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Review Article

Use of uterine manipulators in endometrial cancer surgery: Balancing benefits and uncertainties

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ABSTRACT

Objective: Intrauterine manipulators are commonly used for minimally invasive hysterectomy for endometrial cancer yet concerns regarding tumor spillage and oncologic safety remain debated. This review aims to synthesize comparative evidence regarding their impact on oncologic outcomes.
Methods: A comprehensive literature review up to December 2025 identified 15 comparative studies, including randomized trials, meta-analyses, and observational cohorts. The analysis focused on peritoneal cytology, lymphovascular space invasion (LVSI), recurrence patterns, and survival outcomes in patients undergoing hysterectomy for endometrial cancer.
Results: Most randomized and matched evidence demonstrated no significant detriment in disease-free or overall survival for early-stage endometrioid disease attributable to manipulator use. However, recent large datasets and meta-analytic subgroups signaled modest increases in positive peritoneal cytology (adjusted OR 1.7) and LVSI among manipulator users. Additionally, specific cohorts reported increased isolated vaginal vault recurrences, although overall operative safety remained comparable.
Conclusions: Current evidence suggests that a universal oncologic hazard may not be present for early-stage, low-grade tumors, though the reliance on predominantly retrospective data warrants caution. Until definitive prospective data mature, a selective, technique-conscious approach could be considered.

1. Introduction

Minimally invasive surgery (MIS) has become a cornerstone of the surgical management of apparent early-stage endometrial cancer, reducing perioperative morbidity while maintaining oncologic adequacy in appropriately selected patients [1,2]. To optimize uterine mobilization during MIS hysterectomy, intrauterine manipulators are widely used to improve traction, delineate vaginal margins, and support colpotomy. However, their use in oncologic settings remains debated because of concerns that intrauterine pressure, cervical canalization, or repeated instrumentation could facilitate tumor spillage into the peritoneal cavity, alter lymphovascular space invasion (LVSI) assessment, or shift recurrence patterns—particularly toward the vaginal vault [3].

Over the past two decades, the available literature has explored these issues across randomized trials, prospective cohorts, retrospective series, and meta-analyses. Early single-center experiences suggested that laparoscopic management with intrauterine manipulation did not worsen cytologic or pathologic surrogates of spread, although sample sizes and follow-up were limited [4–6]. Subsequent prospective and randomized studies compared MIS with and without intrauterine manipulation, focusing on operative metrics and short-term outcomes, and generally did not demonstrate clinically meaningful detriment attributable to the manipulator, particularly in low risk endometrioid disease [7,8]. More recently, large multi-institutional and

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population-based cohorts, as well as updated systematic reviews and meta-analyses, have provided a broader view but yielded mixed signals: while several analyses reported no significant impact on disease-free or overall survival, others observed modest increases in adverse surrogate endpoints (e.g., positive peritoneal cytology) or site-specific recurrences among patients exposed to intrauterine devices [3,9–17].

Two key issues have been most extensively examined; first, peritoneal cytology, as uterine manipulation may promote the dissemination of tumor cells into the peritoneal cavity. Observational and pooled analyses variably report neutral findings or small increases in malignant cytology among manipulator users; importantly, the prognostic weight of cytology in the modern staging era remains nuanced and likely context-dependent [3,6,11,12,17]. Second, histopathologic interpretation: LVSI can be influenced by tissue handling and artifact. While most studies do not show consistent LVSI inflation with manipulators, isolated large datasets have suggested a modest increase, warranting careful technique and documentation [5,12].

Survival outcomes, as recurrence and survival, have been the subject of randomized and well-matched cohort analyses. The majority do not show a statistically significant difference in overall recurrence, disease-free survival (DFS), or overall survival (OS) attributable to intrauterine manipulation in early stage endometrioid disease [7,8,14,15]. However, specific retrospective cohorts report higher recurrence hazards or distinct recurrence patterns (e.g., isolated vaginal vault relapse) associated with manipulators, underscoring the possibility that risk is not uniform across clinical scenarios [9,10,13].

Given these uncertainties, this review aims to synthesize the available comparative evidence in patients undergoing hysterectomy for endometrial cancer with or without intrauterine manipulators, to provide a synthesis of current data that may assist surgical decision-making, operative planning, and patient counseling, while acknowledging the inherent limitations of the available literature.

