scissors.

Patients assigned to the closure of uterine vessels at the origin from the internal iliac artery underwent hysterectomy with uterine devascularization performed at the beginning of the procedure by putting two clips per side at the origin of the UA. Access to the retroperitoneum was obtained laterally to the infundibulopelvic ligament. The ureter was visualized and followed along its course. With the opening of pararectal and paravesical spaces, the UA and its origin were identified and reached. The vessel was clipped just medially to its origin from the internal iliac artery using 5-mm titanium clips (LIGAMAX™5 Endoscopic Multiple Clip Applier, Ethicon).[15–17] Advanced electrosurgical devices were not used in the study.

During the in-hospital stay, all patients were treated following the same perioperative care protocol. All patients underwent fasting for solid food at least 8 hours before surgery and for clear liquids at least 2 hours. In all cases, hemoglobin assessment was performed preoperatively and on the first postoperative day. Standardized fluid therapy and routine prophylaxis with low-molecular-weight heparin for thromboembolism prevention were used after all procedures.

2.4 | Study outcomes

The primary outcome was the intraoperative blood loss (mL), which was established from the content of the suction device. The anesthesiologist was in charge of measuring intraoperative blood loss subtracting from the total volume collected in the suction device any volume introduced by irrigation during the procedure. The surgeon was not involved in the primary outcome assessment, being not blinded for the procedure, and directly involved in the trial. The anesthesiologist was not informed regarding the allocation arm, although present during surgery.

Secondary outcomes were the operative time (minutes), the conversion rate from one technique to the other, the hemoglobin drop (g/dL), the length of hospital stay (days), and the minor and major complications rate (Clavien-Dindo Classification grade <3 vs grade ≥3).

The hospital stay was counted starting from the first postoperative day. Operative time for hysterectomy was defined as the time between the first skin incision and the last skin reapproximation. Intraoperative and immediate postoperative complications were recorded at discharge. All patients had a follow-up visit 30 days after surgery and were re-contacted by phone 4 months after surgery to identify postoperative complications. Intraoperative and postoperative complications were graded following the Clavien-Dindo Classification. Investigators performing postoperative, 30-day, and 4-month follow up were masked to the allocation arm and prospectively collected demographic, clinical, perioperative, and follow-up data in an anonymized database.

2.5 | Sample size calculation and statistical analysis

The sample size calculation was performed using software G*POWER 3.115 (Franz Faul, Universität Kiel). We expected an average intraoperative blood loss of 100 mL (standard deviation [SD] = 30 mL) during a TLH performed with uterine vessel closure at the UL.[11] The null hypothesis was that the intraoperative blood loss during TLH does not change whether uterine vessels are closed at the origin or at the UL. With a two-sided type I error (α) of 0.05, we need to enroll 84 women per arm to have a power of 90% to reject the null hypothesis, if the uterine vessel closure at the origin from the internal iliac artery increases or reduces the intraoperative blood loss of 15 mL. Assuming a dropout rate of 5%, we needed 90 patients per arm.

Demographic, clinical, perioperative, and follow-up data were summarized using standard descriptive statistics. Baseline characteristics and study outcomes were compared between the two groups using t test or Mann-Whitney U test as appropriate. Categorical data were analyzed with the chi-squared or Fisher exact test. Simple linear regression was used to investigate the association between uterine weight and intraoperative blood loss. The multilevel linear model analysis was used to test whether this association varies between study groups. All analyses were done by intention to treat. A sensitivity analysis was conducted per protocol, excluding cases with failure and conversion of the procedure. All reported p values were two-sided, and significance was considered at $p < 0.05$. Data analysis was performed using GRAPHPAD PRISM 7.0 (GraphPad Software) and SPSS Statistics 23.0 (IBM).

2.6 | Ethical approval

The institutional review board and the ethical committee of the ASL Biella/University of East Piedmont approved the study in June 2019 (Protocol: 440/CA; Study number: CE40/19). The trial was registered on clinicaltrials.gov before starting recruitment on November 8, 2019 (NCT04156932; https://clinicaltrials.gov/ct2/show/NCT04 156932). Written informed consent was obtained from all patients at the time of preoperative evaluation and was reconfirmed on the day of surgery.

