# Intrauterine manipulator during hysterectomy for endometrial cancer: a systematic review and meta-analysis of oncologic outcomes

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**OBJECTIVE:** This study aimed to assess the effects on oncologic outcomes of intrauterine manipulator use during laparoscopic hysterectomy for endometrial cancer.

**DATA SOURCES:** A systematic literature search was performed by an expert librarian in multiple electronic databases from inception to January 31, 2023.

**STUDY ELIGIBILITY CRITERIA:** We included all studies in the English language that compared oncologic outcomes (recurrence-free, cause-specific, or overall survival) between endometrial cancer patients who underwent total laparoscopic or robotic hysterectomy for endometrial cancer with vs without the use of an intrauterine manipulator. Studies comparing only peritoneal cytology status or lymphovascular space invasion were summarized for completeness. No selection criteria were applied to the study design.

**METHODS:** Four reviewers independently reviewed studies for inclusion, assessed their risk of bias, and extracted data. Pooled hazard ratios with 95% confidence intervals were estimated for oncologic outcomes using the random effect model. Heterogeneity was quantified using the $I^2$ tests. Publication bias was assessed by funnel plot and Egger test.

**RESULTS:** Out of 350 identified references, we included 2 randomized controlled trials and 12 observational studies for a total of 14 studies and 5,019 patients. The use of an intrauterine manipulator during hysterectomy for endometrial cancer was associated with a pooled hazard ratio for recurrence of 1.52 (95% confidence interval, 0.99–2.33; $P$=.05; $I^2$=31%; chi square $P$ value=.22). Pooled hazard ratio for recurrence was 1.48 (95% confidence interval, 0.25–8.76; $P$=.62; $I^2$=67%; chi square $P$ value=.08) when only randomized controlled trials were considered. Pooled hazard ratio for overall survival was 1.07 (95% confidence interval, 0.65–1.76; $P$=0.79; $I^2$=44%; chi square $P$ value=.17). The rate of positive peritoneal cytology or lymphovascular space invasion did not differ using an intrauterine manipulator.

**CONCLUSION:** Intrauterine manipulator use during hysterectomy for endometrial cancer was neither significantly associated with recurrence-free and overall survival nor with positive peritoneal cytology or lymphovascular space invasion, but further prospective studies are needed.

**Key words:** endometrial neoplasms, hysterectomy, intrauterine manipulator, lymphovascular space invasion, overall survival, peritoneal cytology, recurrence-free survival

## Introduction

Endometrial cancer (EC) is the gynecologic malignancy with the highest incidence in Western countries.[1] The American Cancer Society estimates approximately 66,200 new cases and 13,030 deaths owing to EC in the United States in 2023.[2] Total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment represent the primary treatments for apparent early-stage disease,[3,4] and the minimally invasive laparoscopic approach is recommended based on 2 randomized controlled trials (RCTs).[5–8]

The intrauterine manipulator (IUM) has been widely implemented in traditional and robotic-assisted laparoscopic hysterectomies. Its use ensures cranial traction on the uterus, with a consequently more straightforward and comfortable surgery.[9] Nevertheless, in the context of EC, the use of an IUM has been blamed for potentially worsening oncologic outcomes owing to the direct contact with the tumor in the endometrial cavity and the possible spreading of malignant cells.[10–13] Some evidence suggests that using IUM during a hysterectomy for EC is associated with a higher rate of positive peritoneal cytology and lymphovascular space invasion (LVSI).[12–14]

Because the use of IUM is not mandatory for a laparoscopic hysterectomy, and limited evidence supports its routine use—no RCTs and only scant data suggest that the IUM may ease surgery—clarifying whether these iatrogenic effects impair oncologic outcomes is mandatory.[15] This systematic review and meta-analysis aimed to summarize the available literature and provide new evidence on the effects of IUM use during laparoscopic hysterectomy on the oncologic outcomes of patients with apparent early-stage EC.

## Methods

### Eligibility criteria, information sources, and search strategy

The systematic review and meta-analysis were planned before starting the online

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## AJOG at a Glance

### Why was this study conducted?

Intrauterine manipulator use during hysterectomy for endometrial cancer was blamed for worsening oncologic outcomes by spreading the disease. However, available evidence mainly focused on pathologic outcomes, which may represent surgical artifacts without clinical implications.

### Key findings

Few studies have assessed the effects of intrauterine manipulators on oncologic outcomes. Intrauterine manipulation during hysterectomy was not significantly associated with recurrence-free ($P$=.05) or overall survival ($P$=.17). However, pooled hazard ratios for recurrence impede excluding an association.

### What does this add to what is known?

Pooling available evidence, intrauterine manipulators remain potentially associated with endometrial cancer recurrence. Given that their use is not mandatory, even minor increases in recurrence risk can be questioned. Therefore, further investigations on oncologic outcomes instead of pathologic characteristics are recommended.

search, considering the population of interest, treatment and control definitions, outcome measures, study eligibility criteria, and statistical analyses, including subgroup analyses. This study has been prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42022310042) and was deemed exempt from institutional review board approval. The review and meta-analysis was conducted following the Cochrane Handbook for Systematic Reviews of Interventions[16] and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-analysis Of Observational Studies in Epidemiology guidelines.[17,18]

We included all references published in the English language selected based on prespecified Population, Intervention, Comparison, and Outcome criteria. Population: women who underwent total laparoscopic or robotic hysterectomy for EC; Intervention: hysterectomy performed with the use of an IUM; Comparison: hysterectomy performed without the use of an IUM; Primary outcomes: recurrence-free, cause-specific, and overall survival; Secondary outcomes: presence of LVSI at definitive pathology, presence of cancer cells in the peritoneal cytology sampling, and presence of cancer cells in the peritoneal cytology sampling before and after the insertion of the IUM. Outcomes eligibility required reporting at least 1 of the outcomes of interest for completeness. No selection criteria were applied to the study design. We included studies with 10 or more participants per arm in any publication format, eg, full reports or conference abstracts.

A certified professional librarian (Biblioteca Meneghetti—University of Verona) performed a literature search from database inception to January 2023 in the electronic databases EMBASE, Scopus, PubMed/MEDLINE, Web of Science, and the Cochrane Library. The search strategy included the combinations of the medical and MeSH terms "endometrial neoplasms," "endometrial," "neoplasms," "cancer," "endometrial cancer," "hysterectomy," "manipulability," "manipulable," "manipulate," "manipulated," "manipulates," "manipulating," "manipulation," "manipulations," "manipulator," "manipulators," "intrauterine." The detailed search strategy is available as Supplemental Material. The references of all identified studies were systematically revised to identify other eligible publications.

### Study selection and data extraction

Two of 4 reviewers (P.C.Z. and G.B.) independently screened the titles and abstracts of articles identified in the initial literature search. The other 2 reviewers (S.G. and S.U.) retrieved and independently assessed the full text of potentially eligible studies for eligibility. Any disagreement was resolved by reexamining the article with a further reviewer (M.F.). We developed and used a standardized form to extract data from included studies. For each study, we retrieved information on the first author, year of publication, country, study design, characteristics of participants (including age, number of patients per arm, cancer histotypes, FIGO [International Federation of Gynecology and Obstetrics] stages, EC diagnosis method, uterine perforation, and ethnicity), type of IUM, and outcomes measures with details regarding their assessment and used definitions (peritoneal cytology and timing of sampling, LVSI, and definitions and mode of presentation of recurrence-free, cause-specific, and overall survival).

### Assessment of risk of bias

Two reviewers (P.C.Z. and S.G.) independently assessed the risk of bias in included studies according to the Cochrane tools. Version 2 of the Cochrane risk of bias tool for randomized trials was used for the RCTs.[19] The Risk Of Bias In Nonrandomized Studies—of Interventions was used to assess the risk of bias in nonrandomized studies.[20] Any disagreement was resolved by reexamining the article with a further reviewer (S.U.).

### Data synthesis

The meta-analyses were performed using the random-effects model, given that the assumption of having a common treatment effect for all included studies required by the fixed-effects model was absent. We did not expect a common treatment effect for all included studies but rather that the variation of the impact across studies follows the same distribution. The included studies did not have the same composition of study populations (ie, distribution of FIGO staging, histologic type, or the age of patients), interventions received (ie, different techniques used during surgery and type of uterine manipulator), and

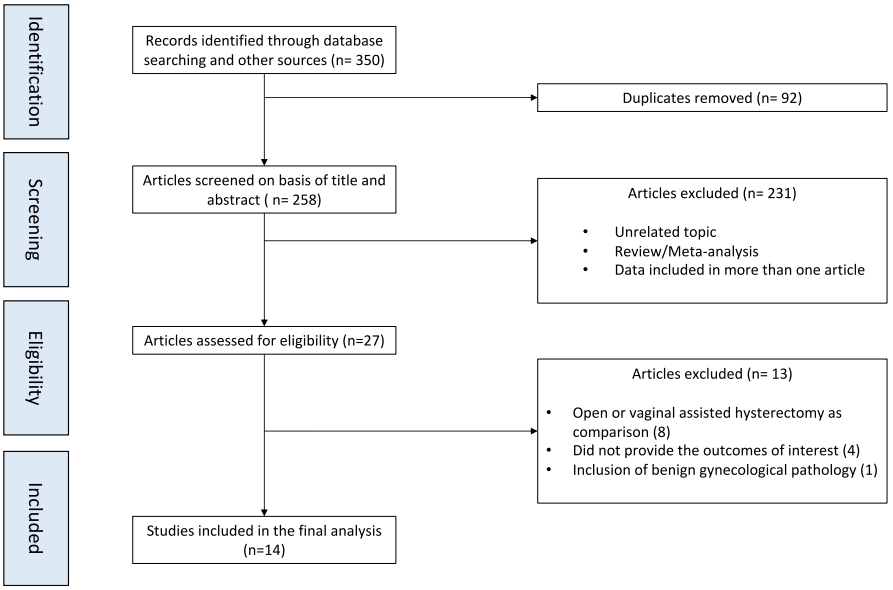
follow-up length; therefore, both within- and between-studies variability must be considered.[21,22] Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used for categorical variables. Pooled hazard ratios (HRs) with 95% CIs were used for time-to-event outcomes (recurrence-free, cause-specific, and overall survival). Meta-analyses of time-to-event data were performed by pooling the log HRs and their variances estimated from each included study. Log HR and its variance were estimated directly from univariate HR and its 95% CI when available, from the *P* value of the log-rank test and the corresponding number of events and patients in each group when univariate Cox regression analysis was not reported.[23] Adjusted HRs from multivariate analyses were not considered because only 2 studies provided such results, and analyses were adjusted for different variables. Heterogeneity was quantified using the $I^2$ tests; $I^2<25\%$ was considered low, and $I^2$ more than 75% was considered high. Publication bias was assessed by funnel plot and Egger test. All analyses were 2-tailed with a statistical significance threshold of $P=.05$. Open Meta version 5 was used to conduct meta-analyses.