2. Methods

2.1. Study design and search strategy

We conducted a structured narrative review of the comparative literature concerning the use of intrauterine manipulators in endometrial cancer surgery. This design was selected to allow for a comprehensive qualitative synthesis of clinical nuances while maintaining the methodological rigor of a systematic search. A literature search was performed across PubMed/MEDLINE and Scopus databases to identify relevant studies published up to December 2025. The search strategy employed a combination of keywords and boolean operators: *"(endometrial cancer OR endometrial carcinoma) AND (uterine manipulator OR intrauterine manipulator) AND (peritoneal cytology OR lymphovascular space invasion OR recurrence OR survival OR oncologic outcomes)"*. In addition to the electronic search, the reference lists of key review articles and meta-analyses were manually screened to identify any additional studies not captured by the initial query.

2.2. Eligibility criteria

To ensure the synthesis of high-quality evidence, study selection was guided by a predefined framework. Studies were included if they met the following criteria.

- Study Design: Original comparative reports, including randomized controlled trials (RCTs), prospective observational cohorts, and retrospective comparative series.
- Population: Patients with histologically confirmed endometrial cancer undergoing primary surgical staging via minimally invasive approaches, such as laparoscopy or robotics.
- Intervention and Comparison: Studies directly comparing the use of an intrauterine manipulator versus no manipulator or alternative uterine mobilization techniques.
- Outcomes: Reports providing extractable data on at least one pathological endpoint (e.g., peritoneal cytology, lymphovascular space invasion) or oncological outcome (e.g., recurrence patterns, disease-free survival, or overall survival).

We excluded non-comparative studies (e.g., case reports, single-arm series), non-peer-reviewed literature (e.g., conference abstracts, editorials, letters), and non-English language publications.

2.3. Study selection and quality assessment

Study selection was performed independently by two authors (M.D.; F.N.), with any discrepancies resolved through consensus. The transition from the initial identification of records to final inclusion was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To assess methodological quality and the risk of bias, we utilized the Cochrane Risk of Bias (RoB 2) tool for randomized trials and the Newcastle-Ottawa Scale (NOS) for observational and retrospective studies. For the NOS, studies scoring $\geq$7 were considered high quality.

2.4. Data synthesis

A total of 15 comparative reports were identified and synthesized (Fig. 1). Due to the substantial heterogeneity in study designs, patient populations, surgical techniques, and adjuvant treatment protocols, a quantitative meta-analysis was not performed. Instead, we conducted a structured narrative synthesis aimed at distilling consistent evidence and identifying potential sources of bias. Primary comparative studies were analyzed to extract granular data on outcomes and surgical techniques, while existing systematic reviews and meta-analyses were utilized to provide a broader context of pooled evidence and to identify areas of divergence in current literature. Potential overlap between study populations was assessed by comparing recruitment periods and participating institutions. This review was based exclusively on published data and adhered to principles of scientific integrity and transparency.

3. Results

3.1. Study selection and characteristics

We synthesized 15 comparative reports: 2 randomized controlled trials, 2 systematic reviews/meta-analyses, 4 prospective observational cohorts, and 7 retrospective studies encompassing single-center, multicenter, and nationwide datasets (Table 1). Sample sizes ranged from 42 to 5205 patients, predominantly with early-stage, low-grade endometrioid histology. Follow-up reporting was heterogeneous, with median durations available in approximately half of the studies. Surgical approaches included total laparoscopic and robotic hysterectomy with standard staging as indicated [3,5–7]. Regarding the quality of the evidence, the two included RCTs showed a low risk of bias, while the retrospective cohorts had a median Newcastle-Ottawa score of 7 (range 5–9), indicating overall good methodological quality despite their retrospective design. Surrogate pathological endpoints (such as positive peritoneal cytology and LVSI) were considered separately from hard oncologic outcomes, including recurrence, disease-free survival, and overall survival.