3 | RESULTS

3.1 | Study sample attrition and clinical-demographic characteristics

Between December 1, 2019 and August 31, 2020, 180 women were enrolled and randomly assigned to the uterine vessel closure at the UL (UL group; n = 90) or uterine vessel closure at the origin (OR group; n = 90). No patients were excluded after randomization, with all 180 patients included in the intention-to-treat analysis. A 30-day follow-up visit was performed for 172 patients (95.5%). The eight patients who did not attend the 30-day follow-up visit had a phone follow up. All 180 women were contacted by phone 4 months after surgery and completed the follow up. Figure 1 shows the CONSORT flow diagram of the study.

Patient demographic and clinical characteristics are summarized in Table 1. Characteristics were well-balanced between the two groups. The mean study population age was 54.2 years (SD 10.8 years). Most patients were premenopausal and of normal weight. Symptomatic uterine fibroids were the main indication for hysterectomy (50.6%). No malignant pathologies were recognized

during surgery. Endometriosis was diagnosed in a relevant percentage of patients in both groups (12 [13.3%] and 17 [18.8%] in UL and OR groups, respectively; p = 0.42). All TLHs were completed without conversion to open surgery. In one case per group, a suprapubic transverse mini-laparotomy was performed to extract the uterus. In all other patients, the uterus was removed vaginally intact or with transvaginal in-bag morcellation.

3.2 | Failure of the UA closure technique

Uterine vessel closure at the origin from the internal iliac artery was completed in all 90 patients (failure rate 0%). Conversely, 11 protocol violations were registered among patients assigned to the UL group (failure rate 12.2%; p < 0.001). In all these cases, the closure at the origin was deemed safer by the operator because of intraoperative detection of severe pelvic anatomical distortion. The conversion was necessary in two circumstances because of fibroids—one isthmic and one occupying the broad ligament. In nine cases, the violation was due to endometriosis infiltrating the lateral paracervix. Endometriosis was diagnosed in 10.1% (8/79)
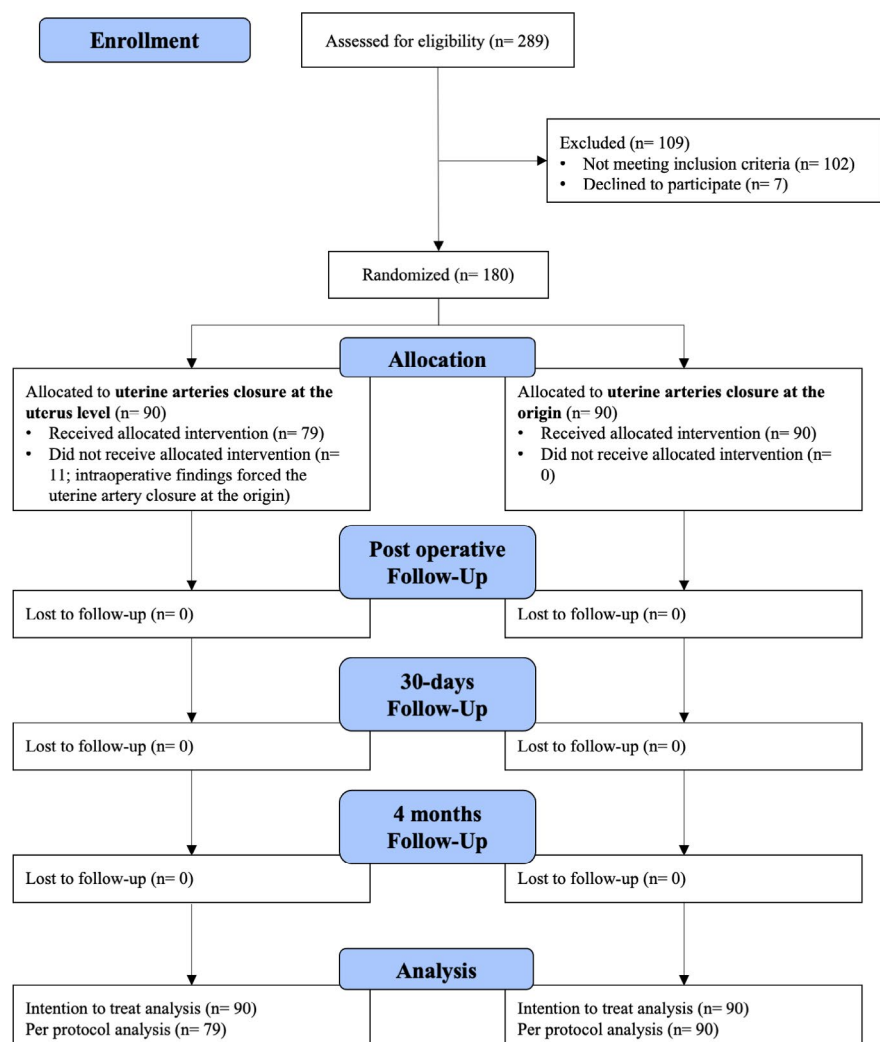

