

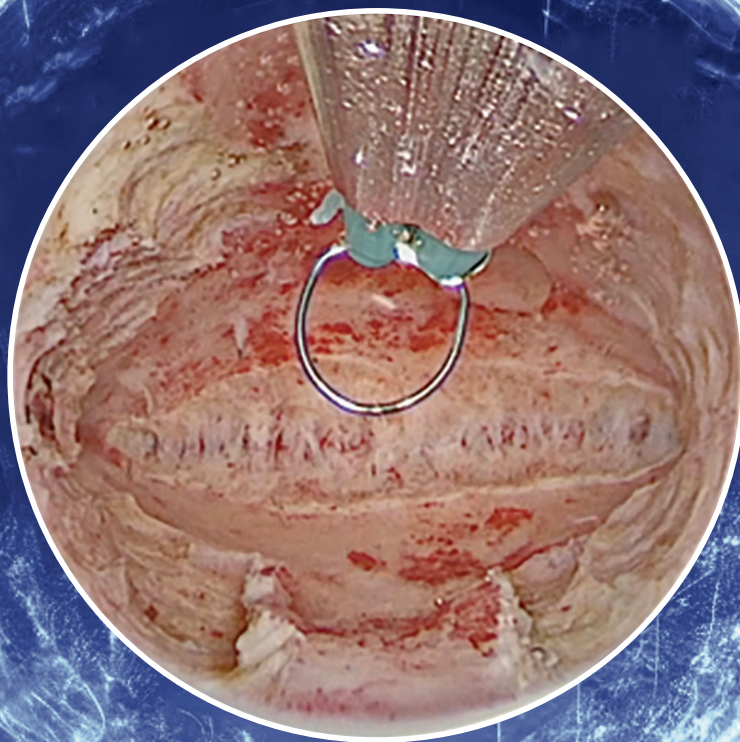
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Seeing the endometrium: time to move beyond blind sampling

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Keywords: Biopsy, endometrium, endometrial cancer, fibroids, hysteroscopy, uterine bleeding

Abnormal uterine bleeding including postmenopausal bleeding remain among the most common reasons for referral to gynaecological services worldwide. For decades, the first-line investigation for assessing the uterus has been transvaginal ultrasonography (TVS). However, TVS is limited when it comes to evaluating the endometrium, being restricted to evaluation of its thickness and regularity. Blind endometrial tissue sampling, using traditional dilation and curettage or a Pipelle®-type aspiration devices, has been the next step. This sequential approach has become embedded in clinical practice because blind sampling is simple, inexpensive, and can often be performed in an outpatient setting. Yet this strategy has always rested on a fundamental limitation, namely, tissue is sampled without actually seeing the pathology. The advent of hysteroscopy has not only allowed visualisation within the uterine cavity but also facilitated targeted endometrial biopsy with the potential to improve diagnostic performance.

Previous systematic quantitative reviews have shown the individual accuracy of TVS,¹ endometrial biopsy^{2,3} and hysteroscopy.⁴ However, the added value of visually directed biopsy has not been so well evaluated. In this issue of FVV Gyn we publish

a joint Society Practice Guideline from the American Association of Gynecologic Laparoscopists (AAGL), the European Society for Gynaecological Endoscopy (ESGE), and the Global Community of Hysteroscopy (GCH) attempts to address this deficiency.⁵

The guideline asks the question as to whether visually directed hysteroscopic biopsy should be favoured over blind endometrial sampling. The answer offered by the guideline is clear. Across the available comparative evidence, hysteroscopy with visually directed biopsy demonstrates superior diagnostic performance for endometrial hyperplasia, endometrial intraepithelial neoplasia (EIN), endometrial cancer, polyps, and submucosal fibroids, and should be incorporated into diagnostic algorithms whenever feasible.

Blind endometrial biopsy performs reasonably well for diffuse endometrial disease, particularly when a substantial proportion of the cavity is affected. However, many clinically important lesions are focal. Endometrial polyps, submucosal leiomyomas, localised EIN, and early endometrial cancer may occupy only a small area of the uterine cavity. It should therefore surprise no one that a blind instrument passed through the endometrial cavity may miss these lesions, sample

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adjacent normal tissue, or yield insufficient material for histological interpretation. The guideline shows that blind biopsy frequently demonstrates lower sensitivity for focal pathology, whereas hysteroscopy allows direct visualisation, targeted biopsy, and confirmation that the suspicious lesion has actually been sampled, thereby improving both detection and exclusion of disease.⁵

Beyond enhancing the diagnostic performance of endometrial biopsy, hysteroscopy allows concomitant treatment such as a polypectomy, myomectomy, retained pregnancy tissue (RPT) removal and adhesiolysis. Moreover, future treatment appropriate for an operating theatre setting can be planned; for example, a submucosal fibroid can be characterised and classified, allowing for better patient counselling, as well as informing decisions for endometrial preparation and selection of the best surgical technologies. Treatment of congenital uterine anomalies, dense adhesions, adherent RPT and cervical niches can similarly be better planned, potentially improving feasibility, efficiency and clinical outcomes. This convergence of diagnosis and treatment has become increasingly important as healthcare systems seek to reduce unnecessary procedures, minimise hospital admissions, and improve patient experience.⁶ The traditional pathway of TVS followed by blind endometrial biopsy and subsequent diagnostic hysteroscopy for ongoing symptoms or equivocal earlier results and eventual operative hysteroscopy in an operating room setting (level 3a to level 5 pain control),⁷ exposes patients to multiple appointments, repeated instrumentation, and prolonged uncertainty. A visually directed outpatient, hysteroscopic biopsy in women who screen positive on TVS has the potential to shorten that journey substantially. However, the acceptability of this approach to patients and its cost effectiveness needs further evaluation.

The guideline supports the view that hysteroscopy is not simply an alternative to endometrial biopsy, but as the optimal method of obtaining endometrial tissue. This distinction matters. Previous guidelines have often reserved hysteroscopy for women with abnormal imaging, persistent bleeding, or non-diagnostic biopsy results. Such recommendations implicitly treat blind sampling as the default and hysteroscopy as a second-line investigation. The present guideline argues instead that once the decision has been made to obtain tissue, hysteroscopic evaluation with directed biopsy should generally be preferred. In doing so, it aligns with an emerging international consensus that blind sampling

should be minimised where hysteroscopic expertise and facilities are available.^{7,8}

Whilst the authors should be commended for undertaking a high quality, systematic review with international involvement in keeping with recommended methodologies,⁹ only four comparative studies met the predefined inclusion criteria, and several had important methodological weaknesses, including lack of blinding of those assessing the reference standard from the test result and heterogeneous reference standards. The quality of evidence supporting many recommendations was judged as only low to moderate which restricts the strength of clinical recommendations. Despite this limitation, contemporary outpatient hysteroscopy using small-diameter hysteroscopes, vaginoscopic techniques, improved optics, and dedicated biopsy instruments has made hysteroscopy more accessible, well tolerated, convenient, feasible and cost-effective.

The future research agenda outlined by the guideline published in this issue of Facts, Views and Vision in ObGyn⁵ deserves equal attention. High-quality prospective, diagnostic accuracy studies, conducted according to recommended methodologies (<https://www.equator-network.org/reporting-guidelines/stard/>) comparing modern outpatient hysteroscopy with contemporary blind sampling techniques are needed, as gauged by the dearth of such studies identified in the systematic review informing this guideline. Integrating clinical data (i.e., patient characteristics)¹⁰ will enhance accuracy and even more exciting is the prospect of integrating hysteroscopic visualisation and directed biopsy with digital imaging, artificial intelligence-assisted lesion recognition, and molecular diagnostics.

The endometrial cavity has remained one of the few anatomical spaces where blind sampling continues to occupy a central role despite the availability of direct endoscopic assessment. The evidence assembled by AAGL, ESGE, and GCH suggests that this historical exception is becoming increasingly difficult to defend. The era of blindly sampling an unseen endometrium is drawing to a close, and this guideline provides the clearest roadmap yet for what should replace it.

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Beyond hysteroscopic metroplasty: time to distinguish fundal from ampliative procedures

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ABSTRACT

Functional intrauterine surgery has recently been proposed as a conceptual framework shifting the focus from anatomical correction alone toward restoration of uterine function and reproductive competence. However, hysteroscopic treatment of congenital uterine anomalies continues to be described under the umbrella term metroplasty, despite substantial differences in uterine morphology, surgical targets, and reconstructive objectives. In this Opinion Paper, we propose distinguishing two categories of hysteroscopic reconstructive procedures: fundal metroplasty and ampliative metroplasty. Fundal metroplasty primarily addresses midline fundal anomalies, most commonly the septate uterus, through a subtractive approach aimed at restoring normal uterine architecture. Conversely, ampliative metroplasty addresses globally restricted or dysmorphic uterine cavities through an expansive approach aimed at enlarging and reshaping the cavity. The use of a single term for these distinct procedures may contribute to conceptual ambiguity in surgical terminology. Rather than proposing a new classification system, we suggest terminology based on the anatomical target and reconstructive objective of hysteroscopic surgery. Distinguishing fundal from ampliative metroplasty may facilitate more precise communication and research and provide a clearer framework for hysteroscopic reconstructive surgery within the broader concept of Functional Intrauterine Surgery.

Keywords: Functional intrauterine surgery, hysteroscopic metroplasty, fundal metroplasty, ampliative metroplasty, septate uterus, dysmorphic uterus

Premise

Functional intrauterine surgery has recently emerged as a new conceptual framework in reproductive gynaecological surgery, shifting the focus from purely anatomical correction toward restoration of uterine function and reproductive competence.¹ Within this perspective, hysteroscopic surgery should not be regarded merely as a tool for removing intrauterine pathology or correcting uterine shape abnormalities,

but rather as a functional intervention aimed at optimising implantation, placentation, and pregnancy development.

Among the conditions most commonly associated with impaired reproductive outcomes are congenital uterine anomalies, particularly septate and dysmorphic uteri. Both conditions have been associated with infertility, pregnancy losses, implantation failure, and obstetric complications, although through

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potentially different anatomical and pathophysiological mechanisms. Hysteroscopic treatment of these abnormalities has become embedded in clinical practice. Despite the heterogeneity of the underlying uterine morphologies and surgical techniques, these procedures have traditionally been grouped under the single term “metroplasty.”

The Limits of Current Terminology

Historically, the term “metroplasty” has been closely associated with the treatment of the septate uterus, presumably because this is the most commonly encountered congenital uterine anomaly. The procedure is conceptually straightforward: a midline structure is incised or resected² in order to unify the uterine cavity. This approach is reflected in the way uterine anomalies are classified and studied.

Both the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy (ESHRE/ESGE) classification systems emphasise fundal morphology as a key diagnostic feature.^{3,4} As a consequence, the conceptual model of metroplasty has remained anchored to the idea of correcting a fundal defect. However, contemporary hysteroscopic practice has evolved beyond this paradigm. Increasingly, surgeons are confronted with uterine cavities that are not divided by a septum, but rather globally restricted, narrow, or dysmorphic. These include T-shaped uteri, tubular cavities, and other forms of subtle uterine cavity dysmorphism, which are classified as dysmorphic uterus within the ESHRE/ESGE system but are not acknowledged by the ASRM classification. In such cases, the surgical objective is not to incise or remove a central part, but rather to reshape and remodel the cavity. Despite this fundamental difference, both types of interventions continue to be labelled under the same term: metroplasty.

Fundal Metroplasty: Restoring Uterine Architecture—Need for a Second Step?

Fundal metroplasty refers to hysteroscopic procedures aimed at correcting midline fundal anomalies, most notably the septate uterus (Figure 1A, B).

Its defining characteristics are:

- a central anatomical target
- a subtractive surgical approach
- the goal of restoring a single unified cavity

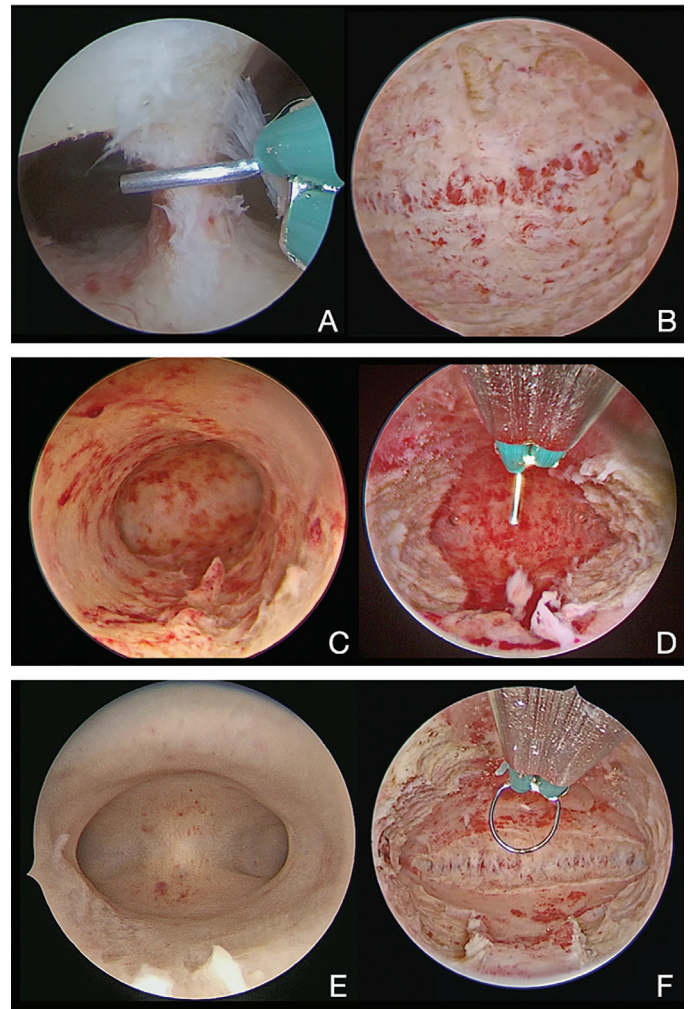


Figure 1. Pre- and post-operative appearance of uterine cavity after fundal, ampliative and combined techniques. (A) Pre-operative appearance of uterine septum. (B) Post-operative appearance of uterine cavity after fundal metroplasty. (C) Pre-operative appearance of T-shaped dysmorphic uterus. (D) Post-operative appearance of uterine cavity after ampliative metroplasty. (E) Pre-operative appearance of Y-shaped dysmorphic uterus. (F) Post-operative appearance of uterine cavity after combined metroplasty (lateral cavity expansion with fundal incision).

The underlying rationale is that a septum may impair implantation or early pregnancy development, and that its removal can improve reproductive outcomes by restoring uterine architecture and endometrial function.

This is the most extensively studied form of metroplasty. However, even in this “classical” indication, the evidence is far from unequivocal. A randomised controlled trial by Rikken et al.⁵ failed to demonstrate a significant improvement in live birth rates following septum resection, thereby challenging long-standing assumptions regarding the reproductive benefits of the procedure; however, despite its prospective design, this

study was subject to several potential sources of bias.^{6,7} At the same time, earlier observational studies and meta-analyses suggested improved reproductive outcomes in selected populations.⁸⁻¹⁰

These conflicting results highlight a key issue: even within a seemingly well-defined condition, variability in patient selection, anatomical definition, and type of septa (thin vs broad, vascularised or not) can profoundly influence outcomes.¹¹ Moreover, fundal metroplasty should not be regarded as a single-step procedure. Emerging evidence demonstrates that, following septum resection, the uterine fundus undergoes a process of myometrial remodelling, leading to progressive changes in cavity shape over time. In a prospective pilot study, Casadio et al.¹² showed that the uterine fundus continues to reorganise after hysteroscopic metroplasty, suggesting that the immediate postoperative anatomy does not represent the final structural outcome. In the framework of a functional intrauterine surgery,¹ this is an important observation because restoration of uterine architecture, rather than an increase in uterine cavity volume, is the key objective of fundal metroplasty.

This observation also has direct clinical implications. Fundal metroplasty should be conceptually reframed as a two-step procedure, in which the initial surgical correction is followed by a second-stage assessment to evaluate the completeness of cavity normalisation after tissue remodelling. Failure to recognise this dynamic process may lead to underestimation of residual anomalies or misinterpretation of surgical success.

Ampliative Metroplasty: Altering Uterine Cavity Dynamics

In contrast, we introduce the concept of ampliative metroplasty, which represents a distinct surgical paradigm. In these cases, the uterine cavity is not divided but constrained. The morphology is often characterised by:

- reduced transverse diameter
- thickened or inwardly protruding lateral walls
- a T-shaped or tubular configuration
- limited endo-cavitary volume

Here, the problem is not the presence of excess tissue in the midline, but rather a globally restricted uterine cavity caused by increased thickness of the lateral and/or fundal uterine walls. Accordingly:

- the target is focused to the lateral walls and global architecture
- the surgical approach is expansive rather than subtractive incising the “excess” of the uterine wall thickness
- the objective is to reshape cavity improving its functional geometry

Procedures of this type have been described, particularly in the context of the T-shaped uterus and uterine dysmorphism (Figure 1C, D).^{13,14} However, they have never been clearly distinguished, at a conceptual level, from septum section.

This lack of distinction obscures a fundamental difference: ampliative metroplasty is not simply a variation of fundal surgery; rather, it is a reconstructive intervention based on a different pathophysiological premise, aimed at restoring uterine function by improving the spatial and biomechanical conditions required for implantation, placentation, and normal pregnancy progression.

Within the framework of functional intrauterine surgery,¹ ampliative metroplasty represents the most explicit example of a procedure aimed at restoring uterine function through spatial and biomechanical optimisation rather than simple anatomical correction.

Importantly, fundal and ampliative principles are not always mutually exclusive. In anatomical variants such as the Y-shaped uterus, the surgical approach may combine lateral cavity expansion with fundal incision, thereby incorporating elements of both procedures (Figure 1E, F).

One Term, Two Different Surgeries

The continued use of a single term “metroplasty” to describe these two procedures creates a structural problem in the literature. When studies evaluate the effectiveness of “metroplasty”, they may include heterogeneous populations comprising:

- patients with a septate uterus
- patients with a dysmorphic uterus

These conditions are biologically and anatomically distinct. The corresponding surgical interventions differ in their targets, techniques, and mechanisms of action. Fundal metroplasty involves incision and/or removal of tissue. Ampliative metroplasty creates space by reshaping the cavity. Fundal metroplasty aims at anatomical and architectural normalisation. Ampliative metroplasty aims at functional optimisation.

Moreover, fundal metroplasty is characterised by a postoperative myometrial reorganisation phase, reinforcing the need to conceptually separate it not only from ampliative procedures, but also from the notion of immediate surgical completeness.

Pooling these entities under a single label risk diluting true treatment effects, generating inconsistent results, and limiting the interpretability of clinical studies.

A Proposed Conceptual Framework

We therefore propose the formal introduction of the following definitions:

- **Fundal metroplasty:** A hysteroscopic procedure aimed at correcting a midline fundal anomaly, primarily the septate uterus, with the goal of restoring a single unified cavity, and requiring a second-step office evaluation due to postoperative myometrial reorganisation.
- **Ampliative metroplasty:** A hysteroscopic procedure aimed at expanding and reshaping a globally restricted or dysmorphic uterine cavity, with the goal of improving its functional geometry and reproductive potential.

This distinction reflects not only different surgical techniques, but also different underlying biological questions.

Implications For Research and Practice

Recognising this dichotomy has immediate implications. First, it calls for greater precision in study design. Clinical trials and observational studies should clearly distinguish between fundal and ampliative indications, rather than grouping them under a generic category. Second, it challenges the interpretation of existing evidence. Meta-analyses that combine heterogeneous forms of metroplasty may be inherently limited in their conclusions. Third, it refines patient selection and counselling. The expected benefits, risks, and mechanisms of action differ between the two procedures, and should be communicated accordingly. In addition, for fundal and combined metroplasty, postoperative office follow-up should be considered an integral part of the procedure itself, rather than an optional step, in order to capture the effects of uterine remodelling. Finally, it opens new avenues for research. In ampliative metroplasty, success may not be adequately captured by traditional endpoints such as cavity “normalisation,” but may require more nuanced assessments of uterine geometry, endometrial function, and implantation dynamics.

Reframing the Central Question

For many years, the field has focused on a single overarching question:

“Does hysteroscopic metroplasty improve reproductive outcomes?”

This question is no longer sufficient.

A more appropriate formulation would be:

“Which metroplasty, for which uterine morphology, and through which mechanism of action?”

Conclusion

Hysteroscopic metroplasty is not a single procedure, but a family of interventions that share an endoscopic approach while differing fundamentally in their anatomical targets and surgical objectives. By introducing the distinction between fundal metroplasty and ampliative metroplasty, we aim to provide a new conceptual framework that better reflects surgical reality and may help resolve long-standing inconsistencies in the literature. This distinction has not been formally described before. Yet, it is already embedded in daily practice.

Recognising it is not merely an exercise in terminology—it is a necessary step toward more precise science and better clinical care.

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Finis coronat opus? What comes after hysteroscopic metroplasty

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ABSTRACT

Hysteroscopic metroplasty is widely regarded as the endpoint of septate uterus care, yet its impact on fertility remains uncertain and the postoperative cavity is seldom reassessed. Evidence on second-look hysteroscopy is equally scarce: mostly retrospective, rarely randomised, and not designed to isolate its reproductive effect. Re-inspection should arguably be reframed as an integral, fertility-oriented step rather than optional surveillance. Routine use in all patients is unjustified and not cost-effective, yet systematic omission may also overlook clinically relevant abnormalities. A selective, risk-stratified strategy is preferable, reserving it for the highest-risk women and triaging the rest with three-dimensional sonohysterography. Prospective, second-look-controlled trials are needed.

Keywords: Hysteroscopy, septate uterus, intrauterine adhesions, infertility, female, pregnancy outcome, live birth

Introduction

The septate uterus remains the most common congenital uterine anomaly, resulting from incomplete resorption of the Müllerian ducts during embryogenesis.¹ Over the past decades, the advent of operative hysteroscopy has profoundly changed the surgical approach to uterine septum, making hysteroscopic metroplasty the most commonly adopted technique in clinical practice.²⁻⁴ However, despite its widespread use, the benefit of hysteroscopic septum resection on reproductive outcomes remains a matter of debate.⁵⁻⁷ This uncertainty has led several authors to question an anatomy-driven approach to septum management and to advocate instead for a more selective, outcome-oriented strategy focused on reproductive benefit rather

than technical completeness alone.⁸⁻¹⁰ Nevertheless, with reproductive outcome as the ultimate goal, the surgical act of septum resection has been extensively debated, whereas far less attention has been paid to what follows the procedure.¹¹ Hysteroscopic metroplasty should be viewed as a critical milestone rather than the endpoint of care.¹² Healing of the uterine cavity, completeness of resection, and the risk of postoperative intrauterine adhesions all represent variables that may significantly influence subsequent fertility, yet they often remain unverified.¹³

In this context, second-look hysteroscopy emerges as a potentially decisive but still underappreciated tool.⁴ Its rationale is straightforward: to confirm adequate anatomical correction, identify residual septal tissue, and detect or treat early intrauterine adhesions before

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they become clinically relevant.¹¹ However, despite its intuitive appeal and increasing adoption in some centres, its role remains controversial, with marked heterogeneity in clinical practice and no shared international recommendations regarding its routine use, timing, or patient selection.^{11,14} This lack of consensus mirrors the broader debate surrounding septum surgery itself, reinforcing the concept that postoperative hysteroscopy should not be regarded as a mandatory extension of surgery, but rather as a selectively applied tool within a personalized care pathway.¹⁵

Why Look Again: The Rationale for Second-Look Hysteroscopy

The rationale for re-inspecting the cavity rests on two findings that metroplasty may leave behind: a residual septum and newly formed intrauterine adhesions. Both are clinically silent and each can compromise implantation and pregnancy.^{11,14}

The most comprehensive synthesis to date pooled 15 studies involving more than 1,400 women undergoing hysteroscopic metroplasty and subsequent second-look hysteroscopy, and its central message is that the postoperative cavity is far less predictable than the surgical literature implies. Clinically significant residual septa greater than 1 cm were identified in a small but non-negligible proportion of patients (2.6%), while intrauterine adhesions were reported with a strikingly variable incidence, ranging from minimal to substantial (1-35%), falling below 10% in series using anti-adhesion barriers.¹¹

Such heterogeneity is unlikely to be coincidental. Rather, it probably reflects differences in surgical technique, operator experience, extent of septum resection, use of postoperative anti-adhesion strategies, and follow-up protocols adopted across centres.^{11,14} Taken together, these findings point to a crucial but often underappreciated issue: hysteroscopic metroplasty should not be regarded as a single, standardised intervention, nor should its postoperative course be assumed to be uniform.⁷ Within this broader variability, the surgical technique itself represents a key determinant.¹⁶ In particular, a useful conceptual distinction has been drawn between septum section and septum resection. Septum section refers to the division of the septum along the midline with preservation of the surrounding myometrium, whereas septum resection involves actual tissue removal, potentially increasing endometrial trauma and the subsequent

inflammatory response.¹⁷ In this context, it would be of particular interest to explore whether and to what extent second-look hysteroscopic findings differ according to the surgical technique adopted, as this could further clarify the relationship between intraoperative tissue handling, postoperative healing patterns, and the need for follow-up intervention.¹¹ Furthermore, in some cases, small residual septa may represent intentional surgical conservatism aimed at avoiding uterine perforation or excessive myometrial damage, particularly in complete septa or anatomically complex uteri.¹⁸ In others, they may reflect incomplete resection or suboptimal healing.¹⁴

Similarly, the wide range in reported adhesion rates (1-35%) across studies underscores how postoperative healing can differ substantially depending on tissue handling, energy source, and preventive measures.^{11,19} Indeed, the use of adhesion-prevention strategies, particularly barrier methods, may reduce the incidence of clinically relevant pathology and, in selected cases, obviate the need for routine second-look hysteroscopy.^{19,20}

When Looking Becomes Treating

Beyond diagnosis, the real value of second-look hysteroscopy lies in its therapeutic potential. Unlike imaging-based follow-up, hysteroscopy allows immediate intervention.²¹ The opportunity to resect a residual septum or lyse early-stage adhesions during the same procedure may prevent progressive distortion of the uterine cavity and reduce the risk of long-term reproductive impairment.^{12,14} This aspect is particularly relevant for women with a history of infertility, recurrent pregnancy loss, or those planning assisted reproductive treatments, for whom even subtle intrauterine abnormalities may have disproportionate clinical consequences.^{11,12}

A complete septate uterus is the clearest example, and the profile most likely to benefit from second-look hysteroscopy (Figure 1). Indeed, such cases involve a longer septum, a more demanding resection and, especially when barrier methods are not used, a higher risk of postoperative sequelae. At second-look hysteroscopy two findings typically emerge: dense fibrous adhesions, or a residual septum, either of which may remain asymptomatic yet compromise reproductive outcomes if left uncorrected. The decisive advantage is that re-inspection allows them to be treated in the same sitting: looking again becomes, in practice, the act of treating (Figure 2).¹¹

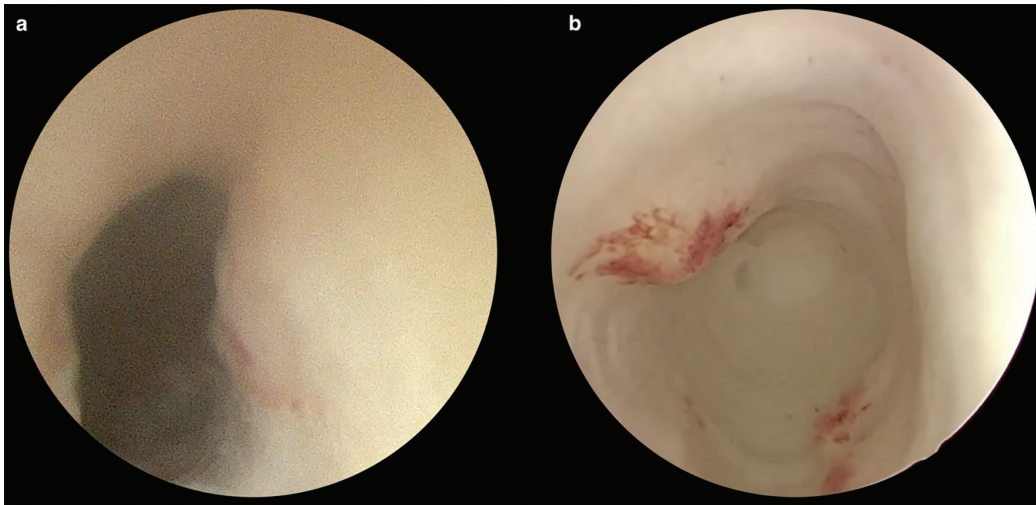


Figure 1. Diagnostic hysteroscopy in a 35-year-old woman with infertility and recurrent pregnancy loss, in whom a complete septate uterus is confirmed (U2bC1V0, according to the ESHRE–ESGE Classification System). (a) Hysteroscopic navigation of the right hemicervix. (b) Hysteroscopic navigation of the right uterine hemicavity showing the right tubal ostium.

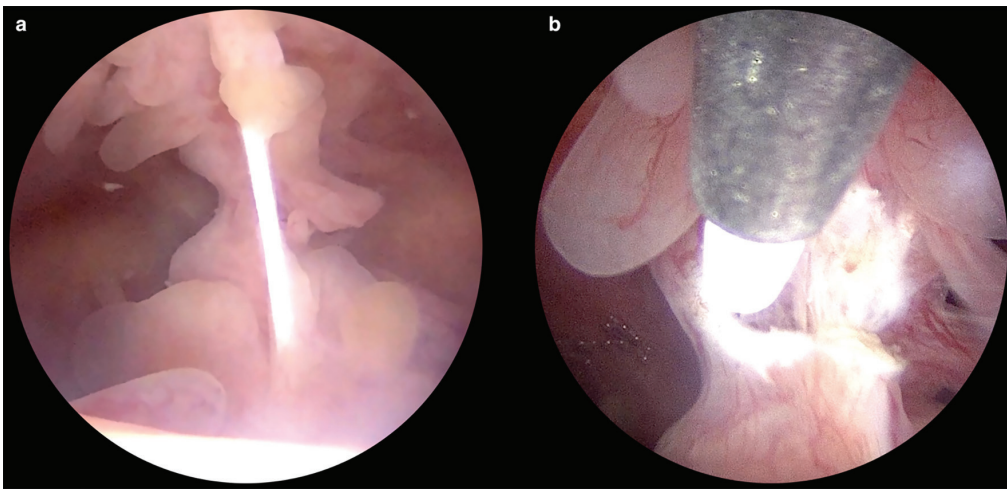


Figure 2. Second-look outpatient hysteroscopy performed 8 weeks after metroplasty (the same patient as in Figure 1). (a) Dense fibrous adhesions bridging the anterior and posterior uterine walls. (b) Careful adhesiolysis under direct vision with a 5-Fr bipolar electrode.

Should it Be Routine? The Case for Selective, Risk-Stratified Use

The question then arises: should second-look hysteroscopy become routine after hysteroscopic septum resection? On the basis of the current evidence, no unequivocal conclusion can be drawn.^{11,12,21} Instead, it could be useful a selective and individualised approach, tailored to patient characteristics and intraoperative findings.²² In our view the clinical challenge lies not only in establishing whether second-look hysteroscopy has value, but in identifying which patients are at high risk and most likely to derive meaningful benefit, and when.¹² Patients with complete septa, technically challenging resections, absence of anti-adhesion measures, or a poor reproductive history appear to be those most likely to

benefit from systematic postoperative evaluation.¹⁴ In these cases, outpatient hysteroscopy represents a low-risk, well-tolerated procedure that combines diagnostic precision with immediate therapeutic capability.¹¹

In this context, adjunctive strategies may further refine patient selection and reduce unnecessary invasive procedures.²³ Among these, non-invasive imaging modalities, particularly three-dimensional sonohysterography (3D-SIS), have demonstrated high diagnostic concordance with hysteroscopy in the postoperative assessment of the uterine cavity.^{16,24} In the studies by Saygili-Yilmaz et al.²⁵ and Casadio et al.,¹⁶ second-look hysteroscopy was not routinely performed in all patients but was instead reserved for selected cases based on abnormal findings at hysterosalpingography or

3D-SIS, respectively. Notably, 3D-SIS has shown diagnostic accuracy, sensitivity, and specificity comparable to hysteroscopy, while being less invasive, better tolerated, and more cost-effective.^{16,25} From this perspective, imaging-based triage may represent a pragmatic strategy to identify among “low-risk” patients, who could benefit from a second-look hysteroscopy (while sparing low-risk women who are unlikely to benefit from an unnecessary procedure) improving cost-effectiveness and patient comfort without compromising diagnostic reliability.²⁶ Overall, these findings highlight the need for a validated diagnostic pathway aimed at tailoring second-look hysteroscopy to individual patient risk profiles.^{16,25}

Once the right candidates have been identified, one objection still remains: cost. Indeed, a further objection often raised against routine second-look hysteroscopy is its cost-effectiveness. This concern, however, has become less compelling now that the examination can be carried out in an outpatient setting without anaesthesia. In this form it requires no operating-theatre time and no further hospital admission, so the additional cost to the patient and to the health system is small.²⁷ The issue, therefore, is not whether the procedure is affordable, but for whom it is worth performing: if it is offered to every woman regardless of risk, the cumulative cost rises without a corresponding clinical gain, whereas if it is reserved for those in whom an abnormality is likely to be found, the same procedure becomes both clinically useful and economically reasonable.²⁷

The Timing of the Second-Look Hysteroscopy

Timing remains another unresolved and clinically relevant issue, as it directly influences both the detection and management of postoperative intrauterine adhesions and the identification of residual septal tissue.^{11,12,28} Most published series adopt an interval from 4 to 20 weeks.^{11,12} Early second-look hysteroscopy may facilitate the management of filmy, newly formed adhesions that are easier to treat and less likely to recur. Proponents of this approach argue that early intervention may interrupt the cascade leading to more fibrotic and clinically significant adhesions.¹² On the other hand, later evaluations may better capture mature abnormalities with clearer anatomical and clinical implications, potentially avoiding overtreatment of transient or clinically insignificant findings.^{11,21} At present, no single time point can be universally recommended, reinforcing the importance of individualised decision-making.¹¹

Both extremes therefore prove unsatisfactory and since the literature defines no optimal interval, the balance of these opposing risks makes an intermediate window advisable. On this basis, assessment at around 6 to 8 weeks appears the most reasonable compromise, late enough for transient findings to resolve, yet early enough to lyse adhesions while they remain filmy and amenable.³

A Fertility-oriented Perspective

To our mind, the most important insight concerns the potential relevance of second-look hysteroscopy from a reproductive medicine perspective.¹¹ Infertility represents the clinical context in which hysteroscopy has progressively assumed a pivotal role, owing to its unique ability to directly assess and treat intrauterine factors that may impair implantation.^{29,30} While the impact of hysteroscopic metroplasty on fertility outcomes has been extensively investigated over the years with conflicting and often controversial results,⁵⁻⁷ virtually no studies have specifically addressed the contribution of second-look hysteroscopy to reproductive outcomes after septum resection.¹¹

Crucially, most studies of fertility outcomes after metroplasty never reassessed the postoperative cavity, so residual septa or early adhesions may have persisted uncorrected in an unknown proportion of women; part of the conflicting fertility results may thus reflect this undocumented variability in the surgical result, not only patient selection and technique. Conversely, the few studies addressing the second look directly are largely retrospective, rarely randomised, and not designed to isolate its reproductive impact, so any benefit is inferred rather than demonstrated. This constitutes a source of bias, not merely a missing endpoint, resolvable only by prospective studies designed to test the reproductive role of the second look directly.^{11,19}

In this regard, the systematic review by Vitale provides the first comprehensive overview of reproductive outcomes in women undergoing postoperative hysteroscopic assessment. Among the 637 women actively attempting to conceive, a pregnancy rate of 66.2% was reported, with a live birth rate of 56.2% and a pregnancy loss rate of 9.6%.¹¹ These figures are uncontrolled and cannot establish causation, but they point to a plausible, testable hypothesis: that detecting and correcting residual septa or early adhesions (which would otherwise pass unnoticed) may contribute to better reproductive outcomes.^{11,12}

Conclusion

Second-look hysteroscopy should be neither routine nor abandoned, but targeted. We reserve it for the women who stand to gain most (those with a complete septum, a technically demanding or incomplete resection, no anti-adhesion prophylaxis, or an adverse reproductive history) and triage the rest with 3D-SIS, proceeding to hysteroscopy only when imaging is abnormal. We schedule it at around 6 to 8 weeks, early enough to lyse filmy adhesions yet late enough to avoid chasing findings that would resolve on their own, and perform it in the outpatient setting so that any residual septum or adhesion is corrected in the same sitting.

In the absence of well-designed prospective trials capable of clearly defining indications, optimal timing, and the true impact of second-look hysteroscopy on reproductive outcomes, clinical practice remains guided more by experience than by evidence. Until such data become available, the challenge is not merely deciding whether to perform a second-look hysteroscopy, but determining how to generate the evidence needed to guide clinicians toward a shared and reproducible direction in patient care.

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Proposals for the #Enzian addendum and update: an international expert survey for item generation

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ABSTRACT

Background: Accurate and standardised characterisation of endometriosis extent is essential for patient counselling regarding pain and fertility outcomes, surgical planning, multidisciplinary communication, and clinical research. The Enzian classification has been applied in Central Europe for over two decades, while the updated #Enzian classification, published in 2021, has subsequently gained broader international acceptance.

Objectives: To evaluate international expert perspectives and generate potential items informing updates to selected compartments of the #Enzian classification.

Methods: Twenty-six internationally recognised experts in endometriosis surgery, imaging, and reproductive medicine were invited to participate in a structured survey. The electronic questionnaire comprised 29 single-choice and open-ended items addressing five #Enzian compartments: T (tuboovarian condition), B (sacrouterine ligaments, cardinal ligaments, pelvic sidewall), C (rectum), FB (bladder), and FA (adenomyosis). Responses were collected anonymously, analysed descriptively, and thematically grouped. Consensus thresholds followed established criteria.

Main Outcome Measures: Expert perspectives regarding the need for revision of selected #Enzian compartments and proposed modifications.

Results: Twenty-three experts responded (88.5%). Strong agreement for revision was observed for compartments B, C, and FB (>80%). Moderate agreement (>60%) supported updates to compartments T and FA. Specific suggested refinements included adding the suffix d within compartment T to reflect tubal dilatation (73.9% in favour) and the suffix P within compartment B to denote pelvic sidewall/parametrial involvement (78.3% in favour). For colorectal disease (compartment C), respondents supported reporting lesion–anal verge distance and multifocality. A graded FA1–FA3 system for adenomyosis was favoured (73.9%). Opinions regarding descriptors of bladder endometriosis were heterogeneous.

Conclusions: Experts identified clear priorities for refining the #Enzian classification, particularly regarding parametrial involvement, colorectal deep endometriosis and adenomyosis extent. These findings could provide a structured framework to inform subsequent Delphi consensus rounds.

What is New? The study identifies international expert-agreed priorities for refinement of selected #Enzian classification compartments.

Keywords: Adenomyosis, colorectal, Delphi consensus, endometriosis, fertility, reproductive medicine

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Introduction

Endometriosis is a chronic, oestrogen-dependent condition characterised by heterogeneous phenotypes, including superficial peritoneal implants, ovarian endometrioma, deep endometriosis (DE) affecting various anatomical locations and adenomyosis.¹ Accurate and standardised description of disease extent is essential for patient counselling regarding pain and fertility outcomes, surgical planning, multidisciplinary communication and clinical research. Traditional staging systems, including the revised American Society for Reproductive Medicine (ASRM) score, have limited ability to describe deep and extragenital disease in anatomical detail, while the American Association of Gynaecological Laparoscopists (AAGL) score reflects surgical complexity rather than providing comprehensive non-invasive anatomical mapping system.²⁻⁴ These limitations prompted the development of anatomically oriented classification systems, including the Enzian classification, used in central European countries over two decades and accepted worldwide since its updated #Enzian version published in 2021.⁵

The #Enzian classification was designed as a comprehensive non-invasive and surgical description system encompassing peritoneal, ovarian, deep and extragenital endometriosis as well as selected adhesions, structured by anatomical compartments, it can be applied using transvaginal ultrasound (TVS), magnetic resonance imaging (MRI), surgical assessment, thereby bridging pre-operative evaluation and intra-operative findings. Several studies have demonstrated high accuracy of the classification when combined with TVS⁶⁻⁸ whose use is supported by a recent consensus statement on imaging and classification of DE.⁹ Diagnostic accuracy and inter-observer agreement for ultrasound¹⁰ and MRI-based #Enzian have been reported as promising, particularly for selected compartments.¹¹

Despite these advances, several limitations of the current #Enzian system have been highlighted. Narrative reviews and comparative studies underline its complexity,¹² variable performance of specific compartments,⁹ and limited descriptors for certain clinically relevant features, such as correlation with pain,^{13,14} fertility outcomes, distal tubal pathology, and parametrial and pelvic sidewall involvement. The absence of standardised non-invasive infertility assessment frameworks underscores the need for more comprehensive, reproducible tools such as #Enzian to bridge this critical diagnostic deficit. Recent

proposals to convert #Enzian into a four-stage system further illustrate the current drive toward harmonisation with other classification schemes.¹⁵

Artificial intelligence (AI) applications in MRI and ultrasound rely heavily on detailed anatomical inputs, with deep learning models achieving substantial improvements in lesion detection and segmentation. Comprehensive and granular datasets may become increasingly relevant for effective AI integration in endometriosis imaging.¹⁶ Against this background, we conducted an international survey among experts in endometriosis surgery, imaging and medically assisted reproduction to evaluate the perceived need for targeted refinement of selected #Enzian compartments and to identify priorities for a future revision of the classification.