## Results

### Study selection

The literature search identified 350 references; after removing 92 duplicates, 258 were available for title and abstract screening. We excluded 231 records based on the title and abstract and reviewed 27 full-texts or conference abstracts for eligibility. We excluded 13 references, because they did not fulfill our inclusion criteria: 8 used open or vaginal assisted hysterectomy as comparison,[24–31] 4 did not provide the outcomes of interest,[32–35] and 1 included benign gynecologic pathology.[36] No records have been excluded for the English language criterion after the initial title and abstract screening for eligibility. A total of 14 studies were finally included in the systematic review and meta-analysis: 2 RCTs[37,38] and 12 nonrandomized studies (9 retrospectives[10,13,14,39–44] and 3 prospective[12,45,46]). The flowchart of reference selection is summarized in Figure 1.

**FIGURE 1**
**PRISMA flow diagram of reference selection**




*PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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### Study characteristics

The 14 studies investigated different types of IUMs (Table 1) for a total of 5,019 patients with differences in the composition of the study populations (eg, distribution of FIGO staging, histologic type, and age of patients), interventions received (eg, different techniques used during surgery), and follow-up length.[10,12–14,37–46] Only 4 out of 14 studies provided information regarding uterine perforation (Table 1): 2 studies excluded cases with uterine perforation (274 patients),[41,44] and the other 2 reported a total of 3 uterine perforations out of 425 patients.[12,43] Details on EC diagnosis were provided by a minority of studies, and only 3 cited hysteroscopy for the EC diagnosis in at least 1 included patient (Table 1).[40,43,44] Only 3 studies provided data regarding ethnicity (Table 1).[41–43]

Oncologic outcomes (recurrence-free, cause-specific, or overall survival) were reported in 8 studies[10,12,37–40,45,46]; of these, 5 had sufficient data to allow the pooled analysis (Table 2).[10,37–40] We were unable to incorporate data from 3 studies for the following reasons: Shinohara et al[46] and Lim et al[12] were excluded, as they did not observe recurrences or deaths probably owing to the short follow-ups (median follow-ups of 3.4 and 18 months, respectively); Eltabbakh et al[45] was excluded, because data regarding oncologic outcomes were insufficient to estimate the log HR and its variance. Given that only 1 study reported data regarding cause-specific survival,[38] pooled analysis was performed only for recurrence-free and overall survival. In the 5 studies included in the meta-analysis of oncologic outcomes, the surgeon was aware of the device used during the surgical procedure. However, recurrence and death are strong outcomes less likely to be biased by the absence of blinding of assigned intervention.[10,37–40]

Peritoneal cytology was assessed in 10 out of 14 studies[12,13,37,38,40–43,45,46]: 4 studies compared the peritoneal cytology sampling collected before and after the insertion of the IUM[12,43,45,46]; 4 studies compared the peritoneal cytology status between patients who

**TABLE 1**
**Characteristics of included studies**

| Author | Year | Year of sample collection | Country | Study design | Interest outcome | IUM/no IUM | Type of IUM | Tubal ligation before IUM insertion | Diagnosis method | Uterine perforation | Ethnicity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Eltabbakh et al[45] | 2006 | 2000–2004 | United States | Prospective | Peritoneal cytology before/after IUM | IUM=42<br>No IUM=42 | Pelosi | No | Endometrial biopsy—method nonreported | NA | NA |
| Lim et al[12] | 2008 | 2004–2006 | Korea | Prospective | Peritoneal cytology before/after IUM | IUM=46<br>No IUM=46 | Rumi | Yes | Endometrial biopsy—method nonreported | 2/92 | NA |
| Krizova et al[13] | 2011 | 2008–2009 | Canada | Retrospective | Peritoneal cytology | IUM=40<br>No IUM=161 | NA | NA | NA | NA | NA |
| Lee et al[37] | 2013 | 2009–2011 | Korea | RCT | Survival; peritoneal cytology; LSVI; peritoneal cytology before/after IUM | IUM=55<br>No IUM=55 | Rumi | Yes | Endometrial biopsy—method nonreported | NA | NA |
| Raji et al[42] | 2011 | 2006–2010 | United States | Retrospective | Peritoneal cytology; LSVI | IUM=18<br>No IUM= 59 | NA | NA | NA | NA | White 83.8%<br>Others 16.2% |
| Machida et al[43] | 2016 | 2000–2015 | United States | Retrospective | Peritoneal cytology before/after IUM | IUM=103<br>No-IUM=230 | V-Care; Rumi; HUMI | No | (71.2%) Endometrial biopsy—method nonreported, (28.8%) hysteroscopic biopsy, dilation and curettage, and Vabra. | 1/333 | White 27.6%<br>African 2.7%<br>Hispanic 55.6%<br>Asian 12.3%<br>Others 1.8% |
| Shinohara et al[46] | 2017 | 2015–2015 | Japan | Prospective | Peritoneal cytology | IUM=13<br>No-IUM=13 | Atom Medical | Yes | NA | NA | NA |
| Tinelli et al[40] | 2016 | 2009–2015 | Italy | Retrospective | Survival; LSVI; Peritoneal cytology before/after IUM | IUM=55<br>No-IUM=55 | Wattiez; Clermont-Ferrand | Yes | Hysteroscopic endometrial biopsy | NA | NA |
| Mitidieri et al[14] | 2017 | 2004–2014 | France | Retrospective | LSVI | IUM=24<br>No-IUM=64 | NA | NA | NA | NA | NA |
| Uccella et al[39] | 2017 | 2000–2013 | Italy | Retrospective | Survival | IUM=579<br>No-IUM=372 | Rumi; Minelli; Clermont-Ferrand; Cohen | NA | NA | NA | NA |
| | | | | | LSVI | IUM=270<br>No-IUM=202 | | | | | |

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(continued)

**TABLE 1**
**Characteristics of included studies** *(continued)*

| Author | Year | Year of sample collection | Country | Study design | Interest outcome | IUM/no IUM | Type of IUM | Tubal ligation before IUM insertion | Diagnosis method | Uterine perforation | Ethnicity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Seifi et al[41] | 2019 | 2012–2016 | United States | Retrospective | LSVI; peritoneal cytology | IUM=59 No-IUM=45 | 2 types of balloon manipulators (not clarified) | NA | NA | Excluded if uterine perforation occurred | White 71.2% African 15.4% Hispanic 1.9% Asian 1.9% Others 9.6% |
| Gueli Alletti et al[38] | 2021 | 2015–2017 | Italy | RCT | Survival; LSVI; peritoneal cytology | IUM=78 No-IUM=76 | Clermont-Ferrand | Yes | NA | NA | NA |
| | | | | | Peritoneal cytology before/after IUM | IUM=78 No-IUM=78 | | | NA | NA | NA |
| Padilla-Iserte et al[10] | 2021 | | Spain | Retrospective | Survival; LSVI | IUM=1756 No-IUM=905 | V-Care; Rumi; Clermont-Ferrand; Cohen Valtchev | NA | NA | NA | NA |
| Hudec et al[44] | 2023 | 2015–2020 | Slovakia | Retrospective | LSVI | IUM=87 No-IUM=83 | Koh-Rumi; Hegar dilator | NA | Hysteroscopic endometrial biopsy or dilation and curettage | Excluded if uterine perforation occurred | NA |

*IUM*, intrauterine manipulator; *LVSI*, lymphovascular space invasion; *NA*, not available; *RCT*, randomized controlled trial.