FIGURE 1 CONSORT flow diagram of the study

TABLE 1 Patient demographic and clinical characteristics

	Total $n = 180$	UL group (closure at the uterus level) $n = 90$	OR group (closure at the origin) $n = 90$	p value*
Age, years (mean, SD, min–max)	54.2 (10.8; 33–91)	54.0 (10.4; 39–84)	54.4 (11.3; 33–91)	0.83
BMI, kg/m^2 (mean, SD, min–max)	25.1 (5.09; 16.9–49.1)	25.0 (5.43; 17–49.1)	25.3 (4.76; 16.9–36.6)	0.73
BMI ≥30 kg/m^2, n (%)	25 (13.9)	12 (13.3%)	13 (14.4%)	0.99
Indication, n (%)				
Fibroids	91 (50.6%)	45 (50%)	46 (51.1%)	0.99
POP	23 (12.8%)	11 (12.2%)	12 (13.3%)	0.99
Adenomyosis	14 (7.8%)	6 (6.7%)	8 (8.9%)	0.78
Abnormal uterine bleeding	26 (14.4%)	15 (16.7%)	11 (12.2%)	0.53
Others	26 (14.4%)	13 (14.4%)	13 (14.4%)	0.99
Previous LPS, n (%)	19 (10.6%)	8 (8.9%)	11 (12.2%)	0.63
Previous open surgery, n (%)	88 (48.9%)	41 (45.6%)	47 (52.2%)	0.46
Comorbidities, n (%)	99 (55%)	47 (52.2%)	52 (57.8%)	0.55
Postmenopausal status, n (%)	69 (38.3%)	35 (38.9%)	34 (37.8%)	0.99
Pre-Op Hb, mg/dL (mean, SD, min–max)	12.6 (1.68; 7.7–15.6)	12.8 (1.57; 7.7–15.1)	12.5 (1.79; 8.8–15.6)	0.22

Abbreviations: BMI, body mass index; Hb, hemoglobin; LPS, laparoscopy; min–max, minimum–maximum; OR group, uterine vessels closure at the origin from the internal iliac artery; POP, pelvic organ prolapses; Pre-Op, preoperative; SD, standard deviation; UL group, uterine vessels closure at the uterus level.

*Comparison between Group A and Group B.

of women with successful closure at the UL vs 81.8% (9/11) of patients with protocol violation ($p < 0.001$). Moreover, higher rates of mono/bilateral parametrectomy (63.6% [7/11] vs 3.8% [3/79]; $p < 0.001$) and ureterolysis (100% [11/11] vs 5.1% [4/79]; $p < 0.001$) were performed in the protocol violation subgroup. We identified a unilateral duplicate ureter in two patients (2/90; 2.2%) of the OR group.