3.2. Peritoneal cytology

Thirteen studies reported peritoneal cytology. Most found no statistically significant difference in positive cytology between manipulator

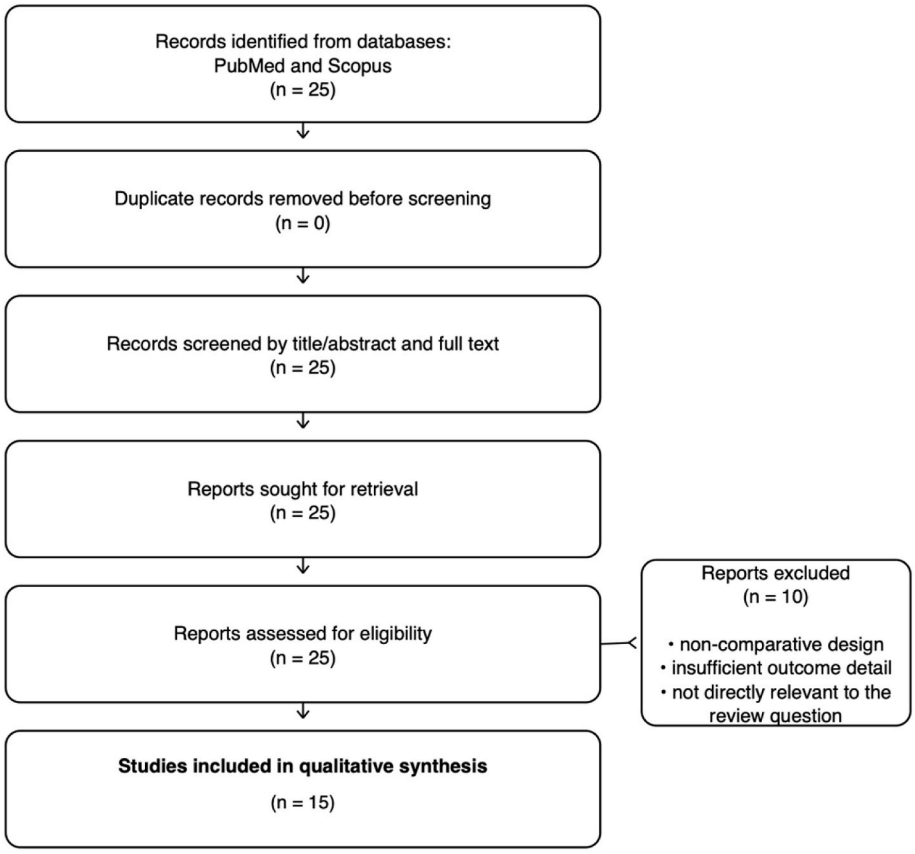

Fig. 1. PRISMA flow diagram of study selection.

and non-manipulator groups, including analyses that controlled for stage and histotype [3,6,11,17]. Nevertheless, some datasets signaled higher odds of malignant cytology with manipulator use. A 2024 multi-institutional analysis observed increased positive cytology in manipulator cases (manipulator 11% vs no manipulator 6%; adjusted odds ratio 1.7) [12]. Meta-analytic subgroup findings similarly suggested a possible elevation in malignant cytology among manipulator users, although pooled estimates across heterogeneous studies were not uniformly significant [3,11]. Studies evaluating the timing of insertion (before vs after pneumoperitoneum or tubal sealing) did not demonstrate a reproducible effect on cytology conversion [6,17].

3.3. Lymphovascular space invasion

Most comparative cohorts showed no significant difference in LVSI rates attributable to manipulator use [3–5,7,8,11,14,15]. However, a large 2024 analysis reported higher LVSI among manipulator users (18% vs 13%; adjusted odds ratio 1.35) [11]. Methodologic limitations include variable pathology protocols and potential artifact from uterine handling [5].

3.4. Operative outcomes and perioperative safety

Across randomized and observational studies, operative time, estimated blood loss, and conversion rates were broadly comparable between groups [4,7,8,14,15]. Some trials and cohorts suggested shorter operative time or less blood loss when avoiding intrauterine devices in purely laparoscopic procedures, whereas robotic platforms showed minimal differences [7,9,11,13]. Overall complication rates were not consistently increased by manipulator use [4,7,8,14,15].