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underwent hysterectomy with vs without the use of an IUM[13,40–42]; and 2 studies provided data regarding both comparisons.[37,38] The pathologic assessment of peritoneal cytology was reported as blind for assigned intervention in 5[13,37,40,45,46] out of 10 studies.[12,13,37,38,40–43,45,46] The rate of LVSI was compared between patients who underwent hysterectomy with vs without using an IUM in 9 out of 14 papers.[10,14,37–42,44] Only 1 retrospective study differentiated between lymphovascular and pseudovascular invasion, which was defined as a "spill artifact" associated with the use of the IUM.[13] The pathologic assessment of LVSI was reported as blind for assigned intervention in 5[37,38,41,42,44] out of 9 studies.[10,14,37–42,44]

### Synthesis of results and risk of bias

*Recurrence-free survival*

Five studies provided enough details to estimate the log HR and its variance for recurrence-free survival, representing 3986 women.[10,37–40] EC histology, grade, and final stage were comparable between women who underwent hysterectomy with and without an IUM in each one of the 5 studies (Table 2). The median follow-up ranged from 9 to 46 months: 4 papers provided a median follow-up from 38.7 to 46 months,[10,38–40] whereas Lee et al[37] had a median follow-up of 9 months. Recurrence-free survival was calculated considering the time from the adjuvant treatment completion to the date of progression or recurrence by Lee et al[37]; from surgery to the first recurrence by Tinelli et al[40]; and from diagnosis to the first recurrence by Gueli Alletti et al.[38] Conversely, Uccella et al[39] and Padilla-Iserte et al[10] did not provide the used definition.

Overall, EC recurrence was observed in 295 out of the 2523 (11.6%) patients who underwent a hysterectomy performed with an IUM and in 122 women out of the 1463 (8.3%) who underwent a hysterectomy without. Pooled HR for

**TABLE 2**
**Characteristics of studies included in the meta-analysis of oncologic outcomes**

| | | IUM Group | | | | | No-IUM Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author, y | Study design | N° | Endometrioid histology | Stage IA/IB | G 1-2 | G 3 | N° | Endometrioid histology | Stage IA/IB | G 1-2 | G 3 | Follow-up length (mo) |
| Lee et al,[37] 2013 | RCT | 55 | 83.6% | 85.4% | 87.3% | 10.9% | 55 | 94.5% | 89.1% | 96.4% | 3.6% | 7–32 |
| Gueli Alletti et al,[38] 2021 | RCT | 78 | 97.4% | 93.6% | 90.4% | 9.6% | 76 | 98.7% | 90.8% | 87.8% | 12.2% | 37.1–40.8 |
| Tinelli et al,[40] 2016 | OBS | 55 | NA | 86% | 84% | 16% | 55 | NA | 84% | 78% | 22% | 3–67 |
| Padilla-Iserte et al,[10] 2021 | OBS | 1756 | 87.69% | 84.9% | 76.27% | 11.41% | 905 | 87.64% | 85.07% | 76.5% | 11.14% | 45.67–43.35 (mean follow-up) |
| Uccella et al,[39] 2017[a] | OBS | 579 | 85.8% | 93.4% | 81.2% | 18.1% | 372 | 86% | 93.5% | 76.6% | 22.9% | 12–163 |

*G*, Grade; *IUM*, intrauterine manipulator; *NA*, not available; *RCT*, randomized controlled trial.

[a] Provided both recurrence-free survival and overall survival.

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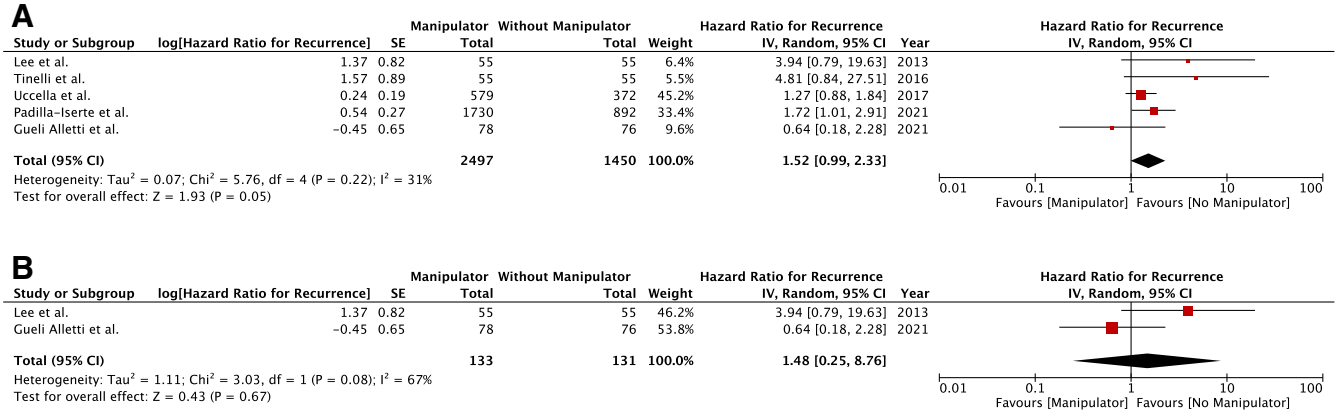
recurrence in patients who underwent hysterectomy with an IUM vs those patients who underwent hysterectomy without an IUM was 1.52 (95% CI, 0.99–2.33; $P$=.05; $I^2$=31%; chi square $P$ value=.22) (Figure 2, A). The funnel plot symmetrical pattern and Egger test (intercept = 0.9013; SE intercept=1.0253; t=0.88, $P$ value=.4441) were indicative of no publication bias (Figure 3, A). Restricting the meta-analysis to the 2 RCTs (264 women),[37,38] recurrence was observed in 9 out of 133 (6.7%) and 7 out of 131 (5.3%) patients who underwent hysterectomy with vs without an IUM, respectively. Pooled HR for recurrence with an IUM was 1.48 (95% CI, 0.25–8.76; $P$=.62; $I^2$=67%; chi square $P$ value=.08) (Figure 2, B). The funnel plot symmetrical pattern was indicative of no publication bias (Figure 3, B).

The risk of bias of included studies considering recurrence-free survival as the intervention effect of interest is reported in Figure 4, A and B. High/Serious and Some concern/Moderate bias risks were reported for randomized and nonrandomized studies. Only the 3 retrospective studies were specifically

**FIGURE 2**
**Forest plot for recurrence-free survival**




Comparison: hysterectomy with vs without IUM. **A,** All studies included in the meta-analysis; **B,** only the 2 randomized controlled trials included in the meta-analysis.

*IUM*, intrauterine manipulator.

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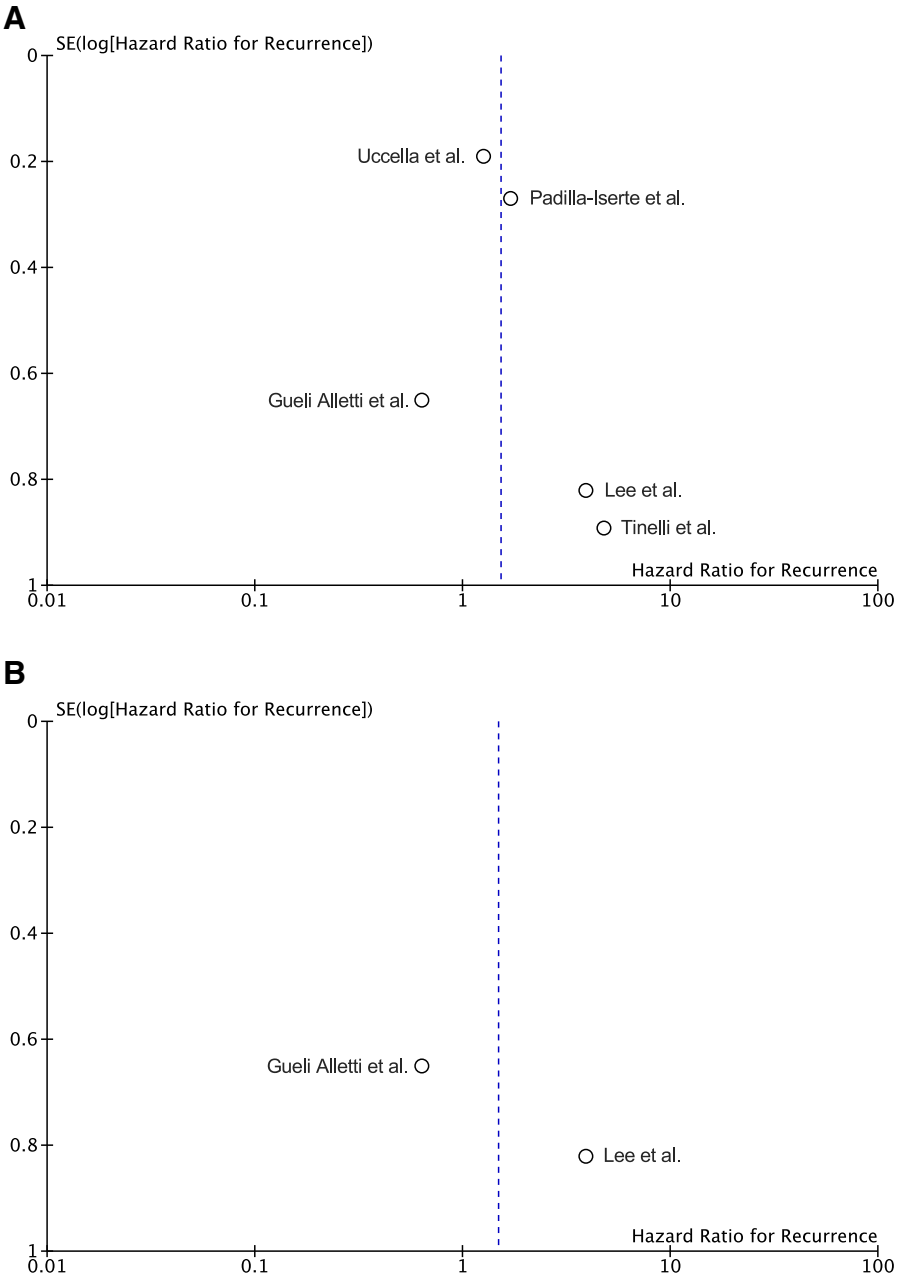
**FIGURE 3**
**Funnel plot for recurrence-free survival**




Comparison: hysterectomy with vs without IUM. **A,** All studies included in the meta-analysis; **B,** only the 2 randomized controlled trials included in the meta-analysis.