3.3 | Intraoperative and postoperative outcomes

Intra- and postoperative outcomes of the two study groups are summarized in Table 2. Uterine weights were comparable between the two treatment arms ($p = 0.56$), with a mean uterine weight of 306.6 g (SD 346.3 g; minimum–maximum 24–2800 g) in the UL group and 338.2 g (SD 381.7 ; minimum–maximum 30–2159 g) in the OR group. The mean intraoperative blood loss was higher in the UL group (108.5 mL) than in the OR group (69.3 mL), with a mean difference of 39.2 mL (95% CI 13.47–64.93 mL; $p = 0.003$). However, preoperative (Table 1) and postoperative (Table 2) hemoglobin levels did not differ. The mean difference in hemoglobin drop between groups was −0.04 g/dL (95% CI −0.29 to 0.22 g/dL; $p = 0.77$). All other outcomes were comparable between the two arms (Table 2).

3.4 | Intraoperative and postoperative complications

Details of complications are provided in Table 3. A single case of intraoperative complication was recorded in each group, and both were recognized and managed laparoscopically during primary surgery. The incidence of minor and major postoperative complications was similar between the UL and OR groups (10% [9/90] vs 6.6% [6/90]; $p = 0.37$). Six (6.6%) vaginal cuff complications were observed in the UL group vs two (2%) in the OR group ($p = 0.28$). All the postoperative infections were successfully managed by antibiotics administration; no drainage or further interventions were required. Among all patients, three women were submitted to reoperation, two because of vaginal cuff dehiscence, and one for postoperative vaginal bleeding. All re-interventions occurred in the UL group and were successfully repaired vaginally.

3.5 | Uterine arteries closure technique, uterine weight, and blood loss

In simple linear regression analysis, intraoperative blood loss was associated with uterine weight ($p < 0.001$). However, the association

TABLE 2 Intraoperative and postoperative outcomes as per the intention-to-treat analysis

	UL group (closure at the uterus level) $n = 90$	OR group (closure at the origin) $n = 90$	p value
Uterine weight, g (mean, SD, min–max)	306.6 (346.3; 24–2800)	338.2 (381.7; 30–2159)	0.56
Intraoperative diagnosis of endometriosis, n (%)	17 (18.8%)	12 (13.3%)	0.42
Intraoperative complications, n (%)	1[a] (1.1%)	1[b] (1.1%)	0.99
Conversion to open surgery, n (%)	0 (0%)	0 (0%)	0.99
Failure with conversion to the other uterine artery closure technique, n (%)	11 (12.2%)	0 (0%)	**<0.001**
Operative time, minutes (mean, SD, min–max)	98.6 (43.6; 35–382)	99.5 (37.5; 55–286)	0.87
Estimated blood loss, mL (mean, SD, min–max)	108.5 (87.2; 0–500)	69.3 (83.8; 0–500)	**0.002**
Hospital stays, day (median, IQR, min–max)	3 (2–10)	3 (1–20)	0.47
Post-Op Hb, g/dL (mean, SD, min–max)	11.5 (1.36; 8–14.1)	11.2 (1.62; 7.3–14.2)	0.23
Hb drop, g/dL (mean, SD, min–max)	−1.33 (0.8; −3.70 to 1.8)	−1.29 (0.92; −5.1 to 3.5)	0.77
Postoperative complications, n (%)	9 (10%)	6 (6.6%)	0.59

Abbreviations: Hb, hemoglobin; IQR, interquartile range; min–max, minimum–maximum; OR group, uterine vessels closure at the origin from the internal iliac artery; Post-Op, postoperative; SD, standard deviation; UL group, uterine vessels closure at the uterus level.

Statistically significant p values are highlighted in bold character.

[a]Bladder lesion recognized and managed laparoscopically during primary surgery.

[b]Small bowel injury recognized and managed laparoscopically during primary surgery.

TABLE 3 Details of intraoperative and postoperative complications as per the intention-to-treat analysis