Methods

This study represents a preliminary, item-generating international expert survey designed to inform subsequent Delphi rounds evaluating potential updates to the #Enzian classification. The survey was created to explore expert views on the established current version of the #Enzian classification of endometriosis.⁵ Twenty-six experts were purposively selected based on academic contribution and recognised clinical expertise in endometriosis, imaging and fertility. The original #Enzian development team was included to preserve continuity. Invitations were distributed by e-mail, and participation was voluntary and anonymous, with no personal identifiers. A structured electronic questionnaire comprising 29 items (single-choice and open-ended) was developed. The instrument targeted five compartments of the #Enzian system, as agreed during the initial in-person core expert group meeting in May 2025: B (sacrouterine ligaments, cardinal ligaments, pelvic sidewall)-questions 1-6; T (tuboovarian condition)-questions 7-12; C (bowel)-questions 13-19; FB (bladder)-questions 20-24 and FA (adenomyosis)-questions 25-29.

All questions addressed both, the perceived need for revision and agreement with proposed modifications (e.g., suffixes, numeric indices, anatomical distances). The questionnaire was distributed electronically using the blind carbon copy function. A 30-day response window was provided, with an estimated completion time of five minutes. The questionnaire is available on <https://www.surveymonkey.com/r/V7QCTRV>.

Quantitative (single choice) responses were tabulated and analysed descriptively. Free-text answers were

standardised and thematically grouped. Consensus thresholds were applied in line with previously published works⁹ as follows: experts provided binary responses (agree/disagree); grades of agreement were defined as strong agreement (more than 80% agree), moderate agreement (more than 60% agree), equipoise (40%-60% agree), or disagreement (less than 40% agree). The summary of this survey and their levels of agreement are presented in this work. The study fulfilled criteria for minimal-risk survey research, and although formal ethical approval was not required, compliance with local survey research standards was ensured.

Results

Of 26 invited experts, 23 completed the survey with a response rate of 88.5%. Respondents represented geographically diverse regions: Australia (1), Austria (2), Belgium (1), Brazil (1), Canada (1), France (1), Germany (5), Hungary (2), Italy (6), Poland (1), Portugal (1), Switzerland (2), and the United Kingdom (2).

Most experts endorsed revising the #Enzian classification according to the following compartments: T (tubo-ovarian condition), B (sacrouterine ligaments, cardinal ligaments, pelvic sidewall), C (rectum), FB (bladder) and FA (adenomyosis) (Table 1). Strong agreement (>80%) was achieved for revising topics concerning compartments (81.6%), C (82.6%), and FB (82.6%). Moderate agreement (>60%) was reached for compartments T and FA (73.9% each).

Participants reached moderate agreement that the current description of compartment T does not provide sufficient information regarding the presence or absence of tubal dilatation, a feature that may suggest impaired tubal function. Within this exploratory item, 73.9% supported adding the suffix d to better describe this possible pathology within compartment T. The proposed suffix was not intended to grade the severity of dilatation or to define management decisions, but rather to

improve structured documentation of potentially fertility-relevant pathology. Opinions diverged on a further subclassification describing tubal content (hydrosalpinx vs. hematosalpinx) with only 21.7% supporting its inclusion, whereas 56.5% considered it an unnecessary level of detail and a further 21.7% did not support the item on the basis on their prior response (disagreement with suggested suffix d addition), indicating an overall lack of agreement.

There was moderate agreement (78.3%) to support the addition of a suffix p within compartment B to denote pelvic sidewall and/or lateral parametrial involvement. In this exploratory survey, lateral parametrial involvement was used to describe disease extending laterally towards the pelvic sidewall, including clinically relevant proximity to or involvement of ureteric or nerve structures. Experts emphasised the surgical relevance of the lateral disease extension, with 78.3% reporting that such involvement always (47.8%) or often (30.4%) influences their operative strategy, and a further 21.8% indicating that it occasionally does so.

Regarding the compartment C (rectum), moderate agreement was reached for documenting distance from the anal verge to the lowermost rectal DE lesion (73.9%) and necessity to record the number of rectal nodules (78.3%), in addition to existing lesion size descriptors used. Respondents also noted that these variables better support surgical planning, particularly for the low rectal lesions: 69.6% survey participants reported lesion proximity to the anal verge as being a frequent determinant in operative decision-making, and 65.2% supported the suffix "L" use within compartment C for lesions <5 cm from the anal verge.

Experts reached moderate agreement (73.9%) regarding exploration of a graded FA1–FA3 system to better characterise according to the estimated proportion myometrial involvement. This proposal should be interpreted as an item for further evaluation rather than

Table 1. Consensus rates for revising the #Enzian classification according to respective compartments.

Compartment	Percent in favour	Level of agreement
B (Parametrium)	81.6%	Strong agreement
C (Bowel)	82.6%	Strong agreement
FB (Bladder)	82.6%	Strong agreement
T (Fallopian tubes)	73.9%	Moderate agreement
FA (Adenomyosis)	73.9%	Moderate agreement
Thresholds: >80% agreed: strong agreement, 60-80% agreed: moderate agreement, 40%-60% agreed: equipoise, <40% agreed: disagreement.		

a validated quantitative grading system. Although strong agreement (82.6%) was observed regarding the need for revising FB descriptors for bladder endometriosis, no single descriptor achieved agreement: 34.8% favoured maximum lesion diameter, 34.8% supported recording the distance between the lesion and the ureteral orifice irrespective of lesion size, 13.0% were uncertain, and 17.4% proposed alternative approaches in free-text comments, including ureteral involvement or trigonal extension descriptions.

Thematic analysis of free-text responses identified several recurring suggestions, summarised in Table 2. Key issues included the need for a more detailed description of compartment B, clinically relevant descriptors of possible tubal pathology within compartment T, inclusion of lesion-to-anal-verge distance and multifocality for colorectal disease within compartment C, and clearer differentiation between focal and diffuse adenomyosis in alignment with MUSA criteria.¹⁷ Views and opinions on bladder endometriosis (FB) classification remained heterogeneous, with many experts preferring simplicity and descriptive annotations rather than additional coding.

Discussion

Main findings

The present work reports the results of an international expert survey conducted as a preliminary item generation step to inform future Delphi-based refinement of the current #Enzian classification. The findings suggest that several clinically relevant anatomical features may currently be insufficiently represented, particularly within compartments B, C and FB. This likely reflects increasing recognition of the importance of parametrial extension, colorectal multifocality, and bladder-related descriptors in contemporary endometriosis imaging and surgical

practice. Nevertheless, variability regarding the preferred implementation of these descriptors highlights the complexity of balancing anatomical details with practical usability within an integrated classification system. Expert support for including lesion-to-anal-verge distance and multifocality in colorectal DE further suggests that lesion size descriptors alone may not adequately reflect the complexity and surgical relevance of rectosigmoid disease. This may be particularly relevant since the surgical literature shows that these variables indeed correlate with operative complexity, choice of technique, and postoperative morbidity.^{18,19} Furthermore, these descriptors may support not only operative planning but also patient counselling and informed consent, particularly in cases of low rectal disease where surgical morbidity may substantially differ. Recent prospective data have additionally demonstrated promising diagnostic accuracy of structured ultrasound assessment for rectosigmoid DE using the IDEA protocol and #Enzian classification framework, supporting the feasibility of more anatomically detailed preoperative reporting.²⁰

The strong interest in refining parametrial and pelvic sidewall descriptors also reflects increasing awareness of the importance of these anatomical regions in both imaging and surgical management of DE. Recently published methodological consensus papers have further standardised ultrasound assessment of the pelvic sidewall and parametrium, potentially facilitating broader implementation and reproducibility of these evaluations in clinical practice.^{21,22}

Moderate agreement regarding modifications to the compartment T reflects growing recognition of the importance of documenting tubal pathology, including tubal dilatation, which may impact reproductive outcomes. The proposed suffix d was intended as an exploratory

Table 2. Thematic synthesis of open-ended responses across compartments.		
Compartment	Key themes	Illustrative comments (paraphrased)
T (Fallopian tubes)	Tubal dilatation; patency and adhesion quality	"Hydrosalpinx vs hematosalpinx distinction is not necessary."
B (Parametrium)	Need for lateral clarity; suffix p; ureter/nerve involvement	"Add suffix p for lateral sidewall involvement."
C (Bowel)	Distance from anal verge; multifocality; number of nodules	"Record in cm and add 'mf' for multifocality."
FB (Bladder)	Heterogeneous views; importance of trigone/ureter proximity; prefer simplicity	"Describe trigonal involvement narratively."
FA (Adenomyosis)	Distinguish focal vs diffuse; consider % myometrial involvement	"Add suffix 'f' or 'd' for focal/diffuse."

descriptor to better integrate documentation of fertility-relevant parameters into the #Enzian classification rather than to directly determine management strategies. Importantly, no agreement was achieved regarding subclassification of hydrosalpinx vs. hematosalpinx, suggesting that experts favoured simplified descriptors at this preliminary stage. Although not formally evaluated within this survey, additional imaging markers such as “kissing ovaries” may also warrant consideration within subsequent Delphi rounds due to their recognised association with posterior compartment disease.²³ Proposed refinements to compartment FB underscore the heterogeneity of bladder endometriosis and the absence of universally accepted descriptors reflecting lesion complexity and surgical relevance. However, no clear agreement emerged regarding whether lesion size and/or proximity to the ureteral orifice should be prioritised within future #Enzian classification descriptors. Interest in exploring a graded FA1–FA3 scheme for adenomyosis may reflect increasing recognition of the need for more structured adenomyosis phenotyping within endometriosis classification systems. Importantly, this proposal should not be interpreted as a validated quantitative grading system, as objective volumetric assessment of adenomyosis remains challenging in both imaging and surgical practice. Furthermore, differentiation between focal and diffuse adenomyosis based on direct and indirect MUSA criteria remains complex and requires further validation for their extent within the classification.

Persistent challenges regarding symptom-disease correlation in endometriosis²⁴ further support the need for more structured and anatomically detailed classification systems. Limited standardised phenotyping may reduce the ability to analyse symptom patterns, reproductive outcomes and disease severity prospectively. However, recent prospective imaging research, particularly the work of Exacoustos and colleagues, demonstrates that when standardised and anatomically detailed descriptors are applied, such as RADAR graphical mapping in conjunction with the #Enzian classification, clinically meaningful correlations with symptoms may indeed be achieved.¹⁰ These findings highlight the need for consistent, prospective data acquisition across all clinical pathways, including assisted reproductive techniques, as robust symptom–disease analyses fundamentally rely on high diagnostic quality. In parallel, contemporary AI applications increasingly rely on high-quality structured anatomical datasets, further emphasising the

potential future relevance of refined and reproducible classification.¹⁶ Nevertheless, implementation of such approaches remains highly dependent on expert imaging assessment, particularly in TVS, and standardised methodology which remains inconsistently implemented across clinical settings.²⁵

Overall, the thematic convergence observed across expert responses indicates that future alterations of the #Enzian classification should prioritise (i) improved delineation of parametrial and pelvic sidewall disease, (ii) more comprehensive characterisation of colorectal involvement, (iii) standardised descriptors for tubal pathology, and (iv) integration of contemporary sonographic criteria for describing the extent of adenomyosis.

Importantly, the absence of universal agreement across several proposed items likely reflects complexity and heterogeneity of endometriosis, differences in surgical approaches, imaging modality expertise and clinical priorities among international experts. Rather than weakening the findings, this observation reinforces the rationale for a structured Delphi process with aim to refine, prioritise and harmonise expert perspectives into even more widely applicable and acceptable classification system.

Strengths and Limitations

The strength of the present work is that it includes the opinion of twenty-three purposively selected experts, including original #Enzian developers reflecting a high external validity within the expert community. Several limitations should be acknowledged. Only selected #Enzian compartments were evaluated, while other potentially relevant domains (e.g. A, O, and F categories outside FB/FA) were beyond the scope of this preliminary survey. Additionally, binary response formats may oversimplify complex anatomical and clinical considerations, making qualitative free-text responses potentially crucial to contextual interpretation. Finally, only moderate agreement was reached on several topics which can be seen as promising but requires refinement and further consensus testing.

Clinical implications

In summary, this work constitutes a structured item-generation phase designed to inform subsequent Delphi consensus processes and to support the further evolution of the #Enzian classification. The proposed exploratory

items aim to enhance its clinical relevance, surgical utility, and compatibility with contemporary imaging and emerging AI-based applications.

Unanswered questions and future research

At this stage, no definitive classification changes are proposed, and further Delphi rounds are necessary to refine, prioritise, and validate the suggested modifications.

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Data sharing: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Transparency: The authors confirm that this manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted.

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Poor knot security when closing running sutures with three threads

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ABSTRACT

Background: Knot security varies with half-knot and half-hitch sequences, rotation sense, and the type and diameter of sutures.

Objectives: To evaluate the security of knots with three threads, as used for tying off running sutures.

Methods: Three-way randomised experiments, with a factorial design and 10 knots/cell. The first experiment evaluated the knot security of a surgical knot (H2H1sH1s) for single stitches (2 threads) or running sutures (3 threads), using polyglactin 910 or polydioxanone, of 2-0 or 1 diameter. The second experiment evaluated the knot security of a running suture with 4 or 5 half-hitch sequences and 2 or 3 blocking knots, using polyglactin 910 or polydioxanone, and with diameters of 2-0 or 1.

Main Outcome Measures: Knot security in Newton, measured with a digital dynamometer. With increasing forces, the knot either slipped open or blocked, causing the suture to break.

Results: In the first experiment, the knot security of surgical knots was less with monofilament ($P=0.0004$) and running sutures ($P<0.0001$), but not with suture diameter (three-way analysis of variance). Variability in outcome was greater with running sutures, especially with monofilament sutures of larger diameter. The second experiment demonstrated that half-hitch sequences occasionally opened with low forces, especially with larger monofilament sutures.

Conclusions: Compared to knots tied with two threads, knots with three threads have a lower and more variable knot security, especially with larger monofilament sutures.

What is New? Knots with 3 threads should be avoided, as they may occasionally open with forces below 30 or 10 Newton.

Keywords: Polyglactin, rotation, sutures, knot security, running suture

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Introduction

In surgery, the choice of sutures and knots is based on tradition, experience, and knowledge. In the absence of documented forces required to keep tissues approximated, the choice of suture diameter and type is a clinical decision based on the estimated forces needed, the suture's tensile strength and resorption time, and surgical handling factors such as gliding. The choice of knots is guided by the estimated forces needed and knowledge of knot security. Knot security is the force (Newton) at which the knot either slides open or blocks, breaking the suture, and is measured with a dynamometer using progressively increasing forces.¹⁻⁵ Unfortunately, the forces required to maintain tissue approximation are poorly understood in gynaecological and abdominal surgery. Clinically, it is logical to postulate that these forces will vary between tissues and that the forces exerted on the abdominal fascia and on the promontory after sacrocolpopexy, especially during coughing, must be higher than after a bowel or vaginal cuff suturing. Instead of indicating the exact knot security in Newton, knots opening with forces <10, <30, and >30 Newtons were called clinically dangerous, insecure, and secure, respectively.^{6,7}

Knot security in surgery increases with the tensile strength of the suture, correct and more sequences of half-knots (H) or half-hitches (S), more throws, correct rotation and stronger tying forces. Knot security is less with easily gliding monofilament sutures. Less understood is the occasional and poorly predictable reorganisation of knots during traction, resulting in a variable knot security, with occasionally dangerous knots opening with forces of a few Newtons.⁶⁻⁹

Knot security is reproducible and increases with the tensile strength of the suture, and with alternating the rotation of the same active end when making successive half-knots or half-hitches.⁶⁻⁹ A similar rotation of 2 one-throw half-knots is known as a granny knot, and opposite rotation results in a flat square knot. The same holds for half-hitch sequences.⁹ Sliding half-hitch (SS) sequences made with opposite rotation remain in one plane and squeeze the passive end symmetrically and more firmly. The surgeon should realise that for blocking half hitches, a similar rotation should be used, since inverting the active and passive ends has the same effect as changing the sense of rotation. Therefore, changing the active and passive ends, as done with bimanual suturing, also has the same

effect as changing the sense of rotation. Knot security increases with the number of throws. With polyfilament sutures, secure knots (>30N) require 4 or 5 throws,⁷ such as a 4-throw surgical knot (H2H1sH1s) or a two- or three-throw half-knot, followed by a two-throw half-knot (H3H2 or H2H2). Surprisingly, for H2H2 and H3H2 knots, rotation only marginally affects knot security, with similar rotation even being slightly better.^{6,7} Secure half-hitch sequences require 5 or 6 throws, two SSs formed by alternate rotation, followed by two to four blocking half-hitches made by similar rotation.

Knot security is lower and more variable with easily gliding monofilament sutures, especially with larger diameters, which have less friction in the tissue and the knot. With monofilament sutures, knot security is low for most half-knot combinations, which should be avoided and replaced by six half hitches with four blocking knots.⁸

Less understood is that the security of individual knots can be variable and difficult to predict because of the occasional three dimensional (3D) reorganisation of the knot during traction. This reorganisation is more likely to happen when tying forces are low, with monofilament sutures and when half knots are destabilised by inadvertent traction on one suture end. For example, the asymmetric traction at one end of a flat square knot (H1H1s) risks transforming it into SSs, opening under forces of a few Newtons. This risk of inadvertent destabilisation increases when the surgeon is less experienced, the suture ends are short, or knot tying is more difficult because it is deeper or less accessible. The mechanism of reorganisation is a poorly understood random effect, and the mechanism is challenging to study, since 40 knots are needed to detect 5% less secure knots.^{6,7} This 3D reorganisation explains that knot security can be unexpectedly and unpredictably low, resulting occasionally in knots opening with forces of a few Newtons.⁶

Knots used to finish a running suture contain three threads instead of two when tying single stitches (Figure 1). Surprisingly, knot security of knots made with 3 threads has not been investigated. Realising the lower and more variable knot security with monofilament sutures, and the recommendation to use 6 half-hitch sequences for monofilament sutures, we evaluated knot security with 3 threads, as used when ending a running suture.

Methods

Terminology and Testing of Knots

Terminology and testing of knots were described in detail previously.^{6-8,10} Knots are defined by their type, an "H" for half-knots or "S" for half-hitches, followed by the number of throws and the rotation of the active end in comparison with the previous knot ("s" for symmetric knots in one plane resulting from alternate rotation and "a" for asymmetric knots after similar rotation). For half-hitches, it is necessary to indicate whether the knot is sliding "s" or blocking "b". For half-hitches, the number of throws and the "s" of sliding are omitted as they are always one, and to avoid confusion with the s of symmetric, respectively. For example, H2H1sH1s is a surgical knot with a 2-throw half knot followed by two 1-throw symmetrical half-knots. SSsSabSab means a second symmetrical and SS (made by alternate rotation) followed by two half-hitches, made by similar rotation, becoming asymmetric and blocking after changing active and passive ends.

Knots were made as described¹¹ by tying a suture around a 15-mm plastic tube. To simulate knot tying when ending a running suture, a loop of one of the suture ends (i.e., two threads instead of one) was tied to the other end (Figures 1 and 2). After knot tying, the suture threads were cut to 10 mm, allowing evaluation of any sliding. The loops were mounted on the hooks of a digital dynamometer (Sauter FH 500) and tested at a speed of 200 mm/min. With



Figure 1. Half-knots with two (left) and three (right) threads as used to secure a running suture. The flat square knot with 3 threads is bulky, squeezing the threads less, which explains why they are less stable.

increasing forces, the knot combination either slipped open, or slid before blocking, or blocked, causing the suture to break. The endpoint is thus the force (N) at which the knot slips open or breaks. Testing was done at the Research Educational Centre of Turin University.

Experiments

The experiments were designed to evaluate the knot security of knots made with 3 threads (as used for running sutures) of monofilament sutures, since with 2 threads, the knot security of half-knots was low and poorly predictable, and, therefore, 5 or 6 half-hitches with 3 or 4 blocking sequences were recommended. In a first experiment, the knot security of a surgical knot (H2H1sH1s) was evaluated with a 3-way randomised factorial design with 10 knots/cell comparing a 2- and 3-thread knot, a polyfilament (polyglactin 910 or Vicryl, Ethicon) and a monofilament (polydioxanone or PDS II, Ethicon) suture and 2 diameters of 2-0 or 1. The second experiment similarly evaluated knot security with 3 threads using 4 or 5 half-hitch sequences with 2 or 3 blocking knots, with polyglactin 910 or polydioxanone, and diameters of 2-0 or 1. In these experiments, the double thread was used as the passive thread for the first 2 sliding half hitches. Exploratory experiments had not shown a difference between SSsSabSab knots made between a single or double thread as the passive thread.

The two endpoints of these experiments were the knot security in Newton, and the number of knots sliding open with forces less than 30 Newton, considered insecure, as an indication of reorganisation, poor predictability, and a potential surgical risk.

All knots were made by the same experienced person (AR), under close supervision by MG to detect any mistakes. For each experiment, knots were block-randomised, i.e., for

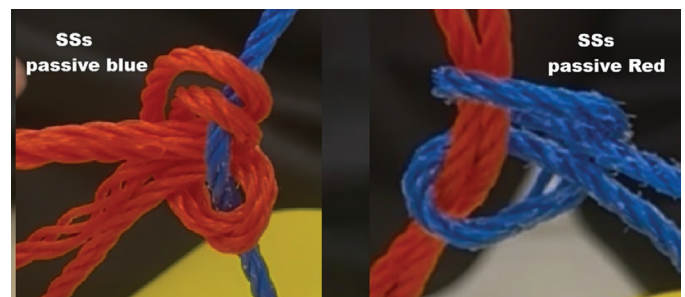


Figure 2. Half-hitch sequences with 3 threads are more bulky. Knot security of 4 and 5 half-hitch sequences with 2 (SSsSabSab) or 3 (SSsSabSabSab) blocking knots was similar whether 2 or 1 thread was used as the passive thread for the first 2 sliding sequences. SS: Sliding half-hitch.

each combination, 1 knot was made before starting the second series.

Institutional Review Board (IRB) approval was not required for *in vitro* experiments that did not involve humans or animals, as previously confirmed in writing by the IRB at Leuven University.^{6,8,9}

Statistical Analysis

Statistical analysis was performed using SAS,¹² and means and standard deviation are reported unless otherwise indicated. The first experiment compared a surgical knot with 2 or 3 threads, two diameters, and two types of sutures. The second experiment compared 4 or 5 half-hitches, two diameters, and two types of sutures. Analysis was performed using a 3-way analysis of variance (PROC GLM) rather than logistic regression, since the endpoint (Newton of opening or breaking) is a continuous variable. A 3-way factorial design with 10 knots/cell was chosen because it yields statistical power of 80 knots per variable, which is similar to performing 3 separate 80-knot trials for each variable. The 3-way factorial design, in addition, permits the evaluation of an eventual interaction between the variables.¹³

Results

In the first experiment (Figure 3), a 3-way analysis of variance showed that the knot security of a surgical knot (H2H1sH1s) was less with running sutures ($P<0.0001$) and with monofilament sutures ($P=0.0004$) but not with suture

diameters. The results confirmed that, with polyfilament sutures, all surgical knots (H2H1sH1s) were secure, except one knot with 4 threads and a larger suture diameter, which slid open, although still secure at $>50\text{N}$. With monofilament sutures, knot security was more variable, and with 2-thread knots, 0/10 and 6/10, and with 3-thread knots, 1/10 and 7/10 of the 2.0 and 1-diameter sutures, slid open, with two 4-thread knots opening at $<30\text{N}$.

A 3-way analysis of variance of the second experiment (Figure 4) confirmed that knot security was less for 4-thread knots ($P<0.0001$), with monofilament sutures ($P<0.0001$), and with 4 half-hitches ($P<0.0001$). This experiment also confirmed that with monofilament sutures, 5 half-hitches with 3 blocking sequences resulted in 100% secure knots, whereas 4 half-hitches with 2 blocking sequences slid open in 6/10 and 7/10 of the 2.0 and 1-diameter sutures. More impressive was the number of sutures opening a less than 30N : with polyfilament sutures in 5/20 of the 4 half hitches knots, but with monofilament sutures in 10/20 and 4/20 of the 4 and 5 half hitches, respectively.

Discussion

Main Findings

These experiments demonstrate that the knot security is less for 3-thread knots than for 2-thread knots. With polyfilament sutures, surgical knots (H2H1sH1s) and 5 half-hitch knots with 3 blocking sequences (SssSabSabSab) are safe. The occasional (10%) 4-hitch sequence sliding

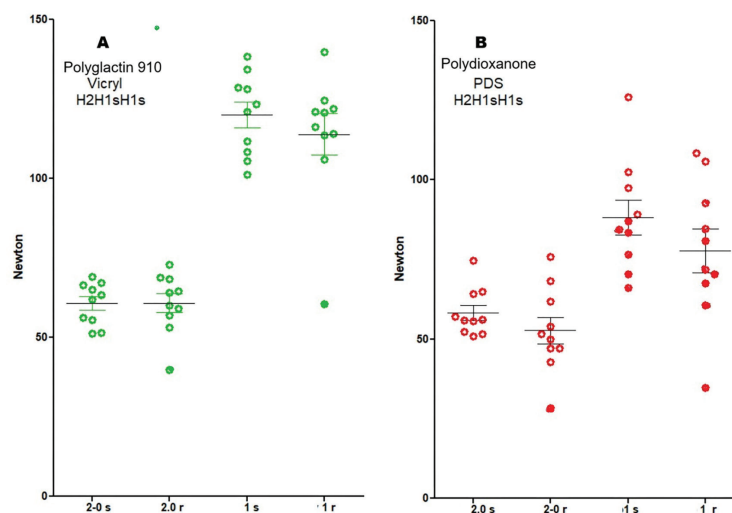


Figure 3. Knot security of a surgical knot (H2H1sH1s) using a polyfilament (polyglactin 910, green) or monofilament (polydioxanone, red) suture, diameter 2.0 or 1 when tied with two threads (s for single stitch) or three threads (r for running suture), as used in single stitches or running sutures, respectively. Open circles indicate knots that break, and filled circles indicate knots that slide open. Mean and SEM are shown. SEM: Standard error of the mean, PDS: Polydioxanone suture.

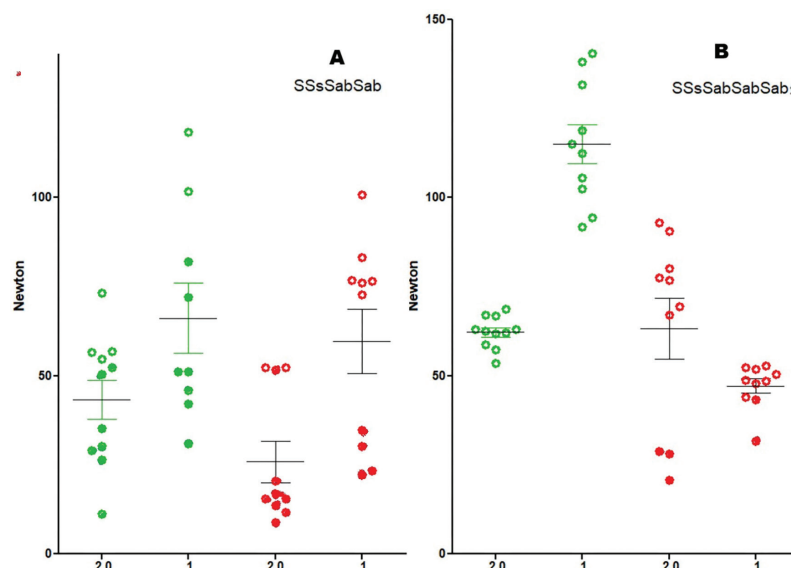


Figure 4. Knot security of polyglactin 910 (green) and polydioxanone (red) with a diameter of 2-0 or 1, to secure a running suture with 3 threads, using 4 or 5 Half-hitches, SSsSabSab or SSsSabSabSab, vicryl (green) or Polydioxanone (red) with diameters 2-0 or 1. Open circles indicate knots that break, and filled circles indicate knots that slide open. Mean and SEM are shown. SEM: Standard error of the mean.

open at a force >30N is probably not clinically significant. However, with monofilament sutures, knot security is lower and more variable, and many slide open,⁸ with some 10% at forces below 30N or 10N. Also, with 5 half-hitch knots and 3 blocking sequences, knot security with 3 threads can be poor and 4/20 knots opened at less than 30N.

Strengths and Limitations

The lower knot security with 3 threads in comparison with 2 threads is statistically solid ($P < 0.0001$ and a power of $N=80$), and not surprising, given the more bulky nature of these knots, squeezing less the opposing threads (Figure 2). However, these data do not permit understanding why only some knots are less secure.

Strengths and Limitations Compared to Other Studies

These data extend and confirm previous observations on knot security with 2 threads. Knot security is inherently variable, with knots occasionally opening with little force. The risk is lower with polyfilament than with monofilament sutures, and the variability emphasises the importance of making knots with correct sequences, rotation, and tying forces, avoiding destabilising knots and risking reorganisation.

Clinical and Policy Implications

The surgeon should realise that these *in vitro* studies showing lower knot security with 3 threads underestimate

the clinical risk, since they reflect knots performed by dedicated experts under visual control of the accuracy of sequences and rotation. During surgery, the risk of minor mistakes is higher, and knots risk being tied with insufficient force, incorrect rotation, and half knots risk destabilisation by inadvertently pulling one end, which occurs more frequently when less experienced surgeons tie knots with short sutures.

The clinical implications of the lower knot security of 3-thread knots are unclear and challenging to investigate. Since knots opening at low forces are rather rare, clinical series will be prohibitively large. In addition, the *in vivo* forces acting on the knots are poorly known. Therefore, clinical implications are speculative today. However, recognising the risk of knots opening unexpectedly with low forces, suggests that some rare complications of running sutures, such as vaginal dehiscence after hysterectomy or problems after vertical fascia closure, could be a consequence of insecure knots. It could be speculated that asymmetric niches following a C-section closed with running sutures might result from (monofilament) 3 thread knots sliding or opening with little forces.¹⁴⁻¹⁶

Unanswered Questions and Future Research

The clinical consequences of variable and unpredictably low knot security after closing a running suture with 3 threads remain to be demonstrated. However, when

closing monofilament running sutures, it might be wise to avoid the risk by adding another single stitch and tying a knot with 2 threads between the end of the running suture and the passive end of the single stitch made with half hitches.

Conclusion

To end a running suture such as a C-section or the fascia of a vertical abdominal incision, the risk of a low-knot security should be considered, especially when using monofilament sutures. It is suggested to avoid half-knot sequences and to use another stitch and tie the end of the additional stitch to the end of the running suture.

Understanding knot security will help the surgeon avoid small mistakes that cumulatively affect it. Examples are tying knots with short ends with the risk of destabilising half-knots, failing to respect rotation, being in a hurry and tying knots with insufficient force for a short time, or using half-knots for monofilament sutures. In surgery, the devil is in the sum of many details, and understanding helps to prevent mistakes.

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Informed consent: Not applicable.

Data sharing: All data will be available upon simple request.

Transparency: The manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and all discrepancies from the study as planned have been explained.

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Safety and efficacy of laparoscopic cornuotomy in the surgical management of complete interstitial ectopic pregnancy

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ABSTRACT

Background: Laparoscopic cornuotomy is a relatively novel surgical approach to manage interstitial ectopic pregnancy (IEP) and there is little information regarding its safety and efficacy.

Objectives: To describe the success, complications and long-term outcomes of women undergoing laparoscopic cornuotomy for IEP.

Methods: Retrospective observational study carried out in a tertiary early pregnancy unit from June 2009 to April 2024.

Main Outcome Measures: The main outcome measure was a complete resolution of the IEP without the need for any additional medical or surgical treatment.

Results: There were 102 cases of complete IEP, of which 71 were managed surgically. The majority of operations were performed laparoscopically (70/71), including 62/70 who underwent a laparoscopic cornuotomy, and 8/70 who underwent an Endoloop-assisted salpingectomy. The remaining patient underwent a planned open procedure. A total of 60/62 [97%, 95% confidence interval (CI), 92-100] laparoscopic cornuotomies were successful, whilst the remaining two patients required further intervention for persistent trophoblast. The median total estimated blood loss for patients undergoing laparoscopic cornuotomy was 50 mLs (interquartile range: 50-150). There were 2/62 (3%, 95% CI, 0-8) intraoperative and 3/62 (5%, 95% CI, 0-10) postoperative complications. Twenty-seven patients (27/62, 44%) subsequently conceived, resulting in a total of 52 pregnancies. There were 25 pregnancies resulting in live birth, 13 of which were vaginal with no cases of uterine rupture.

Conclusions: Laparoscopic cornuotomy is an effective treatment for complete IEP with only a small proportion of patients requiring interventions for retained pregnancy tissue.

What is New? This is the largest study of laparoscopic cornuotomy so far which showed that the procedure is effective with a low-risk of future pregnancy complications.

Keywords: Pregnancy, interstitial, ectopic pregnancy, laparoscopy, intraoperative complications

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Introduction

Interstitial ectopic pregnancies (IEPs) occur when a pregnancy implants in the interstitial portion of the Fallopian tube, defined as the tubal segment traversing the myometrium.¹⁻³ The increased vascularity of the surrounding myometrium, relative to that of the Fallopian tube, increases the risk of rapid blood loss if rupture occurs.^{3,4} These features likely account for the increased mortality rate of IEPs compared to ectopic pregnancies implanted in the more distal aspects of the Fallopian tube.⁵

IEPs can be diagnostically challenging. Their proximity to the uterine cavity means they can be mistaken for normally sited (eutopic) pregnancies which have implanted in the upper lateral aspect of the uterine cavity, previously termed angular pregnancies.^{1,6} This differentiation can be even more difficult in cases of partial IEPs (pIEPs), where the pregnancy implants in the interstitial portion of the Fallopian tube but expands medially, resulting in some of the pregnancy protruding into the uterine cavity.¹

The “interstitial line” sign describes visualisation of the proximal part of the interstitial tube between the lateral aspect of the uterine cavity and the medial aspect of the gestational sac, as a means of accurately diagnosing complete interstitial pregnancies. This has been reported to be 80% sensitive and 98% specific for the diagnosis of IEP and has been included in international guidelines for the diagnosis of ectopic pregnancy.^{1,7}

Historically, management of IEPs involved either hysterectomy or cornual resection, where the pregnancy and surrounding healthy myometrium of the uterine cornu were resected en bloc. Cornual resections are associated with short and long-term morbidity including increased intraoperative blood loss, and increased risk of both pre-term labour and scar rupture in future pregnancies due to the removal of healthy myometrium.⁸⁻¹¹

The development of high-resolution ultrasound and improved access for women to attend early pregnancy units (EPUs) has enabled earlier and more accurate detection of IEP. This has facilitated the use of more conservative management options including expectant management,^{12,13} medical management,^{4,14-16} and laparoscopic cornuotomy.^{4,17} A recent consensus statement on the diagnosis of ectopic pregnancies reclassified IEPs as tubal pregnancies in part to “discourage surgeons from performing uterine wedge

resection which is associated with an increased risk of both intra- and post-operative complications”.¹

The aim of this study is to examine the efficacy and safety of laparoscopic cornuotomy for the surgical management of complete IEP.

Methods

This was a retrospective cohort study conducted at the tertiary referral Early Pregnancy Unit (EPU) at University College London Hospital (UCLH), London, UK. The unit accepts self-referrals from women in addition to referrals from primary care and other EPUs. All women who received a diagnosis of IEP between June 2009 and April 2024 were included in the study. Clinical data was retrieved from electronic patient records on Viewpoint (GE HealthCare, Chicago, Illinois) and EPIC (Epic Systems Corporation, Verona, Wisconsin), including ultrasound images and reports, operative notes, discharge summaries, biochemistry results and histopathology results.

All women underwent pre-operative transvaginal ultrasound using high-end equipment (Voluson E8 or E10; GE HealthCare, Chicago, Illinois). The majority of the examinations were initially performed by clinical fellows in early pregnancy and gynaecology (Level-II operators) under the supervision of expert (Level-III) operators who confirmed the diagnosis in all cases.^{18,19} The diagnosis of IEP was made when pregnancy was seen implanted within the interstitial portion of the Fallopian tube, with morphological features varying from a solid homogeneous swelling to a gestational sac containing

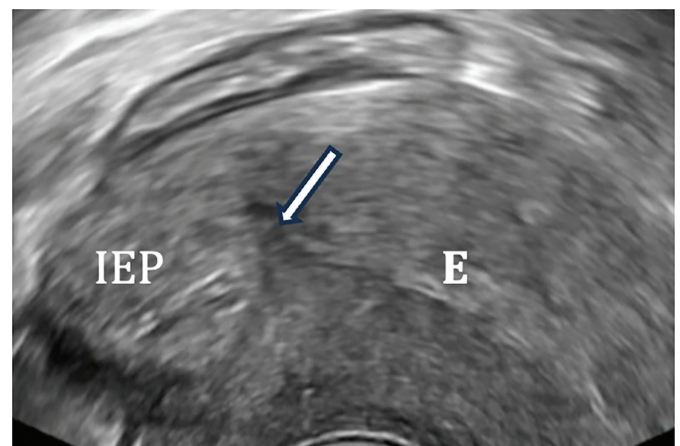


Figure 1. A B-mode ultrasound image of the uterus in the transverse plane. A thin interstitial tube (arrow) is seen adjoining the endometrial cavity (E) and a right interstitial ectopic pregnancy (IEP).

a live embryo.¹⁸ Crucial to the diagnosis of complete IEP was the presence of the “interstitial line sign”, as described above (Figure 1). In addition, the pregnancy had to be at least partially enveloped by myometrium.¹⁹ The diagnosis was supported in many cases by three-dimensional ultrasound scanning (Figure 2). Serum human chorionic gonadotrophin (hCG) and progesterone levels were measured in all clinically stable women diagnosed with complete IEP.

Active surgical management was recommended if patients were experiencing moderate to severe pelvic pain; there was a live embryo; the pregnancy measured >30 mm in the mean diameter, or if there was significant haemoperitoneum defined by the presence of blood clots within the lesser pelvis. All other patients were assessed for suitability of non-surgical management, with consideration given to symptoms, serum hCG and patient preference. The protocols used for expectant and medical management have been described previously.²⁰ Surgery was performed by gynaecologists with expertise in minimally invasive surgery. None of the patients who had surgery for complete IEP underwent cornual resection. pIEPs were surgically treated by transcervical

evacuation under continuous transabdominal or transrectal ultrasound guidance.

Surgical Technique for Laparoscopic Cornuotomy (Figure 3) and Video 1

At diagnostic laparoscopy, prior to starting the cornuotomy, the surgeon would confirm visibility and laterality of the IEP. This would typically appear as a hypervascular purple bulge over the fundo-lateral aspect of the uterus, often partially involving some of the isthmic portion of the Fallopian tube. Visualisation of complete IEP can be challenging at surgery when it is small, relatively medial or in the presence of concurrent uterine pathology such as large or subserous fibroids, or severe adenomyosis. Where the surgeon was uncertain of the location of the IEP, intraoperative transvaginal or transrectal ultrasound would be performed to guide the site of incision. Techniques used to reduce blood loss included the intramyometrial injection of Argipressin (20IU in 20 mLs of normal saline) directly over the IEP prior to the first incision. An incision would then be made in the myometrium or proximal section of the interstitial tube overlying the IEP using laparoscopic scissors, monopolar hook (Karl Storz, Tuttlingen, Germany) or an advanced energy device such as Thunderbeat® (Olympus Medical Systems Corp., Tokyo, Japan) or Harmonic Scalpel® (Ethicon, Johnson & Johnson Med Tech., Raritan, New Jersey, USA). The incision would be large enough to facilitate the introduction of laparoscopic grasping instruments (Johann or Maryland grasper,

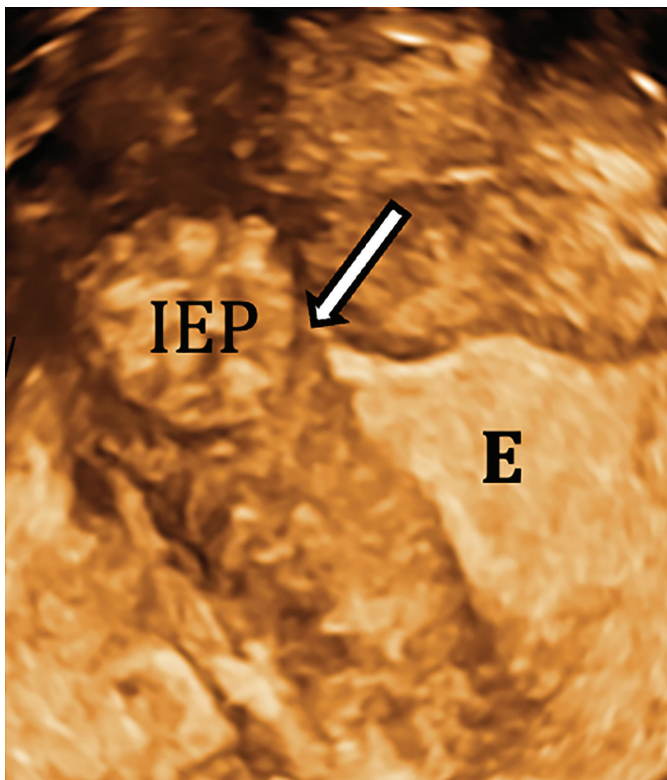


Figure 2. A three-dimensional ultrasound image of the uterus in the coronal plane. The interstitial tube (arrow) is clearly seen adjoining the endometrial cavity (E) and a right interstitial ectopic pregnancy (IEP).