*IUM,* intrauterine manipulator.

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designed to investigate oncologic outcomes.[10,39,40]

*Overall survival*

Three studies provided enough data to estimate the log HR and its variance for overall survival (3766 women).[10,38,39] EC histology, grade, and final stage were comparable between women who underwent hysterectomy with and without an IUM in each one of the 3 studies pooled for overall survival (Table 2). The median follow-up ranged from 38.7 to 46 months. Overall survival was calculated considering the time from the diagnosis to death owing to any cause by Gueli Alletti et al.[38] In contrast, Uccella et al[39] and Padilla-Iserte et al[10] did not provide the used definition.

Pooled HR for death for any cause (overall survival) in patients who underwent hysterectomy with an IUM using as reference those patients who underwent hysterectomy without an IUM was 1.07 (95% CI, 0.65−1.76; $P$=.79; $I^2$=44%; chi square $P$ value=.17) (Figure 5). The funnel plot symmetrical pattern and Egger test (intercept=−0.7442; SE intercept=2.0177; t=−0.37, $P$ value=.775) were indicative of no publication bias (Figure 6).

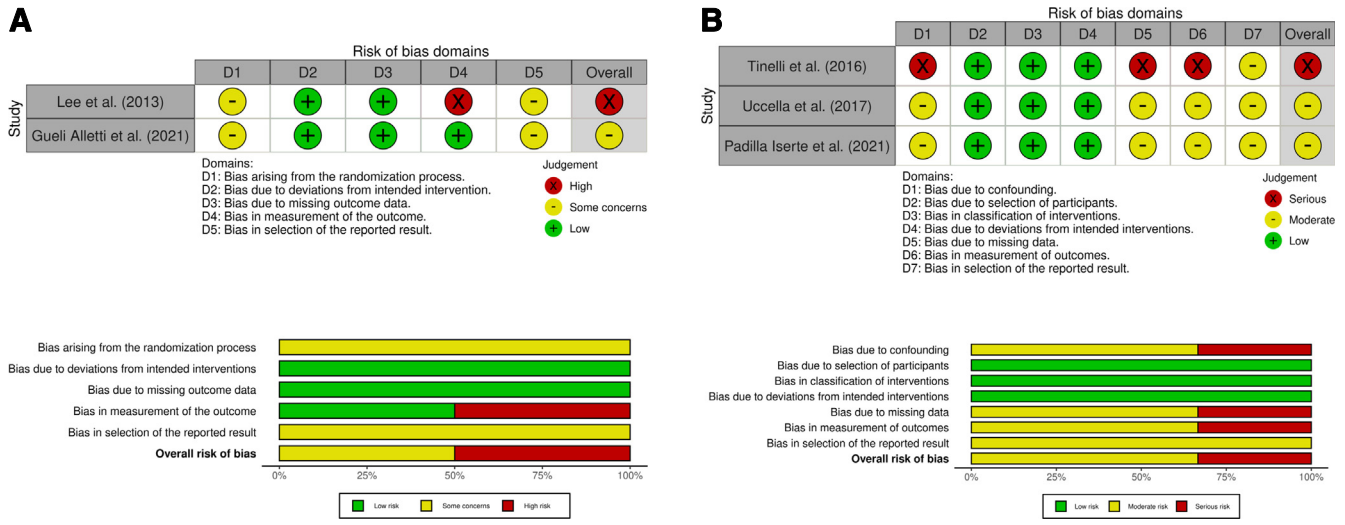
The risk of bias of included studies concerning overall survival as the intervention effect of interest is reported in Figure 7, A and B. A high risk of bias was estimated for the RCT and a moderate risk of bias for nonrandomized studies.[10,38,39] Only the 2 retrospective studies were specifically designed to investigate oncologic outcomes.[10,39]

*Peritoneal cytology status before and after the insertion of the intrauterine manipulator*

We identified 6 studies that assessed the peritoneal cytology status (positive vs negative) in the same patient before and after the insertion of the IUM.[12,37,38,43,45,46] Two of these studies were RCTs.[37,38] Machida et al[43] and Eltabbakh et al[45] performed the peritoneal cytology sampling before and immediately after the insertion of the IUM. In contrast, Shinohara et al,[46] Gueli Alletti et al,[38] and Lee et al[37] performed the sampling before the IUM insertion and at the end of surgery; Lim et al collected all 3 samples.[12]

For the meta-analysis, we excluded the study by Machida et al,[43] because the peritoneal cytology status after the IUM was not reported for all patients of the treatment group (103 out of 230 women). Moreover, we excluded the study by Gueli Alletti et al[38], because no cases with positive peritoneal cytology were observed in both the groups. Pooling data from 4 studies,[12,37,45,46] positive peritoneal cytology was found in 7.1% (11/156) of women before and

**FIGURE 4**
**Risk of bias recurrence-free survival**




Comparison: hysterectomy with vs without IUM. **A,** Randomized controlled trials (risk of bias tool for randomized trials). **B,** Nonrandomized studies (risk of bias in nonrandomized studies—of exposures).

*IUM*, intrauterine manipulator.

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in 6.4% (10/156) of patients after the IUM insertion (OR, 0.90; 95% CI, 0.37−2.19; $P$=.82; $I^2$=0%; chi square $P$ value=.79) (Figure 8). The funnel plot symmetrical pattern and Egger test (intercept = 0.0070; SE intercept = 0.9266; t=0.01, $P$ value=.9947) were indicative of no publication bias (Supplemental Figure 1). Lim et al,[12] Shinohara et al,[46] and Lee et al[37] closed the fallopian tubes before the IUM insertion by applying 5 mm clips or cauterization. Only in 1 study included in the meta-analysis, the IUM was used without closing the fallopian tubes.[45]

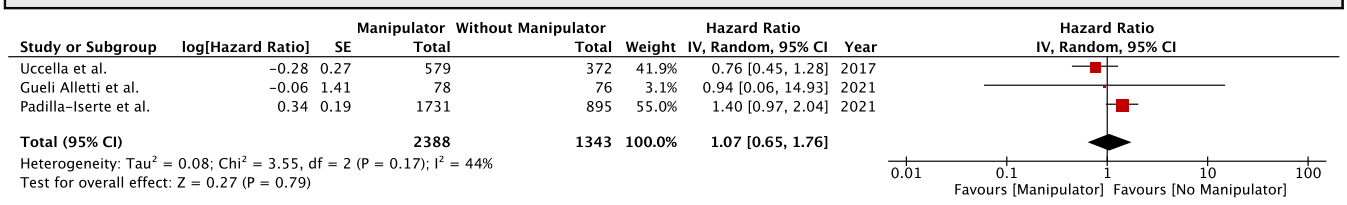
The risk of bias in the included studies concerning peritoneal cytology status before and after the insertion of the IUM as the intervention effect of interest is reported in Supplemental Figure 2, A and B. Some bias concerns were estimated for the RCT and low risk of bias for nonrandomized studies.[12,37,45,46]

*Peritoneal cytology status with vs without the intrauterine manipulator*

Six studies compared the peritoneal cytology status of patients who underwent hysterectomy with vs without using an IUM.[13,37,38,40–42] Two of these studies were RCTs,[37,38] and 4 were retrospective.[13,40–42] Seifi et al[41] and Tinelli et al[40] collected the peritoneal cytology sampling in patients who underwent hysterectomy with the IUM after placing the manipulator. In contrast, Krizova et al[13] and Raji et al[42] did not explain how the pelvic cytology sampling was collected. Gueli Alletti et al[38] and Lee et al[37] sampled both groups before the IUM insertion and at the end of the hysterectomy.

For the meta-analysis, we excluded the study by Gueli Alletti et al[38], because no cases with positive peritoneal cytology were observed in both groups. In total,

**FIGURE 5**
**Forest plot for overall survival**

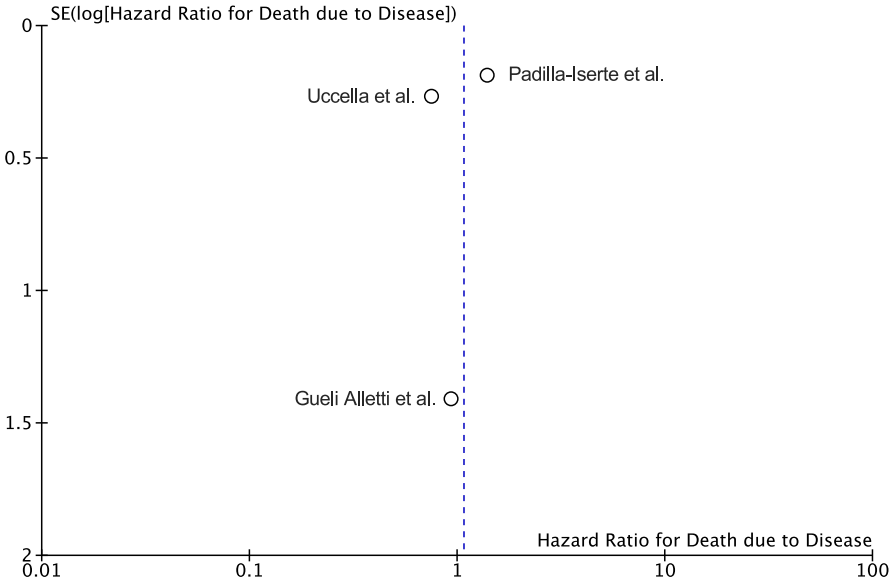



Comparison: hysterectomy with vs without IUM.