	UL group (closure at the uterus level) $n = 90$	OR group (closure at the origin) $n = 90$	p value
Intraoperative complications[a], n (%)	1 (1.1%)	1 (1.1%)	0.99
Bladder lesion	1 (1.1%)	0 (0%)	0.99
Small bowel injury	0 (0%)	1 (1.1%)	0.99
Postoperative complications, n (%)	9 (10%)	6 (6.6%)	0.59
Grade 1–2 complications[b]	6 (6.7%)	6 (6.6%)	0.99
Grade 3 complications[b]	3 (3.3%)	0 (0%)	0.25
Grade 4 complications[b]	0 (0%)	0 (0%)	0.99
Any cuff complication, n (%)	6 (6.6%)	2 (2%)	0.28
Vaginal dehiscence	1 (1.1%)	0 (0%)	0.99
Vaginal evisceration	1 (1.1%)	0 (0%)	0.99
Vaginal cuff hematoma/abscess	2 (2.2%)	2 (2.2%)	0.99
Postoperative vaginal bleeding	2 (2.2%)	0 (0%)	0.50
Vaginal cuff resuture, n (%)	2 (2.2%)	0 (0%)	0.50
Postoperative infection[c], n (%)	3 (3.3%)	4 (4.4%)	0.99

Abbreviations: OR group, uterine vessels closure at the origin from the internal iliac artery; UL group, uterine vessels closure at the uterus level.

[a]Recognized and managed laparoscopically during primary surgery.

[b]Clavien-Dindo classification.

[c]Corrected by the administration of antibiotics, no drainages, neither further interventions were required.

was weak (β = 0.088 mL/g; intercept = 60.6); for every 1000 g of additional uterine weight, intraoperative blood loss increased by 88 mL. In the multilevel linear model analysis, allowing the β coefficient to vary between the two groups did not improve the model fit than the model with fixed coefficients (p = 0.1484). Conversely, the intercept variation between the two groups statistically significantly improved the model fit (intercept = 59.8 mL; random effect SD = 28.5 mL; p = 0.0472). The intraoperative blood loss reduction provided by the UA closure at the origin does not appear to change with the uterine weight (different intercept, equal slope) (Figure 2).
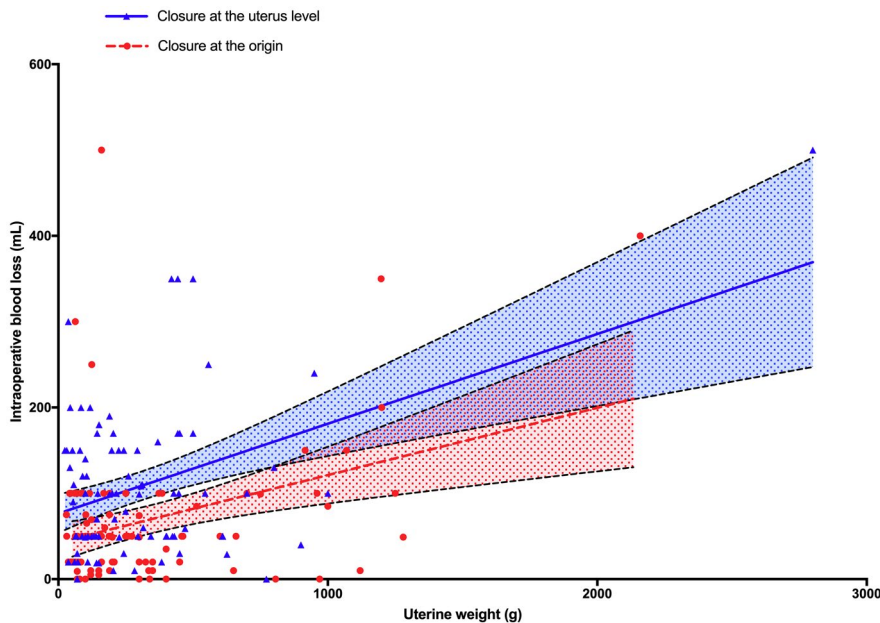
FIGURE 2 Scatter plot with the two regression lines and corresponding 95% CI showing the association between uterine weight (g) and intraoperative blood loss (mL) stratified by treatment group. Blue triangular dots and continuous line = UL group ($\beta = 0.10 \pm 0.02$ mL/g; intercept = 76.5 ± 11.3 mL). Red circular dots and dashed line = OR group ($\beta = 0.08 \pm 0.02$ mL/g; intercept = 42.8 ± 11.1 mL)

3.6 | Study outcome in the per protocol analysis

The analysis was repeated as per protocol, confirming previous results. The intraoperative blood loss was 69.3 mL in the OR group (90 patients) and 104.3 mL in the UL group (79 patients) with a mean difference of 35 mL (95% CI 14.1–64.3 mL; $p = 0.002$). All other outcomes did not differ between treatment arms.