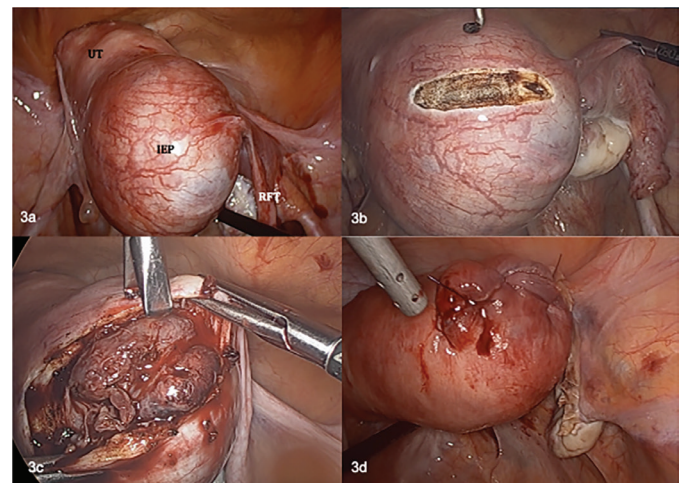


Figure 3. (a) Laparoscopic view of a large right interstitial pregnancy (IEP) (UT, uterus; RFT, distal segment of the right fallopian tube). (b) Initial cornual myometrial incision performed using monopolar diathermy. (c) Evacuation of interstitial pregnancy through the cornuotomy incision. (d) Incision closed using interrupted sutures, with haemostasis achieved.

Karl Storz, Tuttlingen, Germany) which were used to remove the trophoblastic tissue. Hydro-dissection and aspiration were also used as a method to separate and retrieve trophoblast tissue. All retrieved trophoblastic tissue was sent for histological analysis to confirm the diagnosis. In cases where it was uncertain if all of the trophoblastic tissue had been removed, intraoperative ultrasound was used to clarify. Once all the visible trophoblastic tissue had been removed, the incision was then closed laparoscopically using Vicryl, Monocryl, or PDS suture material (Ethicon, Johnson & Johnson Med Tech., Raritan, New Jersey, USA) or V-Loc™ (Medtronic, Minneapolis, Minnesota). An ipsilateral salpingectomy would be performed if the sutures were felt to occlude the Fallopian tube, in order to reduce the risk of recurrent ipsilateral tubal ectopic pregnancy. Blood in the abdomen or pelvis would be aspirated and its volume measured to establish the blood loss. All patients stayed in hospital until they met routine discharge criteria and were followed up as outpatients with repeat serum hCG measurements, usually starting one week post-surgery. If hCG clearance was slower than expected given a half-life of 24 hours,^{21,22} this was diagnosed as residual trophoblast.

The use of Endoloop ligatures (Ethicon, Johnson & Johnson Med Tech., Raritan, New Jersey, USA) can be used as an alternative to cornuotomy in cases where rapid haemostasis is required, or in large interstitial pregnancies that protrude laterally into the fallopian tube. They can be used as a tourniquet to encircle the IEP²³ prior to salpingectomy of the affected fallopian tube. Figure 4 illustrates a proposed decision-making algorithm to guide selection between techniques.

Statistical Analysis

Data was summarised using the mean and standard deviation for normally distributed continuous variables and the median and inter-quartile range for those not following a normal distribution. Logistic regression was used to examine factors associated with residual trophoblast in women undergoing planned laparoscopic cornuotomy. The analysis was performed in two stages.

The first stage examined the separate association between each factor and residual trophoblast in a series of univariable analyses. For some categorical variables, there were no occurrences of residual trophoblast in some categories, therefore logistic regression was unable to be performed and Fisher's exact test was used.

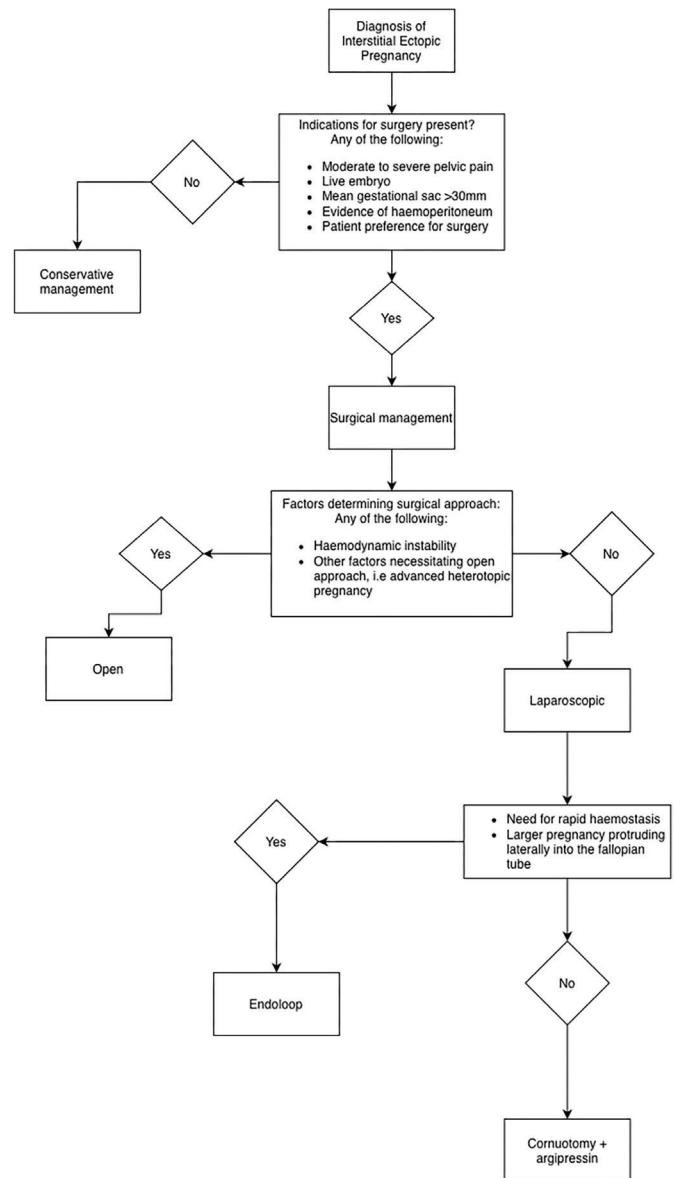


Figure 4. Decision tree to guide management of interstitial ectopic pregnancies.

The second stage examined the joint association between the factors and the outcome in a multivariable analysis. To limit the number of variables, only factors with a *P* value of <0.2 from the univariable analyses were included. A backwards selection procedure was used to retain only the important predictor variables; this involves removing non-significant variables until only the important variables remain.

Results

In the study period between June 2009 and April 2024, 104 patients attending our unit were diagnosed with a total of 106 IEPs, as two women presented with recurrent IEPs.

There were 102 complete and 4 pIEPs. The 102 complete IEPs included four cases of heterotopic pregnancy, where the concomitant normally sited pregnancy was live in all cases. Approximately half of all cases were external referrals from other EPU (56/106, 53%), with the remainder (50/106, 47%) from our clinic population. Several women had undergone some form of medical or surgical intervention (often without a conclusive pre-treatment diagnosis of IEP) at their local hospital prior to being referred to our unit, but for the purpose of this study the primary management was taken to be that following ultrasound diagnosis at our unit.

Patient demographic data are shown in Table 1. The majority of patients were nulliparous, with nearly 40% (39/104) having experienced previous miscarriage. One fifth of patients (21/104) had a previous history of at least one tubal ectopic pregnancy. For these women, the IEP was ipsilateral to the site of a previous tubal ectopic pregnancy in 17/19 [89%, 95% confidence interval (CI): 76-100] cases where the previous site was known (including 2 cases where there had been an ectopic on each side).

The most common presenting symptoms were concurrent vaginal bleeding and pain (43/106, 41%), although one fifth of patients were asymptomatic (22/106, 21%). Of the 106 cases of IEP (complete and partial), 88 (83%) were diagnosed on the initial ultrasound scan and the remaining 18 (17%) during follow up visits. The median gestational age at diagnosis was 7 weeks and 2 days. A conclusive ultrasound diagnosis of IEP was made in all cases prior to a decision regarding management. IEPs were classified into morphological types, where 19/106 (18%) showed evidence of cardiac activity (type 1), whilst the remaining 87/106 (82%) did not (type II-V).¹⁸

A summary of the management of IEPs during the study period is shown in the study flowchart (Figure 5).

Surgical Management of Complete IEP

A total of 71/102 (70%) pregnancies were treated surgically. 70/71 (99%) had planned laparoscopic surgery, including 62/70 (89%) who underwent a laparoscopic cornuotomy, and 8/70 (11%) who underwent an Endoloop assisted salpingectomy. Of the 62 laparoscopic cornuotomies, 54 were the primary management, and the remaining 8 were following unsuccessful expectant or medical treatment (Figure 5). One patient with a heterotopic pregnancy (live eutopic and complete interstitial at 14 weeks') had a planned open cornuotomy to maximise the chance of preserving the normally sited twin. In 69/70 (99%) cases,

Table 1. Demographic information for patients diagnosed with an interstitial pregnancy.

Characteristic	n=104
Age, mean (SD)	34.3 (SD: 5.0)
*BMI, mean (SD)	27.4 (SD: 7.8)
Ethnicity, n (%)	
White	36 (34.6)
Asian or British Asian	11 (10.6)
Black, Black British, Caribbean or African	14 (13.5)
Mixed or multiple ethnic groups	2 (1.9)
Other ethnic group	7 (6.7)
Unknown	34 (32.7)
Gravidity, n (%)	
1	25 (24.0)
2	25 (24.0)
≥3	54 (51.9)
Parity, n (%)	
0	60 (57.7)
1	27 (26.0)
≥2	17 (16.3)
Gynaecology history, n (%)	
Miscarriage	39 (37.5)
Recurrent miscarriage	7 (6.7)
Termination of pregnancy	28 (26.9)
Ectopic pregnancy	21 (20.2)
In vitro fertilization	13 (12.1)
Endometriosis	10 (9.6)
Pelvic infection	4 (3.8)
Adenomyosis	2 (1.9)
Subfertility	14 (13.5)
Fibroids	11 (10.6)
Ovarian cyst	4 (3.8)
Polycystic ovarian syndrome	6 (5.8)
Other (cervical pathology, uterine septum, endometrial hyperplasia)	6 (5.8)
Surgical history, n (%)	
Previous laparoscopic abdominal surgery	32 (30.8)
Previous open abdominal surgery (excluding caesarean section)	8 (7.7)
*Previous surgical management of pregnancy tissue	30 (28.8)
Previous hysteroscopic procedure	7 (6.7)
Obstetric history, n (%)	
Previous caesarean section	15 (14.4)

*n=25, missing data. *Includes surgical management of miscarriage or retained products of conception, and surgical termination of pregnancy. SD: Standard deviation, BMI: Body mass index.

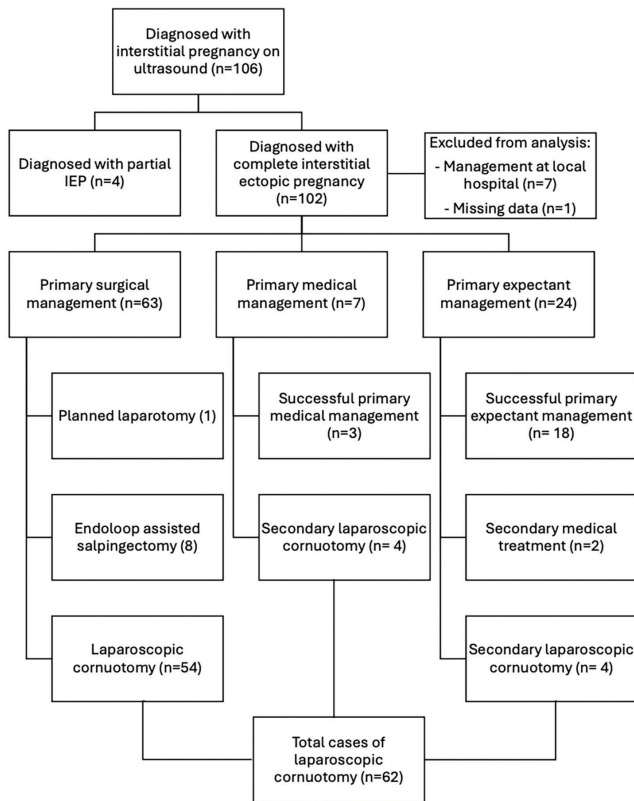


Figure 5. Flowchart showing the management of interstitial pregnancies.

the operation was completed laparoscopically, but in one case the procedure was converted to open surgery due to the presence of extensive bowel adhesions involving the uterine cornu at the site of the interstitial pregnancy.

Laparoscopic Cornuotomy

The median total estimated blood loss (EBL) for cases managed with laparoscopic cornuotomy was 50 mL [$n=53^*$, interquartile range (IQR) 50-150]. An EBL of ≥ 1000 mL was recorded in 3/53 (6%) cases, although in two of these, the blood loss was almost entirely attributed to pre-operative haemoperitoneum. There were no other instances of blood transfusion recorded. Argipressin was used in 71% (42/59^{*}) of cornuotomies, as a measure to further reduce blood loss. Out of 62 cases undergoing planned laparoscopic cornuotomy, 36/62 (58%) had excision of the IEP and ipsilateral salpingectomy (or excision of stump, if previous salpingectomy), whereas the remaining cases had excision of the IEP only.

The mean number of days until discharge from hospital was 1.2 ($n=62$, standard deviation 0.8). Follow-up after laparoscopic cornuotomy involved serial hCG

measurements until levels dropped such that the patient could be discharged, typically <10 IU/L. The median time for hCG resolution following surgery was 20 days ($n=48^*$, IQR: 14-35).

*Patients with missing data were excluded from the analysis.

Residual Trophoblast

Of the 62 interstitial pregnancies managed with planned laparoscopic cornuotomy, there were 9/62 (15%, 95% CI, 6-23) cases of residual trophoblast tissue. Further intervention was required in only 2/62 (3%, 95% CI, 0-8) cases: one case resolved with methotrexate and one case underwent emergency laparotomy, discussed below. The remaining 7 cases were all managed expectantly with serial hCG monitoring and in some cases confirmed with a resolution scan. In total, 60/62 (97%, 95% CI, 92-100) of interstitial pregnancies resolved completely following laparoscopic cornuotomy.

Factors associated with residual trophoblast were examined. Univariable analysis demonstrated that the majority of variables examined were not significantly associated with residual trophoblast (Table 2), however a significant association with previous surgical removal of pregnancy tissue from the uterine cavity (including surgical management of miscarriage or retained products of conception, and surgical termination of pregnancy) was observed.

Multivariable analysis (Table 3) showed that both previous laparoscopic abdominal surgery and surgical management of pregnancy tissue were independently associated with residual trophoblast. After adjusting for the other factors in the analysis, previous laparoscopic abdominal surgery was associated with a 5-fold increase in the odds of residual trophoblast, whilst surgical management of pregnancy tissue was associated with a 6-fold increase (Table 3).

Surgical Complications

Patient records were reviewed up until the time of data collection to capture delayed post-operative complications. Of the 62 cases of IEP managed with planned laparoscopic cornuotomy, 2/62 (3%, 95% CI: 0-8) intraoperative complications and 3/62 (5%, 95% CI: 0-10) postoperative complications were recorded. The intraoperative complications included the case requiring conversion to laparotomy due to adhesions, which resulted in a total blood loss of 1,300 mL, and another

Table 2. Univariable associations with residual trophoblast following laparoscopic cornuotomy.

Variable	Category	Trophoblast n/N (%)	Odds ratio (95% CI)	P value
Age*	-	-	1.10 (0.53, 2.28)	0.80
Ethnicity	White	4/24 (17%)	(+)	0.92
	Asian	1/7 (14%)		
	Black	0/7 (0%)		
	Mixed/other	1/7 (14%)		
Previous	No	7/42 (17%)	1	0.49
Miscarriage	Yes	2/20 (10%)	0.56 (0.10, 2.95)	
Previous TOP	No	4/44 (9%)	1	0.07
	Yes	5/18 (28%)	3.84 (0.90, 16.5)	
Previous ectopic	No	6/46 (13%)	1	0.58
	Yes	3/16 (19%)	1.54 (0.34, 7.04)	
Previous caesarean	No	7/51 (14%)	1	0.71
	Yes	2/11 (18%)	1.40 (0.25, 7.86)	
IVF	No	9/56 (16%)	(+)	0.58
	Yes	0/6 (0%)		
Previous laparoscopic	No	4/44 (9%)	1	0.07
abdominal surgery	Yes	5/18 (28%)	3.85 (0.90, 16.5)	
Previous open	No	8/56 (14%)	1	0.88
abdominal surgery	Yes	1/6 (17%)	1.20 (0.12, 11.7)	
**Previous surgical management of pregnancy tissue	No	4/46 (9%)	1	0.04
	Yes	5/16 (31%)	4.77 (1.09, 20.8)	
Previous transcervical	No	9/60 (15%)	(+)	1.00
Procedure	Yes	0/2 (0%)		
Gestational age (wk)	-	-	0.84 (0.52, 1.36)	0.48
Mean diameter (cm)	-	-	0.69 (0.33, 1.45)	0.33
Appearance	Type I	3/16 (19%)	1	0.58
	Type II-IV	6/46 (13%)	0.65 (0.14, 2.97)	
Type of surgery	Excision of pregnancy only	5/26 (19%)	1	0.38
	Additional salpingectomy/stump excision	4/36 (11%)	0.53 (0.13, 2.18)	

*Odds Ratio given for a 5-year increase in age.

+Unable to calculate odds ratios due to no occurrences of residual trophoblast in one category. Analysis using Fisher's exact test.

**Includes surgical management of miscarriage or retained products of conception, and surgical termination of pregnancy.

CI: Confidence interval, IVF: *In vitro* fertilisation, TOP: Termination of pregnancy.**Table 3.** Multivariable associations with residual trophoblast following laparoscopic cornuotomy.

Variable	Category	Odds ratio (95% CI)	P value
Previous laparoscopic	No	1	0.05
abdominal surgery	Yes	5.18 (1.03, 26.1)	
Previous surgical management of pregnancy tissue*	No	1	0.03
	Yes	6.28 (1.24, 31.7)	

*Includes surgical management of miscarriage or retained products of conception, and surgical termination of pregnancy. CI: Confidence interval.

patient requiring blood transfusion (2 units) for an EBL of 2500 mLs, although the large majority of this was attributed to pre-operative haemoperitoneum.

All three post-operative complications occurred in patients with residual trophoblast. Two cases, with suspected persistent trophoblast based on slowly declining hCG levels, developed acute haemoperitoneum and underwent emergency surgery at their local hospital, at 24 and 43 days post cornuotomy respectively. The first had a laparoscopy and washout; however, the haemoperitoneum was unexplained as no source of bleeding was identified. The second case underwent a laparotomy where bleeding was noted from the right ovary. In both cases, the hCG declined to pre-pregnancy levels following the second surgery. A third patient with residual trophoblast presented with pain 33 days following her primary surgery and underwent a diagnostic laparoscopy and washout of an infected pelvic collection.

Subsequent Pregnancies

Out of 62 women who underwent laparoscopic cornuotomy for complete IEP, 27/62 (44%) had at least one subsequent pregnancy. The total number of subsequent pregnancies was 52. Of these, 44/52 (85%) were eutopic pregnancies, 6/52 (12%) were classified as "pregnancy of unknown location" which resolved, 1/52 (2%) was a tubal ectopic, and 1/52 (2%) was a heterotopic pregnancy including a correctly sited pregnancy and a recurrent IEP. The rate of confirmed miscarriage was 14/52 (27%).

At least one subsequent live birth was recorded for 19/27 (70%) patients who became pregnant following laparoscopic cornuotomy. Of a total of 52 pregnancies, 25 (48%) ended in live delivery of at least one child, including 23 singletons, 1 set of twins and 1 set of triplets, making a total of 28 live births. Outcomes for eutopic pregnancies were unknown for 5 patients, so this may be an underestimate of the number of live births. Of the deliveries, only 2 (8%) were preterm: one woman who delivered at 36 weeks and had previously had a preterm delivery prior to the IEP, and the other was the triplet pregnancy delivered by caesarean. Of the 25 deliveries, 12 (48%) were by caesarean section (none of which were documented to be an emergency) and 13 (52%) were by vaginal delivery, with no recorded intrapartum complications.

Discussion

Main Findings

This is the largest study looking at outcomes of laparoscopic cornuotomy, and our data suggests that it is an effective procedure associated with a short hospital stay, low intraoperative blood loss and low chance of requiring further intervention for persistent trophoblastic tissue. The benefits of laparoscopic surgery have been corroborated by other studies that directly compare laparoscopic and open techniques.^{24,25}

Several factors may have contributed to the low EBL observed in our study. Firstly, most ectopics were diagnosed prior to rupture, meaning patients were clinically stable and had no significant haemoperitoneum at the onset of surgery. Secondly, the technique of laparoscopic cornuotomy avoids transection of large terminal branches of the uterine artery, which are the main cause of excessive bleeding at cornual resection. The use of additional haemostatic measures, including Argipressin, likely also contributed to the low recorded blood loss.

The success rate of 97% compares favourably to non-surgical management. Earlier studies found typically good success rates of conservative management, ranging from around 71-90% for expectant management^{20,12} and 80-94% success for methotrexate (local or systemic).^{20,26} More recent studies have found lower rates of success, such as work by Ben-David et al.¹⁴ demonstrating 70% success with non-surgical management and a 17% risk of uterine rupture during treatment, and a recent systematic review and meta-analysis which found an estimated success rate of 69% for methotrexate treatment from a total of 124 patients.²⁷

The rate of persistent trophoblastic tissue following laparoscopic cornuotomy for IEP is not well established in the literature, with most studies consisting of small sample sizes. Furthermore, there is a lack of studies that distinguish between cases in which residual trophoblast can be managed expectantly, and those where further intervention (typically methotrexate or surgery) is required. Whilst our overall incidence of residual trophoblast was relatively high at 15%, only 3% required further intervention. Our results compare favourably to the existing literature. A study by Ng et al.,⁹ found that 9/52 (17%) of cases undergoing laparoscopic management (both wedge resection and cornuotomy techniques) of IEP required methotrexate for persistently

raised serum hCG. Tulandi and Al-Jaroudi³ found a 1/11 (9%) re-intervention rate following laparoscopic excision of IEP, whilst Moon et al.²³ found that 1 in 24 (4%) cases managed by laparoscopic cornuotomy required subsequent methotrexate.

The rate of persistent trophoblast following salpingotomy for tubal ectopic pregnancy is better established and quoted as between 3 and 20% in the literature.²⁸ A significant proportion of these patients go on to have further treatment in the form of methotrexate or further surgery, often at rates higher than the 3% found in this study.²⁹⁻³¹ Therefore, both the incidence and the risk of intervention for persistent trophoblast in IEPs undergoing laparoscopic cornuotomy appear comparable to that for salpingotomy for tubal ectopic pregnancy.

The finding of a 5-fold increase in the odds of residual trophoblast with previous laparoscopic abdominal surgery, and a 6-fold increase with previous surgical management of pregnancy tissue was interesting and unexpected, and to our knowledge has not been previously reported. However, given a total number of just 9 patients with residual trophoblast, these results lack robustness and need to be interpreted with caution.

Some papers describe performing cornual resection rather than cornuotomy for IEPs above a certain size: 35 mm³ or 40 mm,^{32,33} with the aim of minimising the risk of persistent trophoblast. However, our data did not find an association between size of the IEP and the rate of persistent trophoblast. Nor was there a link between IEPs with cardiac activity and residual trophoblast (Table 2).

Surgical complications are not well established in the context of laparoscopic cornuotomy for IEP. In two of the studies reviewed that looked at surgical outcomes, no major intraoperative or postoperative complications were encountered.^{34,25} However, these sample sizes were relatively small and the time frame over which cases were followed up to assess for complications not always defined. Surgical complications have been better studied in cases of tubal ectopic pregnancy. These are varied, but studies have reported intraoperative complication rates ranging from 0-8% and postoperative complication rates of 0-15% for laparoscopic salpingectomy or salpingotomy.^{35,36} Our intraoperative complication rate of 3% and postoperative complication rate of 5% fall within these reported ranges. Postoperative complications only occurred in women with residual trophoblast. These patients therefore require particularly close monitoring.

Subsequent Pregnancy Outcomes

The true rate of subsequent pregnancy following laparoscopic cornuotomy in our study is uncertain, as our data was limited to the forty-four percent of women who presented at our unit for future early pregnancy or antenatal care. However, our data suggests that pregnancy following laparoscopic cornuotomy is generally safe. Most pregnancies were correctly sited, with a 4% recurrent ectopic pregnancy rate. There were no recorded late second trimester miscarriages, and the rate of preterm birth was low, with neither case likely to be secondary to treatment of the IEP. Half of the deliveries were vaginal, with no reported cases of uterine dehiscence or rupture. Other published studies examining subsequent pregnancy outcome after laparoscopic cornuotomy were small, but they also showed low rates of recurrent ectopic pregnancies and no cases of uterine rupture in late pregnancy or labour.^{23,34}

This data appears favourable compared to a study by Tang et al. who reported a 9.1% rate of recurrent ectopic pregnancy and a 4.5% rate of uterine rupture in women undergoing assisted conception following wedge resection for IEP.¹¹ The reported risk of uterine rupture following cornual resection varies.^{8,11}

Strengths and Limitations

This study is the largest study to our knowledge looking at outcomes from laparoscopic cornuotomy, increasing the reliability of our data. This also means we are likely to pick up less common outcomes (i.e., major complications) that smaller studies may fail to detect. Close post-operative follow-up and the retrospective nature of the study enabled longer term complications to be picked up, including those occurring at other trusts.

Limitations of a single centre retrospective study include selection bias: cases for surgical management were selected based on symptoms and morphology or size, therefore the success rate reported may not apply to other cohorts. There was also significant incomplete data regarding future pregnancies. Data were limited to pregnancies for which the patient had sought early pregnancy or antenatal care at our unit, therefore may not be an accurate reflection of actual subsequent pregnancy outcomes where these were not captured by our data collection, i.e., the patient presented elsewhere. Incomplete or missing data across other outcomes also makes the results vulnerable to selection or loss to follow up bias in these areas.

The multivariable analysis demonstrating a 5-fold increase in the odds of residual trophoblast with previous laparoscopic abdominal surgery, and 6-fold increase with previous surgical management of retained pregnancy tissue was based on a small cohort of patients and this finding has not been corroborated by other studies. Caution is therefore required when interpreting this data. The nature of an observational study means that we are unable to prove causation due to the presence of confounding, although this was considered in the statistical analysis.

Clinical and Policy Implications

Protocols for picking up patients with residual trophoblast (i.e., monitoring serum hCG) should be comprehensive to ensure they are not missed, given this cohort appears to be at higher risk of complications. The association between previous laparoscopic abdominal surgery and surgical management of pregnancy tissue with residual trophoblast has implications for clinical practice. There should be a particularly high index of suspicion when following these women up post-operatively, and meticulous surgical technique should be used, with the aid of intraoperative ultrasound to minimise the chance of residual trophoblast in the first instance.

Unanswered Questions and Future Research

Future research is required on postoperative complications following laparoscopic cornuotomy, particularly looking at complications in women with persistent trophoblast versus those without. Further large multicentre studies are recommended to obtain more robust data regarding the risk of preterm birth and intrapartum uterine rupture.

Conclusion

Laparoscopic cornuotomy is an effective treatment for complete IEP, associated with a low-risk of major intraoperative haemorrhage and short hospital stay. Although residual trophoblast is relatively common, further treatment is required only in a small proportion of patients. The future pregnancy outcomes were good, with a low-risk of recurrent ectopic pregnancy and adverse obstetric outcomes.



Video 1. A video record of a laparoscopic cornuotomy for a left interstitial pregnancy showing key surgical steps

during the procedure. (We are grateful to Mr Martin Hirsh, Consultant Gynaecologist, for providing this video): <https://www.youtube.com/watch?v=ZeSuMmZEJ-s>

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Informed consent: Written informed consent was not required due to the retrospective nature of this analysis.

Data sharing: The datasets used for this study are not available publicly due to legal and confidentiality reasons, although the data analysis can be requested from the author if required.

Transparency: We affirm that this text is an honest, accurate and transparent account of the study and no important aspects have been omitted.

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Complications, recurrence, and survival rates for endometrial and cervical cancer treated by minimally invasive surgery: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background: Consensus is lacking regarding the relative safety and oncological outcomes of minimally invasive compared to abdominal hysterectomy.

Objectives: To estimate complications and survival rates of minimally invasive hysterectomy (MIH) (i.e., laparoscopic or robotic assisted) compared to total abdominal hysterectomy (TAH) for endometrial and cervical cancer.

Methods: A systematic quantitative review of randomised controlled trials (RCTs) comparing MIH with TAH for the treatment of endometrial or cervical cancer. Medline-PubMed, Cochrane Library, Scopus, ongoing clinical trials and the grey literature were searched until December 1, 2024.

Main Outcome Measures: Complications, overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) rates.

Results: Twenty-nine RCTs enrolling 6,127 patients were included. The risk of bladder injury was higher in the MIH group [risk ratio (RR): 1.84, 95% confidence interval (CI): 1.03-3.29, I^2 : 0%], as was the risk of vaginal injury (RR: 12.39, 95% CI: 1.61-95.29, P =0.02, I^2 : 0%) but the risk of wound dehiscence was lower (RR: 0.32, 95% CI: 0.13-0.83, P =0.02, I^2 : 13%) compared to abdominal hysterectomy. Among cervical cancer patients, the risk for blood transfusion was significantly lower with the MIH (RR: 0.42, 95% CI: 0.21-0.84, P =0.01, I^2 : 0%). Among endometrial cancer patients, the OS, DFS, and DSS were comparable between routes of hysterectomy. In contrast, the overall the OS and DFS rates were lower for minimally invasive compared to abdominal hysterectomy (0.94, 95% CI: 0.90-0.98, P =0.005, I^2 : 0%) and (0.89, 95% CI: 0.84-0.94, P <0.001, I^2 : 0%) respectively.

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ABSTRACT

Conclusions: Bladder and vaginal injuries are higher with minimally invasive compared to abdominal hysterectomy. Survival rates for endometrial cancer are comparable but for cervical cancer, minimally invasive hysterectomy is associated with poorer survival outcomes and this should be taken into account when counselling patients and deciding upon the route of hysterectomy.

What is New? TAH has superior survival outcomes compared to minimally invasive hysterectomy.

Keywords: Cancer, laparoscopy, hysterectomy, minimally invasive surgery, postoperative complications, intraoperative complications, survival analysis

Introduction

Endometrial and cervical cancers are the most frequent gynaecological malignancies, together accounting for the majority of cancer cases affecting the female reproductive tract. Endometrial cancer constitutes the most frequently observed malignant gynaecologic disease and the fourth most frequent cancer type in high-income countries, with an incidence of 11.1 per 100,000 women,¹⁻³ and cervical cancer constitutes the fourth cause of cancer-associated deaths among the female population globally.^{4,5} The incidence of uterine malignancies is expected to increase by 2040.² Age, smoking, dietary habits, and medical conditions such as hypertension and diabetes are associated with increased endometrial cancer risk. Higher oestrogen levels observed in situations such as late-onset menopause and obesity constitute risk factors for endometrial cancer development.^{1,2} Cervical cancer is mainly linked to human papillomavirus (HPV) infection,^{4,5} with oncogenic types 16 and 18 being associated with about 70% of the cases.⁵ Other factors related to cervical cancer development are smoking, higher parity, history of sexually transmitted diseases, and long-term contraceptive use. Since vaccination against HPV was implemented, however, the incidence of cervical cancer has declined in high-income countries, and most cases and deaths are observed in low- and middle-income countries.⁵

The typical surgical management of endometrial cancer includes total hysterectomy with bilateral salpingo-oophorectomy (BSO) and lymphadenectomy, including sentinel node biopsy to assess lymph node involvement and define disease stage.^{1,2,6-8} The role of bilateral pelvic and para-aortic lymphadenectomy remains controversial, and some authors suggest that these procedures should only be performed in high-risk patients.² Ovaries may be preserved for select younger patients with low-grade tumours wishing to maintain reproductive capability, but those women need to be meticulously monitored

and concomitantly treated with hormonal therapy.¹ The typical surgical management of early-stage cervical cancer [International Federation of Gynaecology and Obstetrics (FIGO) stages IB1, IB2, and IIA1] includes type C radical hysterectomy and pelvic lymphadenectomy with/without para-aortic lymphadenectomy.^{5,9,10} FIGO stage IA1 is usually managed with cervical conisation or simple extra-fascial hysterectomy. In the case of lymph vascular invasion, type B modified radical hysterectomy and pelvic lymphadenectomy must be considered. FIGO stage IA2 is typically managed with type B modified radical hysterectomy and pelvic lymphadenectomy.^{5,11-13} Adjuvant or neoadjuvant treatment (chemotherapy, radiotherapy, and hormonal therapy) depends on disease stage and is crucial for managing the cancer, complementing the primary surgical treatment.^{1,2,5,7,8,11,12}

Since the laparoscopic hysterectomy was introduced by Reich et al.¹⁴ and the first report of laparoscopic restaging in endometrial cancer was published by Childers et al.,¹⁵ the surgical management of gynaecologic malignancies has evolved significantly; minimally invasive surgery (MIS) techniques, namely, total laparoscopic hysterectomy (TLH), laparoscopically assisted vaginal hysterectomy (LAVH), or robot-assisted laparoscopic hysterectomy (RALH)/total robotic hysterectomy (TRH), are being used more and more in gynaecologic cancers.^{1,2,5,6,9,16,17} Surgical management differs substantially between endometrial and cervical cancer. In presumed uterus-confined endometrial cancer, total hysterectomy with BSO and staging by a MIS approach is currently the preferred surgical strategy. By contrast, in early-stage cervical cancer requiring radical hysterectomy, open surgery remains the standard approach after the LACC trial demonstrated inferior disease-free survival (DFS) and overall survival (OS) with minimally invasive radical hysterectomy. Current guidance allows minimally invasive radical surgery, if at all, only in carefully selected low-risk tumours and in highly specialised high-volume centres after comprehensive counselling.¹⁸⁻²²

In any case, the surgical approach should be individualized according to the patient's characteristics, comorbidities, and intraoperative findings.^{1,2,5,6,9,16,17,23} Total abdominal hysterectomy (TAH) constitutes a widely practiced approach that provides good visual access, haptic feedback, and tactile sensation. The latter is significant in malignant diseases, where removing the entire tumour is of existential importance. The intraoperative spread of cancer cells is less common in TAH. Thus, TAH provides more predictable surgical and oncologic results.^{1,2,6,17,24} However, TAH is associated with higher morbidity, higher postoperative complications rates such as wound infections, haemorrhage, transfusion, bowel perforation, and venous thromboembolic events, prolonged recovery time and hospitalisation, and higher postoperative pain due to the incision size, impacting quality of life postoperatively.^{1,2,6,17,24} By using MIS manoeuvrability and precision are enhanced and these techniques are associated with lower morbidity, reduced blood loss and surgical trauma, reduced infection rates, shorter recovery time and hospitalisation, and less postoperative pain. Thus, MIS is a suitable approach for high-risk patients, namely, obese and older people. However, MIS may not be feasible in patients presenting with anatomical challenges (uterine size, adhesions), which require longer operation times and greater surgical expertise, and is linked to increased risk of intraoperative injuries (due to limited visualisation) and potential tumour dissemination.^{1,2,5,9,10,16,24,25} Recent evidence suggests, moreover, that MIS reliability in terms of oncologic outcomes is debatable, particularly in the case of early-stage cervical cancer.^{5,9,10} Therefore, in the case of cervical cancer, TAH continues to be the standard approach as the long-term cancer results of MIS need to be more extensively evaluated.^{9,10} In the case of endometrial cancer, TAH seems to be neither superior nor inferior to MIS when considering OS and DFS rates.^{6,16}

Several recent systematic reviews and meta-analyses (SRMAs) aimed to compare MIS and TAH.²⁶⁻³³ The SRMAs enrolling cervical cancer patients included observational studies. Of these, one SRMA included 21 observational and only one randomised controlled trial (RCT).³¹ Of the SRMAs enrolling endometrial cancer patients,²⁶⁻²⁹ three included only observational studies, and one SRMA included nine RCTs.²⁶ However, since then, more studies have been published. No reliable conclusions have been drawn yet, however, particularly regarding oncologic outcomes, and thus there is a need to summarise the findings exclusively from randomised studies, given that

the level of evidence of RCTs is higher. We therefore conducted a systematic review and meta-analysis restricted to RCTs to provide a higher-level synthesis of surgical, complication, recurrence, and survival outcomes in endometrial and cervical cancer, with disease-specific interpretation of the findings.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement³⁴ was considered during the conduction of this SRMA. This SRMA conforms to the PRISMA checklist.

A protocol for the present review was prepared a priori and discussed among the coauthors, including members of the ESGE Special Interest Group on Education and Training. However, it was not prospectively registered in PROSPERO or another public registry.

Inclusion and Exclusion Criteria

Prospective RCTs were included that had enrolled patients with endometrial or/and cervical cancer who were treated with total hysterectomy. The intervention arm included those who received MIS, namely, either TLH, or LAVH, or RALH/TRH, and the comparator arm included those women in whom TAH or a different type of MIS (different from the intervention arm) was performed. No limitations regarding BSO or pelvic or para-aortic lymphadenectomy were applied. The outcomes of interest were operative time, intraoperative blood loss, haemoglobin reduction, hospitalisation duration, total number of patients with at least one complication, total number of complications (events), intraoperative and postoperative complications (events), blood transfusion rates, cancer recurrence rates at the end of follow-up, death rates (total and cancer-related) at the end of follow-up, and OS, DFS, and disease-specific survival (DSS). We excluded studies that exclusively assessed pain scores and pain management, pelvic floor function, and quality of life (for detailed criteria, see Supplementary Table 1).

Search Strategy and Sources

The search strategy was formulated based on the Peer Review of Electronic Search Strategies checklist using free text and medical subject heading terms.³⁵ Search terms were "gynaecology", "obstetrics", "laparoscopy", and "laparoscopic hysterectomy" with synonyms and alternatives (for the search queries, see Supplementary Material). We intentionally used an open, highly sensitive search strategy without filters to capture all potentially

eligible studies, while final specificity was ensured during title/abstract and full-text screening according to the predefined inclusion criteria. The following databases were searched: Medline-PubMed, Scopus, Cochrane Library, ClinicalTrials.gov, openGrey, and EU Clinical Trials Register. The PROSPERO database was searched for ongoing SRMAs. Abstracts of congresses and meetings of gynaecological-obstetric and endoscopic surgery societies were also investigated. Our last search was conducted on 1 December 2024.

Study Selection and Data Extraction

After carrying out pilot-calibration procedures, the reviewers separately completed the study selection and data extraction, with another reviewer resolving any disagreements that arose. If there were questions about the eligibility of a study, we tried to communicate with the authors of the paper via email. Zotero 7.0.11 was used as the reference manager software. We used predefined collection forms recommended by the Cochrane Collaboration for Intervention Reviews for data extraction.³⁶ Data were extracted based on a predefined list of variables and outcomes (Supplementary Table 2).

Definitions

Surgical procedures were defined based on the textbook Williams Gynaecology, 3rd edition (MIS,³⁷ TLH,^{37,38} LAVH,³⁹ RALH/TRH,³⁷ TAH,⁴⁰ BSO,^{41,42} and pelvic/para-aortic lymphadenectomy).^{43,44} "Minimally invasive hysterectomy (MIH)" was used by this SRMA during the quantitative synthesis instead of MIS, embracing TLH, or LAVH, or RALH/TRH. Operative time was defined as the time after anaesthesia, including patient and surgery preparation and the procedure time from the first incision to closure. Intraoperative blood loss was defined as the total volume of suctioned blood minus the volume of fluids used for irrigation during surgery. Haemoglobin reduction was defined as the difference between the preoperative value and the value recorded within 2 days postoperatively. Hospitalisation duration was the hospital stay after the surgery until discharge.