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**FIGURE 6**
**Funnel plot for overall survival**




Comparison: hysterectomy with vs without IUM.

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

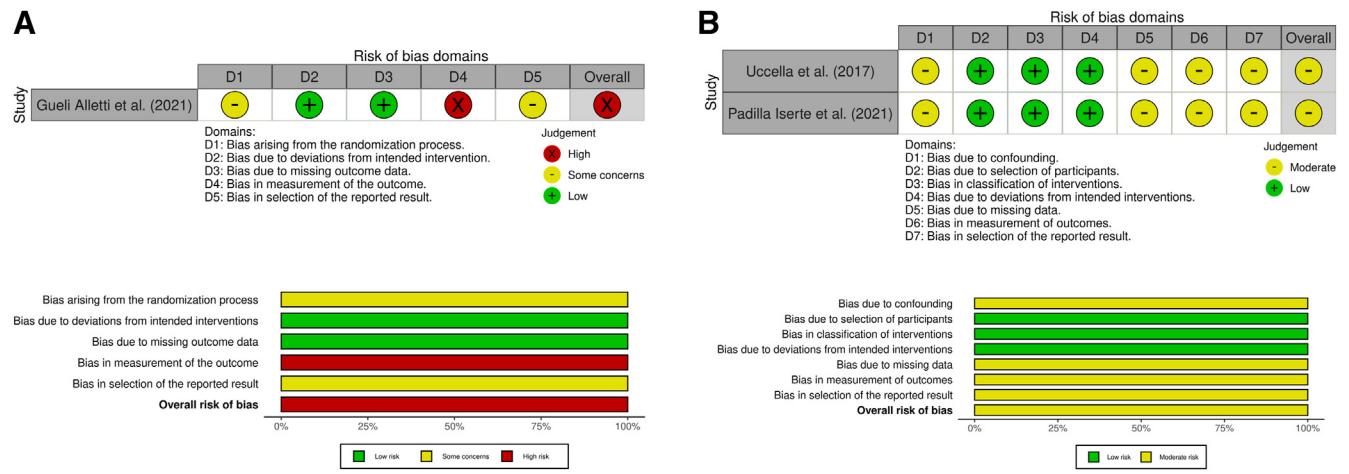
the pooled analysis involved 602 women. Peritoneal cytology was found positive in 21 out of 227 (9.3%) patients who underwent surgery with an IUM vs 20 out of 375 (5.3%) women who underwent hysterectomy without the IUM (Pooled OR, 1.66; 95% CI, 0.67−4.16; $P$=.28; $I^2$=36%; chi square $P$ value=.18) (Figure 9, A). The funnel plot symmetrical pattern and Egger test (intercept=−0.5416; SE intercept=2.3526; t=−0.23, $P$ value=.8327) were indicative of no publication bias (Supplemental Figure 3). After the exclusion of the study by Lee et al,[37] who closed the fallopian tubes before the IUM insertion, the pooled analysis did not change significantly (Pooled OR, 1.42; 95% CI, 0.50−4.07; $P$=.51; $I^2$=46%; chi square $P$ value=.14) (Figure 9, B).

The risk of bias of included studies concerning peritoneal cytology status with vs without the IUM as the intervention effect of interest is reported in Supplemental Figure 4, A and B. Some concern of bias was estimated for the RCT and serious risk of bias for nonrandomized studies.[13,37,40−42]

*Lymphovascular space invasion with vs without the intrauterine manipulator*

Nine studies assessed and reported the outcome[10,14,37−42,44]: 2 RCTs,[37,38] and 7 retrospective studies.[10,14,39−42,44] The impact of IUM use on LVSI was the primary outcome of the ROMANHY RCT by Gueli Alletti et al.[38] Moreover, they performed a subanalysis among the positive LVSI cases demonstrating that the IUM did not affect the pattern of

**FIGURE 7**
**Risk of bias for overall survival**

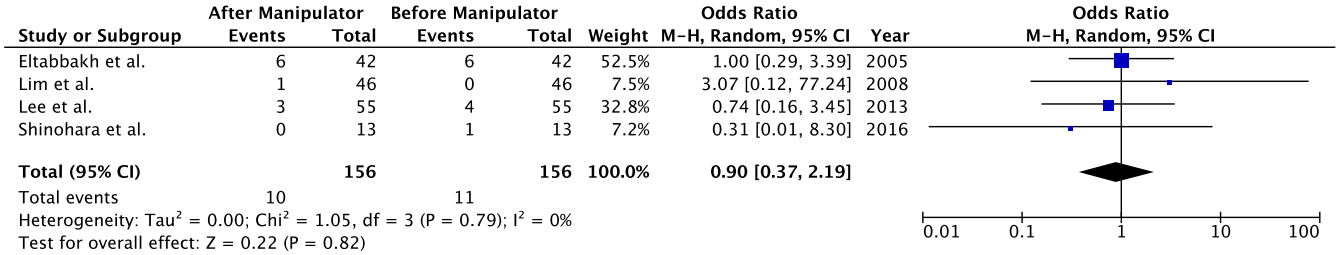



Comparison: hysterectomy with vs without IUM. **A,** Randomized controlled trials (risk of bias tool for randomized trials). **B,** Nonrandomized studies (risk of bias in nonrandomized studies—of exposures).

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**FIGURE 8**
**Forest plot for peritoneal cytology status before and after IUM insertion**




Comparison: hysterectomy with vs without IUM.

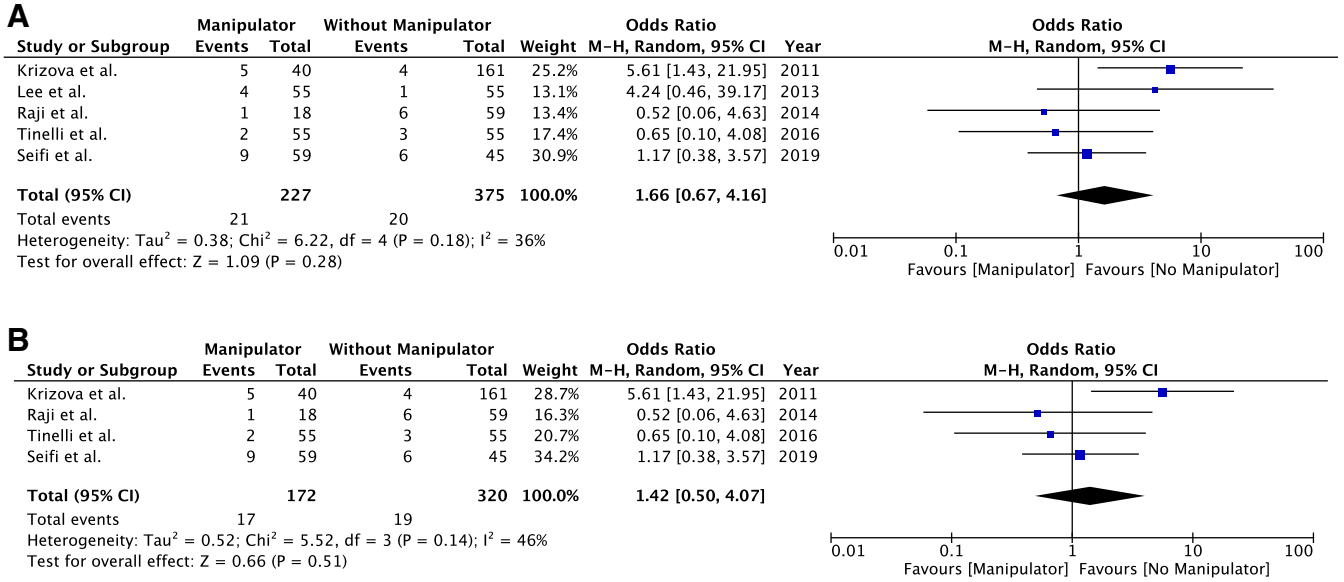
*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

lymphovascular spread (overall focal LVSI vs overall diffused LVSI). All 9 studies compared the presence of LVSI at definitive pathology between women who underwent hysterectomy with an IUM and women who underwent surgery without. In the pooled analysis, the LVSI was present in 470 out of 2402 (19.5%) patients belonging to the IUM group and in 213 out of 1544 (13.8%) women belonging to the control group (OR, 1.11; 95% CI, 0.67−1.90; $P$=.72; $I^2$=77%; chi square $P$ value<.001) (Figure 10, A). The funnel plots symmetrical pattern and Egger test (intercept=−1.7881; SE intercept=1.0090; t=−1.77, $P$ value=.1197) were indicative of no publication bias (Supplemental Figure 5). Including only RCTs for a total of 264 patients,[37,38] LSVI was detected in 22 out of 133 (16.5%) women whose hysterectomy was performed with an IUM and in 23 out of 131 (17.5%) women who underwent surgery without (pooled OR, 0.92; 95% CI, 0.48−1.77; $P$=.81; $I^2$=0%; chi square $P$ value=.38) (Figure 10, B).