4 | DISCUSSION

The UA closure at the origin was associated with a lower intraoperative blood loss and a higher success rate than the closure at the UL, without observing different hemoglobin drop, hospital stay, or complications rate.

Minimally invasive surgery is recommended to perform a total hysterectomy for benign pathologies.[18] However, it is not without surgical morbidity.[2] Among complications, excessive intraoperative bleeding is still an issue. The transfusion rate among hysterectomies for benign pathology is almost 3%,[19] with a higher risk of intraoperative blood loss in large uteri.[20] Nevertheless, despite the strong interest in reducing intraoperative bleeding, limited evidence is available regarding the technical aspects concerning UA management during a TLH.[13] Three randomized controlled trials investigated the UA closure at the origin, providing conflicting results and not reaching definitive conclusions.[10–12] In a recent meta-analysis, significant heterogeneity in intraoperative blood loss and postoperative hemoglobin drop were observed, with only intraoperative blood loss reported with a statistically significant reduction.[13] The low number of included patients, the subjective assessment of outcomes, and an inadequate follow up limited results interpretations.[10–12] One trial was further confounded by using a two-step approach.[12] In this scenario, our randomized, single-blind controlled

trial provides robust evidence of a reduced intraoperative blood loss with the UA closure at the origin, which appears independent from the uterus weight, confirming a small but consistent benefit regardless of the uterine size.

The higher failure rate in the UL group than the OR group reinforces the concept that the UA closure at the origin is more reproducible than closing at the isthmus, which is not always feasible.[21] Notably, the failure to close UAs at the UL was significantly associated with the intraoperative identification of endometriosis and the need for parametrectomy and ureterolysis.[21–23] In these cases, developing the paravesical and pararectal spaces is necessary.[22–24] Consequently, the UA occlusion at the origin appears to be a safer and more reproducible maneuver to complete hysterectomy.[21] Moreover, we observed two (2.2%) cases of ureteral duplication in the OR group. Not recognizing such a condition may lead to a higher risk of ureteral injuries.[25] Therefore, the exposure of the retroperitoneal anatomy may allow a safer surgery, despite one of the main criticisms of the routine closure of UAs at the origin being the risk of damaging retroperitoneal structures.[13]

The main concern is that the observed difference in intraoperative blood loss is not clinically relevant.[13] However, we believe that our data have clinical implications and are not inconclusive regarding the best procedure to secure UAs for a TLH. Anemic patients undergoing hysterectomy[26] could obtain an advantage even from a smaller reduction in intraoperative blood loss.[27] Familiarizing yourself with safely accessing and visualizing the retroperitoneal structures may be beneficial in cases of anatomical distortion that impede the closure of UAs at the UL.[21]

We recognize that our trial was not powered to investigate secondary outcomes, impeding definitive conclusions regarding infrequent complications and procedure safety. Concerning this point, the rate of vaginal cuff complications was three times lower in the OR group, but this discrepancy was not significant and may be due

to chance. On the one hand, vault complications were hypothesized as being associated with oozing from the cuff and subsequent hematoma and inflammation,[8] which may be reduced by closing UAs at the origin; on the other hand, major vaginal vascularization may originate from the UAs rather than directly from the hypogastric or umbilical artery; in this cases, occlusion of the UAs at the origin may reduce (at least partially) the blood supply of the vagina, with possible consequences on the rate of postoperative vaginal cuff complications. Further studies may investigate whether the UA closure at the origin reduces or increases complication rates, clarifying the safety of the procedure and other possible clinical implications.