Complications were divided into intraoperative (occurring from the start of anaesthesia until the end) and postoperative (arising from the end of anaesthesia until 6 months after surgery). Blood transfusion was defined as the transfusion of at least one Red blood cells unit divided into intraoperative and postoperative transfusion. The outcome of "Intraoperative injuries" was a compound one, including bladder, vaginal, bowel,

nerve, vascular, ureteral, urethral, and visceral injuries. Postoperative complications included: ileus (inhibition of gastrointestinal propulsion without signs of mechanical obstruction for more than 48 h),⁴⁵ wound complications, vaginal vault/cuff complications, urinary symptoms, haematoma (at any site and of any duration), fever (≥ 38 °C), postoperative infection (of any type), fistulas, and deep vein thrombosis/pulmonary embolism (DVT/PE).^{46,47} "Wound complications" were a compound outcome, including wound dehiscence and wound infection. "Vaginal vault/cuff complications" were a compound outcome, including vault haematoma, bleeding, infection, dehiscence/laceration, and leakage. "Urinary symptoms" were a compound outcome, including urinary incontinence, ureterostenosis, urinary retention, and urinary tract infection (UTI). "Fistulas" were a compound outcome, including ureterovaginal, vesicovaginal, rectovaginal, and gastrointestinal fistulas.

Definitions of recurrence rates and death (total and cancer-related) were considered self-explanatory. OS, DFS, and DSS were defined based on the National Cancer Institute of the US government.⁴⁸⁻⁵⁰ OS was defined as the time from randomisation until the date of death from any cause. DFS was defined as the time from randomisation to disease recurrence or death from cancer. DSS was defined as the time from randomisation to death because of cancer.

Risk-of-Bias Assessment

We used the RoB 2 Cochrane Tool for RCTs to assess the risk of bias of the initially included studies.⁵¹ We excluded studies with an overall "High" risk from the review and the synthesis. Figures visualising the risk of bias were created with the Robvis tool.⁵² Two reviewers conducted bias assessment separately, while a third reviewer settled disagreements.

Quantitative Synthesis

The quantitative synthesis was conducted using RevMan Web 8.14.0 and R-Studio 2024.12.0 software, and the relevant forest plots were created. The treatment effect was measured using mean and standard deviation (SD) with a 95% confidence interval (CI) for numerical variables, and the standardised mean difference (SMD) was calculated. When only the median, interquartile range, and/or range were reported, data were converted to an estimated mean and SD based on statistical methods described elsewhere.⁵³ The treatment effect was measured using risk ratio (RR) with a 95% CI for categorical

variables. The Mantel-Haenszel method was applied for categorical data and the inverse variance method for numerical data. When a study contained a zero cell in one arm, the standard continuity correction implemented in RevMan was applied by adding 0.5 to all four cells of the corresponding 2 x 2 table. Studies with zero events in both arms did not contribute to RR estimation because the relative effect was undefined. In the case of OS, DFS, and DSS, the effect was measured using the rate ratio and hazard ratio (HR) with a 95% CI after making the necessary logarithmic calculations using statistical software. For survival outcomes, HRs were directly extracted when these were reported in the original studies. HRs were not reconstructed from Kaplan-Meier curves or other published summary data. When studies reported survival rates rather than HRs, rate ratios were used as the effect measure. Because these effect measures reflect different statistical approaches, HR-based and rate ratio-based analyses were performed separately. For OS outcomes, HRs were interpreted as measures of the hazard of death over time. For DFS outcomes, HRs were interpreted as measures of the hazard of recurrence or death over time. Therefore, an HR greater than 1 indicates a higher hazard of the corresponding adverse event in the MIS group compared with TAH.

Statistical heterogeneity was assessed using the Higgins I^2 test and chi-squared Cochran Q-test (α : 0.1). If $I^2 \geq 75\%$, quantitative synthesis was not feasible. The fixed-effects model was used if $I^2 < 50\%$, while the random-effects model was used if $I^2 \geq 50\%$ (or chi-squared Cochran Q-test $P < 0.1$).

Sensitivity analysis was applied in the case of persistent statistical heterogeneity by removing those studies creating it. Subgroup analysis was conducted based on cancer type and surgery type. Further stratification simultaneously by cancer type and specific MIS subtype was not consistently feasible because these data were not uniformly reported in the included studies and because of the small numbers available for individual subgroups. When data were missing, we contacted the authors of the paper. No imputation was necessary.

Publication bias was assessed only when ≥ 10 studies per outcome were available for analysis. Funnel plots were designed by RevMan Web 8.14.0, while Egger's and rank correlation tests were conducted with R-Studio 2024.12.0.

Evidence Quality

Two reviewers independently assessed the quality of evidence for each outcome, and a third reviewer resolved any disagreements. The assessment aligned with the Grading of Recommendations Assessment Development and Evaluation (GRADE) system⁵⁴ and was conducted by using the GRADEpro GDT web application.⁵⁵

Results

Study Selection

Figure 1 summarises the study selection process. After removing duplicate records, 6228 were deemed potentially appropriate, and 5728 studies were removed by screening the titles and abstracts. Five studies were ongoing trials (Supplementary Table 3). The 500 remaining studies, plus 11 new studies found through a reference check, were full-text assessed. The full-text assessment yielded 45 studies to potentially be included. Of these, 14 were excluded⁵⁶⁻⁶⁹ (for the reasons for excluding each study, see Figure 1 and Supplementary Table 4). Thus, 31 studies were included before the risk-of-bias assessment. Two of these 31 studies were judged as "High Risk" (see below) and, therefore, excluded.^{70,71}

Study Characteristics

Twenty-nine studies were included in this SRMA, enrolling 6,127 patients.^{6,9,17,20,72-96} Supplementary Table 5 summarises the study designs and settings, inclusion and exclusion criteria, numbers of participants, interventions, comparators, and primary outcomes.

We included 15 single-center studies,^{72-74,77,79-81,83,87,88,90-92,94,95} two-center studies,^{86,89} and 12 multi-center studies.^{6,9,17,20,75,76,78,79,84,85,93,96} Eighteen studies included only women with endometrial cancer^{6,17,72-87} and ten studies included only those with cervical cancer,^{9,20,88-95} while one study included patients with three types of malignancies (either endometrial, cervical, or ovarian).⁹⁶ Patient characteristics are given in the "Synthesis" section.

TLH was the intervention in 17 studies,^{6,17,72-79,87-91,96} LAVH in six studies,^{79-81,86,92,95} RALH in one study,⁸³ while MIH (either TLH, or LAVH, or RALH/TRH) was performed in six studies.^{9,20,84,85,93,94} In all included studies, patients underwent BSO.^{6,9,17,20,72-96} Pelvic^{6,9,17,20,72-74,78,83-91,93-95} and para-aortic^{84,85,94} lymphadenectomy was carried out for all patients in 20 and three studies, respectively. In four

studies, pelvic lymphadenectomy,^{80-82,96} and in ten studies, para-aortic lymphadenectomy^{6,17,74,78,81-83,91,96} depended on the cancer stage (not carried out for all patients). In all studies, the comparator was TAH, except for four studies: two studies compared TLH with RALH (one regarding endometrial cancer⁸⁷ and another regarding cervical cancer),⁹⁶ one study regarding endometrial cancer compared LAVH with TLH⁸⁶ and, finally, one study

regarding cervical cancer compared LAVH with TRH.⁹⁵ Regarding our outcomes of interest, total operative time was assessed by 19 studies,^{6,17,72,74,75,77,78,80,83,84,86-89,91-94,96} intraoperative blood loss/haemoglobin reduction by 16 studies,^{6,17,72,74,75,77,78,80,82,83,86,87,89,91-94,96} intraoperative and postoperative complications by 21 studies,^{17,72,74-78,80,81,83,84,86-89,91-96} total hospitalisation duration by 18 studies,^{17,72,74,75,77,78,80,82-84,86,87,89,91-95}

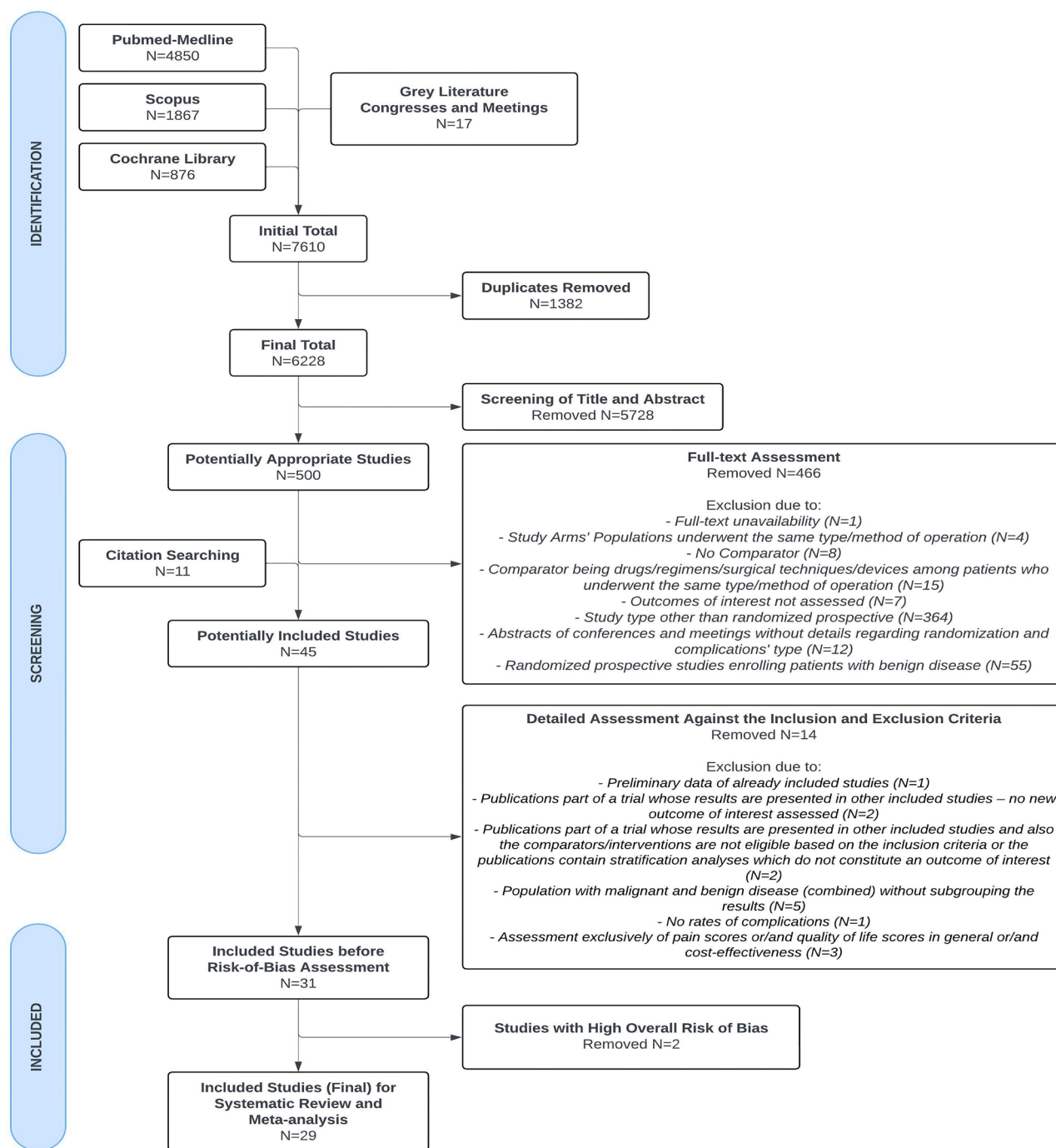


Figure 1. Study selection process.

OS by 11 studies,^{6,9,20,73,74,79,82,85,90,94,96} DFS by 10 studies,^{6,9,20,73,74,79,82,90,94,96} DSS by three studies,^{9,79,82} death rate by 14 studies,^{6,9,20,73,75,77,79,82,85,90,94,96} recurrence rate by 15 studies,^{6,9,20,73,74,77,79,82,85,86,90,91,94-96} and recurrence sites/metastases by 11 studies.^{6,9,73,74,79,82,85,86,90,94,95}

The following articles concerned the same clinical trials but they reported different outcomes of interest: i) Zullo et al.⁷² and Zullo et al.⁷³ (with precisely the same number of participants), ii) Janda et al.,¹⁷ Obermair et al.,⁷⁸ and Janda et al.⁶ (with different participant numbers reported), iii) Mourits et al.,⁷⁵ Bijen et al.,⁷⁶ and Reijntjes et al.⁷⁹ (Mourits et al.⁷⁵ and Bijen et al.⁷⁶ have precisely the same number of participants, while Reijntjes et al.⁷⁹ included fewer participants), iv) Walker et al.⁸⁴ and Walker et al.⁸⁵ (with different participant numbers reported), v) Campos et al.⁸⁸ and Campos et al.⁹⁰ (with precisely the same number of participants), and vi) Ramirez et al.,⁹ Ramirez et al.,²⁰ and Obermair et al.⁹³ (Ramirez et al.⁹ and Ramirez et al.²⁰ have the same number of participants, while Obermair et al.⁹³ included fewer participants).

Risk-of-Bias Assessment

We used the RoB 2 Cochrane Tool for randomised trials to assess the risk of bias of the initially included studies.⁵¹ As stated previously, studies with an overall "High" risk of bias were ultimately excluded. The results per outcome are presented in Supplementary Table 6. Figure 2 depicts the relevant traffic light plots, and Supplementary Figure 1 shows the relevant summary plots. Two studies were excluded because they were judged to be at overall high-risk of bias, in both cases primarily due to concerns in Domain 1 (bias arising from the randomisation process), as the reports stated that randomisation had been performed but did not provide sufficient methodological details regarding sequence generation and/or allocation concealment.

Synthesis

Population Characteristics

The included studies enrolled a total of 6,127 patients; 3,972 were treated by MIS, and among them, 3,006 had

A. ENDOMETRIAL CANCER

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Fram et al. 2002	⬜	⬜	⬜	⬜	⬜	⬜
Zorlu et al. 2005	⬜	⬜	⬜	⬜	⬜	⬜
Tozzi et al. 2005a	⬜	⬜	⬜	⬜	⬜	⬜
Tozzi et al. 2005b	⬜	⬜	⬜	⬜	⬜	⬜
Zullo et al. 2005	⬜	⬜	⬜	⬜	⬜	⬜
Ghezzi et al. 2006	⬜	⬜	⬜	⬜	⬜	⬜
Zullo et al. 2009	⬜	⬜	⬜	⬜	⬜	⬜
Walker et al. 2009	⬜	⬜	⬜	⬜	⬜	⬜
Malzoni et al. 2009	⬜	⬜	⬜	⬜	⬜	⬜
Janda et al. 2010	⬜	⬜	⬜	⬜	⬜	⬜
Mourits et al. 2010	⬜	⬜	⬜	⬜	⬜	⬜
Bijen et al. 2011	⬜	⬜	⬜	⬜	⬜	⬜
Kluivers et al. 2011	⬜	⬜	⬜	⬜	⬜	⬜
Walker et al. 2012	⬜	⬜	⬜	⬜	⬜	⬜
Obermair et al. 2012	⬜	⬜	⬜	⬜	⬜	⬜
Mäenpää et al. 2016	⬜	⬜	⬜	⬜	⬜	⬜
Salehi et al. 2017	⬜	⬜	⬜	⬜	⬜	⬜
Janda et al. 2017	⬜	⬜	⬜	⬜	⬜	⬜
Reijntjes et al. 2022	⬜	⬜	⬜	⬜	⬜	⬜

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
⬜ High
⬜ Some concerns
⬜ Low

B. CERVICAL CANCER

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Naik et al. 2010	⬜	⬜	⬜	⬜	⬜	⬜
Campos et al. 2013	⬜	⬜	⬜	⬜	⬜	⬜
Luo et al. 2018	⬜	⬜	⬜	⬜	⬜	⬜
Ramirez et al. 2018	⬜	⬜	⬜	⬜	⬜	⬜
Xu et al. 2020	⬜	⬜	⬜	⬜	⬜	⬜
Obermair et al. 2020	⬜	⬜	⬜	⬜	⬜	⬜
Campos et al. 2021	⬜	⬜	⬜	⬜	⬜	⬜
Zhu et al. 2022	⬜	⬜	⬜	⬜	⬜	⬜
Xin LV et al. 2023	⬜	⬜	⬜	⬜	⬜	⬜
Ramirez et al. 2024	⬜	⬜	⬜	⬜	⬜	⬜
Xu H et al. 2024	⬜	⬜	⬜	⬜	⬜	⬜

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
⬜ High
⬜ Some concerns
⬜ Low

C. MIXED MALIGNANCIES

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Narducci et al. 2020	⬜	⬜	⬜	⬜	⬜	⬜

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
⬜ Some concerns
⬜ Low

Figure 2. Traffic light plots for the risk-of-bias assessment (regarding all outcomes) using the RoB 2 Cochrane tool. Studies are divided into three categories: (A) those enrolling patients with endometrial cancer, (B) those enrolling patients with cervical cancer, and (C) those enrolling patients with endometrial or cervical or ovarian cancer.

endometrial, 597 cervical, and 369 either endometrial or cervical or ovarian cancer (practically speaking, the latter subgroup only concerns one study).⁹⁶ The rest of the 2,155 women received TAH, and among them, 1,628 had endometrial and 527 had cervical cancer.

There were no significant differences between the two groups (MIS vs. TAH) regarding age, body mass index, parity, tumour FIGO stage, tumour grade, and histopathologic type. However, among the cervical cancer subgroup, women in whom TAH was performed had significantly higher parity than those who underwent MIS. The mean follow-up time in the whole population was 47.5 ± 9.6 months.

Most tumours in both groups were of FIGO stage I (79.8% in the MIS group and 81.5% in the TAH group) and of grade I (39.3% and 33.9%, respectively) and II (34.9% and 38.2%, respectively). Among patients with endometrial cancer, the most common histopathologic type was endometrioid carcinoma in both groups. Among patients with cervical cancer, the most common histopathologic type was squamous carcinoma in both groups.

In most patients MIH was performed (59.9%), referring to the minimally invasive technique. However, MIH (MIS) is a broader term, often used by several studies as a compound intervention, which includes TLH, LAVH, and RALH/TRH together, making it impossible to clarify how many patients received what type of MIH. If we exclude MIH, TLH was the most common technique used in the studies included (28.2%).

Table 1 summarises the aforementioned and further details about the population characteristics per group and cancer-type subgroups.

Operation Time, Intraoperative Blood Loss, Haemoglobin Reduction, and Hospitalisation Duration

Regarding studies comparing MIS and TAH, after sensitivity analysis, the mean operative time was significantly lower in the TAH group for all cancer-type and surgery subgroups and in the whole population (SMD: 0.69, 95% CI: 0.50 to 0.88, $P < 0.001$, I^2 : 68%, Supplementary Figure 2).

Before and after sensitivity analysis, the mean intraoperative blood loss was significantly lower in the MIS group among all cancer-type subgroups and TLH, MIH, and RALH/TRH subgroups. For the whole population SMD was -0.98 (95% CI: -1.29 to -0.66, $P < 0.001$, I^2 : 71%,

favouring MIS, Supplementary Figure 3). Haemoglobin reduction (all studies concerned endometrial cancer and TLH) was significantly lower in the MIS group, but the result presented high statistical heterogeneity.

Before and after sensitivity analysis, the mean hospital stay was significantly shorter in the MIS group for TLH, LAVH, RALH/TRH, and all cancer-type subgroups. The latter was significant for the whole population but presented high statistical heterogeneity (Supplementary Figure 4).

Complications

The risk of a patient presenting at least one complication did not differ between MIS and TAH for surgery subgroups, cancer-type subgroups, and the whole population. The total complication rates were lower in the MIS group among LAVH (23/63 in MIS vs. 58/59 in TAH, RR 0.37, 95% CI 0.27 to 0.52, $P < 0.001$) and endometrial cancer subgroup (580/2359 in MIS vs. 418/1438 in TAH, RR 0.84, 95% CI 0.73 to 0.96, $P = 0.01$, I^2 : 17%). The overall effect for the rest of the surgery, cancer-type subgroups, and the whole population was not significant (Supplementary Figure 5).

Intraoperative Complications and Injuries

No differences were found regarding the risk of intraoperative complications (number of events) among the surgery, cancer-type subgroups, and the whole population. The risk of intraoperative injuries was significantly higher in the MIS group among the entire population (241/3142 in MIS vs. 102/2141 in TAH, RR 1.53, 95% CI 1.23 to 1.91, $P < 0.001$, I^2 : 0%) and among all cancer-type and TLH and MIH subgroups. Still, it was not significant in the LAVH subgroup (Figure 3 and Supplementary Figure 6).

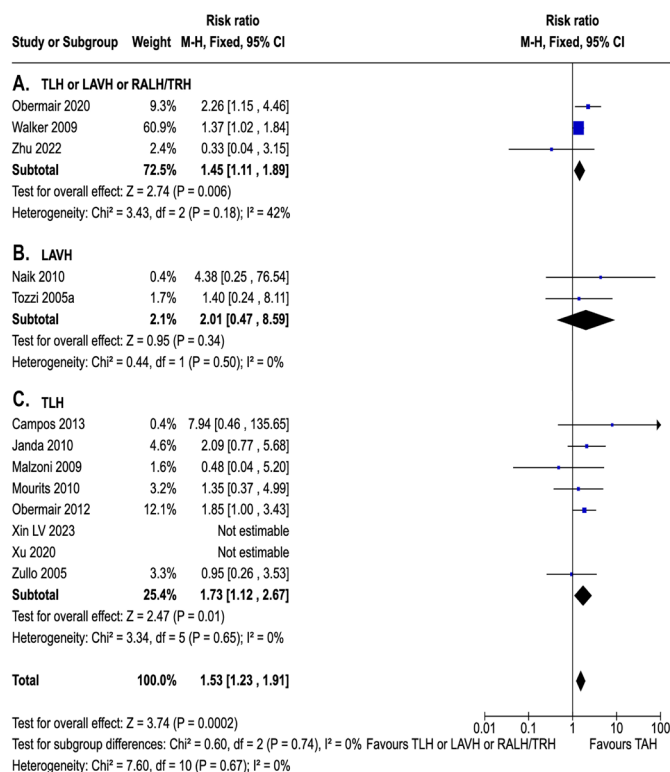
The risk for bladder injury was significantly higher in the MIS group for the whole population (40/2795 in MIS vs. 14/1846 in TAH, RR 1.84, 95% CI 1.03 to 3.29, I^2 : 0%), but not significant for any of the cancer-type and surgery subgroups (Figure 3 and Supplementary Figure 7).

The risk for vaginal injury was significantly higher in the MIS group for the whole population (RR: 12.39, 95% CI 1.61 to 95.29, $P = 0.02$, I^2 : 0%) and in patients who underwent TLH (RR: 21.6, 95% CI 1.28 to 363.58, $P = 0.03$, I^2 : 0%, Supplementary Figure 8). However, this estimate was based on a rare outcome, with 13/467 events in the MIS group vs. 0/408 in the TAH group across two RCTs.

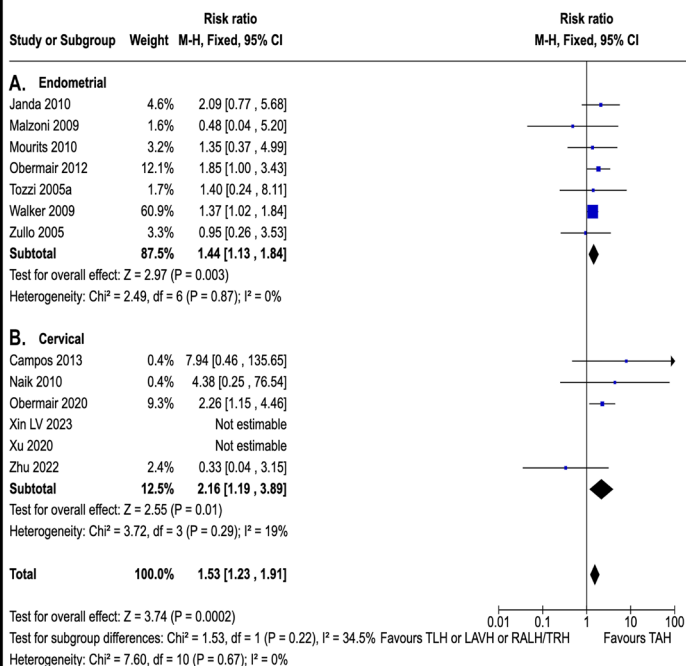
Table 1. Patient characteristics per group and cancer-type subgroups. Note that numerical variables are presented as weighted mean $\pm$ weighted standard deviation based on the relevant values of the included studies.

		Minimally invasive surgery (TLH, LAVH, RALH/TRH)				Open surgery (TAH)		
		Endometrial (n=3006)	Cervical (n=597)	Mixed (n=369)	All (n=3972)	Endometrial (n=1628)	Cervical (n=527)	All (n=2155)
Age (years)		63.3±1.04	47.5±5.9	57.3±10.6	60.3±6.2	63.0±0.8	45.4±1.7	58.6±7.7
BMI (kg/m²)		30.4±2.9	29.1±2	30.5±0.1	30.1±2.8	31.1±3.2	26.1±0.3	30.3±3.5
Parity		2.5±0.6	2.4±0.2	-	2.5±0.5	2.2±0.1	2.9±0.8	2.5±0.6
Surgical stage	FIGO stage I	2057/2635 (78.1%)	528/597 (88.4%)	289/369 (78.3%)	2874/3601 (79.8%)	1232/1561 (78.9%)	469/527 (89%)	1701/2088 (81.5%)
	FIGO stage II	175/2635 (6.6%)	69/597 (11.6%)	56/369 (15.2%)	300/3601 (8.4%)	123/1561 (7.9%)	55/527 (10.4%)	178/2088 (8.5%)
	FIGO stage III	295/2635 (11.2%)	0/597 (0%)	12/369 (3.3%)	307/3601 (8.5%)	162/1561 (10.4%)	527 (0%)	162/2088 (7.8%)
	FIGO stage IV	6/2635 (0.2%)	0/597 (0%)	2/369 (0.5%)	8/3601 (0.2%)	5/1561 (0.3%)	0/527(0%)	5/2088 (0.2%)
	Unspecified	102/2635 (3.9%)	0/597 (0%)	10/369 (2.7%)	112/3601 (3.1%)	39/1561 (2.5%)	3/527 (0.6%)	42/2088 (2%)
Grade	Grade I	495/978 (50.6%)	48/402 (12%)	-	543/1380 (39.3%)	310/644 (48.1%)	42/393 (10.7%)	352/1037 (33.9%)
	Grade II	315/978 (32.2%)	167/402 (41.6%)	-	482/1380 (34.9%)	232/644 (36%)	164/393 (41.7%)	396/1037 (38.2%)
	Grade III	119/978 (12.2%)	104/402 (25.9%)	-	223/1380 (16.2%)	90/644 (14%)	106/393 (27%)	196/1037 (18.9%)
	Unspecified	49/978 (5%)	83/402 (20.5%)	-	132/1380 (9.6%)	12/644 (1.9%)	81/393 (20.6%)	93/1037 (9%)
	Endometrioid	2083/2536 (82%)	0/496 (0%)	166/369 (45%)	2249/3401 (66.1%)	1312/1562 (84%)	0/427 (0%)	1312/1989 (65.9%)
Histopathology	Mucinous	12/2536 (0.5%)	0/496 (0%)	4/369 (1.1%)	16/3401 (0.5%)	5/1562 (0.3%)	0/427 (0%)	5/1989 (0.25%)
	Serous	241/2536 (9.5%)	0/496 (0%)	13/369 (3.5%)	254/3401 (7.5%)	138/1562 (8.8%)	0/427 (0%)	138/1989 (6.9%)
	Clear-cell	38/2536 (1.5%)	0/496 (0%)	10/369 (2.7%)	48/3401 (1.4%)	23/1562 (1.5%)	0/427 (0%)	23/1989 (1.2%)
	Mixed-cell	55/2536 (2.2%)	4/496 (0.8%)	0/369 (0%)	59/3401 (1.7%)	30/1562 (1.9%)	5/427 (1.2%)	35/1989 (1.8%)
	Squamous	4/2536 (0.2%)	343/496 (69.2%)	114/369 (30.9%)	461/3401 (13.6%)	4/1562 (0.3%)	298/427 (69.8%)	302/1989 (15.2%)
	Small-cell	2/2536 (0.08%)	0/496 (0%)	0/369 (0%)	2/3401 (0.1%)	1/1562 (0.06%)	0/427 (0%)	1/1989 (0.05%)
	Adenocarcinoma	1/2536 (0.04%)	106/496 (21.4%)	18/369 (4.9%)	125/3401 (3.7%)	5/1562 (0.3%)	99/427 (23.2%)	104/1989 (5.2%)
	Neuroendocrinoid	0/2536 (0%)	3/496 (0.6%)	0/369 (0%)	3/3401 (0.1%)	0/1562 (0%)	0/427 (0%)	0/1989 (0%)
	Adenoid	0/2536 (0%)	18/496 (3.6%)	0/369 (0%)	18/3401 (0.5%)	0/1562 (0%)	0/427 (0%)	0/1989 (0%)
	Sarcoma	65/2536 (2.58%)	0/496 (0%)	3/369 (0.8%)	68/3401 (2%)	37/1562 (2.4%)	0/427 (0%)	37/1989 (1.9%)
Type of surgery	Others	35/2536 (1.4%)	22/496 (4.4%)	41/369 (11.1%)	98/3401 (2.8%)	7/1562 (0.44%)	25/427 (5.8%)	32/1989 (1.6%)
	TLH	810 (26.9%)	117 (19.6%)	193 (52.3%)	1120 (28.2%)	NA	NA	NA
	LAVH	129 (4.3%)	37 (6.2%)	0 (0%)	166 (4.2%)	NA	NA	NA
	MIH	1969 (65.5%)	413 (69.2%)	0 (0%)	2382 (59.9%)	NA	NA	NA
	RALH	98 (3.3%)	0 (0%)	176 (47.7%)	274 (6.9%)	NA	NA	NA
Total population	TRH	0 (0%)	30 (5%)	0 (0%)	30 (0.8%)	NA	NA	NA
		Patients with endometrial cancer	Patients with cervical cancer	Patients either with endometrial or cervical or ovarian cancer	All enrolled patients			
Mean total follow-up (months)		51.5±6.9	37.9±7.2	32.3±13.2	47.5±9.6			
TLH: Total laparoscopic hysterectomy, LAVH: Laparoscopically assisted vaginal hysterectomy, RALH: Robot-assisted laparoscopic hysterectomy, TRH: Total robotic hysterectomy, TAH: Total abdominal hysterectomy, BMI: Body mass index, FIGO: International Federation of Gynaecology and Obstetrics, NA: Not applicable, MIH: Minimally invasive hysterectomy.								

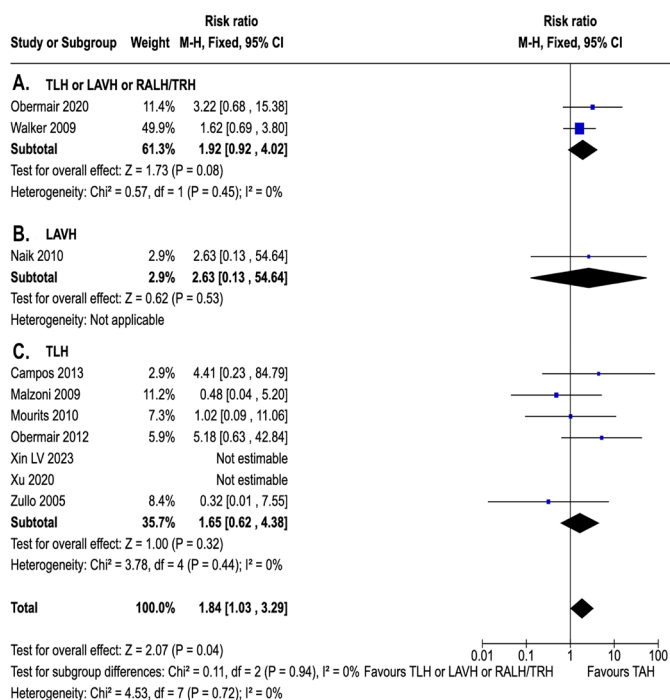
1. Intraoperative Injuries - Surgery Subgroups



2. Intraoperative Injuries - Cancer Subgroups



3. Bladder Injuries - Surgery Subgroups



4. Bladder Injuries - Cancer Subgroups

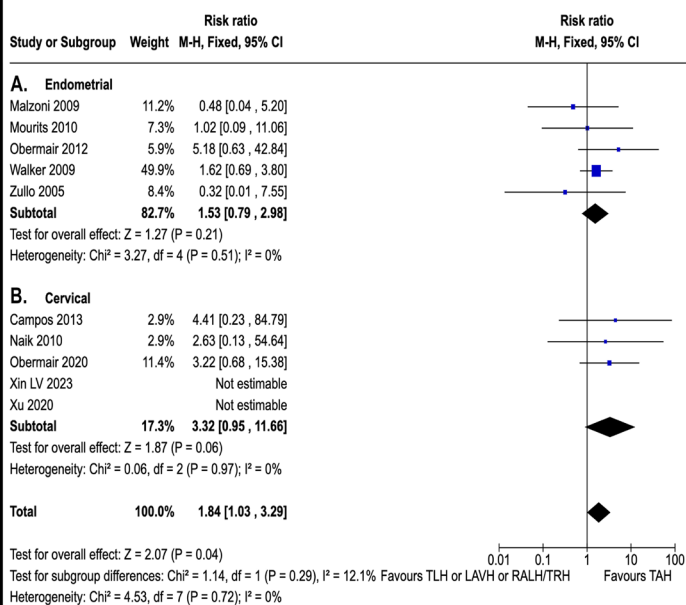


Figure 3. Forest plots regarding (1) intraoperative injuries per surgery subgroups, (2) intraoperative injuries per cancer subgroups, (3) bladder injuries per surgery subgroups, and (4) bladder injuries per cancer subgroups. TLH: Total laparoscopic hysterectomy, LAVH: Laparoscopically assisted vaginal hysterectomy, RALH/TRH: Robot-assisted laparoscopic hysterectomy/total robotic hysterectomy, TAH: total abdominal hysterectomy, CI: Confidence interval.

The risks for bowel, nerve, vascular, ureteral, urethral, and visceral injuries and uterus rupture did not differ between the groups in the whole population or subgroup analyses.

Blood Transfusion Rates

The risk for blood transfusion (intra- and postoperatively) was significantly lower in the MIS (4/92) vs. the TAH (14/91) for the LAVH subgroup (RR: 0.28, 95% CI 0.10 to 0.82, $P=0.02$, I^2 : 0%). It was also significantly lower in the MIS (11/296) vs. the TAH (25/274) for the cervical cancer subgroup (RR: 0.42, 95% CI 0.21 to 0.84, $P=0.01$, I^2 : 0%) (Supplementary Figure 9). However, this estimate was based on a rare outcome. The risk of transfusion did not differ between the groups for the whole population and the rest of the subgroups. Intraoperative and postoperative blood transfusion rates were assessed in one study, and no significant difference was noted.⁹³

Postoperative Complications

The risk of postoperative complications was lower in the MIS for the TLH subgroup (19/73 in MIS vs. 32/69 in TAH, RR: 0.57, 95% CI 0.36 to 0.90, $P=0.02$, I^2 : 0%), LAVH subgroup (20/63 in MIS vs. 49/59 in TAH, RR: 0.38, 95% CI 0.26 to 0.56, $P<0.001$), and endometrial cancer subgroup (31/103 in MIS vs. 67/97 in TAH, RR: 0.44, 95% CI 0.30 to 0.65, $P<0.001$, I^2 : 24%). However, the result was not significant among the entire population, MIH, and cervical cancer subgroups (Supplementary Figure 10).

The risk for ileus development was significantly lower in the MIS group for the whole population (69/2249 in MIS vs. 73/1357 in TAH, RR: 0.52, 95% CI 0.38 to 0.72, $P<0.001$, I^2 : 0%) and for MIH and endometrial cancer subgroups (Supplementary Figure 11).

The risk for wound complications was significantly lower in the MIS group regarding the whole population (74/2948 in MIS vs. 98/2000 in TAH, RR: 0.42, 95% CI 0.23 to 0.76, $P=0.004$, I^2 : 42%), the TLH, and the endometrial and cervical cancer subgroups (Supplementary Figure 12). Wound dehiscence risk was significantly lower in the MIS group for the whole population (4/559 in MIS vs. 12/411 in TAH, RR: 0.32, 95% CI 0.13 to 0.83, $P=0.02$, I^2 : 13%) and the TLH subgroup. These studies enrolled only women with endometrial cancer (Supplementary Figure 13). The results for wound infection risk were analogous: risk was significantly lower in the MIS group for the whole population (64/2559 in MIS vs. 60/1621 in TAH, RR: 0.65, 95% CI 0.46 to 0.92, $P=0.02$, I^2 : 19%) and TLH and endometrial cancer subgroups (Supplementary Figure 14).

Risk of vaginal vault/cuff complications was higher in the MIS group regarding the MIH subgroup (11/279 in MIS vs. 2/257 in TAH, RR: 5.07, 95% CI 1.13 to 22.64, $P=0.03$). Still, conclusions cannot be drawn since only one study assessed this outcome among patients in the MIH subgroup.⁹³ The latter risk did not significantly differ between the two groups regarding the whole population and the rest of the subgroups (Supplementary Figure 15).

The risk for developing urinary symptoms (compound outcome including urinary incontinence, urinary retention, UTI, and uterostenosis) did not significantly differ between the two arms regarding the whole population and all subgroups. Particularly, the risk for UTI and urinary retention did not differ between MIS and TAH among the entire population, surgery type, and cancer-type subgroups. The risk for haematoma development (compound outcome), fever development, postoperative infection, fistulas, and DVT/PE did not differ between the two groups overall and for any subgroup.

Recurrence and Death Rates-Survival

After sensitivity analysis, the risks for total and 4.5/5-year recurrence were significantly higher in the MIS group regarding the cervical cancer subgroup (40/352 in MIS vs. 12/343 in TAH, RR: 3.23, 95% CI 1.73 to 6.04, $P<0.001$, I^2 : 0%). Regarding the MIH subgroup, the latter results presented high statistical heterogeneity even after the sensitivity analysis. No significant differences were noted among the whole population and the rest of the subgroups (Supplementary Figures 16 and 17).

The risk for local recurrence was significantly higher in the MIS group among the cervical cancer and MIH subgroups (18/319 in MIS vs. 4/312 in TAH, RR: 4.40, 95% CI 1.51 to 12.86, $P=0.007$, Supplementary Figure 18). The risk for recurrence at multiple sites was significantly higher in the MIS group only among the cervical cancer subgroup (10/319 in MIS vs. 2/312 in TAH, RR: 4.89, 95% CI 1.08 to 22.14, $P=0.04$, Supplementary Figure 19). The risk for vaginal vault/cuff, pelvic, wound/port-site recurrence, and distant metastasis did not significantly differ between the two groups in the whole population and for any subgroup.

The risk for death by the disease (cancer) was significantly higher in the MIS group for the cervical cancer subgroup after sensitivity analysis (18/352 in MIS vs. 3/343 in TAH, RR: 5.69, 95% CI 1.72 to 18.84, $P=0.004$, I^2 : 0%, Supplementary Figure 20). The risk of death (general) did not significantly differ for the whole population and the

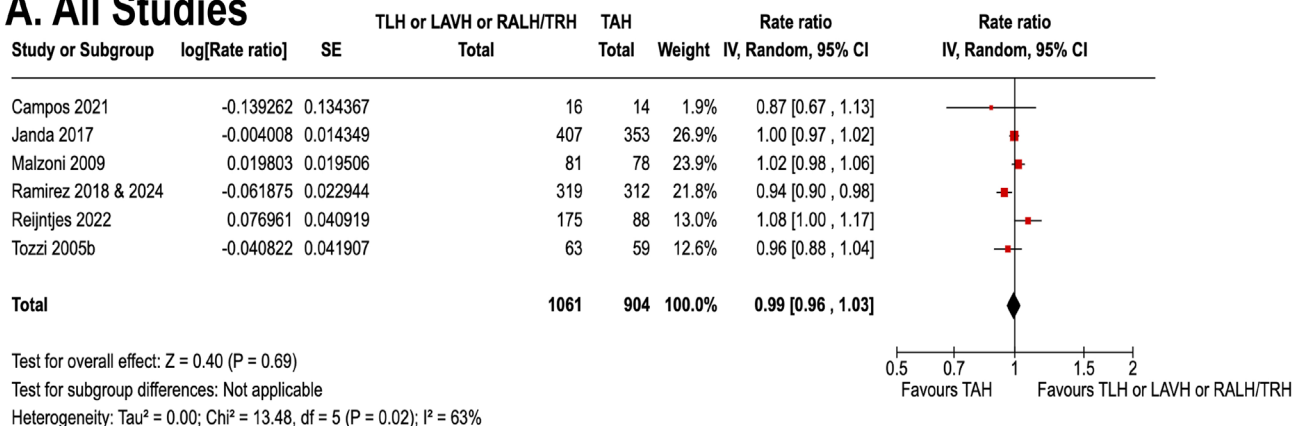
subgroups. The MIH subgroup results presented high statistical heterogeneity even after sensitivity analysis.