The risk of bias of included studies concerning LVSI with vs without the IUM as the intervention effect of interest is reported in Supplemental Figure 6, A and B. Some bias concerns were estimated for the 2 RCTs and a

**FIGURE 9**
**Forest plot for peritoneal cytology status with vs without IUM**

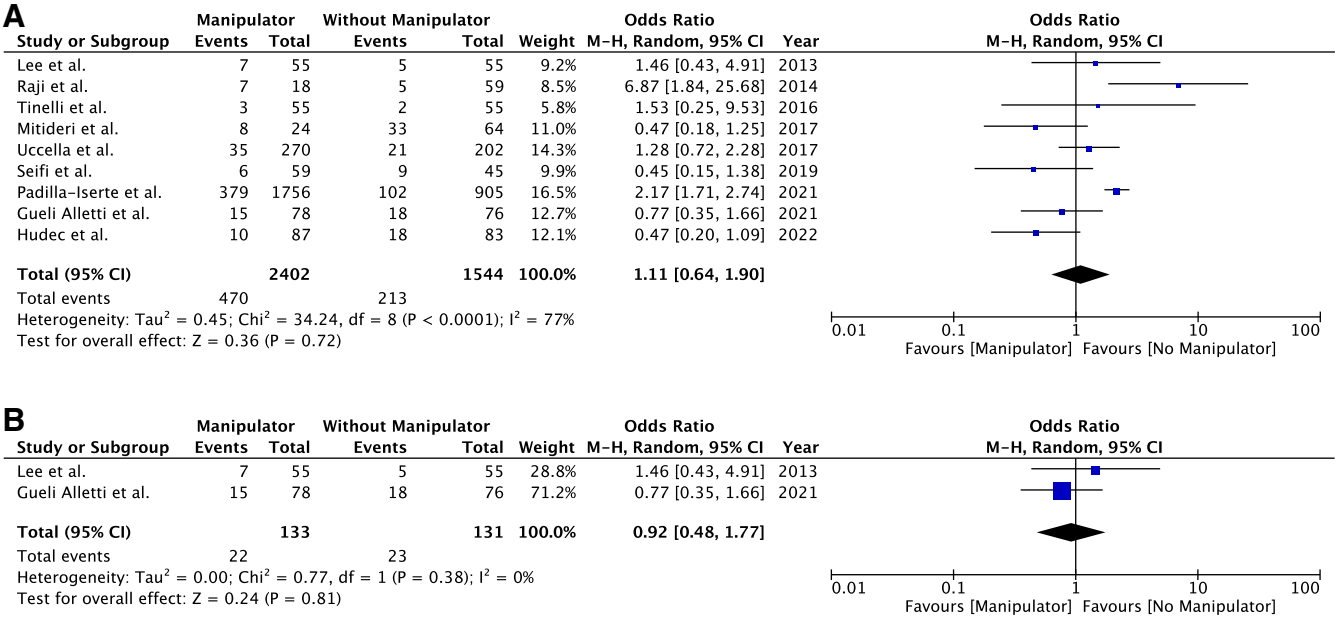



Comparison: hysterectomy with vs without IUM. **A,** All studies included in the meta-analysis; **B,** meta-analysis after the exclusion of the study by Lee et al,[37] who closed the fallopian tubes before the IUM insertion.

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**FIGURE 10**
**Forest plot lyphovascular space invasion**




Comparison: hysterectomy with vs without IUM. **A,** All studies included in the meta-analysis; **B,** only the 2 randomized controlled trials included in the meta-analysis.

*IUM,* intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

serious risk of bias for nonrandomized studies.[10,14,37–42,44]

## Comment

### Principal findings

In pooled analyses incorporating 14 studies for a total of 5019 patients,[10,12–14,37–46] we did not observe a statistically significant association between IUM use during hysterectomy for EC and recurrence-free and overall survival or peritoneal cytology status and LVSI. The analysis limited to the RCTs did not provide additional insights.

### Comparison with existing literature

After the results of the LAP2 and LACE trials,[5–8] laparoscopic surgery was assumed as the gold standard for the surgical treatment of apparent early-stage EC. These trials demonstrated that laparoscopic surgery for EC was feasible and safe, providing fewer complications and shorter hospital stay than open surgery without affecting oncologic outcomes.[5–8]

Despite trial results,[5–8] the survival of EC is worsening in the United States, with an age-adjusted death rate rising on average 1.6% each year over 2011 to 2020 vs an age-adjusted rate for new uterine cancer cases rising on average 0.7% per year.[47] Multiple factors have potentially affected the oncologic outcomes of EC in the last few decades, such as the increasing obesity prevalence[48] and the persistence of disparities in prevention, diagnosis, and treatment of EC, especially in minority communities.[49] However, changes in the treatment of EC have been questioned, such as the implementation of the IUM use, which was blamed for worsening oncologic outcomes of EC by spreading malignant cells in the abdominal cavity or lymphatic and blood vessels.[10–13] Notably, in the LACE trial, an intrauterine device was not used; in the LAP2 trial, the vaginal laparoscopic-assisted technique was frequently performed without requiring an intrauterine device.[5–8]

Nevertheless, although the presence of these concerns and the assumed wide use of an IUM during total laparoscopic and robotic hysterectomy for EC, our systematic review and meta-analysis revealed that only a few studies had been specifically conducted to investigate the impact of the IUM on EC. Moreover, most of the 14 identified studies and all RCTs were designed to investigate the association between using an IUM and a higher rate of positive peritoneal cytology and LVSI. However, an increased incidence of positive peritoneal cytology or LVSI positivity does not imply worsened oncologic outcomes being potentially only artifacts.[25,36] In this regard, our meta-analysis showed no statistically significant differences in positive peritoneal cytology before and after the insertion of the uterine manipulator and with and without the use of an IUM. Similarly, the presence of LVSI did not differ significantly with and without using an IUM.

**TABLE 3**
**Characteristics of previous systematic reviews and meta-analyses**

| Author | Year | Studies included | Outcomes | Test | Overall survival | Recurrence | LVSI | Positive peritoneal cytology | Peritoneal cytology before and after | Supports the use of uterine manipulator |
|---|---|---|---|---|---|---|---|---|---|---|
| Scutiero et al[50] | 2022 | 3 prospective<br>13 retrospectives<br>2 RCT | LVSI, positive peritoneal cytology, recurrence | Random-effects model | Not considered | RR, 1.11; 95% CI, 0.71−1.74 | RR, 1.18; 95% CI, 0.76−1.85 | RR, 1.89; 95% CI, 0.74−4.83 | RR, 1.21; 95% CI, 0.68−2.16 | Yes |
| Meng et al[51] | 2020 | 3 prospective<br>7 retrospectives<br>1 RCT | LVSI, positive peritoneal cytology, recurrence | Fixed-effects model | Not considered | RR, 1.25; 95% CI, 0.89−1.74 | RR, 1.18; 95% CI, 0.66−2.11 | | RR, 1.53; 95% CI, 0.85−2.77 | Yes |

*IUM*, intrauterine manipulator; *LVSI*, lymphovascular space invasion; *NA*, not available; *RCT*, randomized controlled trial; *RR*, relative risk.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

A direct investigation of oncologic outcomes is mandatory to clarify whether IUM use worsens the EC prognosis. Nevertheless, none of the previous systematic reviews and meta-analyses specifically focused on these outcomes (Table 3).[50,51] A minority of identified studies provided data about recurrence-free and overall survival with a relevant follow-up, and only 2 retrospective studies had a sample size providing discrete power. Uccella et al[39] included 951 patients affected by early-stage EC and did not observe an association between IUM use and worse oncologic outcomes. In contrast, the study involving 2661 patients by Padilla-Iserte et al[10] reported an association between IUM use and a higher risk of recurrence and death. The 2 studies have different inclusion criteria, which may have determined the discrepancy in survival outcomes[52]: Uccella et al[39] included only clinical stage I EC, whereas Padilla-Iserte et al[10] included more advanced stages. In this context, the pooled analysis for the recurrence-free survival did not report a statistically significant association between IUM use and lower recurrence-free survival. However, we recognize that an HR of 1.52 with a 95% CI of 0.99−2.33 ($P$=.05; $I^2$=31%) suggests a possible association between the IUM use and a higher risk of recurrence as supported by Padilla-Iserte et al.[10]

Fewer included studies reported data on overall survival, and no statistically significant differences were observed. The pooled HR for death for any cause in patients who underwent hysterectomy with an IUM was almost 1, suggesting no association between IUM use and overall survival. Therefore, the potential lower recurrence-free survival does not seem to imply the risk of death. Nevertheless, given that the pooled HR for recurrence may translate into an absolute difference in recurrence-free survival lower than 5%, and considering that some types of EC recurrences can be subject to treatment,[4,53,54] a larger sample size is needed to show an effect on survival. Moreover, the provided results are based on overall survival, and data regarding cause-specific survival are almost absent.

On that basis, further investigations are required to clarify the effects on oncologic outcomes of IUM use during hysterectomy for EC. Considering that a laparoscopic hysterectomy performed with an IUM is not mandatory nor necessary, even a minor increase in recurrence risk can be questionable if confirmed.

### Strengths and limitations

Several limitations of this systematic review and meta-analysis must be discussed to interpret study results and weigh possible conclusions appropriately. Regarding primary outcomes, most included studies did not focus on recurrence-free, cause-specific, or overall survival; furthermore, used definitions were heterogenous and in some cases questionable. Recurrence-free survival should be calculated considering the time from the hysterectomy rather than from the adjuvant treatment completion, because prolonged but ineffective adjuvant treatments would result in a shorter time to recurrence. Only the randomized design that worked well in adjuvant treatment distribution allowed us to include the study by Lee et al.[37] Moreover, an appropriate follow-up length was not reported by all studies. A limited follow-up was one of the main reasons for the serious and high risk of bias.