3.5. Device characteristics and timing

Reporting on device brand, balloon inflation, sealing of fallopian tubes, and insertion timing was inconsistent. Studies explicitly comparing insertion timing did not demonstrate adverse cytology or oncologic outcomes attributable to early vs late placement [17].

A critical aspect often underestimated in general analyses of tumor spillage is iatrogenic uterine perforation. Although generally considered rare in standard laparoscopic series, recent focused studies have highlighted that the risk is not negligible. For instance, Laskov et al. reported a uterine perforation rate of up to 11% in specific cohorts undergoing uterine manipulation, demonstrating a direct correlation between mechanical trauma and adverse oncologic signals [12]. This complication is not merely a surgical event but acts as a catalyst for neoplastic dissemination: the combination of a full-thickness breach in the uterine wall and intrauterine pressure establishes a direct communication between the endometrial tumor and the peritoneal cavity. Notably, uterine perforation has been statistically associated with increased lymphovascular space invasion (LVSI), suggesting that intracavitary pressure may mechanically force tumor cells into vascular channels opened by the trauma [12]. However, the true impact of this complication on overall survival is difficult to quantify in current meta-analyses. Large multicenter retrospective studies, such as the one by Padilla-Iserte et al., frequently exclude cases complicated by intraoperative uterine rupture from their primary analyses to avoid staging bias [9]. Paradoxically, this methodological practice may lead to an overestimation of the oncologic safety of uterine manipulators, as the adverse events with the worst prognostic potential are systematically removed from recurrence datasets.

Table 1
Characteristics of included studies.

STUDY	STUDY DESIGN	POPULATION SIZE	STAGE DISTRIBUTION	HISTOLOGY	MANIPULATOR TYPE	TIME OF CITOLOGY/ WASHING	PRIMARY OUTCOMES	FOLLOW-UP	QUALITY SCORE (NOS OR ROB 2)
Scutiero et al., 2022 [3]	Systematic review	18 studies	Predominantly early-stage in included studies	Mostly endometrioid; mixed histologies across studies	Mixed/ heterogeneous	Heterogeneous/ NR	LVSI, recurrence, peritoneal cytology	No mention found	High Quality (AMSTAR-2)
Tinelli et al., 2016 [4]	Retrospective	110	Early-stage	Predominantly endometrioid	NR	NR	Recurrence, surgical outcomes	No mention found	6/9 (Moderate - NOS)
Fanfani et al., 2011 [5]	Case-control	314	Early-stage	Endometrioid predominant	Intrauterine manipulator	NR	Manipulator and frozen section accuracy	No mention found	6/9 (Moderate - NOS)
Eltabbakh & Mount, 2006 [6]	Prospective cohort, single center	42	Early-stage	NR	NR	Peritoneal cytology assessed	Manipulator and positive cytology	Median 28 months (7–56)	7/9 (High - NOS)
Lee et al., 2012 [7]	Randomized controlled trial	110	Apparently early-stage	Predominantly endometrioid	NR	NR	Surgical outcomes, positive cytology, LVSI	Median 19 months	Low Risk (RoB 2)
Gueli Alletti et al., 2021 [8]	Randomized controlled trial (ROMANHY)	154	Early-stage	Low-grade endometrioid predominant	NR	Assessed before/ after manipulation protocol-dependent	LVSI after MIS staging	Median 38.7 months	Low Risk (RoB 2)
Uccella et al., 2017 [9]	Retrospective cohort, multicenter	951	Early-stage predominant	Endometrioid predominant	NR	NR	Risk of disease recurrence	Median 46 months (12–163)	8/9 (High - NOS)
Padilla-Iserte et al., 2020 [10]	Retrospective multicenter	2661	Uterine-confined/early-stage predominant	Endometrioid predominant	NR	NR	Relapse rate	No mention found	8/9 (High - NOS)
Meng et al., 2020 [11]	Systematic review/meta-analysis	11 studies	Predominantly early-stage in included studies	Mixed; mostly endometrioid	Heterogeneous	Heterogeneous/ NR	LVSI, positive cytology, recurrence	No mention found	High Quality (AMSTAR-2)
Yoshida et al., 2024 [12]	Retrospective cohort, nationwide	3846	Early-stage predominant	Mixed, including endometrioid predominant	Intrauterine manipulator	NR	Pathological factors, oncologic outcomes	No mention found	7/9 (High - NOS)
Laskov et al., 2024 [13]	Retrospective	699	Early-stage predominant	NR	Intrauterine manipulator	NR	Manipulator and outcomes	Median 44 months (29–67)	6/9 (Moderate - NOS)
Ye et al., 2024 [14]	Retrospective, multicenter	5205	Early-stage, low-grade	Low-grade endometrioid	NR	NR	IU vs non-IU manipulator, oncologic outcomes	No mention found	7/9 (High - NOS)
Eoh et al., 2023 [15]	Retrospective cohort, single center	574	Endometrial cancer, stage NR	NR	Uterine manipulator/ alternative approach	NR	Oncologic outcomes (robotic vs open)	Median 42.5 months (12–71)	6/9 (Moderate - NOS)
Gerçek et al., 2025 [16]	Prospective observational	108	Endometrial cancer, stage NR	NR	NR	Peritoneal cytology timing evaluated	Manipulator and peritoneal cytology	No mention found	7/9 (High - NOS)
Machida et al., 2016 [17]	Case-control, multicenter	333	Endometrial cancer, stage NR	NR	Intrauterine manipulator	Before vs after cytology/staging steps	Timing of manipulator and pelvic cytology	No mention found	7/9 (High - NOS)