Cervical cancer patients in whom TAH was performed presented significantly higher OS and DFS rate ratios and decreased OS and DFS HR than those of the MIS group. The cervical cancer OS rate ratio was 0.94 (95% CI 0.90 to 0.98, $P=0.005$, $I^2=0\%$), and the relevant OS-HR was 2.55

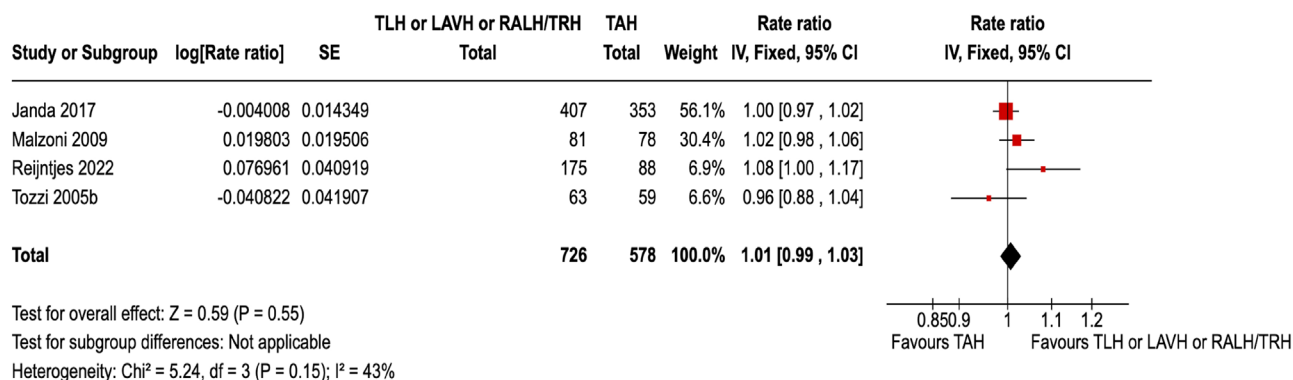
(95% CI 1.35 to 4.85, $P=0.004$, $I^2=0\%$). The cervical cancer DFS rate ratio was 0.89 (95% CI 0.84 to 0.94, $P<0.001$, $I^2=0\%$), and the relevant DFS HR was 3.61 (95% CI 1.95 to 6.69, $P<0.001$, $I^2=0\%$). The OS and DFS rate ratios and OS and DFS HRs for the whole population and among endometrial cancer patients did not reach statistical significance (Figures 4 and 5).

1. OVERALL SURVIVAL (Rate Ratio)

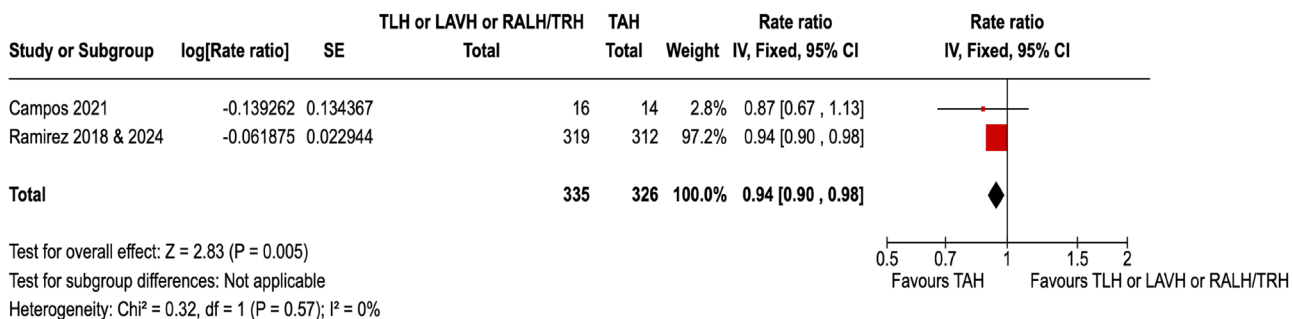
1A. All Studies



1B. Endometrial Cancer

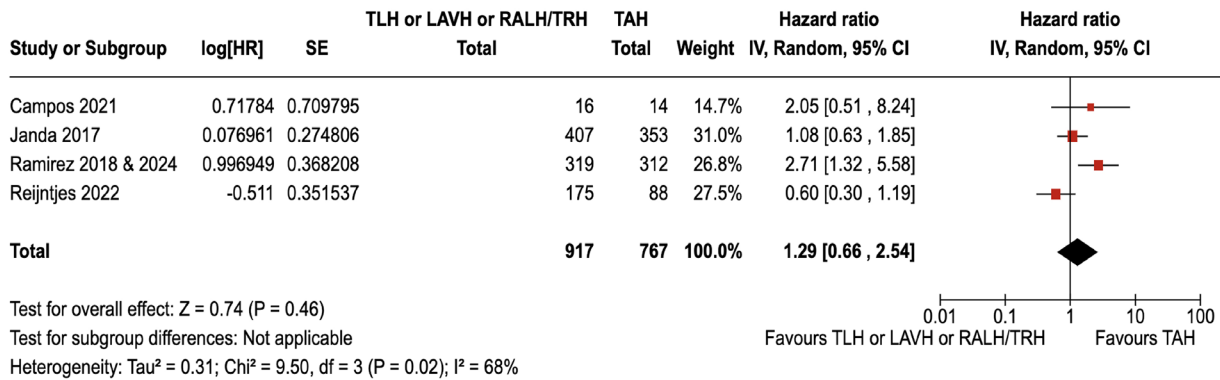


1C. Cervical Cancer

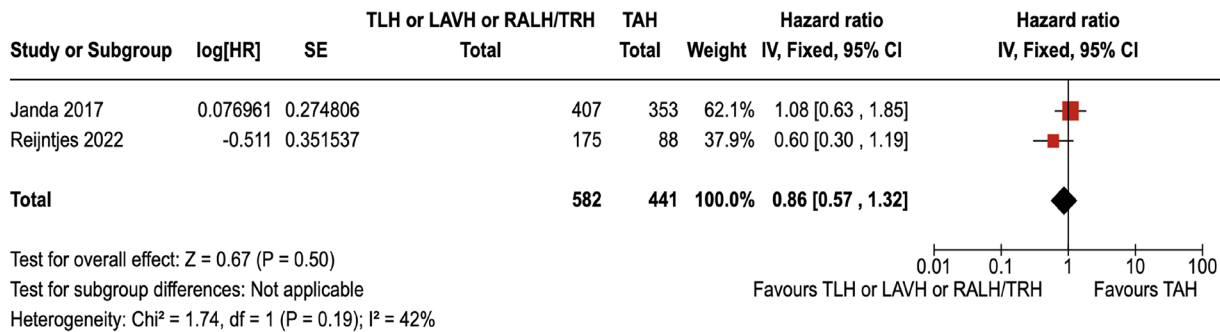


2. OVERALL SURVIVAL (Hazard Ratio)

2A. All Studies



2B. Endometrial Cancer



2C. Cervical Cancer

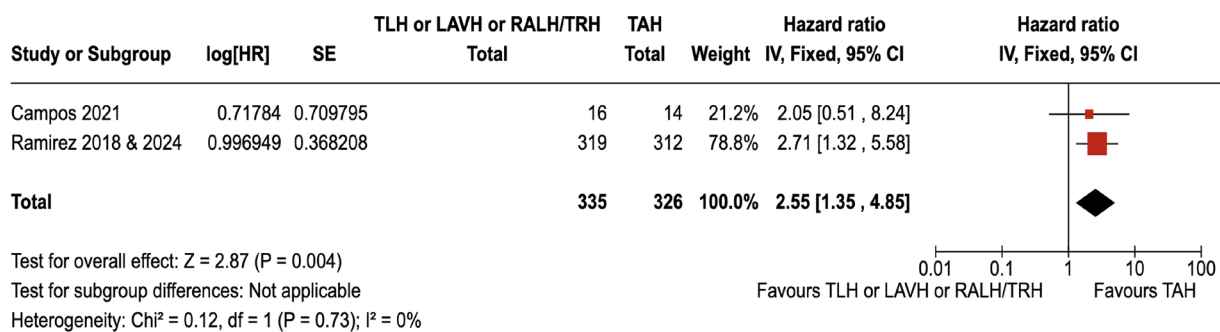
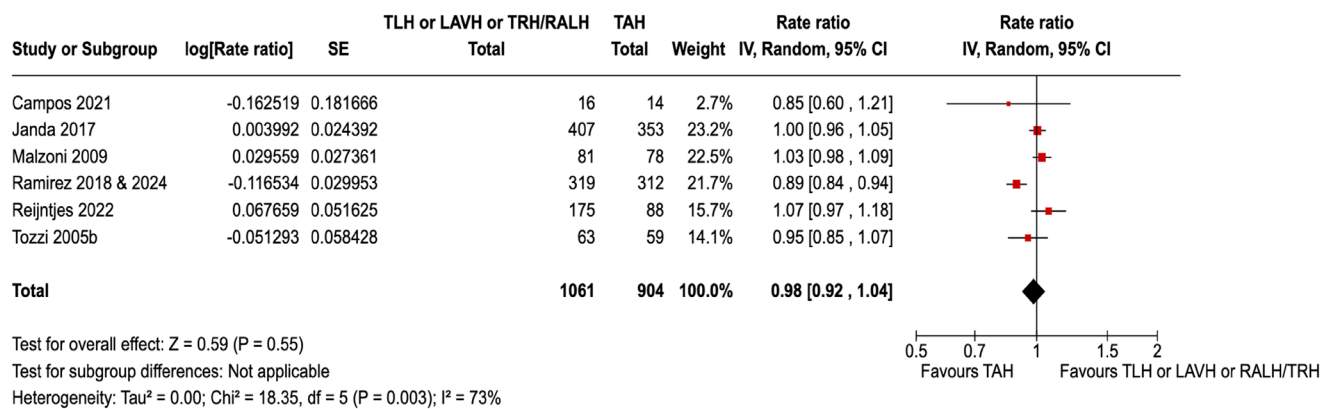


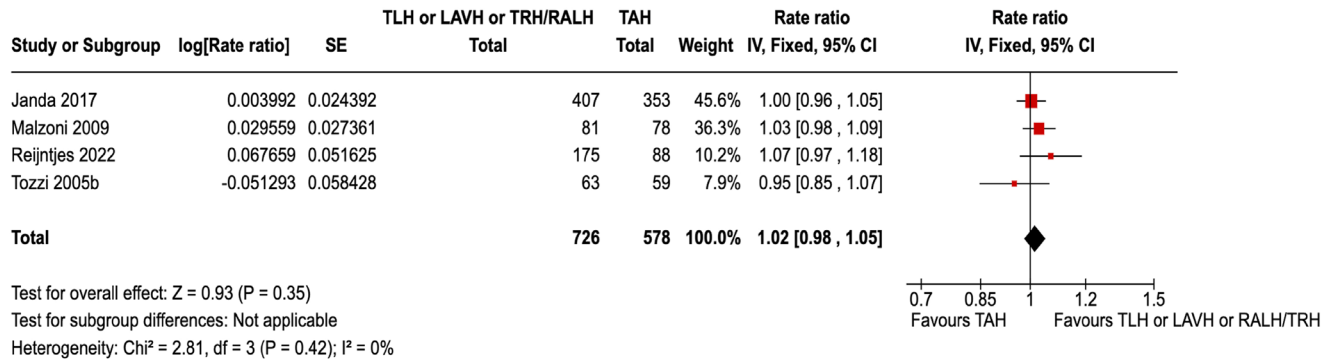
Figure 4. Forest plots regarding overall survival rate ratios (1) and hazard ratios (2) for the entire population (1A and 2A), endometrial cancer patients (1B and 2B), and cervical cancer patients (1C and 2C). All effect estimates compare minimally invasive surgery (MIS)—TLH, LAVH, RALH/TRH—with total abdominal hysterectomy (TAH). For survival rate ratios, values below 1 indicate lower overall survival rates in the MIS group and therefore favour TAH, whereas values above 1 favour MIS. For hazard ratios, values above 1 indicate a higher hazard of death (i.e., lower overall survival) in the MIS group and therefore favour TAH. Values below 1 indicate a lower hazard in the MIS group and therefore favour MIS. TLH: Total laparoscopic hysterectomy, LAVH: Laparoscopically assisted vaginal hysterectomy, RALH/TRH: Robot-assisted laparoscopic hysterectomy/total robotic hysterectomy, OS: Overall survival, SE: Standard error, CI: Confidence interval, IV: Inverse variance.

1.DISEASE FREE SURVIVAL (Rate Ratio)

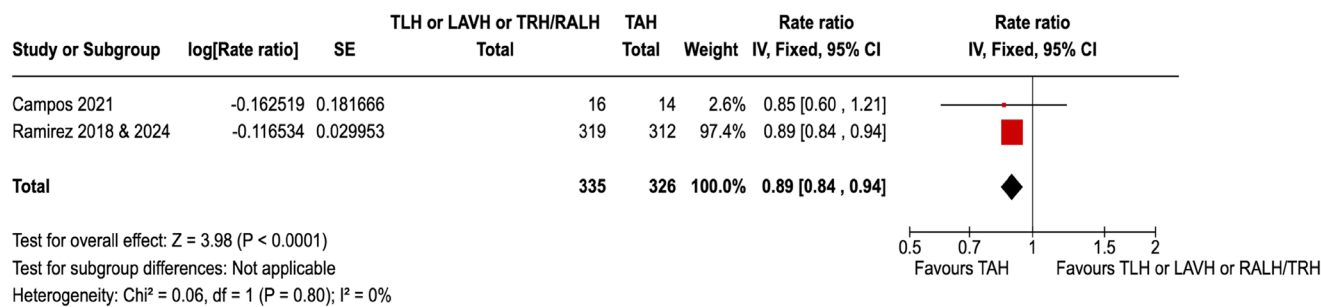
1A. All Studies



1B. Endometrial Cancer

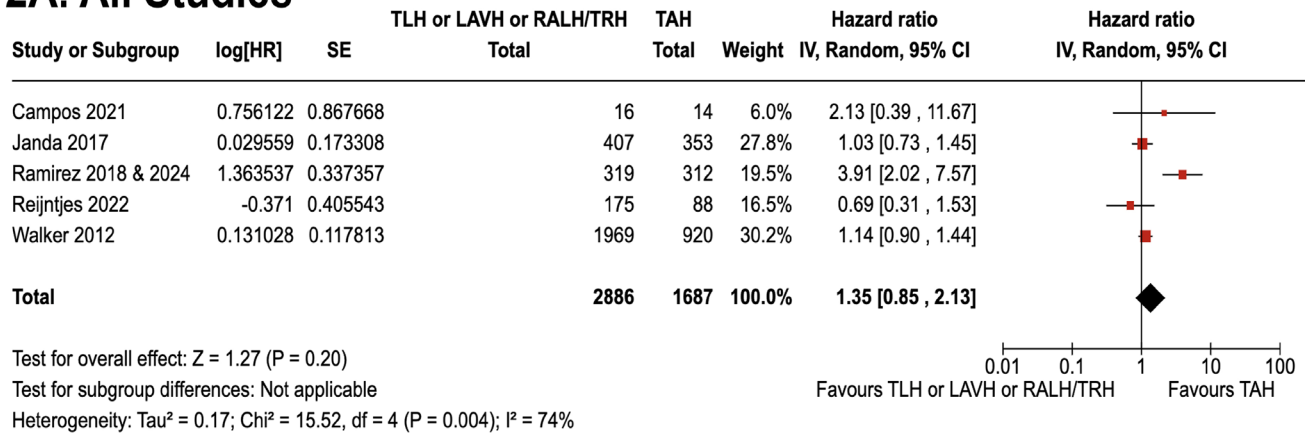


1C. Cervical Cancer

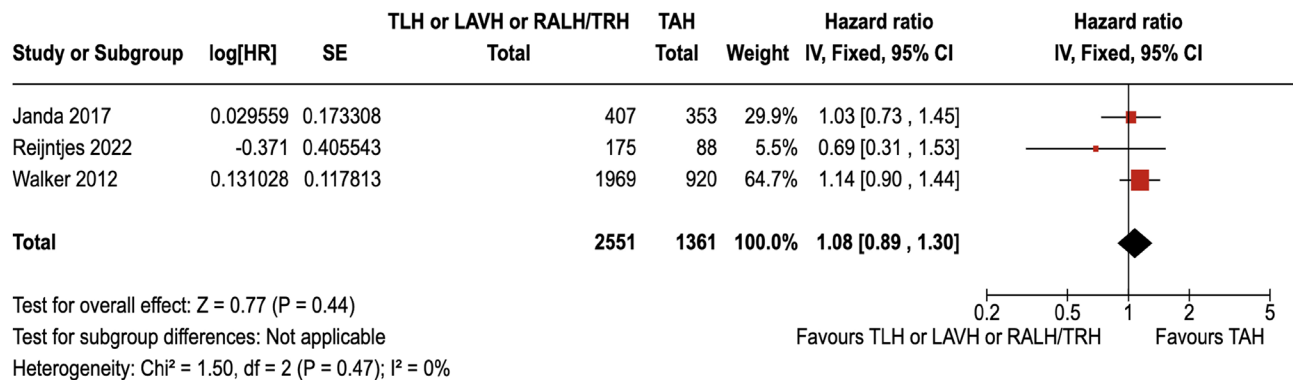


2. DISEASE FREE SURVIVAL (Hazard Ratio)

2A. All Studies



2B. Endometrial Cancer



2C. Cervical Cancer

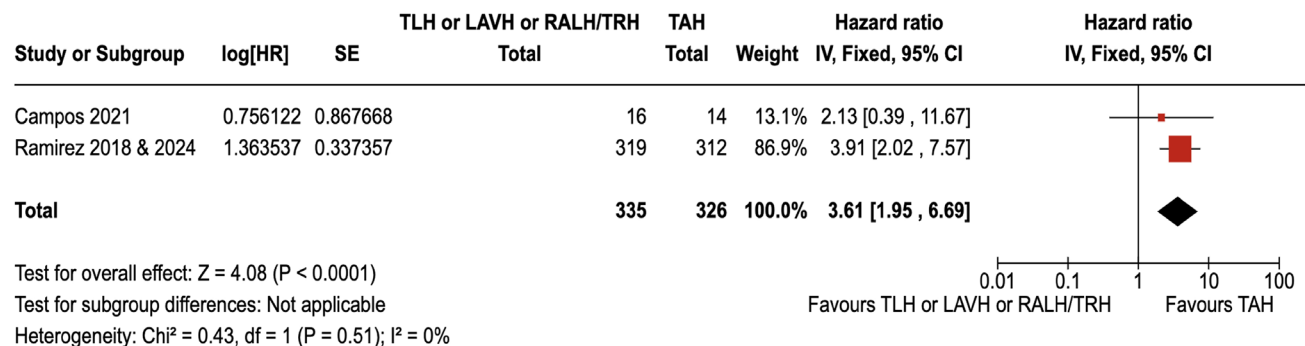


Figure 5. Forest plots regarding disease-free survival rate ratios (1) and hazard ratios (2) for the entire population (1A and 2A), endometrial cancer patients (1B and 2B), and cervical cancer patients (1C and 2C). All effect estimates compare minimally invasive surgery (MIS)—TLH, LAVH, RALH/TRH—with total abdominal hysterectomy (TAH). For disease-free survival rate ratios, values below 1 indicate lower disease-free survival rates in the MIS group and therefore favour TAH, whereas values above 1 favour MIS. For hazard ratios, values above 1 indicate a higher hazard of recurrence or death (i.e., lower disease-free survival) in the MIS group and therefore favour TAH. Values below 1 indicate a lower hazard in the MIS group and therefore favour MIS. TLH: Total laparoscopic hysterectomy, LAVH: Laparoscopically assisted vaginal hysterectomy, RALH/TRH: Robot-assisted laparoscopic hysterectomy/total robotic hysterectomy, DFS: Disease-free survival, SE: standard error, CI: Confidence interval, IV: Inverse variance.

DSS rate ratio was assessed by two studies enrolling patients with endometrial cancer,^{79,82} and no significant overall effect was noted (rate ratio 1.03, 95% CI 0.96 to 1.11, $P=0.42$, I^2 : 43%). DSS-HR was assessed by two studies (one enrolling patients with endometrial and the other patients with cervical cancer), and no significant overall effect was noted (HR: 1.32, 95% CI 0.32 to 5.45, $P=0.70$, I^2 : 80%). However, the latter result is characterised by high statistical heterogeneity, and no reliable conclusions can be drawn (Supplementary Figure 21).

Studies Comparing Outcomes Between Different Minimally Invasive Techniques

Regarding studies comparing TLH and RALH, the SMD was not significant concerning operative time and intraoperative blood loss, but reliable conclusions cannot be drawn due to the high heterogeneity. Haemoglobin reduction and hospitalisation duration did not differ.

The risk of a patient presenting at least one complication did not differ between the groups. Similarly, the risk for total, intraoperative, and postoperative complications (number of events) and intraoperative injuries did not differ across the groups. The risk for blood transfusion, infection, fistulas, wound complications, and DVT/PE did not differ between the groups. Similarly, the risk for intraoperative and postoperative blood transfusion, fever, and vaginal vault/cuff complications did not differ, but these outcomes were only assessed by one study.⁹⁶ The risk for UTI and urine retention did not differ between the two groups, but it was only evaluated by one study.⁸⁷ The risk for developing urinary symptoms was significantly lower in the RALH group than TLH (RR: 2.99, 95% CI 1.12 to 8.04, $P=0.03$, I^2 : 0%).

Death rates, OS, and DFS were assessed by one study, and no significant differences were noted.⁹⁶

The study comparing TLH and LAVH revealed a significantly longer operative time in the LAVH subgroup. Still, no other significant differences were noted regarding intraoperative blood loss, hospitalisation duration, total number of patients with at least one complication, total complications (number of events), intraoperative complications and injuries, postoperative complications, blood transfusion, recurrence rates, and recurrence sites.⁸⁶

The study comparing LAVH and TRH revealed a significantly shorter hospitalisation duration and fewer total postoperative complications (compound outcome—number of events) in the TRH group. No other differences were noted regarding the rest of the outcomes of interest of this SRMA. Similarly, no differences were recorded regarding recurrence, cancer-related death, and overall death rates.⁹⁵

Publication Bias

Ten or more studies were available for analysis for the following outcomes: operative time, intraoperative blood loss, hospitalisation duration, intraoperative injuries, bladder injuries, blood transfusion, wound complications, recurrence, and death by cancer. Based on the funnel plots, Egger's test (mixed-effects meta-regression and weighted regression), and rank correlation test, publication bias was detected for the following: operative time, intraoperative blood loss, hospitalisation duration, wound complications, recurrence, and death by cancer (Supplementary Figure 22). Publication bias was not detected for intraoperative injuries, bladder injuries, and blood transfusion (Supplementary Figure 23).

Strength of Evidence GRADE Reporting System

For each outcome of interest, we took under consideration the number of studies, the design, the inconsistency in results across the studies, the directness/indirectness and the precision/imprecision of the reported results, the publication bias probability, the effect size, the plausible confounding influence, and the dose-response gradient. Table 2 shows the results of the above evaluation.

The certainty of the evidence was judged as "high" for the following outcomes: operative time, intraoperative blood loss, hospitalisation duration, bladder injuries, vaginal injuries, blood transfusion, wound complications, wound dehiscence, 4.5/5-year recurrence, OS (rate ratio and HR), DFS (rate ratio and HR), and DSS (rate ratios).

Possible publication bias was detected for several key outcomes, including recurrence and death, based on funnel plot asymmetry and/or formal testing. This reduces confidence in the corresponding pooled estimates, which should therefore be interpreted with caution.

Table 2. Summary of findings for the included studies after evaluation with GRADE reporting system.

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Study event rates (%)		Anticipated absolute effects		
				With total abdominal hysterectomy	With minimally invasive surgery (MIS)	Risk with total abdominal hysterectomy	Risk difference with MIS	NNH/NNTB (95% CI)
Operative time (minutes)	2149 (10)	High	-	984	1165	-	SMD 0.69 SD more (0.5 more to 0.88 more)	NA
Intraoperative blood loss (mL)	1053 (7)	High	-	466	587	-	SMD 0.98 SD fewer (1.29 fewer to 0.66 fewer)	NA
Hospitalisation duration (days)-cancer subgroups	3105 (5)	High	-	1120	1985	-	SMD 1.3 SD fewer (1.84 fewer to 0.75 fewer)	NA
Hospitalisation duration (days)-surgery subgroups	3880 (8)	High	-	1548	2332	-	SMD 1.99 SD lower (2.73 lower to 1.24 lower)	NA
Total number of complications (intra- and postoperative- number of events)-cancer subgroups	4397 (8)	Low	RR 0.88 (0.74 to 1.06)	582/1726 (33.7%)	778/2671 (29.1%)	337 per 1,000	40 fewer per 1,000 (88 fewer to 20 more)	NNTB 22 (14-56)
Total number of complications (intra- and postoperative- number of events)-surgery subgroups	4519 (1)	Moderate	RR 0.77 (0.60 to 0.99)	640/1785 (35.9%)	801/2734 (29.3%)	359 per 1,000	82 fewer per 1,000 (143 fewer to 4 fewer)	NNTB 16 (11-27)
Intraoperative injuries	5283 (13)	Moderate	RR 1.53 (1.23 to 1.91)	102/2141 (4.8%)	241/3142 (7.7%)	48 per 1,000	25 more per 1,000 (11 more to 43 more)	NNH 35 (24-64)
Bladder injury	4641 (10)	High	RR 1.84 (1.03 to 3.29)	14/1846 (0.8%)	40/2795 (1.4%)	8 per 1,000	6 more per 1,000 (0 fewer to 17 more)	NNH 149 (79-2688)
Vaginal injury	875 (2)	High	RR 12.39 (1.61 to 95.29)	0/408 (0.0%)	13/467 (2.8%)	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)	NNH 36 (22-77)
Blood transfusion (intra- and postoperative)	4709 (10)	High	RR 0.60 (0.34 to 1.07)	113/1881 (6.0%)	167/2828 (5.9%)	60 per 1,000	24 fewer per 1,000 (40 fewer to 4 more)	NNTB 979 (CI crosses null)
Total number of postoperative complications (number of events)	800 (5)	Moderate	RR 0.61 (0.33 to 1.12)	205/385 (53.2%)	191/415 (46.0%)	532 per 1,000	208 fewer per 1,000 (357 fewer to 64 more)	NNTB 14 (8-344)

Table 2. Continued

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Study event rates (%)		Anticipated absolute effects		NNH/NNTB (95% CI)
				With total abdominal hysterectomy	With minimally invasive surgery (MIS)	Risk with total abdominal hysterectomy	Risk difference with MIS	
Wound complications	4948 (11)	High	RR 0.42 (0.23 to 0.76)	98/2000 (4.9%)	74/2948 (2.5%)	49 per 1,000	28 fewer per 1,000 (38 fewer to 12 fewer)	NNTB 42 (29-76)
Wound dehiscence	970 (5)	High	RR 0.32 (0.13 to 0.83)	12/411 (2.9%)	4/559 (0.7%)	29 per 1,000	20 fewer per 1,000 (25 fewer to 5 fewer)	NNTB 46 (23-186)
Wound infection	4180 (9)	Moderate	RR 0.65 (0.46 to 0.92)	60/1621 (3.7%)	64/2559 (2.5%)	37 per 1,000	13 fewer per 1,000 (20 fewer to 3 fewer)	NNTB 84 (43-720)
Vaginal vault/cuff complications	1806 (8)	Low	RR 1.98 (0.66 to 5.94)	23/861 (2.7%)	48/945 (5.1%)	27 per 1,000	26 more per 1,000 (9 fewer to 132 more)	NNH 42 (24-163)
Total recurrence-cancer subgroups	4710 (10)	Low	RR 1.21 (0.86 to 1.69)	173/1885 (9.2%)	324/2825 (11.5%)	92 per 1,000	19 more per 1,000 (13 fewer to 63 more)	NNH 44 (25-198)
Total recurrence-surgery subgroups	4267 (10)	Moderate	RR 1.01 (0.82 to 1.25)	177/1667 (10.6%)	294/2600 (11.3%)	106 per 1,000	1 more per 1,000 (19 fewer to 27 more)	NNH 145 (CI crosses null)
4.5/5-year recurrence-cancer subgroups	4287 (8)	High	RR 1.48 (1.02 to 2.15)	148/1718 (8.6%)	300/2569 (11.7%)	86 per 1,000	41 more per 1,000 (2 more to 99 more)	NNH 33 (21-83)
4.5/5-year recurrence-surgery subgroups	4688 (8)	High	RR 1.11 (0.92 to 1.34)	152/2344 (6.5%)	270/2344 (11.5%)	65 per 1,000	7 more per 1,000 (5 fewer to 22 more)	NNH 20 (15-30)
Local recurrence	1175 (4)	Very low	RR 1.26 (0.38 to 4.25)	18/537 (3.4%)	32/638 (5.0%)	34 per 1,000	9 more per 1,000 (21 fewer to 109 more)	NNH 61 (CI crosses null)
Recurrence in multiple sites	4270 (4)	Low	RR 1.25 (0.43 to 3.67)	26/1673 (1.6%)	49/2597 (1.9%)	16 per 1,000	4 more per 1,000 (9 fewer to 41 more)	NNH 301 (CI crosses null)
Death by cancer-cancer subgroups	4710 (10)	Moderate	RR 1.19 (0.95 to 1.48)	111/1885 (5.9%)	213/2825 (7.5%)	59 per 1,000	11 more per 1,000 (3 fewer to 28 more)	NNH 61 (33-568)
Death by cancer-surgery subgroups	4267 (10)	Low	RR 1.06 (0.84 to 1.32)	118/1667 (7.1%)	203/2600 (7.8%)	71 per 1,000	4 more per 1,000 (11 fewer to 23 more)	NNH 138 (CI crosses null)
Overall survival (hazard ratio)-endometrial cancer	661 (2)	High	HR 0.86 (0.57 to 1.32)	326 participants	335 participants	209 per 1,000	26 fewer per 1,000 (84 fewer to 57 more)	NA
Overall survival-cervical cancer	661 (2)	High	Rate ratio 0.94 (0.90 to 0.98)	326 participants	335 participants	945 per 1,000	57 fewer per 1,000 (94 fewer to 19 fewer)	NA

Table 2. Continued

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Study event rates (%)		Anticipated absolute effects		
				With total abdominal hysterectomy	With minimally invasive surgery (MIS)	Risk with total abdominal hysterectomy	Risk difference with MIS	NNH/NNTB (95% CI)
Overall survival (hazard ratio)-cervical cancer	661 (2)	High	HR 2.55 (1.35 to 4.85)	326 participants	335 participants	56 per 1,000	81 more per 1,000 (19 more to 188 more)	NA
Disease-free survival-endometrial cancer	1306 (4)	High	Rate ratio 1.02 (0.98 to 1.05)	578 participants	728 participants	905 per 1,000	18 more per 1,000 (18 fewer to 45 more)	NA
Disease-free survival (hazard ratio)-endometrial cancer	3912 (3)	High	HR 1.08 (0.89 to 1.30)	1,361 participants	2551 participants	103 per 1,000	8 more per 1,000 (11 fewer to 29 more)	NA
Disease-free survival-cervical cancer	661 (2)	High	Rate ratio 0.89 (0.84 to 0.94)	326 participants	335 participants	963 per 1,000	106 fewer per 1,000 (154 fewer to 58 fewer)	NA
Disease-free survival (hazard ratio)-cervical cancer	661 (2)	High	HR 3.61 (1.95 to 6.69)	326 participants	335 participants	37 per 1,000	90 more per 1,000 (34 more to 186 more)	NA
Disease-specific survival	385 (2)	High	Rate ratio 1.03 (0.96 to 1.11)	147 participants	238 participants	918 per 1,000	28 more per 1,000 (37 fewer to 101 more)	NA
Disease-specific survival (hazard ratio)	894 (2)	Moderate	HR 1.32 (0.32 to 5.45)	400 participants	494 participants	28 per 1,000	9 more per 1,000 (19 fewer to 115 more)	NA

Abbreviations: CI: Confidence interval, HR: hazard ratio, RR: risk ratio, SMD: standardised mean difference, NNH: Number needed to harm, NNTB: Number needed to treat for benefit.

Notes:

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

NNH/NNTB: The values were approximated from the crude study event rates using the absolute risk difference (MIS minus TAH) with 95% CI. NNH is shown when MIS increased event risk. NNTB is shown when MIS reduced event risk. "CI crosses null" indicates that the risk-difference 95% CI included 0, so a bounded NNH/NNTB CI was not estimable. NA indicates that NNH/NNTB was not applicable to quantitative, rate-ratio, or hazard-ratio outcomes.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Discussion

Main Findings

Based on the findings, the publication bias, and the strength-of-evidence assessment, the primary and most reliable findings of our SRMA concerned bladder and vaginal injuries rates, blood transfusion rates, wound dehiscence complications, and the OS, DFS, and DSS. The risk for bladder injury was 84% higher in the MIS group for the whole population (RR: 1.84, 95% CI 1.03 to 3.29, I^2 : 0%). The risk for vaginal injury was increased 12.4-fold in the MIS group for the whole population (RR: 12.39, 95% CI 1.61 to 95.29, $P=0.02$, I^2 : 0%). Wound dehiscence risk was 68% lower in the MIS group for the whole population (RR: 0.32, 95% CI 0.13 to 0.83, $P=0.02$, I^2 : 13%). Among endometrial cancer patients, the OS, DFS, and DSS did not differ between MIS and TAH. Among cervical cancer patients, the risk for blood transfusion was 58% lower for the MIS group (RR: 0.42, 95% CI 0.21 to 0.84, $P=0.01$, I^2 : 0%). Among cervical cancer patients, the OS rate was 6% lower (0.94, 95% CI 0.90 to 0.98, $P=0.005$, I^2 : 0%) with a 1.55-fold increased HR (2.55, 95% CI 1.35 to 4.85, $P=0.004$, I^2 : 0%). The DFS rate was 11% lower (0.89, 95% CI 0.84 to 0.94, $P<0.001$, I^2 : 0%) with a 2.61-fold increased HR (3.61, 95% CI 1.95 to 6.69, $P<0.001$, I^2 : 0%).

Strength and Limitations

Our SRMA has some limitations. First, we included heterogeneous studies in terms of the population included. We divided the studies into cervical and endometrial cancer and performed a subgroup analysis. Still, even among these subgroups, the population differed in terms of cancer stage, tumour grade, and histopathology. Most studies included early-stage cancers. However, the surgical staging may have ultimately differed (after the procedure) from the one assumed before the operation. The type of surgery was not homogeneous. We used the terms TLH, LAVH, RALH/TRH, and TAH, but little differences existed among the studies. There is no need to mention the differences regarding lymphadenectomies, which depended on the cancer stage but could influence the pooled effects since lower-stage cancers generally lead to better oncologic and survival outcomes. The latter may also have influenced the pooled effects regarding complications; advanced cancer stages are associated with lower general health and, thus, higher complication rates. Another issue was the type of studies and outcomes. All studies were by nature not blinded, and the outcome

assessment was, in most cases, conducted by the surgical team, thus potentially introducing bias. The definition of outcomes was not always the same among the included studies, and although we attempted to incorporate each study's outcomes into our broader compound outcomes, that limitation may have introduced bias. Although the PROSPERO database was searched for ongoing SRMAs, the protocol for the present review was not prospectively registered. This should be considered a limitation in terms of transparency and reproducibility. Possible publication bias was detected for operative time, intraoperative blood loss, hospitalisation duration, wound complications, recurrence, and death by cancer based on funnel plot asymmetry and/or formal testing. This reduces confidence in the corresponding pooled estimates, which should therefore be interpreted with caution.

Nonetheless, our effort has some strengths. First, our search was broad and comprehensive, limiting the possibility of excluding significant reports and studies. Our methodology was indeed systematic. To the best of our knowledge, this SRMA is the first to simultaneously assess cervical and endometrial cancer management, providing a universal view. This approach is enhanced by the decision to include all types of MIS, not to focus on only one approach, and to search various complications based on the literature. Although differences did exist among the studies, the subgroups created diminished this issue. At the same time, we were attentive to reporting the conclusions since they were based on the level of evidence and publication bias. More importantly, our SRMA included only randomised trials, which represent de facto the best evidence available.

Strengths and Limitations Compared to Other Studies

Endometrial Cancer

Regarding the MIS approach, we noted among studies enrolling endometrial cancer patients: longer operative time, lower intraoperative blood loss, shorter hospitalisation duration, lower total complication and postoperative complication rates, higher intraoperative injuries (total), and lower risk for ileus and wound complications (including wound dehiscence and infection). No difference was noted regarding intraoperative complications, risk for specific injuries (bladder, vaginal, bowel, nerve, vascular, ureteral, urethral, and visceral), recurrence rates, sites of recurrence, death, and OS, DFS, and DSS.

Several observational studies assessed the issues addressed in our SRMA among women with endometrial cancer. As expected, the total operative time was longer for MIS than TAH, while blood loss measured in mL was lower and hospitalisation duration was shorter.⁹⁷⁻¹⁰⁰ However, one study comparing TLH and TAH noted a significant difference in hospitalisation duration and not in operative time and blood loss.¹⁰¹ Regarding complication rates, studies comparing LAVH and TLH with TAH showed fewer postoperative complications in general among the MIS groups.^{97,98,100} Three studies comparing TLH with TAH likewise noted significantly fewer wound infections.^{97,101} Analogous results regarding wound infections were pointed out in a third study, where, at the same time, fewer rates of DVT/PE were likewise recorded in the MIS group.¹⁰⁰ Another study showed significantly lower rates of wound infections when comparing RALH/TRH with TAH and lower transfusion rates in the RALH/TRH group than in the TLH group. However, the total complication rates were similar across all groups.⁹⁹ Another study comparing LAVH with TAH noted more vascular and bowel injuries and higher rates of PE, wound complications, and transfusions among patients in the TAH group.¹⁰² Other complications such as UTIs,¹⁰¹ wound dehiscence, and ileus¹⁰⁰ did not differ significantly. A recent retrospective study did not report any significant differences regarding intraoperative and postoperative complications in general between TLH, RALH/TRH, and vaginal hysterectomy.¹⁶ The OS and DSS were similar in a study comparing LAVH and TAH, noting no disease recurrence in the LAVH group.⁹⁸ Similarly, recurrence rates were not elevated in either the LAVH or TAH group in another study.¹⁰⁰ No difference regarding recurrence and survival rates was observed in two studies comparing TLH and TAH^{97,101} and in one study comparing TLH, RALH/TRH, and vaginal hysterectomy.¹⁶ In the latter study, it is reported that the risk of death (HR) was associated with non-endometrioid histological type, FIGO grade 3 tumour, and serosal/adnexal invasion.¹⁶

A SRMA of 21 retrospective studies enrolling patients with endometrial cancer compared the robotic and laparoscopic approach with TAH. The robotic approach presented OS, recurrence-free survival, and DSS similar to those for the laparoscopic approach, and higher OS, recurrence-free survival, and DSS rates than for TAH.²⁷ Another SRMA that included 37 cohort studies (including one non-randomised, controlled study) compared RALH/TRH with TLH and TAH for the management of endometrial cancer did not observe any significant

differences in survival and recurrence rates. Although RALH/TRH was associated with longer operative time and higher rates of vaginal cuff dehiscence, reduced blood loss, shorter hospitalisation duration, and lower intraoperative complication rates were found in the RALH/TRH group than in the TAH and TLH groups. The overall complications and postoperative complications were significantly higher in the RALH/TRH group than in the TAH group.²⁸ Another SRMA that included retrospective cohort studies assessed the perioperative outcomes of the robotic approach vs. laparotomy for the management of endometrial cancer in elderly patients. The hospitalisation duration and the overall complication rate were found to be reduced by using the robotic approach. The robotic approach was more beneficial regarding complications as age increased. However, no significant differences were noted regarding intraoperative complications.²⁹ A 2018 Cochrane meta-analysis, including nine randomised trials, reported no significant difference in OS, DFS, and recurrence-free survival between laparoscopy and laparotomy. No significant findings were noted regarding perioperative mortality, overall complication rates, and intraoperative injuries (bladder, ureteric, vascular, and bowel). Reduced blood loss, shorter hospitalisation duration, and fewer postoperative complications were noted for the laparoscopy approach.²⁶ Note that this is the only meta-analysis that included randomised trials. Our effort included 19 randomised trials assessing endometrial cancer.