Only 2 RCTs underpowered for oncologic outcomes were identified,[37,38] and most of the 12 observational studies included <100 EC patients per arm.[10,12−14,39−43,45,46] The nonrandomized design and the small number of patients increase the weight of possible confounders or modifiable factors, such as the heterogeneous population composition (different EC histotypes and stages), the different types of IUMs, the performed surgical techniques, and the adjuvant treatment policies. These concerns are supported by the moderate or high heterogeneity observed in most pooled analyses on oncologic outcomes and the increased risk of bias in most

observational studies. In addition, the multiple types of IUMs employed in included studies impede to consider conclusive study results, which may not be relevant to all currently available devices.

Moreover, some areas of neglect are present in the available evidence. Only 4 out of 14 studies provided information regarding uterine perforation, and most did not provide details regarding EC diagnosis. Therefore, separating the potential effect of hysteroscopy and uterine perforation in spreading cells into the peritoneal cavity from the IUM use was not possible. In addition, demographic characteristics associated with EC diagnosis, treatment, and prognosis, such as ethnicity, were rarely considered (Table 1), raising concern regarding appropriate population representativeness.[49]

Finally, we stress that pooled HRs are univariate; therefore, the provided results are not adjusted for possible confounders related to differences between the group that underwent hysterectomy with IUM and the group that underwent hysterectomy without. Being pooled analysis of oncologic outcomes mainly based on the observational studies by Padilla-Iserte et al[10] and Uccella et al,[39] the risk of possible confounders is present. However, the strength of the potential association may be increased or reduced. In the multivariate analysis by Padilla-Iserte et al,[10] IUM use resulted in an increased association with worse oncologic outcomes. Regarding peritoneal cytology and LSVI, our systematic review and meta-analysis present similar limitations of oncologic outcomes, though the meta-analysis includes 2 RCTs specifically designed to answer this question that strengthens obtained results.[37,38]

## Conclusions and implications

Although IUM has been blamed for potentially worsening oncologic outcomes of EC patients by spreading malignant cells in the abdominal cavity or lymphatic and blood vessels,[10–13] only 14 studies have been specifically conducted to investigate the impact of the IUM on EC.[10,12–14,37–46] Moreover, most evidence is limited to the association between using an IUM and a higher rate of positive peritoneal cytology and LVSI. In this regard, our results do not support this association. Only a few studies provided data regarding oncologic outcomes with appropriate follow-up, and pooled analysis did not demonstrate a significant association between IUM use during hysterectomy for EC and a lower recurrence-free and overall survival. Nevertheless, definitive conclusions are impossible owing to several limitations, and observed results raise the concern of a higher risk of recurrence with IUM use. Considering that a higher rate of positive peritoneal cytology and LVSI do not seem associated with IUM use and likely are surgical artifacts without clinical implications,[25,32,55] future trials must focus on oncologic outcomes instead of pathologic characteristics. A laparoscopic hysterectomy performed with an IUM is not mandatory nor necessary; therefore, we await future trials to exclude even minor increases in recurrence risk. Clarifying the role of IUM use in EC is part of the continuous challenge to improve EC prevention, diagnosis, and treatment. ■

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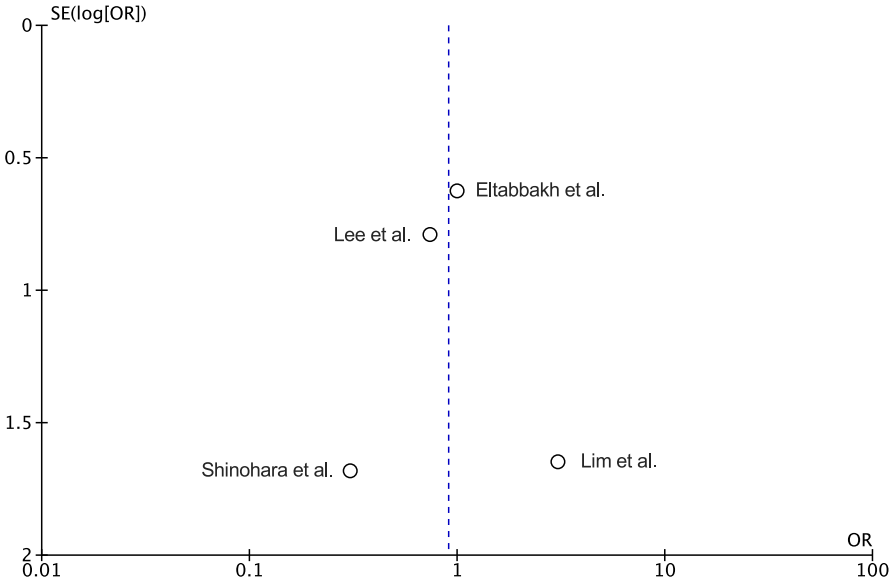
**SUPPLEMENTAL FIGURE 1**
**Funnel plot for peritoneal cytology status before and after IUM insertion**

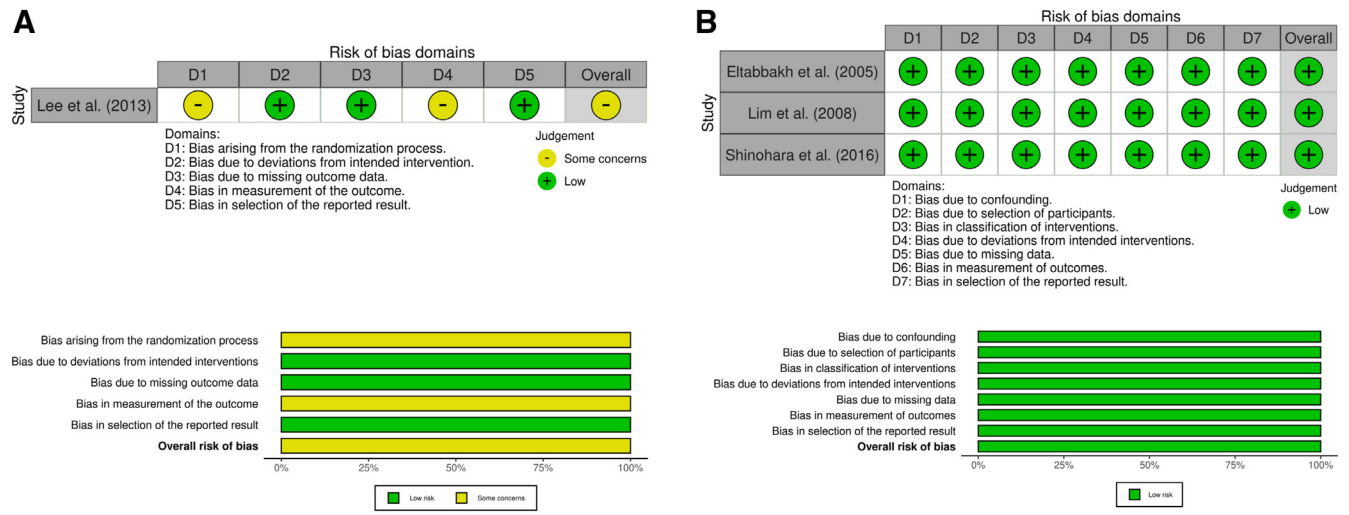



Comparison: hysterectomy with vs without IUM.

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**SUPPLEMENTAL FIGURE 2**
**Risk of bias for peritoneal cytology status before and after IUM insertion**

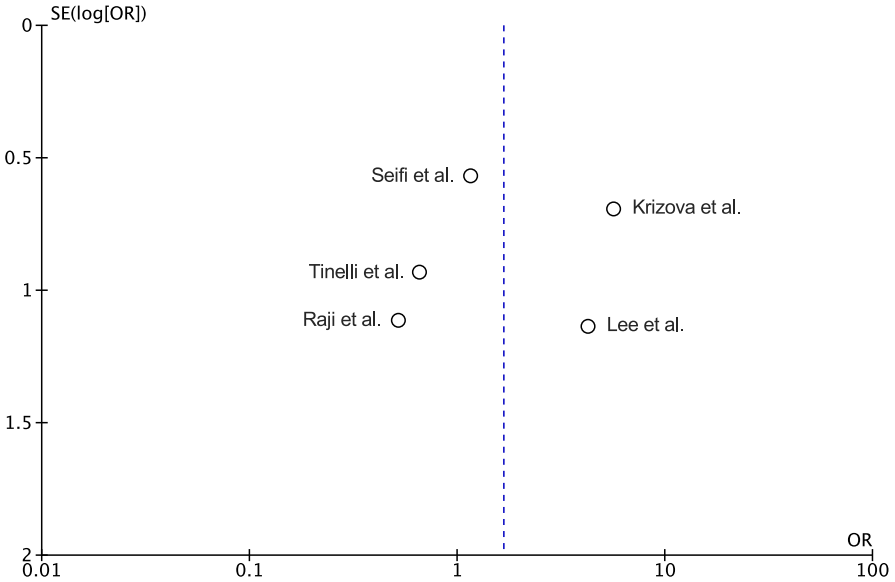



Comparison: hysterectomy with vs without IUM. **A,** Randomized controlled trials (risk of bias tool for randomized trials). **B,** Nonrandomized studies (risk of bias in nonrandomized studies—of exposures).