LVSI: Lymphovascular Space Invasion; IU: intra-uterine; MIS: minimally invasive surgery; NR: not reported.

3.6. Recurrence patterns

Regarding recurrence outcomes, randomized trials and well-matched cohorts generally found no significant difference in overall recurrence associated with intrauterine manipulator use in early-stage endometrioid disease [7,8,14,15]. In contrast, some retrospective series observed higher composite recurrence rates among manipulator users, although these findings may be influenced by residual confounding related to case selection and staging extent [9,10]. One multicenter series also reported a higher rate of isolated vaginal vault recurrence among manipulator users, suggesting the possibility of site-specific effects [13].

3.7. Survival outcomes

Across randomized studies and adjusted comparative cohorts, disease-free survival and overall survival were generally similar between manipulator and no-manipulator groups in early-stage, low-grade endometrioid disease [7,8,14,15]. Although some retrospective studies suggested worse survival outcomes in selected populations [9,10], these findings were not consistent across the literature and should be interpreted with caution given potential confounding, variable follow-up, and differences in adjuvant treatment [3,9–15].

3.8. Overall interpretation

Taken together, the analyzed evidence does not consistently demonstrate a universal oncologic hazard from intrauterine manipulation in early-stage, low-grade endometrioid cancers treated with MIS. Yet, consistent with biological plausibility, modest increases in malignant peritoneal cytology and, in selected cohorts, LVSI or site-specific (vaginal vault) recurrences have been observed (Table 2). Data for high-risk histologies (serous/clear cell) remain limited; extrapolation should be cautious and individualized [3,8–15]. These findings reinforce a selective, technique-conscious approach and underscore the need for high-quality prospective studies with device/timing standardization and sufficient follow-up [3,5–7,15].

4. Discussion

The use of an intrauterine manipulator during minimally invasive hysterectomy for endometrial cancer sits at the intersection of surgical ergonomics and oncologic prudence. The concern is biological: uterine instrumentation and transient increases in intrauterine pressure could theoretically promote transtubal dissemination of exfoliated tumor cells, confound pathologic interpretation (particularly LVSI), or influence site-specific recurrence patterns.

Across the highest-quality comparative evidence available to date, most studies do not demonstrate a clinically meaningful detriment in recurrence-free or overall survival attributable to uterine manipulator use in predominantly early-stage, low-grade endometrioid cancers. The ROMANHY randomized trial [8] found no differences in peritoneal cytology, LVSI, survival or recurrence rates between manipulator and no-manipulator arms, while showing small perioperative differences (operative time and blood loss) that were platform-dependent. Large multicenter retrospective data have similarly reported no increase in recurrence or mortality with intrauterine manipulator use [3–11]. Systematic reviews and meta-analyses generally did not demonstrate a measurable oncologic detriment attributable to the manipulator [7,8].