Additionally, our study supports that UA closure at the origin reduces intraoperative blood loss regardless of the uterine weight. However, caution is required. Conversely to previous trials, we included very large uteri and observed only a weak association between uterine weight and blood loss. This result highlights a possible further limitation represented by the surgeon's experience,[3–6,28,29] which may have reduced the benefits of closing UAs at the origin.[13,20] In this regard, surgical experience and practice may have affected other results, such as the observed failure rate in the UL group. Although surgeons involved in the trial do not close UAs at the origin in their routine practice, their approach may be more prone to close at the origin than other surgical schools with a possible inflated failure rate. Finally, the single-blind design—it being impossible to mask surgeons—is a possible source of bias for the primary outcome, which was assessed by the anesthesiologist to limit this measure bias. Moreover, regardless of limitations, our trial results are strengthened by the study design and methods: the randomization, the objective assessment of primary outcome, the long-term follow up with minimal attrition, and the concealment of patients and assessors of the postoperative course.

5 | CONCLUSION

The UA closure at the origin is superior to the closure at the UL in terms of lower intraoperative blood loss and higher reproducibility. However, the absence of translation into clinical benefits impedes the support of its clinical superiority in all cases. The routine uses of this approach may provide advantages in specific conditions, such as in the presence of severe preoperative anemia, deep infiltrating endometriosis, or ureteral duplication. Further studies should investigate whether UA closure at the origin reduces or increase complication rates, such as vaginal cuff complications,[8] and further characterized clinical benefits.

CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
SU conceptualized the study. SUccella and PCZ designed the study. SU, PCZ, GL, and DG performed laparoscopic total hysterectomies. SU, PCZ, GL, DG, MB, and IP prospectively collected data. SG, SU, and PCZ managed the data set and performed statistical analyses. SU, SG, PCZ, SG-A, SC, and MF wrote the manuscript. All authors contributed to the interpretation of the results, as well as to the writing and editing of the manuscript.

ORCID
Simone Garzon https://orcid.org/0000-0002-5840-699X

REFERENCES

1. Morgan DM, Kamdar NS, Swenson CW, Kobernik EK, Sammarco AG, Nallamothu B. Nationwide trends in the utilization of and payments for hysterectomy in the United States among commercially insured women. *Am J Obstet Gynecol.* 2018;218:425.e1-425.e18.
2. Aarts JWM, Nieboer TE, Johnson N, et al. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev.* 2015;8:CD003677.
3. Uccella S, Cromi A, Bogani G, Casarin J, Formenti G, Ghezzi F. Systematic implementation of laparoscopic hysterectomy independent of uterus size: clinical effect. *J Minim Invasive Gynecol.* 2013;20:505-516.
4. Uccella S, Casarin J, Morosi C, et al. Hysterectomy for uteri weighing ≥1kg: laparoscopic vs. open approach. *J Minim Invasive Gynecol.* 2015;22:S87.
5. Uccella S, Casarin J, Marconi N, et al. Laparoscopic versus open hysterectomy for benign disease in women with giant uteri (≥1500 g): feasibility and outcomes. *J Minim Invasive Gynecol.* 2016;23:922-927.
6. Uccella S, Morosi C, Marconi N, et al. Laparoscopic versus open hysterectomy for benign disease in uteri weighing >1 kg: a retrospective analysis on 258 patients. *J Minim Invasive Gynecol.* 2018;25:62-69.
7. Uccella S, Cromi A, Serati M, Casarin J, Sturla D, Ghezzi F. Laparoscopic hysterectomy in case of uteri weighing ≥1 kilogram: a series of 71 cases and review of the literature. *J Minim Invasive Gynecol.* 2014;21:460-465.
8. Uccella S, Malzoni M, Cromi A, et al. Laparoscopic vs transvaginal cuff closure after total laparoscopic hysterectomy: a randomized trial by the Italian Society of Gynecologic Endoscopy. *Am J Obstet Gynecol.* 2018;218:500.e1-500.e13.
9. Uccella S, Zorzato PC, Kho RM. Incidence and prevention of vaginal cuff dehiscence after laparoscopic and robotic hysterectomy: a systematic review and meta-analysis. *J Minim Invasive Gynecol.* 2021;28:710-720.
10. Pan H-S, Ko M-L, Huang L-W, Chang J-Z, Hwang J-L, Chen S-C. Total laparoscopic hysterectomy (TLH) versus coagulation of uterine arteries (CUA) at their origin plus total laparoscopic hysterectomy (TLH) for the management of myoma and adenomyosis. *Minim Invasive Ther Allied Technol.* 2008;17:318-322.
11. Kale A, Aksu S, Terzi H, Demirayak G, Turkay U, Sendag F. Uterine artery ligation at the beginning of total laparoscopic hysterectomy reduces total blood loss and operation duration. *J Obstet Gynaecol.* 2015;35:612-615.
12. Yen Y-K, Liu W-M, Yuan C-C, Ng H-T. Comparison of two procedures for laparoscopic-assisted vaginal hysterectomy of large myomatous uteri. *J Am Assoc Gynecol Laparosc.* 2002;9:63-69.
13. Gingold JA, Chichura A, Harnegie MP, Kho RM. Perioperative interventions to minimize blood loss at the time of hysterectomy for uterine leiomyomas: a systematic review and meta-analysis. *J Minim Invasive Gynecol.* 2019;26:1234-1252.e1.
14. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Obstet Gynecol.* 2010;115:1063-1070.