Cervical Cancer

Regarding the MIS approach, we noted among studies enrolling cervical cancer patients: longer operative time, lower intraoperative blood loss, shorter hospitalisation duration, higher intraoperative injuries, lower blood transfusion rates, wound complications (compound outcome), higher risk for recurrence in total and at 4.5/5 years, higher risk for local and multiple-site recurrence, higher death by disease rates, and lower OS and DFS rates. No differences were noted regarding total complication rates, the risk for specific injuries (bladder, vaginal, bowel, nerve, vascular, ureteral, urethral, and visceral), and postoperative complications.

Regarding observational studies enrolling women with cervical cancer, as again expected, blood loss was reduced¹⁰³⁻¹⁰⁵ and hospitalisation duration was shorter^{103,104,106} for the MIS group. Interestingly, two studies noted longer operative times among patients in the TAH group,^{103,105} another found no difference,¹⁰⁴ and a

third study found no difference regarding hospitalisation duration.¹⁰⁵ In most observational studies, no difference was found between MIS and TAH regarding the total number of complications.^{103,107} One study comparing TLH and TAH noted lower rates of intraoperative and postoperative complications in the TLH group even after propensity score balancing.¹⁰⁶ In contrast, another study reported increased odds of intraoperative and postoperative complications in the TLH group, particularly reporting significantly higher odds for ureteral and bowel injuries and vesicovaginal fistulas.¹⁰⁸ In another study, reported complications included ureteral and bladder injuries and vaginal vault bleeding and dehiscence, which were more frequent in the TAH group but did not reach statistical significance.¹⁰³ In another study, postoperative gastrointestinal issues such as ileus or incomplete defecation were reported as significantly higher in the TAH than in the TLH group.¹⁰⁵ Likewise, a study comparing abdominal and laparoscopic radical trachelectomy for early cervical cancer management showed no difference in the reported total complication rates.¹⁰⁴ One study found no differences between OS and DFS between MIS and TAH. Recurrence rates between the two groups were also similar.¹⁰³ One study comparing TLH and TAH reported significantly higher rates of pelvic recurrences, peritoneal carcinomatosis, and a significantly shorter progression-free survival in the TLH group without noting a significant difference in OS.¹⁰⁹ Similarly, another study observed lower DFS rates and an increased rate of recurrence or death after adjusting for adjuvant therapy in the TLH group. However, the same study noted that the DFS and OS in high-volume centers did not significantly differ, showing that there might be selection bias in the result.¹⁰⁷ In contrast, another study noted a significantly higher OS in the TLH than in the TAH group, even after adjusting for covariates.¹⁰⁶ The study comparing abdominal and laparoscopic radical trachelectomy noted no difference in recurrence rates, OS, DFS, and DSS.¹⁰⁴ Poorer survival outcomes were associated with age, FIGO stages III-IV, tumour FIGO grade 2-3, lymph vascular invasion,¹⁰³ and the presence of residual postconisation.¹⁰⁷

A SRMA that included 21 retrospective cohort studies and one randomised trial enrolling early-stage cervical cancer patients found a 1.9-fold higher risk for peritoneal carcinomatosis in the MIS group; peritoneal carcinomatosis represented 22.2% of recurrences following MIS compared with 8.8% following TAH.³¹ Another SRMA of 10 observational studies enrolling

patients with early-stage cervical cancer and tumour size ≤ 2 cm found that MIS was associated with worse progression-free survival compared to TAH, observing at the same time a non-significant trend towards a lower OS rate in the MIS group. The rate of distant recurrence was similar between the two groups.³² A third SRMA, which included 22 cohort studies, compared RALH/TRH with TLH and TAH for managing cervical cancer and noted that overall complication rates, particularly wound infection, fever, and UTI rates, were lower for the robotic approach than TAH. Likewise, blood loss was found to be reduced and hospitalisation duration was shorter. Overall complications (intraoperative and postoperative) did not differ between RALH/TRH and TLH. No significant differences were observed regarding OS and DFS between RALH/TRH and TLH, and RALH/TRH and TAH.³³ The results of another SRMA that included 12 cohort studies enrolling women with cervical cancer were analogous: TLH was associated with longer operative time, reduced blood loss, faster recovery, lower total postoperative complication rates, and, particularly, lower wound infection, fever, and wound dehiscence rates. OS and DFS rates were similar between TLH and TAH.³⁰

Clinical and Policy Implications

Hysterectomy using a MIS approach may be associated with disadvantages regarding bladder and vaginal injuries for the whole population. Findings concerning rare events should be interpreted cautiously, because statistically significant relative estimates may be imprecise when based on very small absolute numbers and wide CIs. Vaginal injury is an illustrative example of this issue, as the high relative risk was derived from few events.

The oncologic and survival outcomes of MIS for managing endometrial cancer seem to be similar to those for TAH. Among cervical cancer patients, caution is advised regarding oncologic and survival outcomes, particularly since MIS is associated with lower OS and DFS rates.

Therefore, in early-stage endometrial cancer, MIS appears to provide oncologic outcomes comparable to those of open surgery, while preserving perioperative advantages, in compliance with current guideline recommendations that support MIS as the preferred approach.

In cervical cancer, however, MIS is associated with less favourable survival outcomes, consistent with the findings of the LACC trial and with current ESGO recommendations supporting open radical surgery as the standard approach for radical procedures. Accordingly,

the findings of the present review should be interpreted in a disease-specific context, and MIS in cervical cancer should be considered, if at all, only in carefully selected low-risk cases and in high-volume expert centers.^{9,18–20} The cervical cancer survival findings in the present SRMA should be interpreted with caution; they are largely driven by the LACC trial and its follow-up analyses. Post-LACC literature has raised several potential explanations for the unfavourable MIS results, including surgeon learning-curve effects, center variability, limited representation of robotic surgery, and the absence of uniformly applied tumour-containment or no-touch techniques. These issues are important when considering the contemporary applicability of older MIS data, particularly in the robotic era.

Likewise, it is essential to underline that many of the randomised trials in this SRMA were conducted in a laparoscopy-dominant era and preceded the widespread adoption of robotic platforms. In addition, several technical refinements now commonly used in contemporary MIS practice are potentially important effect modifiers. These were not uniformly reported across the included studies, including tumour size distribution, use of uterine manipulators, and perioperative or intraoperative practices (closure of the vaginal cuff under direct vision, tumour-containment strategies, use of protective bags, and no-touch surgical principles), intending to reduce tumour spillage and optimise oncologic outcomes. Therefore, these factors could not be evaluated consistently in the present analysis. Accordingly, although the synthesised evidence is methodologically rigorous, it may not fully reflect present-day MIS practice, particularly robotic surgery performed in high-volume oncologic centers. Ongoing randomised trials such as RACC¹¹⁰ and ROCC/GOG-3043¹¹¹ are expected to clarify further the role of modern robotic surgery in cervical cancer.

Unanswered Questions and Future Research

Our review suggests that MIS is associated with lower OS and DFS rates. More randomised studies are needed to better understand the long-term oncologic outcomes of surgical management with MIS in cervical cancer.

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Supplementary Materials: <https://d2v96fxpocvxx.cloudfront.net/8a9ff4da-541a-42fa-9980-1a9a3ab6d6c5/documents/3-2026.220-supplemantry.docx>

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Aetiology of pelvic neuropathies in women: a narrative review

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ABSTRACT

Pelvic neuropathy is an under-recognised contributor to chronic pelvic pain in women, yet a structured overview of its identifiable causes has been lacking. In this narrative review we searched PubMed, Embase and Web of Science from inception to 1 March 2024 for clinical studies describing pelvic neuropathy in women with a defined or inferable aetiology, and synthesised them thematically. We included 306 studies (215 case reports, 53 case series, 24 retrospective and 14 prospective cohort studies) describing 2,413 women. Five recurring aetiological categories emerged: iatrogenic injury (the most frequent), nerve invasion or traction by disease processes (notably endometriosis and tumours), pregnancy- and childbirth-related injury, external trauma, and compression by muscular, vascular, benign or malignant structures. Aetiologies of particular relevance to gynaecological practice included nerve-invasive endometriosis, which characteristically produces cyclical (catamenial) symptoms, and obstetric neuropathies, which are usually self-limiting. Specific neuropathic syndromes—piriformis, May–Thurner, pelvic congestion and Alcock’s canal (pudendal) syndrome—were inconsistently defined across studies. Diagnostic strategies and reporting quality varied widely, neuropathy was frequently recognised late, and the evidence base was dominated by case reports and small series; the overall certainty of evidence is therefore low and no randomised controlled trials were identified. Greater awareness of nerve-specific injury mechanisms—particularly endometriosis-related and obstetric neuropathies—together with standardised diagnostic pathways, is needed to improve recognition and outcomes for women with neuropathic pelvic pain.

Keywords: Endometriosis, iatrogenic disease, neuralgia, peripheral nervous system diseases, pelvis

Introduction

Chronic pelvic pain (CPP) affects an estimated 7-24% of women globally and represents a significant clinical and economic burden on healthcare systems and patients alike.¹ It is defined as persistent or recurrent pain in pelvic structures that lasts more than 6 months and often has no clearly identifiable cause.^{1,2} In many cases, CPP is multifactorial, involving gynaecological, urological, gastrointestinal,

musculoskeletal, neurological, and psychological components.³ Effective treatment typically requires a multidisciplinary approach, including physical therapy, pharmacological management, and psychological support.^{4,5}

Pain perceived in the pelvis can arise through distinct mechanisms, and distinguishing between them is clinically important. Nociceptive pain results from actual or threatened damage to non-neural tissue

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with an intact somatosensory system; neuropathic pain is caused by a lesion or disease of the somatosensory nervous system itself; and nociplastic pain arises from altered nociceptive processing without clear evidence of tissue or nerve damage, as seen in central sensitisation states. These mechanisms frequently coexist in CPP, but only neuropathic pain reflects a definable structural or functional nerve lesion that may be amenable to nerve-targeted treatment. The present review focuses specifically on pelvic neuropathies—that is, the neuropathic component of pelvic pain for which an identifiable aetiology can be determined.

Within this complex framework, pelvic neuropathies are a potentially underdiagnosed and undertreated cause of CPP. Neuropathic pelvic pain is characterised by moderate to severe symptoms such as burning, tingling, paraesthesia, muscle weakness, or organ dysfunction.⁶ It is caused by damage or disease affecting the somatosensory nervous system.⁷ These neuropathies may arise from various mechanisms, including iatrogenic injury, compression, inflammation, invasion by endometriosis or tumours, or obstetric trauma. Although neuropathic mechanisms are increasingly recognised in pelvic pain syndromes, their specific aetiologies remain poorly synthesised, leading to suboptimal diagnostic accuracy and symptom-focused rather than cause-targeted treatment.

This narrative review aims to address this gap by mapping the existing literature on the causes of pelvic neuropathies in women. We do not aim to evaluate treatment effectiveness or diagnostic accuracy, but rather to systematically explore and categorise the reported aetiologies of pelvic neuropathies, thereby offering clinicians a comprehensive overview of possible causes to consider in their diagnostic reasoning.

Understanding these aetiologies is crucial, as accurate diagnosis may enable nerve-targeted treatment strategies, such as surgical decompression, pharmacological neuromodulation, or physical therapy. Even when the aetiology is known, however, multimodal pain management remains essential, given the neuroplastic and psychosocial dimensions of chronic pain. Furthermore, these findings may inform preventive strategies, especially for iatrogenic neuropathies—by far the most frequently reported group in the literature.

To support clinical decision-making, this narrative review provides an overview of all currently described causes of pelvic neuropathies in women, categorising them into meaningful subtypes, and identifies knowledge gaps.

Because CPP is a core part of gynaecological practice, we give particular attention throughout to the aetiologies most relevant to gynaecologists, including nerve-invasive endometriosis, neuropathies related to pregnancy and delivery, and pudendal (Alcock's canal) entrapment. In doing so, we aim to contribute to better diagnostic practices, targeted treatments, and improved outcomes for women with neuropathic pelvic pain.

Methods

This study was conducted as a structured narrative review to map the breadth and diversity of reported aetiologies of pelvic neuropathies in women. A narrative review approach was chosen because the topic encompasses heterogeneous study designs, rare conditions, and predominantly descriptive evidence, for which quantitative synthesis or formal effectiveness assessment is neither feasible nor appropriate. To enhance transparency and reproducibility, an explicit and systematic literature search and predefined eligibility criteria were nevertheless applied.

Definition of Pelvic Neuropathy and Its Application in Study Selection

For the purposes of this review, pelvic neuropathy was defined as a condition involving structural or functional impairment of a specific pelvic nerve or nerve plexus, accompanied by symptoms consistent with neuropathic pain or dysfunction. This definition was aligned with the International Association for the Study of Pain definition of neuropathic pain and with descriptions commonly used in the neuropelveology literature.⁶⁻¹¹

During study selection, we required that pelvic neuropathy be explicitly diagnosed or confirmed in the original publication. Confirmation could be based on clinical evaluation with a nerve-specific symptom distribution, imaging findings suggestive of nerve involvement, neurophysiological testing such as electromyography (EMG) or nerve conduction studies (NCS), intraoperative findings, or the use of established diagnostic criteria where applicable (e.g., the Nantes criteria for pudendal neuralgia). Studies describing pelvic pain without neuropathic features, or in which neuropathy was only hypothesised without diagnostic confirmation, were excluded. This approach was chosen to ensure conceptual clarity and specificity. However, it also introduces essential limitations. Pelvic neuropathies are frequently underdiagnosed in clinical practice, and diagnostic confirmation is often incomplete or absent

in the literature. By requiring explicit confirmation, this review likely underrepresents cases in which neuropathy was present but not recognised or formally documented.

Eligibility Criteria

Eligibility criteria were structured using the Population–Concept–Context framework. We included peer-reviewed case reports, case series, and observational cohort studies that described patients with a diagnosed pelvic neuropathy and an identifiable underlying cause. Studies were eligible regardless of publication year or language.

We excluded reviews, editorials, and opinion articles, as well as studies reporting idiopathic pelvic neuropathies without an identifiable aetiology. Studies describing pelvic conditions (such as endometriosis or fibroids) without explicit confirmation of nerve involvement were also excluded. This strategy was chosen to enable a focused exploration of reported causes rather than symptom-based associations.

Information Sources and Search Strategy

A comprehensive literature search was performed on 1 March 2024 in PubMed, Embase, and Web of Science (Core Collection). The search was designed and carried out in collaboration with a medical information specialist (R.d.V.), who developed the database-specific syntax and ran the searches. The search strategy combined MeSH and free-text terms related to pelvic neuropathy, pelvic nerves, neuralgia, nerve compression, and neuropelvelogy. The complete search strategy is provided in Appendix A. Reference lists of included studies were screened to identify additional relevant publications.

Study Selection

Two authors (RLE, ED) independently screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Disagreements were resolved through discussion until consensus was reached. This dual-reviewer approach was used to reduce selection bias and enhance reproducibility.

Data Extraction

Data were extracted using a standardised form, capturing study characteristics, patient demographics, diagnostic methods, type of neuropathy, reported aetiology, and treatment where described. Extraction focused on how the authors of the original studies defined and substantiated the cause of neuropathy.

Quality of the Evidence

Given that the included literature consisted predominantly of case reports and small case series, a formal risk-of-bias or certainty-of-evidence assessment was not performed, in keeping with the descriptive aim of a narrative review. Instead, study design was used as a pragmatic indicator of evidential strength. Case reports and small series provide low-certainty evidence: they lack control groups, are prone to selection and reporting bias, and cannot support reliable estimates of incidence or causal attribution. The cohort studies, although larger, were generally retrospective and heterogeneous in their diagnostic criteria. The overall certainty of the evidence base is therefore low, and the frequencies reported below should be interpreted as descriptive rather than epidemiological.

Data Synthesis

We employed an inductive, thematic synthesis approach to analyse the extracted data. Reported aetiologies and mechanisms of pelvic neuropathy were descriptively coded and compared across studies. Codes were then grouped into broader thematic categories through iterative discussion and refinement, based on similarities in anatomical involvement, clinical context, and pathophysiology. This data-driven process allowed us to organise diverse cases into coherent categories that reflect shared underlying mechanisms and facilitate meaningful clinical interpretation.

Results

The search was performed in PubMed, Embase, and Web of Science on 1 March 2024 and yielded 7,234 references. After the title-abstract screening, 344 articles were evaluated for eligibility; 306 met our inclusion criteria (selection is shown in Figure 1).

Characteristics of Included Studies

The included studies were published between 1964 and 2024 and originated from a wide range of clinical specialties, including gynaecology, urology, neurology, general surgery, orthopaedic surgery, radiology, and pain medicine. The great majority of studies appeared from 2000 onward (Figure 2), coinciding with the wider availability of cross-sectional imaging and magnetic resonance neurography, whereas only a small minority (approximately 7%) predated 1990; this temporal skew should be borne in mind when interpreting the apparent rarity of conditions described mainly in older

literature. Study designs included case reports ($n=215$), case series ($n=53$), retrospective cohort studies ($n=24$), and prospective cohort studies ($n=14$). No randomised controlled trials were identified. Sample sizes ranged from single-patient case reports to prospective cohorts with up to 200 participants. The studies covered a wide age range, from infancy to postmenopausal age. Diagnostic confirmation of pelvic neuropathy was established through various modalities, including clinical examination, imaging [magnetic resonance (MRI), computed tomography (CT), ultrasound], neurophysiological testing (e.g., EMG), intraoperative visualisation, and, in selected cases, formal diagnostic criteria such as the Nantes criteria for pudendal neuralgia. A complete overview of the study characteristics is presented in Table 1. Most studies were conducted in the obstetrics and gynaecology department (24%). However, studies were also conducted in orthopaedic surgery (15%), neurology (10%), and rehabilitation medicine (10%) (according to the department of the first author). All departments are displayed in Figure 3. Most of the included studies were

conducted in the United States of America ($n=97$, 32%). Twenty-three studies (8%) were performed in Turkey, 5% in South Korea, France, Italy, and Japan, and 4% in Canada, Taiwan, Spain, and the United Kingdom.

Aetiologies

Following the inductive, thematic synthesis approach, we arranged all the included studies by aetiology. We have described five main categories: iatrogenic, nerve invasion (e.g., by endometriosis or infection), pregnancy and birth, trauma, and compression. In addition, we added subcategories as displayed in Table 2 and visualised in Figure 4. The included 306 studies described 2,413 patients in total. Some studies described patients from more than one (sub)category, so the total number of studies per subcategory exceeds 306. The number of studies and patients per category and subcategory is shown in Table 3.

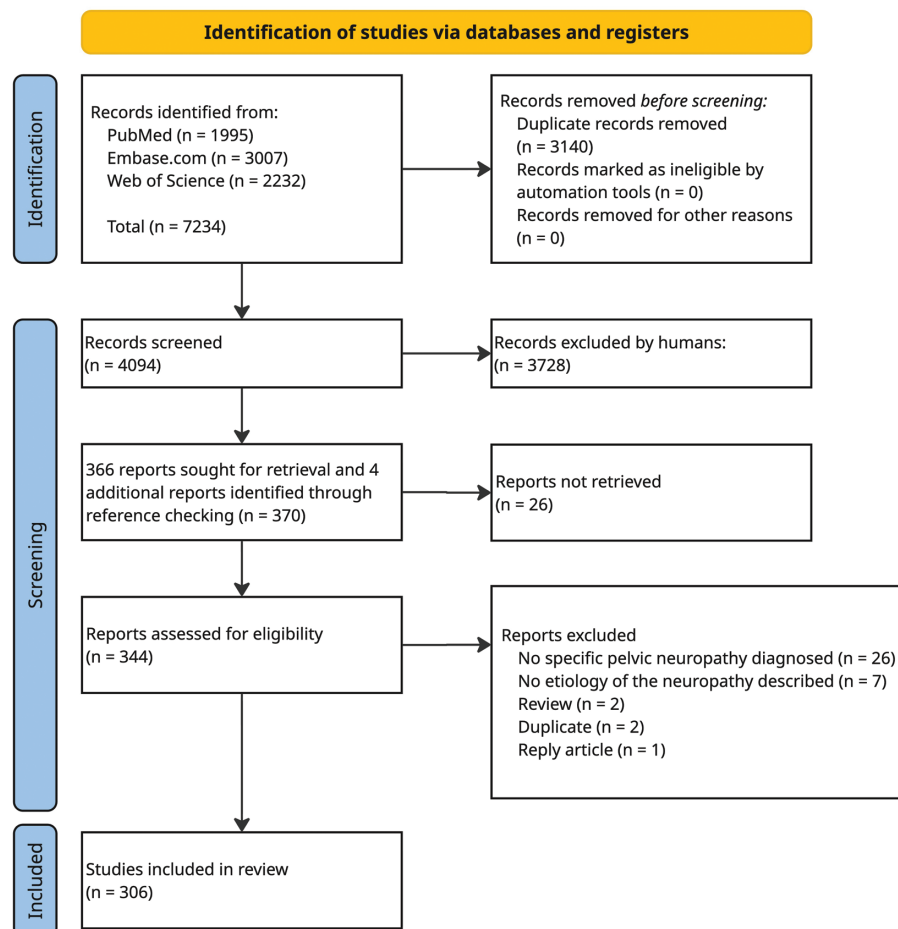


Figure 1. PRISMA flowchart.

Iatrogenic Causes

Most of the neuropathies were seen after surgery in the lower abdomen or pelvis and were mainly labelled as “not specified surgical complications” (n=955 patients, 40%). Only 11 of these 71 studies performed MRI and/or CT; however, most did perform an EMG and/or NCS to diagnose the neuropathy. Another 30 studies (n=85 patients, 4%) specifically indicate the aetiology of post-surgical neuropathy as compression. The compression was caused by the positioning of the patient or sandbag, oedema, haematoma, aneurysm or entrapment of the nerve by sutures.^{3,7-9,12-14} Also, mesh or urethral sling for urinary incontinence or vaginal prolapse, an acetabular reconstruction ring, wear debris, granulomatous

tissue, and intrapelvic cement or screws after total hip replacement were indicated as post-surgical compression aetiologies for pelvic neuropathies.¹⁵⁻²² As seen in Appendix B, most neuropathies were reported after gynaecologic surgery, and femoral, lateral femoral cutaneous, obturator, ilioinguinal, iliohypogastric, genitofemoral, lumbosacral root, sciatic and pudendal neuropathies are described. After gynaecologic surgery, multiple cases of post-surgery pelvic neuropathies are also described for orthopaedic, urologic and general surgery. Only one study described a femoral neuropathy after abdominoplasty, a plastic surgery procedure.²³ Five studies reported a transection of the obturator nerve during gynaecologic surgery, which was intraoperatively recognised and repaired, of which only one patient had transient symptoms post-operatively.²⁴ Next to surgery, other descriptions of iatrogenic causes of pelvic neuropathies are radiation therapy, radiofrequency ablation, iliac bone graft and bone marrow harvesting, manoeuvre by an osteopath, local nerve block and a superior gluteal artery pseudoaneurysm after transvaginal follicle aspiration or needle biopsy.²⁵⁻³² The time between surgery, treatment or procedure and presentation was very divergent, as symptoms could start directly after intervention or had a long interval. Interval periods were described up to nine years after total hip arthroplasty,³³ 36 years after radiation therapy³⁴ or even 40 years after iliac bone grafting.³⁵

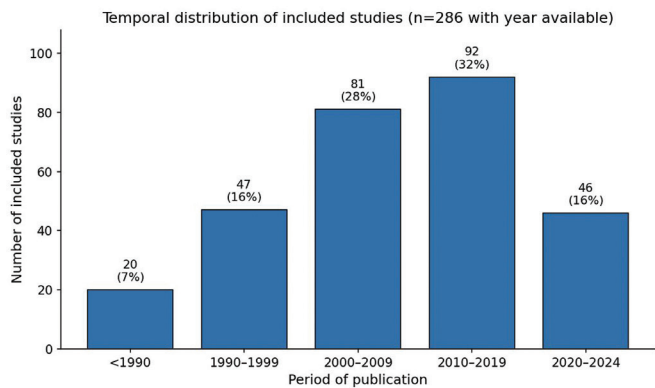


Figure 2. Temporal distribution of the included studies by period of publication.

Nerve Invasion and Traction

The second largest group of patients demonstrated pelvic neuropathy due to nerve-invasive endometriosis (n=557 patients, 23%). This invasion and/or traction is mainly seen in the sciatic nerve, as sciatic neuropathy after invasion of endometriosis is described in 18 studies (18/23 studies). Femoral, lateral femoral cutaneous, pudendal, obturator and lumbosacral root neuropathies were also described due to endometriosis, as seen in Appendix B. Endometriotic infiltration most often involves the sacral plexus and the sciatic nerve, and the hallmark clinical clue is catamenial (cyclical) symptomatology, with pain, paraesthesia or motor deficit that intensifies in the perimenstrual period.³⁶ Symptoms may nonetheless become continuous once perineural fibrosis and axonal damage are established, and Possover³⁷ demonstrated progressive nerve destruction within two years in untreated cases. The diagnosis is frequently delayed because symptoms are attributed to lumbar disc disease; magnetic resonance neurography and laparoscopic

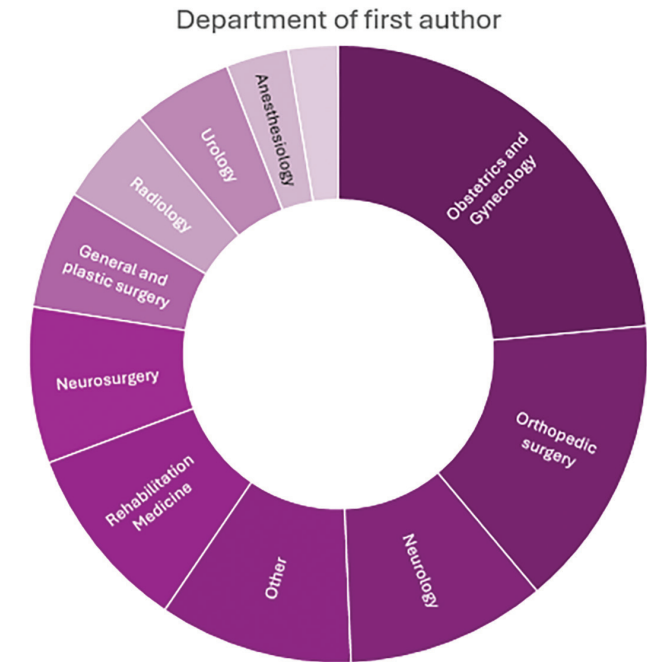


Figure 3. Diagram of the department of the included studies.

Table 1. Inclusion and exclusion criteria of the search.

	Inclusion criteria	Exclusion criteria
Population	• A located pelvic neuropathy that can occur in women	• Women with endometriosis, adhesions, MESH complications, nervous tumors or venous congestion syndromes without a pelvic neuropathy
Outcomes	• Etiologies for pelvic neuropathy	• Idiopathic neuropathy
Study design	• Randomized controlled trial • Case control • Cohort study • Case reports	• Reviews • Meta-analysis • Reply, editorials or opinion articles

Table 2. Aetiological categories of pelvic neuropathy, by mechanism and condition.

Mechanism	Condition
Iatrogenic	Surgical: Surgical complication, compression, post-repair Non-surgical
Nerve invasion	Neuritis Endometriosis Invasive nerve tumours
Pregnancy and birth	Pregnancy Birth Caesarean section
Trauma	Acute Chronic Haematoma e.g., due to clotting disorders
Compression	Muscular: Hypertrophy/nerve variation, rhabdomyolysis Vascular: Aneurysm; venous compression syndrome Tumour: Benign cysts; fibrosis; malignant tumours

exploration of the pelvic sidewall and sacral plexus are the most informative investigations. Laparoscopic neurolysis with excision of perineural endometriosis can relieve symptoms and, if performed before irreversible axonal loss, may allow neurological recovery—underscoring the value of early recognition by gynaecologists. Pelvic neuropathy caused by invasion of the nerve by a tumour is rare and only reported in case reports and small case series. The benign schwannoma is most documented and most often described in the sciatic nerve.³⁸ Other benign nerve tumours are intraneural perineuriomas, neurofibromas and lipomatosis of the nerves.³⁹⁻⁴¹ In addition, four case reports present a sciatic neuropathy by the invasion of a malignant tumour, namely malignant nerve sheath tumours, neurolymphomatosis, and extramedullary anaplastic ependymoma,⁴²⁻⁴⁵ and one

Table 3. Categories of pelvic neuropathy aetiologies.

Etiology category-number of included patients	Subcategory (number of studies)-number of included patients
Iatrogenic-1094 patients (45%)	Surgery: Surgical complication (71)-955
	Surgery: Compression (30)-85
	Surgery: Post-repair (5)-5
	Non-surgical (20)-49
Nerve invasion and traction-614 patients (25%)	Endometriosis (23)-557
	Neuritis (1)-1
	Nerve tumors (21)-56
Pregnancy and birth-93 patients (4%)	Pregnancy (4)-6
	Birth (12)-77
	Caesarean section (4)-10
Trauma-202 patients (8%)	Acute (16)-158
	Chronic (13)-28
	Hematoma (6)-9
	Clotting disorder (7)-7
Compression-409 patients (17%)	Muscular (18)-41
	Vascular (16)-220
	Tumor benign: Cysts (23)-29
	Tumor benign: Fibrosis (1)-1
	Tumor benign: Other (40)-58
	Malignant tumors (17)-60

study reported a lumbosacral root neuropathy caused by malignant pelvic neuroblastoma.⁴⁶ Another rare presentation of nerve invasion is a case report by Lazaro and Butt⁴⁷ describing femoral neuropathy/neuritis caused by Lyme disease.

Pregnancy and Birth

Pelvic neuropathy after pregnancy or childbirth entails the smallest proportion of patients of all five main categories (n=95 patients, 4%). Sciatic, femoral, and lumbosacral

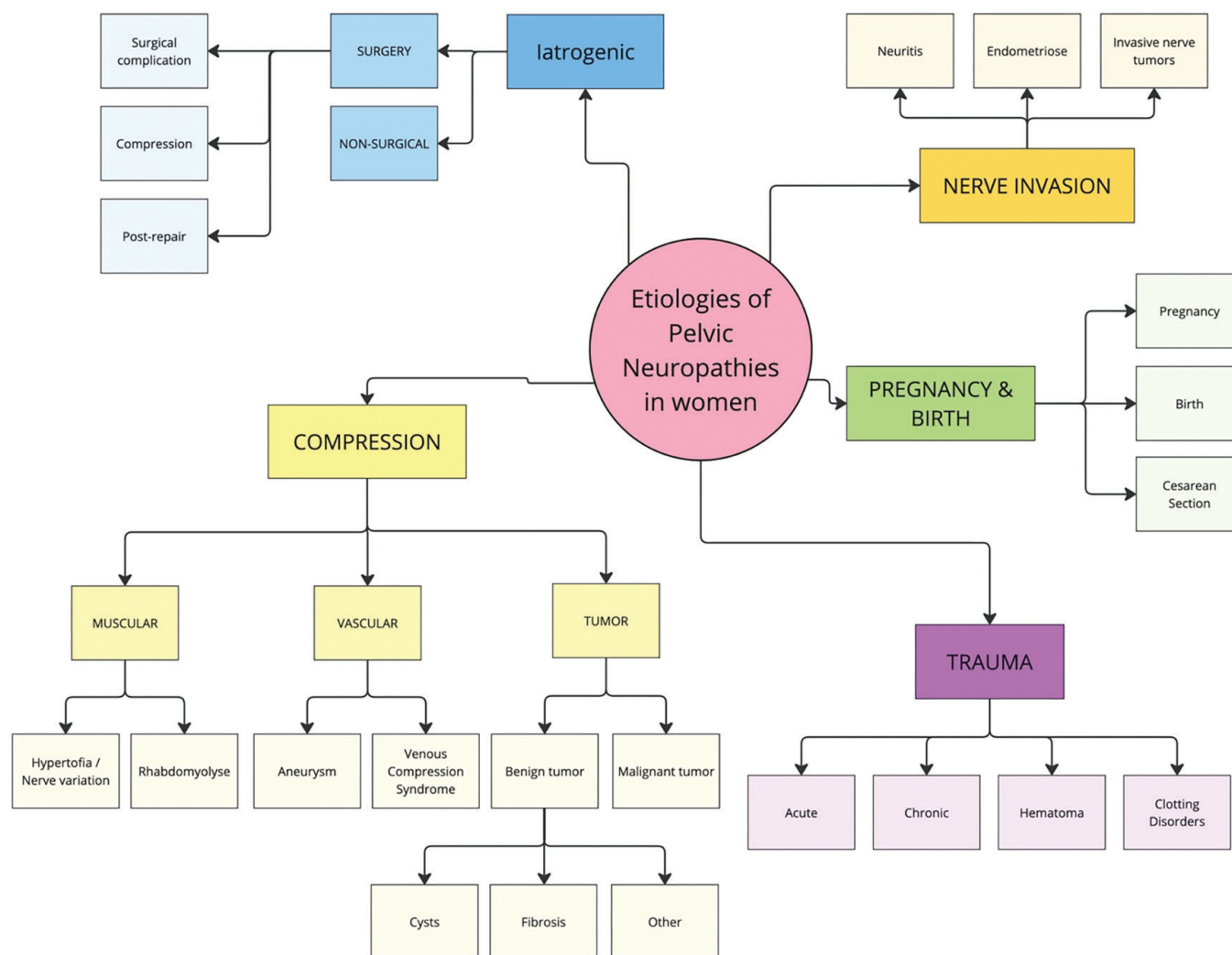


Figure 4. Aetiological categories of pelvic neuropathy.

root neuropathies were described during normal pregnancies of 30-34 weeks of gestation. Additionally, an obturator neuropathy was reported after an ectopic pregnancy.⁴⁸ Femoral and obturator neuropathy have been described both after uncomplicated vaginal birth and after prolonged vaginal birth.^{49,50} As seen in Appendix B, pudendal and cluneal neuropathy were also reported after uncomplicated birth, and lumbosacral root neuropathies were seen after prolonged vaginal births. One case report describes an obturator neuropathy after forceps delivery.⁵¹ Moreover, four studies report on cases of pelvic neuropathies after caesarean section.⁵²⁻⁵⁵ Another rare observation after birth with massive postpartum haemorrhage is reported by Rohilla et al.,⁵⁶ describing lumbosacral root neuropathy because of uterine necrosis after pelvic vessel embolization.

Although the least frequent category, pregnancy- and childbirth-related neuropathies merit closer attention given their direct relevance to obstetric practice. Antepartum lesions are usually compressive, arising as the gravid uterus or the descending fetal head compresses the lumbosacral trunk against the pelvic brim, most commonly affecting the lumbosacral trunk, femoral and obturator nerves. Intrapartum mechanisms include prolonged lithotomy positioning, which stretches the femoral and common peroneal nerves, and instrumental (forceps) delivery. Recognised risk factors are nulliparity, a prolonged second stage of labour, cephalopelvic disproportion, and short maternal stature. Importantly, the great majority of obstetric neuropathies are demyelinating and self-limiting, resolving within weeks to a few months with conservative management; this probably explains both their low representation in the

literature and their frequent under-reporting. Persistent or progressive deficits, by contrast, should prompt imaging to exclude haematoma or another structural cause.

Trauma

Trauma was the aetiology in 8% (n=202 patients) of all included patients with pelvic neuropathies. We subdivided these patients into acute, chronic, haematoma and clotting disorders. Most studies in the acute trauma group described sciatic neuropathy after a fracture because of a fall, road traffic or sports accident (as displayed in Appendix B). In addition, blunt trauma, gunshot, stab wounds and lacerations were also described.^{41,57} An avulsion fracture after a short run leading to sciatic or lateral femoral cutaneous neuropathy was reported by Dosani et al.⁵⁸ and Thanikachalam et al.,⁵⁹ respectively. More cases of neuropathies due to sport are described in the chronic category, for example a posterior femoral cutaneous neuropathy after a marathon⁶⁰ and a pudendal neuropathy after 2-3 hours of pilates exercises per day.⁶¹ Other reported cases in the chronic trauma group mainly describe neuropathies after prolonged periods in certain positions. This could be in an altered state of consciousness due to medication, drugs, coma or by choice, like a sciatic neuropathy after hospitalisation with a pharmacologically altered state of consciousness⁵⁷ or after long-term gluteal pressure of a wallet.⁶² All described haematomas after trauma led to femoral neuropathy specifically. We divided the cases with a haematoma and a clotting disorder into a separate group, possibly due to haemophilia or anticoagulants. Similarly, these haematomas caused femoral neuropathies, except for one case of sciatic neuropathy due to a pelvic haematoma as a first presentation of haemophilia.⁶³

Compression-Muscular and Vascular

Neuropathy by muscle compression was only reported in case reports and small case series (n=41 patients, 2%). Hypertrophy of the muscle surrounding the pelvic nerves leading to neuropathy could be caused by muscle overuse or by imbalance from scoliosis or leg-length discrepancy.^{62,64} Furthermore, abnormal piriformis muscle bundles or abnormal orientation of the nerve could lead to neuropathy in certain circumstances (described as piriformis syndrome). As seen in Appendix B, these included cases described neuropathies in the sciatic and pudendal nerves. In addition, five other studies described sciatic, femoral, obturator and lumbosacral root neuropathies due to rhabdomyolysis.^{65,66} While neuropathy by compression of vessels was reported in

fewer studies than muscular compression (16 studies vs. 18 studies), more patients were described (n=220, 9% vs. n=41, 2%). As displayed in Appendix B, compression of nerves by vessels could be due to aneurysms of arteries or dilation of veins. The largest two cohorts showed sciatic, pudendal, and lumbosacral root neuropathies by intrapelvic aberrant dilated veins.^{67,68} Vascular entrapment syndromes are also described as a cause, but there was very little consensus about the definitions of the various pelvic congestion syndromes.⁶⁷⁻⁷³

Compression-Benign Tumours: Cysts, Fibrosis and Other

Only 1% of the included patients had pelvic neuropathy due to cysts (n=29). Most described were hydatid cysts (or echinococcosis), ganglion or synovial cysts, and Tarlov (also perineural or meningeal) cysts (as seen in Appendix B). One rare description of femoral neuropathy was presented in the case series of Ducic et al.³⁰ This neuropathy was idiopathic, as extensive workup had not yielded a direct cause or diagnosis; however, during neurolysis, tissues surrounding the femoral nerve appeared fibrotic and fixed to the inguinal ligament, which led to local swelling and hyperaemia of the nerve.³⁰ As displayed in Appendix B, other benign tumour aetiologies were very diverse, and 40 studies described 58 patients (2%). Multiple studies presented a patient with sciatic neuropathy after pyomyositis,⁷⁴ osteochondromas,⁷⁵ adenomyosis,⁷⁶ schwannomas⁷⁷ and lipomas.⁷⁵ Furthermore, next to sciatic neuropathy, uterine fibroids were described as the aetiology in obturator, lateral femoral cutaneous and lumbosacral root neuropathy.⁷⁸⁻⁸¹

Compression-Malignant Tumours

In total, 17 case reports and series described 60 patients with pelvic neuropathies caused by malignant tumours (2%). Primary tumours or metastases mostly caused sciatic, femoral or lumbosacral root neuropathies (as seen in Appendix B). The largest case series, by Bickels et al.,⁸² describes 18 cases with metastatic, bone or soft-tissue tumours, such as sarcomas. Another rare entity is described by Cucinella et al.,⁸³ presenting a case of sciatic neuropathy induced by retroperitoneal squamous cell carcinoma originating from endometriosis.

Specific Neuropathic Syndromes

Several aetiologies in this review are clinically grouped under named neuropathic syndromes, which deserve specific comment because their definitions are

inconsistent and they are frequently encountered—yet under-recognised—in gynaecological practice.

Piriformis syndrome denotes sciatic nerve irritation at the greater sciatic notch, attributed variously to piriformis hypertrophy, anatomical variants of the sciatic nerve, or post-traumatic scarring; as discussed below, the term is applied inconsistently and lacks agreed diagnostic criteria.

May-Thurner syndrome classically describes compression of the left common iliac vein by the overlying right common iliac artery. In the neuropelvic context it is implicated when the resulting venous congestion and dilated pelvic veins compress the lumbosacral plexus or sacral nerve roots, producing sciatic or pudendal symptoms.⁶⁸

Pelvic congestion syndrome refers to CPP associated with dilated, refluxing pelvic veins. Its relationship to neuropathy is indirect—through perineural venous compression—and the literature shows little consensus on its definition or its distinction from other vascular entrapment syndromes.⁶⁷⁻⁷³

Alcock's canal (pudendal canal) syndrome is entrapment of the pudendal nerve within the fascial canal formed by the obturator internus fascia, and is probably the syndrome most relevant to—and most under-diagnosed by—gynaecologists. It produces neuropathic pain in the pudendal territory (clitoris, labia, perineum and anorectum), characteristically worsened by sitting and relieved by standing or by sitting on a toilet seat. Diagnosis rests on the clinical Nantes criteria,⁸⁸ supported where available by pudendal nerve motor latency testing and image-guided diagnostic nerve blocks. Management ranges from conservative measures and nerve blocks to laparoscopic or transgluteal pudendal nerve decompression. Greater familiarity with this syndrome would help gynaecologists distinguish pudendal neuralgia from vulvodynia and other causes of chronic perineal pain.