At the same time, several credible "signals" warrant attention and nuance in counseling. A large Spanish retrospective cohort (2600 patients) reported higher recurrence risk and worse survival associated with uterine manipulator use in uterine-confined disease [10], findings that diverge from the Italian experience and pooled analyses [3,9,11]. A recent multi-institutional analysis observed higher rates of LVSI among patients operated with a manipulator [12]. Another cohort described a greater frequency of positive peritoneal cytology and a shift toward isolated vaginal vault relapse with manipulation, even though overall recurrence and survival did not differ [13]. Therefore, these patterns do not establish causality, but they do underscore that manipulator-related risk, if present, may appear context-dependent, and more consistently detectable in intermediate endpoints than in survival.

How should clinicians interpret LVSI and cytology in this setting? LVSI is prognostically meaningful, yet its assessment can be confounded by tissue handling. Most series show no reproducible LVSI inflation with intrauterine manipulator use [3–5,7,8,11,14,15] but at least one large dataset suggests a modest increase [12]. Similarly, while many cohorts found no difference in peritoneal cytology [3,6,11,17], others reported higher odds of malignant cytology with manipulation [12,13]. The available data suggest that, if uterine manipulator-related increases in LVSI or cytology occur, they have not consistently translated into inferior disease-free or overall survival across studies [3,7–9,11,14,15].

Importantly, surrogate findings such as positive peritoneal cytology or LVSI should not be interpreted as direct evidence of worsened oncologic outcome, as their clinical significance in this setting remains uncertain and has not consistently translated into higher recurrence rates or worse survival.

Platform and technique also matter. In robotic surgery, propensity-matched analyses suggest that uterine manipulator use does not compromise progression-free or overall survival compared with open

Table 2
Selected oncologic outcomes.

STUDY	PERITONEAL CYTOLOGY	LVSI	RECURRENCE RATE*	STATISTICAL SIGNIFICANCE
Scutiero et al., 2022 [2]	RR 1.89 (0.74–4.83)	RR 1.18 (0.76–1.85)	RR 1.11 (0.71–1.74)	None**
Lee et al., 2012 [6]	UM: 7.2% No UM 1,8% (p: 0.147)	UM: 12.7% No UM: 9.1% (p: 0.761)	UM: 9.1% No UM: 1.8% (p: 0.206)	None
Gueli Alletti et al., 2021 [7]	0% in both groups	UM: 19.2% No UM: 23.7% (p: 0.501)	UM: 5.1% No UM: 7.9% (p: 0.486) Multivariate analysis for DFS HR 0.92 (0.24–3.59)	None
Uccella et al., 2017 [8]	Not assessed	Not assessed	UM: 13.5% No UM: 11.6% (p: 0.37) Multivariate analysis for DFS odds ratio, 1.00 (95% CI, 0.60-1.7059)	None
Padilla-Iserte et al., 2020 [9]	Not assessed	Not assessed	UM: 11.69% No UM: 7.4% (p < 0.001) HR 2.31 (1.27–4.20); p = 0.006	**UM associated with risk of recurrence**
Meng et al., 2020 [10]	RR 1.53 (95% CI 0.85–2.77)	RR 1.18 (95% CI 0.66–2.11)	RR 1.25 (95% CI 0.89–1.74)	None
Yoshida et al., 2024 [11]	UM: 10.8% No UM: 6.4% (p: <0.001) Odds Ratio 1.35 (1.08–1.69)	UM: 17.8% No UM: 13.3% (p: 0.009) Odds Ratio 1.77 (1.29–2.31)	No mention	**UM associated with risk of peritoneal cytology and LVSI**
Laskov et al., 2024 [12]	UM: 8.8% No UM: 4.4% (p: 0.002)	Not assessed	UM: 12.3% No UM: 11.9% (p: 0.08)	**UM associated with risk of peritoneal cytology**
Ye et al., 2024 [13]	Not assessed	Not assessed	UM: 4.0% No UM: 3.2% (p: 0.78)	None
Eoh et al., 2023 [14]	Not assessed	Not assessed	UM: 8.4% VT: 4.7% No UM: 15.8% (p: <0.001)	None ***