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**SUPPLEMENTAL FIGURE 3**
**Funnel plot for peritoneal cytology status with vs without IUM**

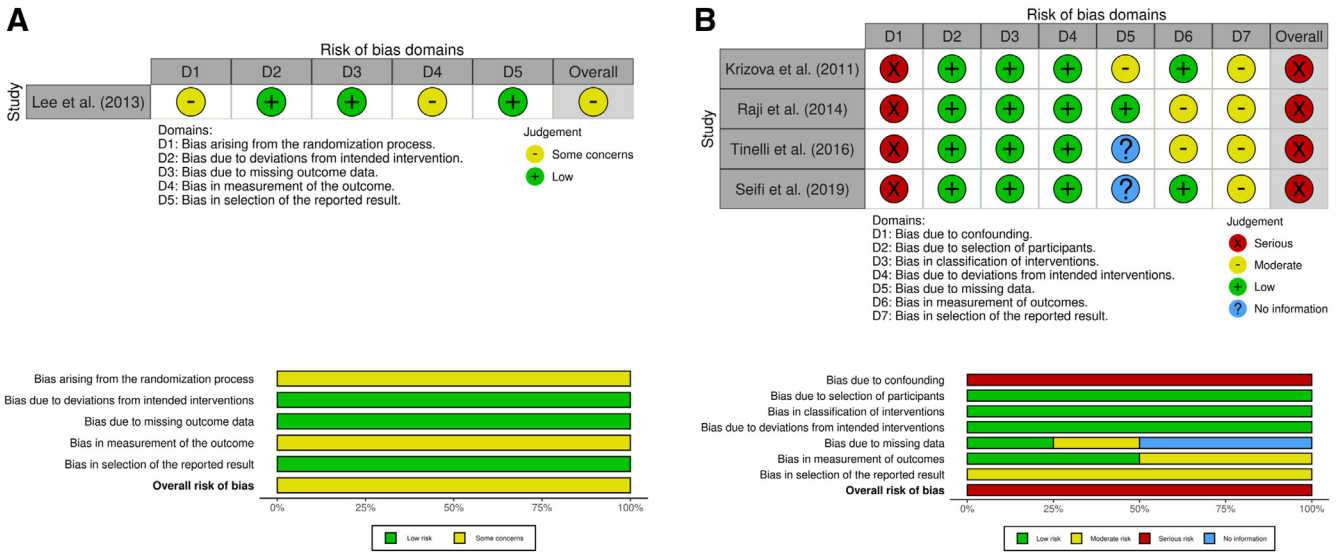



Comparison: hysterectomy with vs without IUM.

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**SUPPLEMENTAL FIGURE 4**
**Risk of bias for peritoneal cytology status with vs without IUM**

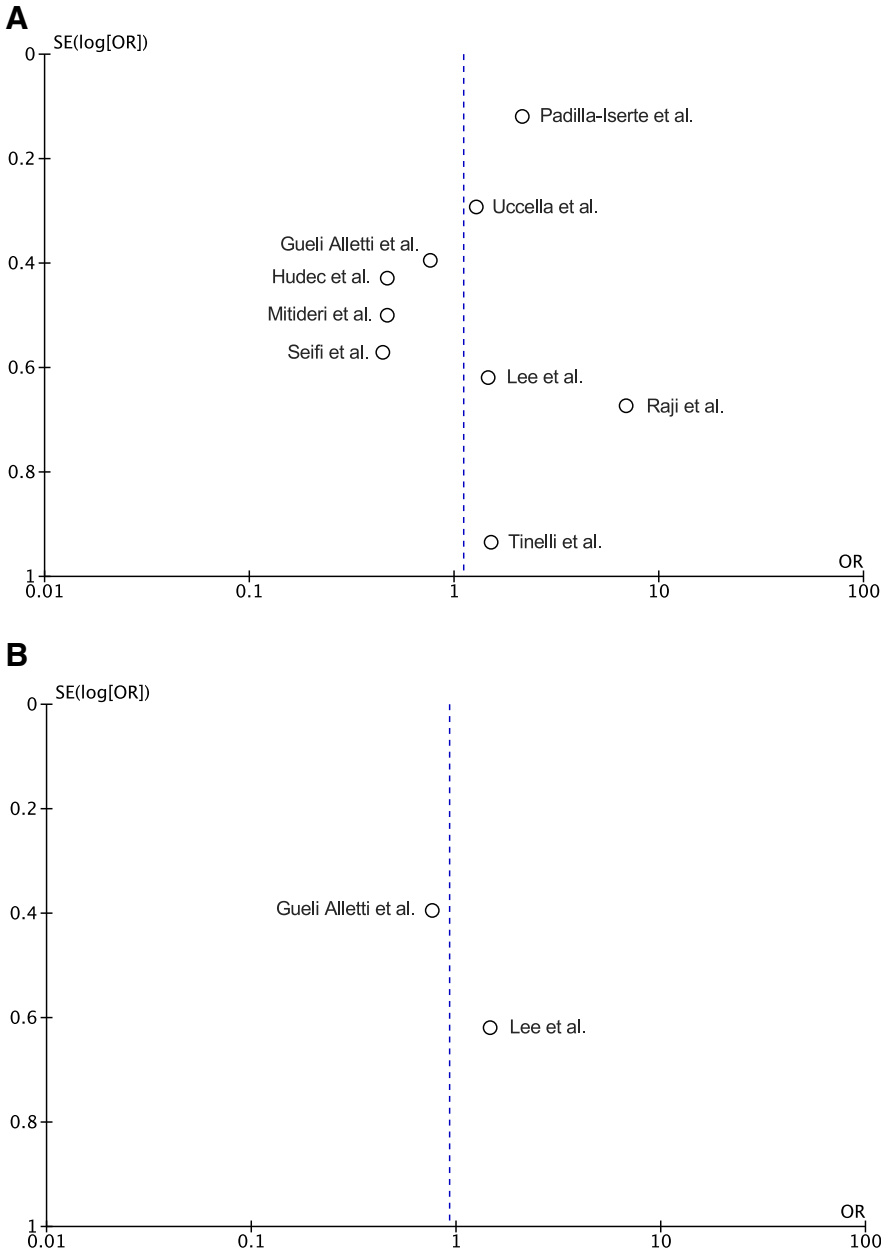



Comparison: hysterectomy with vs without IUM. **A,** Randomized controlled trials (risk of bias tool for randomized trials). **B,** Nonrandomized studies (risk of bias in nonrandomized studies—of exposures).

*IUM*, intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**SUPPLEMENTAL FIGURE 5**
**Funnel plot for lymphovascular space invasion**



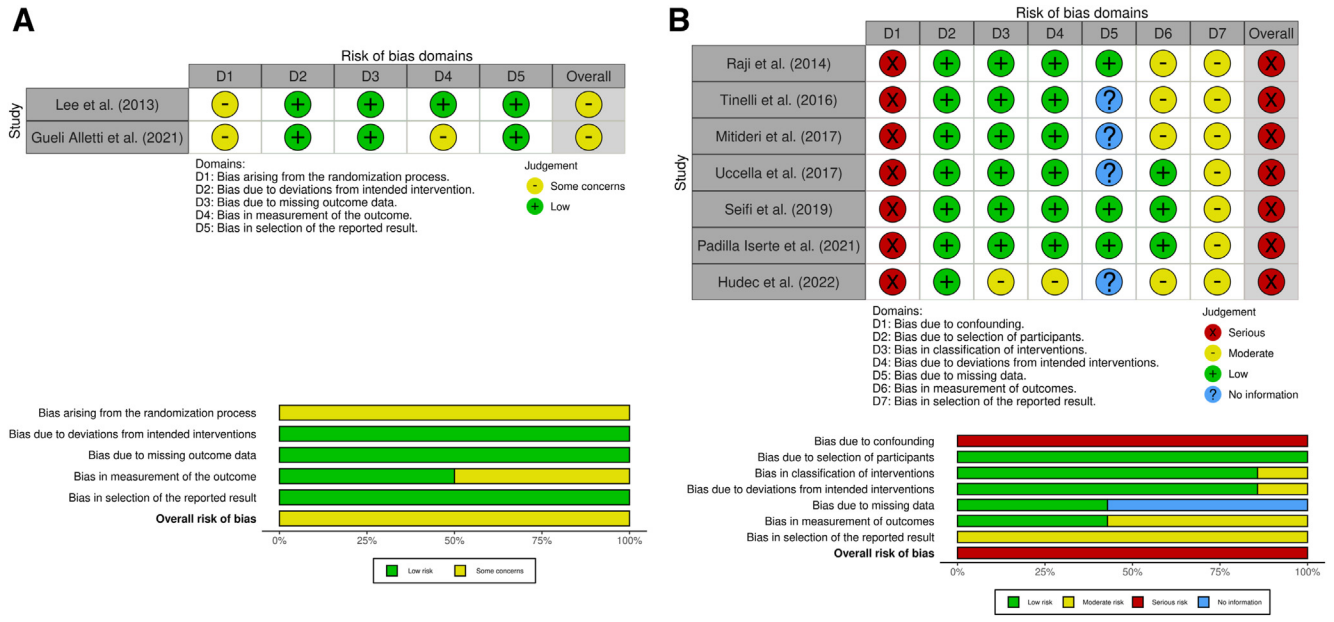

Comparison: hysterectomy with vs without IUM. **A,** All studies included in the meta-analysis. **B,** Only the 2 randomized controlled trials were included in the meta-analysis.

*IUM,* intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*

**SUPPLEMENTAL FIGURE 6**

## Risk of bias for lymphovascular space invasion




Comparison: hysterectomy with vs without IUM. **A,** Randomized controlled trials (risk of bias tool for randomized trials). **B,** Nonrandomized studies (risk of bias in nonrandomized studies—of exposures).

*IUM,* intrauterine manipulator.

*Zorzato. Intrauterine manipulator during hysterectomy for endometrial cancer and oncologic outcomes. Am J Obstet Gynecol 2024.*