Discussion

Main Findings

This narrative review synthesises the published evidence on the identifiable aetiologies of pelvic neuropathy in women, encompassing 306 studies published between 1964 and 2024. Consistent with the literature, iatrogenic causes—particularly nerve injuries associated with pelvic surgery—were the most frequently reported mechanism of pelvic neuropathy. Other well-described mechanisms

included nerve invasion or traction by pathological processes (including endometriosis and tumours), pregnancy- and childbirth-related injury, trauma, and extrinsic compression by benign or malignant structures.

Across the themes, a wide range of pelvic nerves was implicated, including the obturator, femoral, sciatic, pudendal, ilioinguinal, and lumbosacral plexus. Diagnostic approaches varied substantially, with many cases relying on clinical features alone, while others incorporated advanced imaging or neurophysiological testing. These themes provide a comprehensive framework for understanding the breadth of identifiable causes documented in the current literature.

Several included studies described a specific neuropathic syndrome, such as piriformis syndrome, May–Thurner syndrome, pelvic congestion syndrome and Alcock's canal syndrome. The problem with these terms is that there is very little consensus about their definitions, and the same syndrome label is used for patients with different aetiologies. For example, piriformis syndrome was used by Dere et al. (2009) to describe a patient with sciatic neuropathy because of hypertrophy of the unilateral piriformis muscle due to leg-length discrepancy.⁸⁴ However, Kraus et al. 2016 diagnosed piriformis syndrome in a patient with sciatic neuropathy because of variant anatomy of the left sciatic nerve,⁸⁵ while Siddiq et al. 2017 used the diagnosis of piriformis syndrome for patients with sciatic neuropathy after a fall or blunt trauma of the buttock.⁶²

For the gynaecologist specifically, three messages stand out. First, nerve-invasive endometriosis should be considered in any woman with cyclical sciatic, gluteal or pudendal pain, since timely diagnosis can prevent irreversible nerve damage. Second, most obstetric neuropathies are self-limiting and can be managed conservatively with reassurance and physiotherapy, whereas persistent deficits warrant imaging. Third, pudendal (Alcock's canal) neuralgia is an under-recognised but treatable cause of chronic perineal pain that is frequently mislabelled as vulvodynia. Incorporating these considerations into the routine gynaecological assessment of CPP could reduce diagnostic delay and unnecessary symptom-only treatment.

Pelvic neuropathies in or after pregnancy were the smallest group of patients in our study (n=95 patients, 4%), possibly meaning that pelvic neuropathies are a rare complication of pregnancy and birth, perhaps because many pregnancy-related neuropathies are self-limiting.

Strengths and Limitations

A major strength of this review is its broad, inclusive approach, which allows us to map a large and heterogeneous body of evidence without excluding studies based on design or sample size. The use of inductive thematic synthesis enabled the identification of clinically meaningful groupings that reflect real-world mechanisms of nerve injury. The evidence base is, however, dominated by case reports and small case series, which provide only low-certainty evidence; we therefore refrained from a formal risk-of-bias assessment and instead interpret the findings descriptively. Several further limitations must be acknowledged. By design, the review included only studies in which a clear underlying aetiology of pelvic neuropathy was described, thereby excluding reports of idiopathic neuropathies or those lacking definitive diagnostic confirmation. This exclusion criterion—while enhancing specificity—may have led to underrepresentation of clinically relevant neuropathic presentations encountered in practice. Furthermore, diagnostic criteria were highly heterogeneous across studies, with many relying on clinical judgement without objective corroboration. Some case reports attributed causality based on temporal associations rather than definitive evidence, potentially introducing causal uncertainty. Finally, the predominance of case reports and small series limited the ability to derive robust epidemiological estimates.

Interpretation

The findings from this review confirm that pelvic neuropathy can result from a broad spectrum of identifiable causes, many of which remain under-recognised in clinical settings. The high prevalence of iatrogenic injuries emphasises the importance of surgical planning and anatomical awareness to prevent avoidable nerve damage. Other mechanisms, such as nerve invasion by disease, mechanical compression, and obstetric stretch injuries, underscore the need to consider neuropathic processes in patients presenting with chronic or atypical pelvic pain.

These results must be interpreted within the wider framework of CPP, a condition known to be multifactorial, involving nociceptive, myofascial, visceral, nociplastic, and central-sensitisation components alongside neuropathic contributions. Even when a neuropathic aetiology is confirmed, multidisciplinary management—including physical therapy, psychological support, pharmacological

treatment, and interventional strategies—remains essential for optimal outcomes.^{4,10}

This review also highlights a pressing need for standardised diagnostic frameworks. The lack of uniform imaging protocols and inconsistent application of neurophysiological testing limit diagnostic accuracy and reproducibility. Most studies relied on imaging (ultrasound, CT, or MRI), which often failed to detect neuropathy in the absence of a compressive lesion. EMG and NCSs were inconsistently used, and their diagnostic value remains uncertain. Pudendal neuropathy was occasionally assessed using the Nantes criteria,⁸⁸ but equivalent diagnostic frameworks are lacking for other pelvic nerves.

When a patient presents with suspected neuropathic pelvic pain, clinical reasoning should first distinguish between visceral and somatic pain, then localise the affected nerve and lesion site. The distinction between neurogenic (complete nerve lesion) and non-neurogenic (partial lesion) mechanisms, as described by Possover⁵ can assist in refining the differential diagnosis. The aetiological categories synthesised in this review may support clinicians in structuring their diagnostic approach. However, the diagnostic process remains challenging. In addition to the absence of validated criteria, there is limited consensus on overlapping syndromes such as pelvic congestion or piriformis syndrome, further contributing to underdiagnosis.

Future research should prioritise the development of clear diagnostic criteria for pelvic neuropathies, enabling earlier recognition and facilitating access to structured, evidence-based care.

Conclusion

Pelvic neuropathy remains an under-recognised but clinically significant cause of CPP, with aetiologies ranging from iatrogenic injury to nerve invasion, trauma, compression, and obstetric complications. This review highlights the diversity of mechanisms and the diagnostic challenges associated with these conditions. Improved awareness, earlier recognition, and structured diagnostic pathways are essential to prevent misdiagnosis and enable timely, multidisciplinary intervention. Future research should aim to broaden the epidemiological understanding of pelvic neuropathies, including idiopathic cases, and evaluate treatment strategies that address both neuropathic and non-neuropathic contributors to pelvic pain.

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Appendix A Link: <https://d2v96fxpocvxx.cloudfront.net/68ab204c-182b-49da-b227-bc7efe058632/content-images/99a04a40-6e9a-4799-85e2-9679a36663f7.pdf>

Appendix B Link: <https://d2v96fxpocvxx.cloudfront.net/bda9171a-fae8-4995-8276-2138323f1e16/content-images/721f9ea8-4ecd-4bc6-93a6-c021cb013baf.pdf>

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Visually directed hysteroscopic biopsy in the evaluation of abnormal uterine bleeding and postmenopausal bleeding: a Joint Society Practice Guideline

Joint Society Practice Guideline from AAGL–ESGE–GCH*

*This guideline was developed through the collaborative efforts of representatives from international professional societies and the AAGL Practice Guidelines Committee.

**All members of the Joint Society Practice Guideline from AAGL–ESGE–GCH and their institutional affiliations are listed in the Acknowledgements section.

ABSTRACT

Background: Abnormal uterine bleeding (AUB) and postmenopausal bleeding (PMB) require systematic evaluation to exclude clinically significant intrauterine pathology, including premalignant and malignant endometrial disease.

Objectives: To provide evidence-based recommendations for the histopathologic evaluation of patients with AUB or PMB undergoing assessment for suspected intrauterine pathology.

Methods: The American Association of Gynecologic Laparoscopists, European Society of Gynaecological Endoscopy, and Global Community on Hysteroscopy developed a Joint Society Guideline using the PICO framework. Diagnostic hysteroscopy performed in outpatient or inpatient settings, including hysteroscopy alone, hysteroscopy combined with ultrasound, or hysteroscopy with biopsy, was compared with blind endometrial sampling performed without preceding hysteroscopy. Risk of bias and study quality were assessed using established methodological frameworks.

Main Outcome Measures: The primary outcome was diagnostic accuracy, measured by sensitivity and specificity, using histopathology from endometrial sampling or hysterectomy specimens as the reference standard.

Results: Meta-analysis showed that hysteroscopy, with or without concomitant endometrial sampling, had higher diagnostic accuracy than blind endometrial biopsy for detecting and excluding endometrial cancer, endometrial intraepithelial neoplasia, endometrial hyperplasia with or without cytological atypia, endometrial polyps, and submucous myomas. Accuracy estimates were generally higher for detecting than excluding intrauterine pathology. Evidence for endometritis was limited to one comparative study, and no comparative data were available for other conditions, including uterine niches or retained pregnancy tissue.

Conclusions: Hysteroscopy is a valuable diagnostic modality for AUB and PMB, particularly when focal pathology is suspected or prior imaging or sampling is inconclusive. When endometrial tissue assessment is indicated, visually directed biopsy performed with hysteroscopic evaluation is favored over blind sampling.

What is New? Hysteroscopy with or without endometrial biopsy is more accurate than blind endometrial sampling alone for benign structural, premalignant and malignant endometrial pathology. This practice guideline recommends that visually directed biopsy is favored over blind biopsy in the evaluation of AUB or PMB.

Keywords: Biopsy, diagnosis, endometrial cancer, endometrial hyperplasia, hysteroscopy, postmenopausal, ultrasound, uterine bleeding

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Introduction

Abnormal uterine bleeding (AUB) and postmenopausal bleeding (PMB) are common indications for gynecologic evaluation across the lifespan.¹⁻⁴ In non-pregnant, reproductive-aged individuals, AUB is defined as bleeding that is abnormal in frequency (amenorrhea or cycles occurring <24 or >38 days apart), regularity (cycle-to-cycle variation ≥ 8 -10 days, depending on age), duration (>8 days), or volume (heavy menstrual bleeding that negatively affects quality of life).^{1,2} In contrast, any uterine bleeding occurring 12 months or more after cessation of menses is considered PMB.⁵ Although the underlying causes of abnormal bleeding differ between premenopausal and postmenopausal populations, both require systematic evaluation to exclude premalignant and malignant disease.

AUB affects up to 30% of individuals over their lifetime and accounts for approximately one-third of outpatient gynecologic visits.^{3,4} Beyond its clinical implications, AUB substantially affects quality of life and is associated with significant direct and indirect health care costs.⁴ In contrast, PMB occurs in up to 10% of postmenopausal individuals and accounts for approximately 5% of outpatient gynecologic visits.^{6,7} Importantly, depending on age and underlying risk factors, up to 14% of individuals presenting with PMB are ultimately diagnosed with endometrial cancer, underscoring the need for prompt and thorough evaluation.⁸

In reproductive-aged individuals, the International Federation of Gynecology and Obstetrics (FIGO) classifies causes of AUB using the PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy and hyperplasia-coagulopathy, ovulatory disorders, endometrial causes, iatrogenic, not classified) system, distinguishing structural from non-structural etiologies (Figure 1).^{1,2} Current guidelines recommend transvaginal ultrasonography as the initial imaging modality after exclusion of pregnancy.^{3,8,9} However, ultrasonography has limited sensitivity for focal intracavitary lesions.¹⁰ Saline infusion sonography (SIS) improves detection of endometrial polyps and submucosal leiomyomas. For patients with fibroids, SIS is also more accurate in the FIGO classification of leiomyomas and evaluation of the adnexa than transvaginal ultrasonography alone. When intracavitary lesions are detected with SIS, operative hysteroscopy is required for further evaluation and removal of pathology.¹¹

Histopathologic assessment is essential for accurate diagnosis of intracavitary lesions, including endometrial polyps, submucosal fibroids, endometrial hyperplasia and malignancy.¹² Although blind endometrial sampling has traditionally served as the initial step in histologic evaluation, hysteroscopy allows for direct visualisation of the uterine cavity, targeted biopsy, and simultaneous treatment of focal pathology.¹³ A 2024 international consensus statement advocated for incorporating hysteroscopic evaluation in patients with suspected intrauterine pathology and minimising blind sampling where feasible.¹³

Despite demonstrated diagnostic accuracy, safety, and therapeutic capability, hysteroscopy is not uniformly recommended as a first-line diagnostic modality for AUB or PMB.¹⁴ Several guidelines, including those from the British Gynaecological Cancer Society, Spanish Society of Medical Oncology-Spanish Group for Ovarian Cancer Research, and the American College of Obstetrics and Gynecology (ACOG) recommend a stepwise diagnostic approach, reserving hysteroscopy for select cases with abnormal imaging findings, persistent symptoms, high-risk features, or non-diagnostic endometrial sampling.^{8,15,16}

More recently, ACOG updated its guidance for PMB, recommending that transvaginal ultrasonography and endometrial tissue sampling be incorporated into the initial evaluation for most patients with PMB, reflecting concern that reliance on endometrial thickness alone may miss malignant or premalignant disease in select patients.^{5,8} This focused update represents an important evolution in the initial evaluation of PMB, while still leaving unresolved the optimal method of obtaining tissue when histopathologic assessment is indicated. Direct comparative data between first-line hysteroscopy and traditional sequential diagnostic approaches remain limited, and randomised trials are sparse. Accordingly, the American Association of Gynecologic Laparoscopists (AAGL), the European Society for Gynaecological Endoscopy (ESGE), and the Global Community of Hysteroscopy (GCH) created a Joint Society Practice Guideline to systematically evaluate the available evidence on the role of hysteroscopy in the assessment of AUB and PMB. In particular, the current evaluation focused on the diagnostic accuracy of diagnostic hysteroscopy (alone, with ultrasound, or with biopsy), in comparison with blind endometrial sampling, to provide evidence-based recommendations and inform clinical practice.

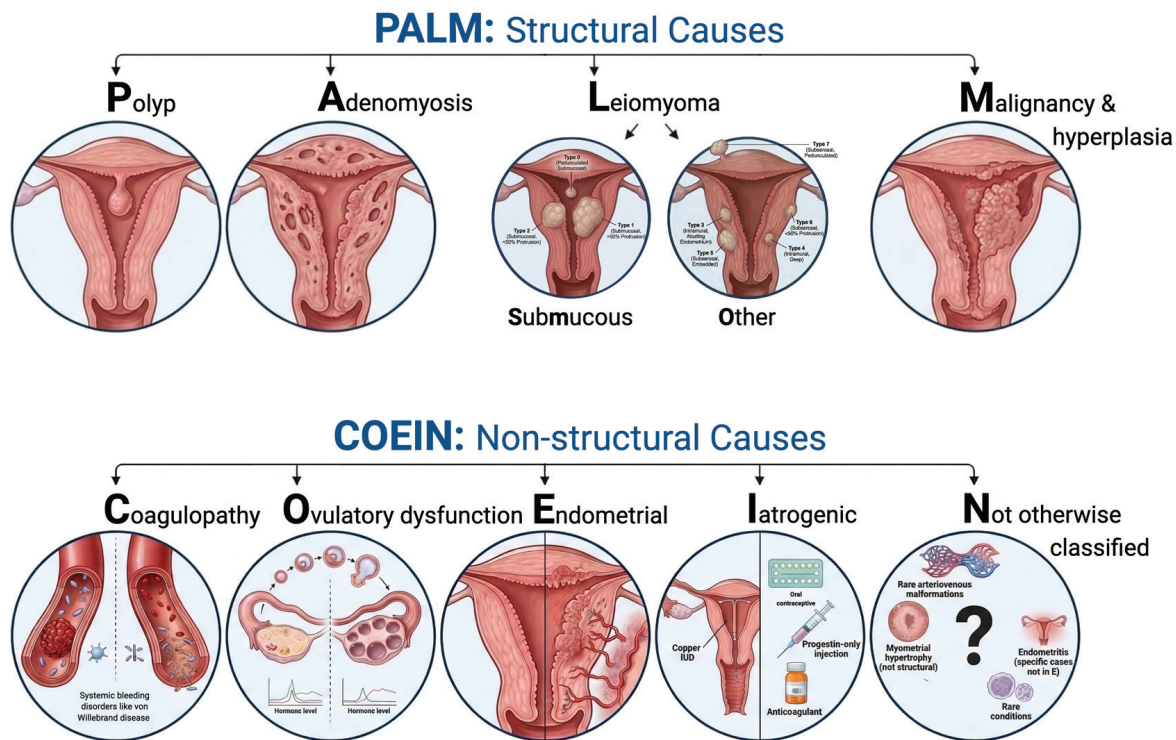


Figure 1. The International Federation of Gynecology and Obstetrics (FIGO) PALM–COEIN classification system for causes of abnormal uterine bleeding in reproductive-aged individuals and postmenopausal bleeding. Structural etiologies are summarised by the acronym PALM and include polyp, adenomyosis, leiomyoma, and malignancy and hyperplasia, which are generally identifiable by imaging or histopathology. Non-structural causes are represented by COEIN and include coagulopathy, ovulatory dysfunction, endometrial disorders, iatrogenic causes, and entities not otherwise classified. Figure created with assistance from Gemini (Google, CA, USA), subsequently modified, verified for accuracy and approved by the authors.

Summary of Recommendations and Clinical Practice Points

When evaluating patients with AUB or PMB, hysteroscopy with visually directed biopsy offers superior diagnostic accuracy compared with blind endometrial sampling for multiple intrauterine pathologies and should be incorporated into the diagnostic algorithm when feasible.

• Hyperplasia/endometrial intraepithelial neoplasia (EIN)

In patients with AUB or PMB undergoing evaluation for suspected endometrial hyperplasia without atypia, atypical endometrial hyperplasia (AEH) or EIN, hysteroscopy with visually directed biopsy is recommended over blind or ultrasound-guided aspiration sampling (Strong recommendation. Low-moderate quality of evidence).

• Malignancy

When evaluation of AUB or PMB raises concern for endometrial malignancy, hysteroscopy with visually directed endometrial biopsy is recommended over

blind endometrial sampling when feasible. (Strong recommendation. Low-moderate quality of evidence).

• Polyps

When endometrial polyps are suspected in patients undergoing evaluation for AUB or PMB, hysteroscopy with visually directed biopsy or resection is recommended over blind endometrial sampling. (Strong recommendation. Moderate quality of evidence).

• Submucosal leiomyomas

When submucosal leiomyomas are suspected in patients undergoing evaluation for AUB or PMB, hysteroscopy with or without resection is recommended over blind endometrial sampling for diagnostic evaluation. (Strong recommendation. Low-moderate quality of evidence).

• Endometritis

When endometritis is suspected, hysteroscopy with or without visually directed biopsy is suggested to improve diagnostic accuracy compared with blind endometrial

sampling. (Conditional recommendation. Low quality of evidence).

- The Joint Society Guideline recommends hysteroscopic visualisation with directed endometrial sampling, rather than hysteroscopy followed by blind endometrial sampling. Blind sampling may fail to adequately capture focal lesions and does not allow confirmation that visually identified pathology has been completely removed. (Clinical Practice Point)
- The Joint Society Guideline recommends hysteroscopy, with or without visually directed biopsy, to aid diagnosis in patients with complex presentations, including those with suspected uterine anatomic variants (e.g., Müllerian anomalies), intrauterine adhesions, retained products of conception, a large uterine cavity, uterine niche, endocervical lesions, or lesions that are difficult to access. In these scenarios, blind endometrial sampling has limited diagnostic accuracy. (Clinical practice point)

Methods

The joint AAGL-ESGE-GCH Society Practice Guideline developed clinical recommendations for visually directed hysteroscopic biopsy in the evaluation of patients with AUB and PMB based on a systematic review that was designed using the PICO (i.e., Patient, Intervention, Comparison, Outcome) framework.¹⁷ The patient population consisted of patients presenting with AUB and PMB. The intervention of interest was hysteroscopy, performed in either outpatient or inpatient settings, as a diagnostic procedure, including hysteroscopy used alone, hysteroscopy with ultrasound, or hysteroscopy with biopsy. Biopsy in the intervention group included both biopsy obtained under direct hysteroscopic visualisation as well as blind tissue sampling which occurs immediately following visualisation by diagnostic hysteroscopy. The comparison group was defined as blind biopsy with no concurrent or preceding hysteroscopy, with or without the incorporation of ultrasound. Biopsy in the comparison group included blind tissue sampling [Pipelle (CooperSurgical, CT, USA), dilation and curettage (D&C), Novak (BR Surgical, CO, USA) Pipelle, or Vabra (Cooper Laboratories, NJ, USA) aspiration] that was obtained with no concurrent or preceding hysteroscopy. For the purpose of this literature review, ultrasound was defined as two or three dimensional-transvaginal ultrasound or SIS. The reference standard used across the included studies was histopathologic diagnosis obtained from hysterectomy, blind D&C, or visually directed biopsy.

The primary outcome of interest was diagnostic accuracy, with sensitivity and specificity as the principal measures. Other measures of diagnostic accuracy were also evaluated as secondary outcomes if available, including positive predictive value, negative predictive value, likelihood ratio for positive test result, likelihood ratio for negative test result, and diagnostic odds ratio (DOR). We evaluated diagnostic accuracy of hysteroscopy for the following conditions: 1) endometrial hyperplasia without atypia, AEH, EIN, or endometrial malignancy, 2) polyps or submucosal myomas, and 3) other intrauterine pathologies if available such as adenomyosis, endometritis, niche or retained products of conception.

Literature Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines,¹⁸ a systematic review was undertaken. The search strategy was designed by an expert medical librarian with feedback from the guideline development team. Medical search headings (MeSH), other controlled vocabulary terms, and keywords were used to collect relevant publications. Electronic searches were performed in Ovid Medline, Embase, and Cochrane Library from the inception of these bibliographic databases to September 1, 2023 (supplemented by an updated search through March 21, 2025). The search strategy is reported in Appendix A. The references of relevant systematic reviews identified during the article screening were also hand-searched to identify potential additional citations not retrieved by the search.

Study Selection and Data Extraction

We included studies that addressed the PICO defined above and met the following criteria: 1) reported diagnostic accuracy data for patients with AUB or PMB; 2) provided adequate data to enable calculation of diagnostic accuracy for the specific pathologies of interest; 3) involved original research (i.e. excluded registered studies/methods papers without data available, editorials, and commentaries); 4) compared diagnostic accuracy of hysteroscopy and blind biopsy using an independent reference standard; and 5) published as full length articles (excluding conference abstracts, case reports, and video articles). Studies were excluded if they did not have an independent histological reference standard or did not provide pathology-specific diagnostic accuracy data. No language restrictions were applied. The process of study selection included an initial title and abstract review, followed by full text review to determine study eligibility.

A standardised data extraction form was developed to collect key information about each included study. The list of extracted data elements was developed based on the Standards for Reporting Diagnostic Accuracy Studies guidelines,¹⁹ along with input from the team's clinical experts. A draft data extraction form was pilot tested using a small number of studies and then modified/refined prior to final use. For both study selection and data extraction, each study was independently reviewed by two team members. Discrepancies were resolved by discussion among team members and/or consultation with a third team member. If not already reported in the study, measures of diagnostic accuracy were calculated.

Assessment of the Quality of Included Studies

The quality of each included study was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool with comparative extension (QUADAS-C).²⁰ The QUADAS-C tool assesses risk of bias and applicability concerns for studies that compares diagnostic accuracy of one test vs. another test regarding patient selection, index test, reference standard, and flow and timing. Each domain was rated as low, high or unclear risk of bias. A study was rated as having low overall risk of bias if all domains had low risk of bias or rated as having high overall risk of bias or unclear overall risk of bias if one or more domains had high or unclear risk of bias, respectively. Two team members independently assessed each study with discrepancies resolved by discussion and consultation with a third team member.

Synthesis of Results and Formulation of Recommendations

Study characteristics and quality assessments were summarised by pathology, and the diagnostic accuracy of hysteroscopy was compared with blind endometrial biopsy. When studies were sufficiently homogeneous, pooled estimates were calculated using random-effects meta-analysis. Sensitivity and specificity were pooled using a bivariate random-effects model with Clopper-Pearson 95% confidence intervals (CI), while likelihood ratios and DORs were pooled on the logarithmic scale using Hartung-Knapp-Sidik-Jonkman 95% CI. Predictive values were calculated for individual studies but not pooled due to variability in disease prevalence across studies. Analyses were performed using Stata 18.5 (College Station, TX, USA).

To rate the strength of recommendation and quality of evidence, we utilised a modified framework of criteria

from ACOG²¹ and the American Society for Reproductive Medicine Clinical Practice Guidelines (Box A).²²

Results

The flow diagram of study selection is shown in Figure 2. A total of four articles met the predefined eligibility criteria for inclusion.²³⁻²⁶ These studies compared the diagnostic accuracy of hysteroscopic diagnostic techniques with blind endometrial sampling across a broad spectrum of intrauterine pathology. Key characteristics of these four studies are summarised in Table 1, with detailed description of each study included in Appendix B.²³⁻²⁶

Among the four included studies, three were prospective investigations (Leone et al.,²³ Angioni et al.,²⁴ Karageyim Karsidag et al.²⁶), and one was a retrospective analysis (Gao et al.²⁵). Leone et al.²³ enrolled both premenopausal and postmenopausal women with AUB and endometrial thickening on ultrasound, whereas the remaining three studies focused exclusively on postmenopausal women with bleeding. Angioni et al.²⁴ evaluated a large cohort of postmenopausal patients undergoing blind biopsy followed by outpatient hysteroscopy. Gao et al.²⁵ retrospectively compared patients who underwent primary hysteroscopy with those who underwent diagnostic curettage. Karageyim Karsidag et al.²⁶ studied a highly select population of postmenopausal women with persistent or recurrent bleeding despite a prior negative blind D&C.

Across studies, outcomes assessed included hyperplasia (with or without atypia, EIN) (Leone et al.,²³ Angioni et al.,²⁴ Gao et al.²⁵), malignancy of endometrial carcinoma (Leone et al.,²³ Gao et al.²⁵), and benign focal intracavitary lesions (endometrial polyps and submucosal myomas) (Angioni et al.,²⁴ Gao et al.,²⁵ Karageyim Karsidag et al.²⁶); Gao et al.²⁵ additionally evaluated endometritis.

Reference standards varied across studies. In Leone et al.,²³ histopathology from blind D&C served as the reference standard. In Angioni et al.,²⁴ visually directed operative hysteroscopy specimens constituted the reference standard for benign intracavitary lesions, whereas hysterectomy specimens were used for hyperplasia with atypia and carcinoma. Patients with negative findings from diagnostic hysteroscopy underwent an unspecified endometrial biopsy which served as the reference standard. In Gao et al.²⁵ and Karageyim Karsidag et al.,²⁶ visually directed hysteroscopy specimens functioned as the reference standard.

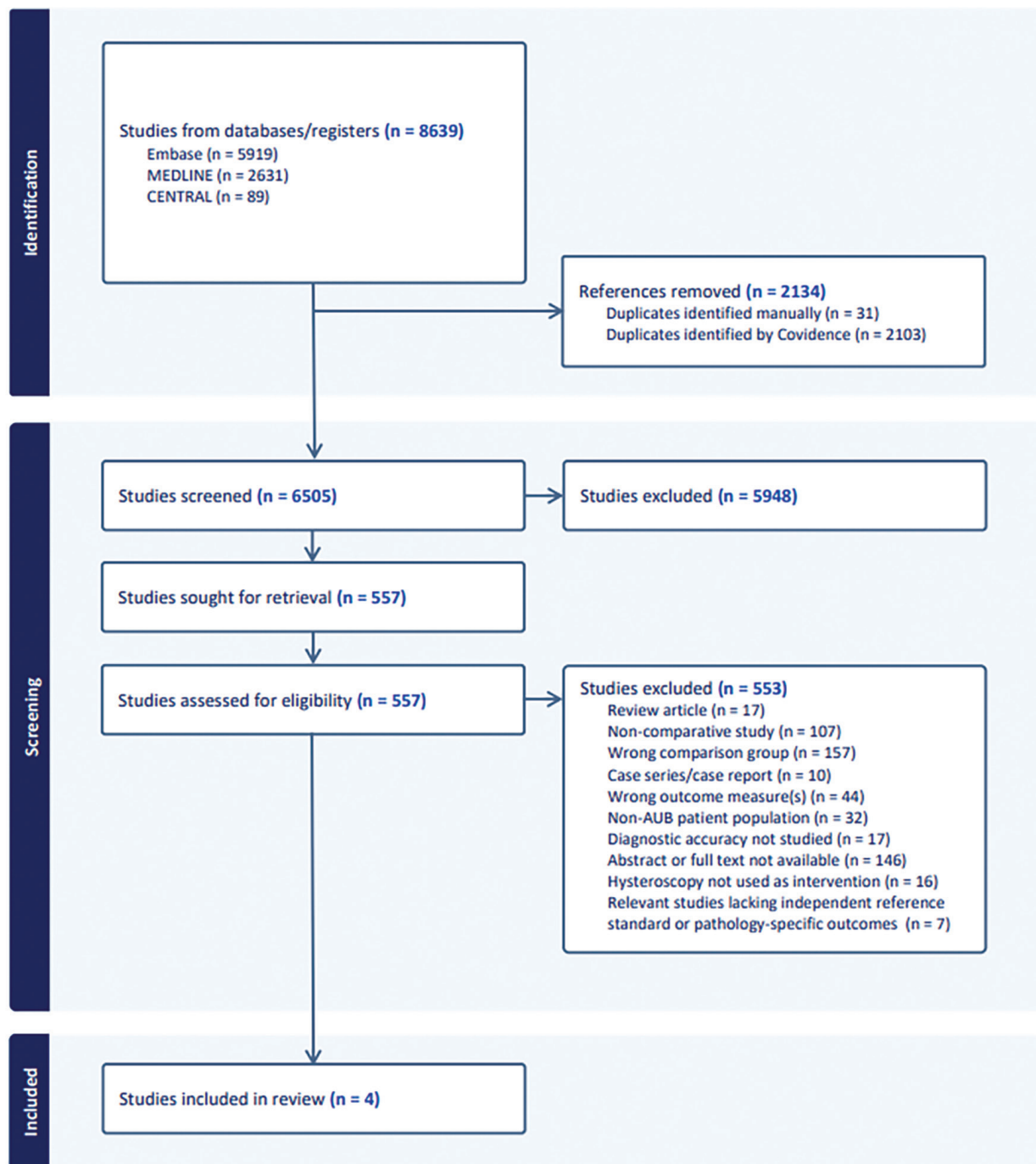


Figure 2. Flow diagram of study selection. AUB: Abnormal uterine bleeding.

Assessment of methodological quality of the four included studies according to the QUADAS-C tool identified variable risk of bias across the included studies (Table 2) (more detailed findings from the QUADAS-C assessment are provided in Appendix C).²³⁻²⁶ Overall risk of bias was high for three studies (Leone et al.,²³ Angioni et al.,²⁴ Gao et al.²⁵) primarily due to concerns regarding

lack of blinding in the conduct and interpretation of the index tests relative to the reference standard, the use of varying reference standards across different pathologies or patient groups, and the absence of prespecified diagnostic criteria. The other study (Karageyim Karsidag et al.²⁶) was rated as having unclear risk of bias due to insufficient detail about patient selection.

Box A. Criteria for strength of recommendation and quality of evidence.^a**Strength of Recommendation***Strong Recommendation*

Indicates high confidence that the desirable effects of the intervention substantially exceed potential harms or burdens. In most clinical situations, this intervention should be offered to eligible patients.

- *Conditional Recommendation*

Reflects a variable balance between benefits and potential risks or burdens. The most appropriate course of action may differ based on individual patient characteristics, values, and preferences; shared decision-making between clinician and patient is therefore encouraged.

Recommendation Against

Indicates that potential harms or burdens outweigh the anticipated benefits. In most circumstances, the intervention should generally be avoided.

Quality of Evidence**High**

Evidence based on well-conducted randomised trials, systematic reviews, or meta-analyses with minimal methodological limitations, or on highly consistent and robust observational studies. Confidence in the reliability of the estimated effect is high, and future research is unlikely to substantially change the findings.

Moderate

Evidence based on randomised trials with certain methodological limitations or on well-designed observational studies with generally consistent results. The estimated effect is considered reasonably reliable.

Low

Evidence based on randomised trials with serious methodological flaws, observational studies with serious methodological flaws, or a very limited number of studies or studies with inconsistent findings. Confidence level on the estimated effect is considered low.

Clinical Practice Points

Clinical practice points are included when clinical guidance is considered important despite very limited or absent direct evidence. These statements are not formally graded and are informed by expert consensus together with careful consideration of the available literature.

a: Criteria modified from the framework used in ACOG²¹ and ASRM Clinical Practice Guidelines.²²

Outcomes of Interest

The outcomes of the included studies are reported according to the following pathology categories: hyperplasia without atypia, EIN and/or AEH, malignancy, polyp, leiomyoma, and endometritis.

Hyperplasia without Atypia, and EIN and/or AEH using D&C as Reference Standard

One study (Leone et al.²³) compared the diagnostic accuracy of hysteroscopy against blind endometrial sampling for hyperplasia without atypia as well as EIN and/or AEH using blind D&C as the reference standard. Specifically, this study compared aspiration-guided biopsy performed at the time of SIS and visually directed hysteroscopic biopsy. Both techniques demonstrated high diagnostic performance; however, hysteroscopic-directed biopsy showed higher sensitivity, specificity, and overall diagnostic accuracy compared with SIS-guided aspiration biopsy (Table 3).²³ This difference was particularly evident for the detection of AEH and EIN, where hysteroscopy-directed biopsy demonstrated

substantially greater diagnostic sensitivity and overall accuracy. Notably, this improved performance was observed despite the sequential design of the study, in which all patients had previously undergone aspiration-guided biopsy at the time of SIS. These findings demonstrated that direct visualisation and targeted sampling during hysteroscopy enhanced detection of premalignant endometrial lesions, even after recent endometrial instrumentation.

Combined Grouping of Hyperplasia without Atypia and EIN/AEH

Two studies (Angioni et al.,²⁴ Gao et al.²⁵) compared the diagnostic accuracy of endometrial evaluation techniques for the combined pathologic grouping of hyperplasia without atypia and EIN and/or AEH. Hysteroscopy-directed biopsy was used as the reference standard in Gao et al.,²⁵ whereas in Angioni et al.,²⁴ reference standards varied by histologic outcome, with operative hysteroscopy used for hyperplasia without atypia and hysterectomy for EIN/AEH. Diagnostic discordance was noted in several

Table 1. Description of included studies.

Study	Country	Data year(s)	Patient age range	Patient menopausal status	Overall sample size	Prospective or retrospective design	Intervention	Comparator	Reference standard	Condition(s) with diagnostic performance measures available
Angioni et al. ²⁴	Italy	1992-2004	46-88	Post-menopausal	319	Prospective	Hysteroscopy (visualisation only)	Blind biopsy performed by Novak curette	Hysterectomy if performed; otherwise operative hysteroscopy if available or unspecified endometrial biopsy	Combined grouping of hyperplasia without atypia and EIN/AEH; polyp; Submucosal myoma
Gao et al. ²⁵	China	2009-2011	44-75	Post-menopausal	177	Retrospective	Hysteroscopy (visualisation only)	Blind biopsy performed by D&C	Hysteroscopy-directed biopsy	Combined grouping of hyperplasia without atypia and EIN/AEH; polyp; Submucosal myoma; Endometritis
Karageyim Karsidag et al. ²⁶	Turkey	2006-2007	46-70	Post-menopausal	36	Prospective	Hysteroscopy (visualisation only)	Blind biopsy performed by D&C	Hysteroscopy-directed biopsy	Polyp; submucosal myoma
Leone et al. ²³	Italy	Not reported	Not reported	Pre- and post-menopausal	128	Prospective	Hysteroscopy (visually-directed biopsy)	Blind biopsy (guided aspiration with SIS)	Blind D&C	Hyperplasia without atypia; EIN/AEH

AEH: Atypical endometrial hyperplasia, D&C: Dilation and curettage, EIN: Endometrial intraepithelial neoplasia, SIS: Saline-infused sonography.

cases where diagnostic hysteroscopy or blind biopsy suggested hyperplasia without atypia but subsequent hysteroscopic resection indicated normal endometrium or other pathology (Table 4).^{24,25} Likewise, there were cases of suspected other pathology (by hysteroscopy or blind biopsy) that ultimately showed findings of hyperplasia. Blind endometrial biopsy generated insufficient tissue for a large proportion of patients (24.0% in Angioni et al.²⁴ and 23.5% in Gao et al.²⁵). Meta-analysis from these two studies demonstrated markedly improved sensitivity for hysteroscopy (75.1%) compared to blind biopsy (41.9%), while specificity was comparable between hysteroscopy (94.0%) and blind biopsy (94.3%) for the detection of hyperplasia and EIN/AEH.^{24,25}

Malignancy

Two studies (Leone et al.;²³ Gao et al.²⁵) compared blind endometrial sampling with diagnostic hysteroscopy for the detection of endometrial malignancy. In Leone et al.,²³ using blind D&C as the reference standard, hysteroscopy-directed biopsy demonstrated higher sensitivity and overall diagnostic accuracy than guided aspiration biopsy performed at the time of SIS, while maintaining excellent specificity (Table 5).²⁵ In Gao et al.,²⁵ using hysteroscopic-directed biopsy as reference standard, diagnostic performance of hysteroscopy was superior compared to blind D&C, although both hysteroscopy alone and blind sampling missed several malignancies. Although no meta-analysis could be performed due to the different hysteroscopy tests and different reference standards used in the two studies, their findings suggest that while blind endometrial sampling demonstrates high specificity, its lower sensitivity may result in missed malignancies. In contrast, hysteroscopy (alone or with visual-directed biopsy) provides improved diagnostic performance through direct visualisation and targeted sampling.

Polyps

Three studies (Angioni et al.;²⁴ Gao et al.;²⁵ Karageyim Karsidag et al.²⁶) evaluated the diagnostic accuracy of endometrial evaluation techniques for the detection of endometrial polyps, comparing blind endometrial sampling

Table 2. Risk of bias assessment of included studies based on QUADAS-C.

Study	Condition	Test	Risk of bias (QUADAS-2)				Applicability concerns (QUADAS-2)			Risk of bias (QUADAS-C)				
			P	I	R	FT	P	I	R	P	I	R	FT	Overall
Angioni et al. ²⁴	Combined grouping of hyperplasia without atypia and EIN/AEH	Hysteroscopy ^a	✓	✗	✗	✓	✓	✓	✓					
		Blind biopsy ^b	✓	✓	✗	✓	✓	✓	✓	✓	✗	✗	✓	✗
	Polyp	Hysteroscopy ^a	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	✓	✗
		Blind biopsy ^b	✓	✓	✗	✓	✓	✓	✓					
	Submucosal myoma	Hysteroscopy ^a	✓	?	✓	✓	✓	✓	✓	✓	✗	✗	✓	✗
		Blind biopsy ^b	✓	✓	✗	✓	✓	✓	✓					
Gao et al. ²⁵	Malignancy	Hysteroscopy ^a	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
	Combined grouping of hyperplasia without atypia and EIN/AEH	Hysteroscopy ^a	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
	Polyp	Hysteroscopy ^a	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
	Submucosal myoma	Hysteroscopy ^a	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
	Endometritis	Hysteroscopy ^a	✓	✓	✗	✓	✓	✓	✓	✓	✓	✗	✗	✗
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
Karageyim Karsidag et al. ²⁶	Polyp	Hysteroscopy ^a	?	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	?
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
	Submucosal myoma	Hysteroscopy ^a	?	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	?
		Blind biopsy ^c	✓	✓	✓	✓	✓	✓	✓					
Leone et al. ²³	Malignancy	Hysteroscopy ^d	✓	?	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗
		Blind biopsy ^e	✓	✓	✓	✓	✓	✓	✓					
	Hyperplasia without atypia	Hysteroscopy ^d	✓	?	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗
		Blind biopsy ^e	✓	✓	✓	✓	✓	✓	✓					
	EIN/AEH	Hysteroscopy ^d	✓	?	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗
		Blind biopsy ^e	✓	✓	✓	✓	✓	✓	✓					

a: Visualisation alone, b: Performed by Novak curette; c: Performed by D&C, d: Visually directed biopsy, e: Guided aspiration with SIS.
 ✓ indicates low risk; ✗ indicates high-risk; ? indicates unclear risk.
 AEH: Atypical endometrial hyperplasia, D&C: Dilation and curettage, EIN: Endometrial intraepithelial neoplasia, P: Patient selection, I: Index test, R: Reference standard, FT: Flow and timing, SIS: Saline infusion sonography, QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2, QUADAS-C: Quality Assessment of Diagnostic Accuracy Studies-Comparative.

with hysteroscopic approach (Table 6). In Angioni et al.,²⁴ where hysteroscopic-directed biopsy served as the reference standard, blind endometrial biopsy using a Novak curette demonstrated very low sensitivity for polyps despite relatively high specificity, resulting in poor overall diagnostic accuracy. In contrast, hysteroscopic-directed biopsy demonstrated markedly higher sensitivity

and overall diagnostic performance. Similarly, Karageyim Karsidag et al.²⁶ found that blind D&C identified only a minority of polyps when compared with hysteroscopy-directed biopsy as the reference standard, whereas diagnostic hysteroscopy detected all polyps. Gao et al.,²⁵ using hysteroscopy-directed biopsy as reference standard, reported consistent findings, with diagnostic

hysteroscopy demonstrating substantially higher sensitivity for endometrial polyps than blind D&C, while maintaining high specificity. Several cases where polyps

were missed or inadequately sampled during blind curettage were subsequently identified on hysteroscopic-directed biopsy.