LVSI: Lymphovascular Space Invasion; **CI**: confidence interval; **UM**: uterine manipulator; **VT**: vaginal tube.
*Manipulator vs no manipulator.
** a positive association between malignant cytology and hysterectomies was found in a subgroup analysis where LH/LAVH were compared to TAH. (RR = 2.26, 95% CI, 1.08-4.71. P = 0.03).
***after propensirty score matching.

approaches or with alternatives such as a vaginal delineator [15]. Trials and cohorts that examined timing found that inserting the manipulator before versus after peritoneal washings did not consistently influence cytology conversion [17], and case-control data indicate that the uterine manipulator does not bias frozen section evaluation of invasion depth, histotype, or grade [5]. Historical laparoscopic series similarly found no increase in positive cytology attributable to manipulation [6].

Even when overall recurrence rates are similar, the possibility of a site-specific effect is clinically relevant. In a recent study cohort [13], vaginal vault recurrence occurred more often in the uterine manipulator group, while overall recurrence and OS did not differ after adjustment. This pattern suggests a hypothesis that manipulation may influence local contamination or dissemination pathways without necessarily shifting long-term survival in populations where salvage and/or adjuvant therapies mitigate risk.

Methodology likely explains some of the discrepancies. Studies vary in case mix (stage distribution, histology), surgical details (device type, degree of instrumentation), and adjuvant therapy. Residual confounding may influence retrospective findings, particularly where manipulator use correlates with uterine size, cervical canalization difficulty, or surgeon preference. Moreover, LVSI artifacts from traction or retraction can mimic true invasion, emphasizing the importance of standardized grossing and pathology reporting.

The cumulative evidence suggests that the uterine manipulator may be utilized in MIS for early-stage endometrial cancer, provided that surgical caution is exercised. For most patients with low-risk, endometrioid tumors, its use has not been associated with worsened survival outcomes in the majority of the analyzed cohorts. [3,7–9,11,14,15]. Nonetheless, surgeons should remain attentive to settings where theoretical risk might be higher—bulky intracavitary disease, cervical involvement, or situations where adjuvant therapy is unlikely—because even a small shift toward vaginal vault relapse could be clinically meaningful [10,12,13].

Potential risk-mitigation strategies grounded in surgical prudence include and align with good surgical hygiene: obtain peritoneal washings before uterine manipulation when feasible; minimize endouterine pressure and avoid repeated reinstrumentation; consider early tubal occlusion or clipping in cases with abundant intracavitary tumor; choose devices judiciously; and collaborate closely with pathology to reduce LVSI misinterpretation [4–6,17]. Incorporating these steps into standardized pathways can help balance ergonomic gains with oncologic caution. Despite the biological plausibility of tumor dissemination related to manipulator-induced pressure, current data suggest a 'decoupling' between surrogate markers and clinical outcomes. The increase in malignant peritoneal cytology or LVSI observed in some datasets has not consistently translated into a reduction in DFS or OS. This indicates that it remains to be definitively determined whether such biological signals, while warranting technical caution, possess sufficient prognostic weight to alter the oncologic fate of patients with early stage disease.

Finally, the field would benefit from prospective comparative studies powered for oncologic endpoints, with rigorous reporting of device characteristics, insertion timing, cytology sequencing, and adjuvant therapy. Stratification by histologic subtype, molecular factors and intrinsic risk will be crucial. Until such data mature, a selective, technique-conscious approach—grounded in shared decision-making and transparent documentation—represents a cautious clinical strategy. [10,12–14,18,19]. The ongoing MANEC Trial, a randomized controlled study, is expected to complete accrual in 2028 and will present results in 2032, potentially clarifying the oncologic safety of intrauterine manipulators in endometrial cancer surgery and influencing future clinical guidelines.

Its results—on recurrence, disease-free survival, and peritoneal dissemination—will clarify the device's oncologic safety, inform patient selection, technical standardization, and future guidelines, and may also identify pragmatic surrogate endpoints to accelerate research and implementation in clinical practice [20]. Interpretation of these findings is inherently limited by confounding by indication. Surgeons may preferentially use or avoid intrauterine manipulators based on uterine size, tumor burden, cervical involvement, or technical difficulty, which may bias retrospective comparisons. In addition, variability in adjuvant treatment and follow-up duration may further influence recurrence outcomes. Potential immortal time and follow-up biases should also be considered when interpreting retrospective survival analyses.