15. Holub Z, Jabor A, Lukac J, Kliment L, Urbanek S. Laparoscopic myomectomy with lateral dissection of the uterine artery. *JSLS.* 2005;9:447-453.

16. Holub Z, Lukac J, Kliment L, Urbanek S. Variability of the origin of the uterine artery: laparoscopic surgical observation. *J Obstet Gynaecol Res.* 2005;31:158-163.

17. Ercoli A, Delmas V, Iannone V, et al. The lymphatic drainage of the uterine cervix in adult fresh cadavers: anatomy and surgical implications. *Eur J Surg Oncol.* 2010;36:298-303.

18. Committee opinion no 701: choosing the route of hysterectomy for benign disease. *Obstet Gynecol.* 2017;129:e155-e159.

19. Wallace SK, Fazzari MJ, Chen H, Cliby WA, Chalas E. Outcomes and postoperative complications after hysterectomies performed for benign compared with malignant indications. *Obstet Gynecol.* 2016;128:467-475.

20. Brummer THI, Jalkanen J, Fraser J, et al. FINHYST, a prospective study of 5279 hysterectomies: complications and their risk factors. *Hum Reprod.* 2011;26:1741-1751.

21. Peters A, Stuparich MA, Mansuria SM, Lee TTM. Anatomic vascular considerations in uterine artery ligation at its origin during laparoscopic hysterectomies. *Am J Obstet Gynecol.* 2016;215:393.e1-3.

22. Gingold JA, Falcone T. The retroperitoneal approach to endometriosis. *J Minim Invasive Gynecol.* 2017;24:896.

23. Gingold JA, Falcone T. Retroperitoneal anatomy during excision of pelvic side wall endometriosis. *J Endometr Pelvic Pain Disord.* 2016;8:62-66.

24. Cunha FLD, Arcoverde FVL, Andres MP, et al. Laparoscopic treatment of ureteral endometriosis: a systematic review. *J Minim Invasive Gynecol.* 2021;28:779-787.

25. Sharp HT, Adelman MR. Prevention, recognition, and management of urologic injuries during gynecologic surgery. *Obstet Gynecol.* 2016;127:1085-1096.

26. Tyan P, Taher A, Carey E, et al. The effect of anemia severity on postoperative morbidity among patients undergoing laparoscopic hysterectomy for benign indications. *Acta Obstet Gynecol Scand.* 2020;99:112-118.

27. Alvarez JB, Alvarez PM, Shepherd JA. Factors associated with symptomatic anemia and indication for blood transfusion after total laparoscopic hysterectomies. *J Minim Invasive Gynecol.* 2015;22:S90.

28. Bretschneider CE, Frazzini Padilla P, Das D, Jelovsek JE, Unger CA. The impact of surgeon volume on perioperative adverse events in women undergoing minimally invasive hysterectomy for the large uterus. *Am J Obstet Gynecol.* 2018;219:490.e1-490.e8.

29. Naveiro-Fuentes M, Rodríguez-Oliver A, Fernández-Parra J, González-Paredes A, Aguilar-Romero T, Mozas-Moreno J. Effect of surgeon's experience on complications from laparoscopic hysterectomy. *J Gynecol Obstet Hum Reprod.* 2018;47:63-67.