This review has several limitations that should be acknowledged. First, its narrative rather than systematic design may influence the breadth and generalizability of the synthesized evidence. The available literature is largely characterized by a predominance of retrospective data, which are inherently subject to selection bias and residual confounding. Furthermore, there is significant heterogeneity across the included studies regarding surgical platforms—spanning both laparoscopic and robotic approaches—and the administration of adjuvant therapies. Finally, follow-up reporting was inconsistent across the analyzed cohorts, with median durations available for only approximately half of the included studies. Furthermore, it is essential to consider the impact of potential methodological biases typical of retrospective data. Specifically, **immortal time bias** and **follow-up bias** may have influenced survival and recurrence outcomes, as patients must survive long enough to receive certain treatments or be included in specific analysis groups. Additionally, the **variability in adjuvant treatment** protocols (e.g., radiotherapy or chemotherapy) across the included studies represents a significant confounding factor. These discrepancies in post-operative management can materially influence recurrence comparisons, making it difficult to isolate the independent effect of the uterine manipulator on oncologic safety. Consequently, results from retrospective series should be interpreted with caution.

It is also critical to acknowledge that uterine manipulators (UM) do not constitute a homogeneous category. Different designs—including balloon-based systems, Clermont-Ferrand-type devices, and reusable versus disposable systems—may have distinct biological and mechanical effects on the uterus. For instance, balloon devices may exert different intracavitary pressures compared to simple vaginal delineators. These technical nuances, alongside the lack of standardized reporting on device specifics in current literature, contribute to the complexity of comparing oncologic outcomes across studies."

A relevant question arises from this synthesis: if hard oncologic outcomes like DFS and OS remain unaffected, why does the surgical community maintain such a strong focus on surrogate signals like peritoneal cytology or LVSI? This persistence is likely rooted in biological plausibility and the 'precautionary principle.' The idea that mechanical manipulation could facilitate the hematogenous or transtubal spread of malignant cells—even if those cells are subsequently cleared by the immune system or adjuvant therapy—remains inherently concerning to the oncologic surgeon.

Furthermore, the limitations of current literature cannot be ignored. Most available studies are retrospective or, if prospective (such as the ROMANHY trial), may be underpowered to detect subtle differences in survival within a patient population that inherently possesses an excellent prognosis. Finally, the clinical relevance of surrogate markers often extends beyond survival: the presence of LVSI or malignant cytology—even if suspected to be artifactual—can lead to the upstaging of disease or the prescription of unnecessary adjuvant treatments, thereby increasing patient morbidity without a proven survival benefit."

5. Conclusion

In conclusion, while available literature does not definitively show that uterine manipulators significantly impair hard oncologic outcomes in early-stage disease, this observation is inherently limited by the retrospective and heterogeneous nature of the evidence.

However, a **nuanced clinical approach** is mandatory. The observed increase in surrogate markers (e.g., peritoneal cytology and LVSI) in

some series—while not currently linked to worse survival—highlights the need for **strict technical standardization**. This includes minimizing intrauterine pressure and considering strategies like tubal ligation to prevent potential cell dissemination. Finally, given the lack of robust data, **utmost caution** should be exercised in high-risk histological subtypes or advanced stages, where the biological impact of uterine manipulation remains to be fully elucidated.

Disclosure statement

The authors report no conflicts of interest.

Ethics

Not applicable — synthesis of published studies.

Contributions

Study concepts: MD, MB, AF, FF, Study design:MD, AF, FF.
Data acquisition:FN, FP, SR, GV, AR, EP, AF, FF.
Quality control of data and algorithms:MD, MB.
Data analysis and interpretation: MD, MB, FN, FP, SR, GV, AR, EP, AF, FF.
Statistical analysis:MD, MB.
Manuscript preparation:MD, MB, FN, FP, SR, GV, AR, EP.
Manuscript editing:MD, MB, AF, FF.
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Conflicts of interest

The author declares no conflicts of interest.

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