Table 3. Diagnostic accuracy of hysteroscopy-directed biopsy for hyperplasia without atypia, and EIN/AEH compared to blind biopsy, using D&C as reference standard (Leone et al.²³).

Diagnostic performance	Hyperplasia without atypia		EIN/AEH	
	Blind biopsy ^a	Hysteroscopy ^b	Blind biopsy ^a	Hysteroscopy ^b
Sensitivity	89.5%	91.2%	50.0%	100%
	(81.5, 97.4)	(83.9, 98.6)	(6.8, 93.2)	(39.6, 100)
Specificity	94.4%	98.6%	98.4%	99.2%
	(89.1, 99.7)	(95.8, 100)	(94.3, 99.8)	(97.6, 100)
PPV	92.7%	98.1%	50%	80.0%
	(85.8, 99.7)	(94.5, 100)	(6.8, 93.2)	(28.4, 99.5)
NPV	91.8%	93.3%	98.4%	100%
	(85.2, 98.4)	(87.2, 99.4)	(94.3, 99.8)	(97.0, 100)
LR+	15.9	64.7	31.3	125
	(6.1, 42.3)	(9.2, 456)	(5.0, 191)	(17.0, 907.0)
LR-	0.11	0.09	0.51	0
	(0.05, 0.23)	(0.04, 0.21)	(5.0, 191.0)	NC
Diagnostic odds ratio	142.4	727.3	60.9	NC
	(37, 546)	NC	NC	-

a: Guided aspiration with SIS, b: Visually directed biopsy. EIN: Endometrial intraepithelial neoplasia, AEH: Atypical endometrial hyperplasia, PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, NC: Not calculable, D&C: Dilation and curettage.

Table 4. Diagnostic accuracy of hysteroscopy-directed biopsy compared to blind biopsy for the combined grouping of hyperplasia without atypia and EIN/AEH.

Diagnostic performance	Combined grouping of hyperplasia without Atypia and EIN/AEH					
	Angioni et al. ²⁴		Gao et al. ²⁵		Pooled estimates	
	Blind biopsy ^a	Hysteroscopy ^b	Blind biopsy ^c	Hysteroscopy ^b	Blind biopsy ^d	Hysteroscopy ^b
Sensitivity	24.6%	73.7%	66.7%	83.3%	41.9%	75.1%
	(15.8, 36.0)	(61.0, 83.7)	(35.4, 87.9)	(55.2, 95.3)	(11.0, 80.8)	(63.6, 83.9)
Specificity	92.4%	93.1%	97.2%	96.4%	94.3%	94.0%
	(88.8, 94.9)	(89.4, 95.6)	(90.4, 99.2)	(90.2, 98.8)	(86.5, 97.7)	(90.1, 96.4)
PPV	41.2%	70.0%	75.0%	76.9%	NC	NC
	(24.4, 57.7)	(57.5, 80.2)	(40.9, 92.9)	(49.7, 91.8)	-	-
NPV	84.9%	94.2%	95.9%	97.6%	NC	NC
	(80.5, 88.4)	(90.9, 96.4)	(89.2, 98.5)	(91.8, 99.4)	-	-
LR+	3.23	10.7	24.0	23.3	7.87	13.2
	(1.82, 5.75)	(6.3, 18.2)	(5.6, 102.7)	(7.7, 69.4)	NC	NC
LR-	0.82	0.28	0.34	0.17	0.60	0.27
	(0.69, 0.97)	(0.18, 0.43)	(0.12, 0.94)	(0.04, 0.66)	NC	(0.04, 1.83)
Diagnostic odds ratio	3.9	38.0	70.0	135.0	14.29	52.3
	(1.9, 8.1)	(18.8, 76.8)	(8.5, 576.0)	(21.0, 869.0)	NC	NC

a: Performed by Novak curette, b: Visualisation alone, c: Performed by dilation and curettage, d: Performed by Novak curette or dilation and curettage. EIN: Endometrial intraepithelial neoplasia, AEH: Atypical endometrial hyperplasia, PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, NC: Not calculable.

Meta-analysis from these three studies demonstrated that blind endometrial sampling has limited sensitivity for detecting endometrial polyps and frequently misses focal intracavitary lesions (Table 6).²⁴⁻²⁶ In contrast, hysteroscopy provides superior diagnostic performance through direct visualisation of the uterine cavity and targeted biopsy of suspected lesions.

Submucosal Myomas

Three studies (Angioni et al.,²⁴ Gao et al.,²⁵ Karageyim Karsidag et al.²⁶) evaluated the diagnostic accuracy of hysteroscopic evaluation, in comparison to blind endometrial sampling, for the detection of submucosal myomas (Table 7). In Angioni et al.,²⁴ hysteroscopic-directed biopsy served as the reference standard. Blind endometrial biopsy with Novak curette demonstrated very low sensitivity for submucosal myomas despite high specificity, resulting in missed lesions and limited diagnostic utility. In contrast, hysteroscopy demonstrated high sensitivity and overall diagnostic accuracy. Similarly, Karageyim Karsidag et al.²⁶ reported that blind D&C failed to identify submucosal myomas, whereas diagnostic hysteroscopy correctly identified all lesions with high diagnostic accuracy, although estimates were limited by the small number of cases. Gao et al.²⁵ reported consistent

findings, with diagnostic hysteroscopy demonstrating excellent sensitivity and specificity for submucosal myomas. In contrast, blind curettage demonstrated substantially lower sensitivity, with several myomas missed or yielding insufficient tissue for diagnosis.

Meta-analysis from all three studies demonstrate that blind endometrial sampling has limited sensitivity for detecting submucosal myomas and may fail to identify focal intracavitary lesions (Table 7).²⁴⁻²⁶ Hysteroscopy provides superior diagnostic performance through direct visualisation of the uterine cavity and targeted evaluation of suspected lesions.

Endometritis

Only one study (Gao et al.²⁵) evaluated the diagnostic accuracy of hysteroscopy for the detection of endometritis, in comparison to blind diagnostic curettage, using hysteroscopy-directed biopsy as the reference standard. Diagnostic hysteroscopy demonstrated perfect concordance with histopathology, whereas blind diagnostic curettage showed substantially lower sensitivity despite high specificity (Table 8).²⁵ Several cases of endometritis confirmed on hysteroscopy-directed biopsy were not detected on blind curettage because of insufficient tissue sampling, and one case

Table 5. Diagnostic accuracy of hysteroscopy compared to blind biopsy for malignancy.

	Malignancy of endometrial carcinoma			
	Leone et al. ²³ (reference standard: D&C)		Gao et al. ²⁵ (reference standard=hysteroscopy-directed biopsy)	
	Blind Biopsy ^a	Hysteroscopy ^b	Blind Biopsy ^c	Hysteroscopy ^d
Sensitivity	90.9%	95.5%	62.5%	88.9%
	(72.2, 97.5)	(78.2, 99.2)	(30.6, 86.3)	(56.5, 98.0)
Specificity	100%	100%	100%	98.9%
	(96.5, 100)	(96.5, 100)	(95.0, 100)	(93.8, 99.8)
PPV	100%	100%	100%	88.9%
	(83.9, 100)	(84.5, 100)	(56.6, 100)	(56.5, 98.0)
NPV	98.2%	99.1%	96.1%	98.9%
	(93.5, 99.5)	(94.9, 99.8)	(89.0, 98.7)	(93.8, 99.8)
LR+	NC	NC	NC	77.3
	-	-	-	(10.9, 550.3)
LR-	0.09	0.05	0.38	0.11
	(0.03, 0.35)	(0.01, 0.31)	(0.17, 0.89)	(0.02, 0.71)
Diagnostic odds ratio	1747	3053	231	688
	NC-	NC	NC	NC

a: Guided aspiration with SIS, b: Hysteroscopic-directed biopsy, c: Dilation and curettage, d: Visualisation alone. EIN: Endometrial intraepithelial neoplasia, AEH: Atypical endometrial hyperplasia, SIS: Saline infused sonography, PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, NC: Not calculable, D&C: Dilation and curettage.

Table 6. Diagnostic accuracy of hysteroscopic-directed biopsy compared with blind biopsy for polyps.

	Polyp		Angioni et al. ²⁴		Gao et al. ²⁵		Karageyim Karsidag et al. ²⁶		Pooled estimates	
	Blind biopsy ^a	Hysteroscopy ^b	Blind biopsy ^c	Hysteroscopy ^b	Blind biopsy ^c	Hysteroscopy ^b	Blind biopsy ^c	Hysteroscopy ^b	Blind biopsy ^d	Hysteroscopy ^b
Sensitivity	11.3%	88.7%	60.0%	95.2%	60.0%	95.2%	34.8%	100%	30.7%	90.6%
	7.0, 17.8	(82.2, 93.1)	(35.8, 80.2)	(77.3, 99.2)	(35.8, 80.2)	(77.3, 99.2)	(18.8, 55.1)	(85.7, 100)	(9.3, 65.9)	(83.0, 95.0)
Specificity	93.0%	93.0%	98.5%	96.0%	98.5%	96.0%	92.3%	69.2%	94.1%	90.3%
	88.4, 95.9	(88.4, 95.9)	(91.9, 99.7)	(88.9, 98.6)	(91.9, 99.7)	(88.9, 98.6)	(66.7, 98.6)	(42.4, 87.3)	(88.6, 97.1)	(74.2, 96.8)
PPV	53.6%	90.1%	90.0%	87.0%	90.0%	87.0%	88.9%	85.2%	NC	NC
	(35.8, 70.5)	(83.8, 94.1)	(59.6, 98.2)	(67.9, 95.5)	(59.6, 98.2)	(67.9, 95.5)	(56.5, 98.0)	(67.5, 94.1)	-	-
NPV	59.5%	92.0%	91.5%	98.6%	91.5%	98.6%	44.4%	100%	NC	NC
	(53.7, 64.9)	(87.3, 95.1)	(82.8, 96.1)	(92.6, 99.8)	(82.8, 96.1)	(92.6, 99.8)	(27.6, 62.7)	(70.1, 100)	-	-
LR+	1.61	12.7	39.6	23.8	39.6	23.8	4.52	3.25	5.62	9.36
	(0.79, 3.28)	(7.48, 21.5)	(5.43, 288.9)	(7.83, 72.4)	(5.43, 288.9)	(7.83, 72.4)	(0.63, 32.3)	(1.52, 6.97)	NC	(0.72, 122.5)
LR-	0.95	0.12	0.41	0.05	0.41	0.05	0.71	0.03	0.72	0.11
	(0.89, 1.03)	(0.08, 0.20)	(0.22, 0.76)	(0.01, 0.34)	(0.22, 0.76)	(0.01, 0.34)	(0.50, 0.99)	(0.00, 0.49)	(0.27, 1.93)	(0.05, 0.28)
Diagnostic odds ratio	1.69	104.7	97.5	480.0	97.5	480.0	6.40	99.2	8.68	120.8
	(0.78, 3.69)	(48.1, 228.1)	NC	NC	NC	NC	(0.70, 58.5)	NC	NC	NC

a: Performed with Novak curette, b: Visually directed biopsy, c: Performed by dilation and curettage, d: Performed by Novak curette or dilation and curettage. PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio.

interpreted as endometritis on blind curettage was subsequently classified as hyperplasia without atypia. These findings suggest that hysteroscopic visualisation may improve detection of endometrial inflammation compared with blind sampling techniques.

Discussion

This guideline systematically evaluated the available evidence comparing hysteroscopy, visually directed hysteroscopic biopsy, and endometrial sampling in the diagnostic assessment of AUB and PMB. Across the included studies, hysteroscopy consistently demonstrated good diagnostic accuracy for premalignant and malignant endometrial disease, as well as focal intrauterine lesions such as endometrial polyps and submucosal myomas, particularly for detection of these pathologies. In addition, hysteroscopic visualisation enabled targeted tissue sampling for histologic confirmation of suspected pathology and provided interpretation when blind endometrial samples were insufficient or non-diagnostic. However, limitations in the methodological quality of included studies restrict the strength of clinical inferences and recommendations. Future studies evaluating the diagnostic accuracy and clinical effectiveness of hysteroscopy in women with AUB and PMB should adhere to established reporting and methodological standards to generate more robust evidence capable of informing clinical practice.

Several limitations within the current evidence base should be acknowledged. Substantial heterogeneity exists across studies in patient selection, sequence of sampling, reference standard, and outcome reporting. In addition, we identified very few studies that conducted head-to-head comparisons between hysteroscopy and blind biopsy with an independent reference standard. Several studies had to be excluded because they reported global measures of diagnostic performance rather than pathology-specific metrics, limiting the clinical interpretability of findings for intracavitary lesions (Appendix D).²⁷⁻³³ Evaluation of diagnostic accuracy is further complicated by the use of imperfect reference

Table 7. Diagnostic accuracy of hysteroscopy over blind biopsy for the detection of submucosal myomas.

Leiomyoma		Angioni et al. ²⁴		Gao et al. ²⁵		Karageyim Karsidag et al. ²⁶		Pooled estimates	
		Blind biopsy ^a	Hysteroscopy ^b	Blind biopsy ^c	Hysteroscopy ^b	Blind biopsy ^c	Hysteroscopy ^b	Blind biopsy ^d	Hysteroscopy ^b
Sensitivity		12.5%	100%	66.7%	100%	66.7%	100%	29.9%	93.3%
		(2.2, 47.1)	(67.6, 100)	(30.0, 90.3)	(67.6, 100)	(39.1, 86.2)	(51.0, 100)	(6.6, 72.0)	(72.5, 98.6)
Specificity		100%	99.4%	98.7%	98.9%	100%	96.9%	99.2%	98.3
		(98.8, 100)	(97.7, 99.8)	(92.8, 99.8)	(93.8, 99.8)	(89.3, 100)	(84.3, 99.4)	(96.8, 99.8)	95.5, 99.4
PPV		100%	80.0%	80%	88.9%	100%	80.0%	83.3%	83.3%
		(20.7, 100)	(49.0, 94.3)	(37.6, 96.4)	(56.5, 98.0)	(67.6, 100)	(37.6, 96.4)	(35.9, 99.6)	(62.6, 95.3)
NPV		97.8%	100%	97.4%	100%	88.9%	100%	97.0%	100%
		(95.5, 98.9)	(98.8, 100)	(90.9, 99.3)	(95.8, 100)	(74.7, 95.6)	(88.9, 100)	(94.9, 98.5)	(99.1, 100)
LR+		NC	155.5	50.0	88.0	NC	32	42.7	55.7
		-	(33.9, 409.2)	(6.58, 379.7)	(11.4, 276.1)	-	(4.04, 97.2)	NC	NC
LR-		0.88	0	0.34	0	0.33	0	0.83	0.07
		0.62, 1.12	NC	(0.11, 1.05)	NC	(0.17, 0.74)	NC	(0.43, 1.60)	0.03, 0.17
DOR		122.8	2104.5	148.0	991.7	124.6	189.0	76.1	775.9
		NC	NC	NC	NC	NC	NC	NC	NC

a: Performed with Novak curette, b: Visualisation only, c: Performed by dilation and curettage, d: Performed by Novak curette or dilation and curettage. PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, NC: Not calculable.

standards in some studies—particularly blind D&C, which may underestimate the true diagnostic capability of direct hysteroscopic visualisation. Comparability between index tests was also limited in some studies because of non-randomised and non-paired designs or conditional verification strategies. Lastly, although this review sought to incorporate evidence on balancing factors, such as adverse events, costs, and pain/patient acceptability, into the formulation of the recommendations, scarce data on those outcomes were available in the studies meeting the eligibility criteria of this review. These areas warrant further investigation in future research.

Despite these limitations, the present guideline applied rigorous inclusion criteria based on the PICO framework to ensure a structured and transparent evaluation of the evidence. Several additional studies were identified that were relevant to the clinical question but did not meet the predefined criteria for inclusion because they compared hysteroscopy against blind biopsy or vice versa, without an independent reference standard. Those studies are summarised in Appendix D.²⁷⁻³³

Future research should prioritise well-designed prospective studies with clearly defined reference standards and standardised reporting of pathology-specific outcomes. Incorporating modern hysteroscopic techniques and technologies, including directed biopsy and office-based operative hysteroscopy, will be important to reflect contemporary clinical practice. In addition, standardised reporting frameworks and consensus definitions across studies would improve comparability and facilitate more robust meta-analysis. Advances in digital imaging, artificial intelligence-assisted interpretation, integration with molecular or histology markers and incorporation of these findings have the potential to enhance diagnostic precision of hysteroscopy and refine patient-centered diagnostic pathways.

Conclusion

In summary, once the decision has been made to obtain endometrial sampling in the

Table 8. Diagnostic accuracy of hysteroscopy for detection of endometritis.²⁵

	Endometritis	
	Blind biopsy ^a	Hysteroscopy ^b
Sensitivity	62.5%	100%
	(30.6, 86.3)	(64.6, 100)
Specificity	98.6%	100%
	(92.6, 99.8)	(95.9, 100)
PPV	83.3%	100%
	(43.6, 97.0)	(64.6, 100)
NPV	96.0%	100%
	(88.9, 98.6)	(95.9, 100)
LR+	45.6	NC
	(6.06, 343.7)	-
LR-	0.38	0
	(0.16, 0.93)	NC
Diagnostic accuracy	120.0	2685
	NC	NC

a: Performed by dilation and curettage, b: Visualisation only. PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio, NR: Not reported, NC: Not calculable.

evaluation of patients with AUB or PMB, the available evidence supports hysteroscopy as the superior diagnostic approach. Hysteroscopy offers direct visualisation of the uterine cavity, enabling accurate identification of focal lesions such as endometrial polyps and submucosal myomas and facilitating targeted biopsy. Although histologic confirmation remains necessary for definitive diagnosis of endometrial hyperplasia and malignancy, hysteroscopy enhances diagnostic yield by guiding targeted tissue sampling. Within contemporary gynecologic practice, blind sampling has a limited role, particularly when focal pathology is suspected. Continued methodological rigor and standardised outcome reporting in future studies will be essential to further define the role of hysteroscopy within diagnostic algorithms for AUB and PMB and to support high-quality, patient-centered care.

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Appendices: <https://d2v96fxpocvxx.cloudfront.net/dd8262ff-66e6-418e-b233-a064eb1ea82f/content-images/5f0b692b-7512-417f-a9c7-2d2a23cb4f48.pdf>

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Structured Reporting of Diagnostic Hysteroscopy Findings in Women with Reproductive Disorders: An ESGE–ESHRE–IFFS International Consensus

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ABSTRACT

Background: Despite its widespread use in women with reproductive disorders, no standardised framework currently exists for reporting of hysteroscopic findings. This lack of uniformity may limit the utility of the procedure and contribute to substantial heterogeneity among operators and centres. As a result, the reproducibility of hysteroscopy is limited, making it difficult to conduct robust studies that define its prognostic value in specific patient subgroups.

Objectives: To develop an international consensus on the structured reporting of diagnostic hysteroscopy findings in women with reproductive disorders.

Methods: A dedicated working group from the European Society for Gynaecological Endoscopy (ESGE), European Society of Human Reproduction and Embryology (ESHRE), and International Federation of Fertility Societies (IFFS) collaborated to develop a consensus for comprehensive structured reporting of diagnostic hysteroscopy findings in women with reproductive problems. This consensus paper focuses on grouping diagnostic hysteroscopic findings, structuring their reporting, and adopting standardised terminology for women with reproductive disorders. The virtual Nominal Group Technique, a structured consensus-building method, was adopted to ensure equal contribution from all members in the development of the final consensus.

Main Outcome Measures: A consensus for comprehensive structured reporting of diagnostic hysteroscopy findings in women with reproductive problems.

Results: This collaborative document by ESGE, ESHRE and IFFS provides the first detailed framework for structured reporting of diagnostic hysteroscopy findings in women with reproductive disorders. The document provides a structured reporting of hysteroscopic findings into five sections, each systematically capturing patient characteristics, procedural findings, and pathological observations as follows: patient characteristics, findings from the vagina, cervix, uterine cavity, endometrium and tubal ostia.

Conclusions: The standardised reporting of hysteroscopic findings promotes consistent data collection across centres and could help inform research and exchange of clinical experience, enhancing the value of hysteroscopy in fertility evaluation. This report could be used as a validation tool for further research.

What is New? This collaborative document by ESGE, ESHRE and IFFS provides the first detailed structured reporting of diagnostic hysteroscopy findings in women with reproductive disorders.

Keywords: Consensus, hysteroscopy, infertility, reproduction, reproductive disorders, International consensus

Introduction

Hysteroscopy is widely recognised as the gold standard for the diagnosis and treatment of intrauterine pathologies.¹⁻³ Technological advancements, including smaller-diameter scopes with operative channels and the use of saline distension media, have greatly simplified hysteroscopy, making it more patient-friendly and enabling outpatient procedures without the need for cervical dilation or analgesia.⁴⁻⁶

As with other specialised diagnostic procedures, the use of hysteroscopy should be guided by specific clinical indications and diagnostic objectives. Reproductive disorders such as infertility, recurrent pregnancy loss, late miscarriage, and repeated Assisted Reproductive Technologies (ART) failures represent common indications, requiring evaluation by operators with expertise in reproductive medicine. In patients with reproductive disorders, hysteroscopy provides valuable information on the vagina, cervix, cervical canal, uterine cavity, endometrium, and tubal ostia. It should be regarded not merely as an anatomical inspection, but as a comprehensive functional assessment of factors

relevant to reproduction, as well as a tool that may improve the performance of ARTs (e.g., resolution of cervical canal stenosis, anatomical assessment for embryo transfer), especially in patients experiencing recurrent implantation failure.⁷ Among its key advantages, the procedure enables detailed assessment of endometrial morphology and its concordance with the menstrual phase, while allowing the identification of common congenital and acquired uterine abnormalities, including uterine malformations, niches, fibroids, and intrauterine adhesions (IUA). Hysteroscopy also permits a limited evaluation of tubal patency through indirect visualisation of the morphological and dynamic characteristics of the tubal ostia, potentially revealing infertility-related factors that may escape detection by ultrasound. Overall, hysteroscopy represents a technically refined procedure with substantial diagnostic value.

Despite its widespread use in women with reproductive disorders, no standardised framework currently exists for reporting of hysteroscopic findings. This lack of uniformity may limit the utility of the procedure and contribute to substantial heterogeneity among operators and centres.

As a result, the reproducibility of hysteroscopy is limited, making it difficult to conduct robust studies that define its prognostic value in specific patient subgroups.

In recent years, progress has been made toward harmonising hysteroscopic terminology at the global level, based on expert consensus.⁶ However, no comparable scientific efforts have been directed toward standardising the execution and reporting of diagnostic hysteroscopy in women with reproductive disorders. Given its potential global value, there is an urgent need for a scientifically validated and universally accepted framework.

To address this gap, a joint working group was established, composed of representatives from the European Society for Gynaecological Endoscopy (ESGE), the European Society of Human Reproduction and Embryology (ESHRE), and the International Federation of Fertility Societies (IFFS). The objective of the established working group was to develop a structured reporting framework for diagnostic hysteroscopy findings in women with reproductive disorders. The overarching objective was to standardise terminology and facilitate global adoption of this framework in both clinical practice and research settings. The present document represents the outcome of this collaborative effort.

Methods

Organisational Framework and Participants

This project was implemented as an international, multidisciplinary consensus initiative jointly endorsed by three leading organisations in the field of reproductive medicine and gynaecological endoscopy: the ESGE, the ESHRE, and the IFFS.

A total of 17 experts were nominated by the three societies based on recognised expertise in hysteroscopy and reproductive medicine, as well as significant academic contributions to the field. To strengthen the global relevance of the consensus, experts were selected to ensure representation from diverse geographic regions.

Draft Development and Consensus Methodology

A preliminary draft of a structured hysteroscopy recording template was prepared by a steering committee composed of three members (U.C., Am.V., A.A.) and critically revised by one member (G.G.). This draft was developed following a critical review of the current

literature and existing recording systems in gynecology and served as the basis for the consensus process. The consensus process was completed in two virtual meetings and one final round of written feedback. The entire process was conducted between July 2025 and February 2026. After finalising the reporting template, the manuscript was prepared by U.C. and G.G. and sent for comments and final approval by the members of the working group.

To refine and validate the draft template, we adopted the virtual Nominal Group Technique, a structured consensus-building method designed to ensure equal contribution from all participants.⁸

Step 1-Silent Generation of Comments

Each expert independently reviewed the draft template and documented its strengths, limitations, and potential modifications.

Step 2-Round-Robin Sharing

During a moderated videoconference, each participant in turn presented a proposed modification. All suggestions were recorded without immediate discussion until the full set of comments was collected.

Step 3-Structured Discussion

Each proposed modification was then discussed by the group to ensure clarity, avoid redundancy, and consolidate overlapping proposals. The discussion was moderated to maintain focus and equitable participation.

Step 4 -Voting and Ranking

All participants subsequently rated each proposed modification anonymously using an electronic survey tool (five-point Likert scale: strongly disagree to strongly agree). A predefined threshold of $\geq 75\%$ agreement (scores 4-5) was required for inclusion. Items with $< 50\%$ agreement were excluded, whereas those with 50-74% agreement were revised and re-discussed before re-voting in the same session.

Step 5-Consolidation

The steering committee synthesised the voting outcomes, integrated approved modifications, and produced a revised version of the recording template. This version was circulated electronically among all 17 experts for final written comments. At this stage, only minor editorial

adjustments were accepted, and no new items were introduced.

The final text was reviewed and approved by the ESGE Academic Faculty, ESHRE and IFFS Executive Committees.

Ethical Considerations

As this initiative did not involve patient recruitment or the collection of clinical data, formal ethical approval was not required. Nonetheless, the process was conducted in full compliance with the principles of transparency, inclusivity, and respect for intellectual contributions, following Good Consensus Practice recommendations for scientific societies.⁹

Results

Development of the Structured Reporting Template

To ensure a comprehensive and reproducible evaluation of uterine anatomy and pathology in women with reproductive disorders, a structured hysteroscopic reporting template was developed. The report is organised into five sections, each systematically capturing patient characteristics, procedural findings, and pathological observations.

A total of 35 items were reviewed (Supplementary File 1). Of these: 17 (48.6%) were approved unanimously; 18 (51.4%) required modification following group discussion before final approval (Supplementary File 2).

Hysteroscopic Report

The structured reporting template for hysteroscopic procedures in women with reproductive disorders (Figure 1) includes:

Patient Characteristics

The initial section records baseline demographic and reproductive data, including age, anthropometric parameters (height, weight), hormonal profile [anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH)], and menstrual history. It further includes previous hysteroscopic or uterine interventions (e.g., caesarean section, myomectomy, conisation, uterine artery embolisation) and possible previous infections [e.g. pelvic inflammatory disease (PID)]. Reproductive history, including infertility, previous implantation failures, gravidity, parity, miscarriages/abortions (with or without dilation and curettage), preterm deliveries, is also reported. Indications for hysteroscopy (baseline

assessment, failed ART attempts and pregnancy losses) are specified, together with relevant imaging findings from ultrasound or magnetic resonance imaging (MRI).

Hysteroscopic Findings

Vagina, Cervix and Cervical Canal

The second section addresses the anatomical and pathological findings in the vagina, cervix, and cervical canal.

Potential vaginal anomalies are listed: longitudinal non-obstructive or obstructive vaginal septum, transverse septum, others.¹⁰

Cervical morphology and orientation/course of the endocervical canal (anteverted, axial, retroverted) are documented, along with potential abnormalities such as congenital malformation (single cervix with cervical septum or double cervix),^{11,12} intracervical synechiae, or stenosis of the internal or external uterine orifice. Cervical lesions, if present, should also be described.

Congenital anomalies of the vagina and the cervix follow the ESGE/ESHRE classification system.^{10,12}

Uterine Cavity

As a first step, the difficulty in accessing the uterine cavity should be reported; if the access to the uterine cavity is not possible, an explanation is required. Evaluation of the uterine cavity includes distension quality (optimal/non-optimal), wall irregularities, uterine orientation (anteverted, axial, retroverted), and overall uterine morphology. The presence of foreign bodies is also documented.

Regarding uterine morphology, the report may include a diagnostic suspicion of a dysmorphic uterus (T-shaped or Y-shaped), unicornuate uterus or other (e.g., I-shaped, infantilis).^{10,12-14} Further differential diagnoses (e.g., between septate uterus and bicornuate uterus) cannot be made based solely on intrauterine hysteroscopic visualisation.¹² In the hysteroscopic report, the description of the fundal indentation is also required following the ESHRE/ESGE classification system: partial (including also the indentation length) or complete. In case of fundal indentation, a 3D ultrasound examination is recommended, as only the combination of hysteroscopy and 3D ultrasonography ensures the highest diagnostic accuracy.^{5,12}

PATIENTS CHARACTERISTICS			
Name _____ Age _____ H _____ W _____ Last menstrual period _____ AMH _____ FSH _____ Other _____			
Current medical therapy: _____ Previous hysteroscopies: _____			
Previous uterine procedures (i.e. caesarean sections, abdominal or hysteroscopic myomectomy, conization, uterine artery embolization): _____			
Previous infections (type) _____			
Reproductive anamnesis: Infertility (duration in months: _____) ☐ Primary ☐ Secondary			
Previous implantation failures (number): _____ Gravidity _____ Parity _____			
Miscarriages/Abortion _____ D&C: ☐ YES ☐ NO Preterm delivery _____			
Indication: ☐ baseline examination ☐ failed ART ☐ Recurrent pregnancy loss			
☐ Ultrasound findings: _____ ☐ MRI findings: _____			
☐ Other: _____			
HYSTEROSCOPIC FINDINGS			
VAGINA ☐ Normal ☐ Abnormal: ☐ Longitudinal obstructive septum ☐ Longitudinal non-obstructive septum ☐ Transverse septum ☐ Other: _____		CERVIX AND CERVICAL CANAL ☐ Normal ☐ Septate ☐ Double Stenosis: ☐ External uterine os ☐ Internal uterine os Intracervical adhesions ☐ obstructive ☐ non obstructive Orientation: ☐ Anteverted ☐ Axial ☐ Retroverted Cervical lesions: _____	
UTERINE CAVITY Access to the uterine cavity ☐ Easy ☐ Difficult ☐ Not possible (reason) _____ Distention: ☐ Optimal ☐ Non-optimal (reason) _____ Wall irregularities _____ Orientation: ☐ Anteverted ☐ Axial ☐ Retroverted Other (i.e. foreign bodies): _____ Presence of fluid in the uterine cavity ☐ YES ☐ NO Morphology: ☐ Normal ☐ Dysmorphic ☐ T-shaped ☐ Y-shaped ☐ Unicorporeal ☐ Others (i.e. I-shaped, infantilis) _____ ☐ Fundal indentation ☐ Partial (specify according to the cavity length) _____ ☐ Complete			
ENDOMETRIAL FEATURES Synchronous ☐ YES ☐ NO Abnormal findings ☐ Hypotrophic endometrium ☐ Diffuse polypoid thickening ☐ Focal polypoid thickening ☐ Highly vascularized ☐ Easily bleeding areas ☐ Strawberry pattern ☐ Cystic dilations of the uterine glands ☐ Micropolyps ☐ Stromal edema ☐ Microcalcifications ☐ Ulcerated areas ☐ Crumbly consistency ☐ Haemorrhagic cysts ☐ Small opening on the surface ☐ Endometrial vascular dystrophia ☐ Endometrial compaction ☐ Other: _____			
Polyps (number) _____ ☐ Pedunculated ☐ Sessile Wall (anterior, posterior, lateral right, lateral left): _____ Location (fundus, corpus, isthmus): _____ Size (mm): _____			
Fibroids (number) _____ ☐ Type 0 ☐ Type 1 ☐ Type 2 ☐ Suspicion of Type 3 Wall (anterior, posterior, lateral right, lateral left): _____ Location (fundus, corpus, isthmus): _____ Size (mm): _____			
Suspicion of malignancy ☐ Focal lesion ☐ Diffuse lesion ☐ <50% of the cavity ☐ >50% of the cavity ☐ Suspicion of myometrial infiltration ☐ Suspicion of cervical infiltration			
Adhesions ☐ Central ☐ Lateral right ☐ Lateral left ☐ Right cornua ☐ Left cornua ☐ Extension <1/3 ☐ Extension >1/3 ☐ Extension >2/3 Consistency: ☐ Dense ☐ Filmy			
Isthmocele Location ☐ Isthmus ☐ Cervix Classification ☐ Simple niche ☐ Simple niche with one branch ☐ Complex niche Size ☐ Small ☐ Medium ☐ Large ☐ Extreme ☐ Fluid/blood retention ☐ Vascularization: _____			
Other pathologies (e.g. RPOC, foreign bodies) _____			
Tubal ostia right ☐ Normal ☐ Abnormal Adhesions ☐ YES ☐ NO Polyps ☐ YES ☐ NO Vascularization ☐ YES ☐ NO Others _____		Tubal ostia left ☐ Normal ☐ Abnormal Adhesions ☐ YES ☐ NO Polyps ☐ YES ☐ NO Vascularization ☐ YES ☐ NO Others _____	

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Figure 1. Final structured reporting template for diagnostic hysteroscopy in women with reproductive disorders.

Endometrial Features

A dedicated section focuses on findings from the endometrium.

It is recommended to describe whether the endometrium appears synchronous with the phase of the menstrual cycle or consistent with ongoing hormonal therapy, if any.

The following abnormal findings, if present, should be described:¹⁵

- Hypotrophic endometrium
- Diffuse polypoid thickening
- Focal polypoid thickening
- Highly vascularised endometrium
- Easily bleeding areas
- Strawberry pattern
- Cystic dilations of the uterine glands
- Micropolyps
- Stromal oedema
- Microcalcifications
- Ulcerated areas
- Crumbly consistency
- Haemorrhagic cysts
- Small opening on the surface
- Endometrial vascular dystrophia
- Endometrial compaction
- Other

This section additionally records intrauterine lesions. Polyps are described according to morphology (pedunculated, sessile), position on the uterine walls (anterior, posterior, lateral right, lateral left), location (fundus, corpus, isthmus), and dimensions.

Fibroids are classified following the FIGO system (Type 0-Type 2),¹⁶ with systematic documentation on wall involvement (anterior, posterior, lateral right, lateral left), location (fundus, corpus, isthmus) and size. Suspected Type 3 fibroids may also be reported.

Suspected malignant findings are categorised as focal or diffuse lesions, with quantification of cavity involvement (<50% vs. >50%) and potential extension toward the myometrium or cervix.¹⁵

IUAs are classified by site (central, lateral, cornua), extent (<1/3, >1/3, >2/3 of the cavity), and consistency (filmy vs. dense).¹⁷

Isthmocele is described according to its location from the internal uterine os (isthmus or cervix), classification

(simple niche, simple niche with one branch, complex niche), size (small, medium, large, extreme).¹⁸ Additional characteristics are fluid/blood retention and vascularisation.

Other intrauterine pathologies, such as retained products of conception (RPOC) or foreign bodies, are also documented when present. The size and the location of RPOCs may be specified in the report.¹⁹

Tubal Ostia

The characteristics of right and left tubal ostia are reported, together with the presence of adhesions, polyps, or abnormal vascularisation.

Discussion

The development of a structured template for reporting diagnostic hysteroscopy findings in women with reproductive disorders represents an important step toward standardisation of reproductive diagnostics. This initiative provides a consensus-based tool designed to improve consistency across centres, enhance communication among clinicians, and facilitate the design of robust scientific studies. In this section, we discuss the rationale and evidence supporting the inclusion of each section and item within the final report.

Patient Characteristics

Accurate documentation of baseline characteristics is essential for patient stratification and the evaluation of hysteroscopic findings. Age, body mass index, hormonal profile (AMH, FSH), and reproductive history have all been shown to impact endometrial receptivity and treatment outcomes.²⁰ Previous uterine surgery (e.g., myomectomy, caesarean section) or infections (e.g., PID) are relevant as they may predispose to IUAs or niche formation.²¹ Although this information is usually included in the patient's main records and inclusion in the hysteroscopy report might be a duplication, the working group considers that it is important to be included in the record due to their clinical significance and as a way to avoid ignoring them.

Hysteroscopic Findings

Vagina, Cervix and Cervical Canal

The evaluation of vaginal and cervical anomalies is necessary to identify congenital malformations or structural barriers that may hinder conception or *in vitro* fertilisation (IVF) procedures. Cervical anomalies such as

stenosis or synechiae can interfere with embryo transfer or sperm migration.¹ Cervical duplications and septa may also indicate Müllerian anomalies.^{10,22}

Vaginal anomalies, although rare, may include longitudinal non-obstructive or obstructive septa and transverse vaginal septa. These anomalies can have significant implications for reproductive outcomes and may be associated with obstructive symptoms, hematocolpos, or dyspareunia. Importantly, their identification can suggest the presence of more complex Müllerian anomalies.²³

Differentiating between a single cervix with a cervical septum and true cervical duplication is crucial for accurate diagnosis and management planning.²⁴ This distinction cannot be made solely by hysteroscopy but requires integration with clinical and imaging data.²⁵ The combined use of hysteroscopy, transvaginal ultrasound, and three-dimensional imaging enhances the diagnostic accuracy in distinguishing these conditions.^{11,12,26} In cases of a single cervix with a septum, hysteroscopy may reveal a central longitudinal ridge without duplication of cervical canals, whereas true duplication will typically present as two distinct cervical orifices, often associated with complete uterine septum or bicornuate uterus.

Uterine Cavity

Documenting any difficulties in accessing the uterine cavity is important for procedures like embryo transfer.²⁷ Uterine cavity shape anomalies, such as T-shaped or Y-shaped uterus, have been reported as potential factors impairing fertility and pregnancy outcomes; the need for more robust data makes their report useful for further research.²⁸ Further subclassification of dysmorphic uteri, including T-shaped, Y-shaped, I-shaped, and uterus infantilis, has been proposed in recent years, with an increasing need for simultaneous hysteroscopic and ultrasound evaluation of the cavity.^{13,14,29} Furthermore, hysteroscopy alone cannot differentiate between septate bicornuate uterus and/or bicornuate septate uterus underlining the need to use 3D ultrasound to improve diagnostic precision.^{12,30} This combined approach is supported by the concept of the digital hysteroscopic clinic, where real-time hysteroscopy and three-dimensional ultrasound are employed synergistically to enhance diagnostic accuracy.⁵

Congenital uterine anomalies are well-documented factors impairing reproductive outcome despite an existing debate for the need of their treatment.³¹⁻³⁴ Thus, the documentation of fundal indentation characteristics

by hysteroscopy is extremely important in cases of women with infertility and impaired pregnancy outcome.³⁵

Endometrial Features

A comprehensive description of endometrial appearance is a key feature in this consensus. Several hysteroscopic patterns have been associated with endometrial dysfunction, endometritis, or implantation failure. For example, the presence of micropolyps, stromal oedema, or increased vascularity has been correlated with chronic endometritis.^{36,37} Glandular-cystic changes and irregular vascular patterns may indicate hormonal imbalance or underlying endometrial pathology. The recognition of endometrial post-ovulatory compaction has recently been proposed as a marker of receptivity.³

Endometrial polyps are associated with abnormal uterine bleeding and infertility, with evidence suggesting improved implantation and pregnancy rates following hysteroscopic polypectomy in selected patients.^{38,39} Their systematic documentation by size, morphology (sessile or pedunculated), and location is fundamental for evaluation of their clinical impact and management.

Submucosal fibroids are linked to impaired implantation and increased miscarriage rates. Their classification using the FIGO system (Type 0-Type 2 for submucosal types) allows reproducibility and better surgical planning.¹⁶ Studies have demonstrated improved reproductive outcomes following hysteroscopic myomectomy in women with symptomatic submucosal fibroids.⁴⁰⁻⁴² FIGO type 3 fibroids, which are entirely intramural but overlying the endometrium, are increasingly recognised as potentially relevant in the context of infertility.⁴³ Although they do not distort the endometrial cavity per se, some studies have suggested a possible detrimental effect on implantation due to their proximity to the endometrial-myometrial interface.^{43,44} The management of Type 3 fibroids remains controversial, with ongoing debate regarding the indication for surgical removal in asymptomatic women seeking fertility treatment. Their potential documentation in hysteroscopic reports, as they are only partially visible by alterations in the overlying endometrium, is important for their management.

Although rare, the systematic recording of suspicious endometrial lesions is necessary to guide timely histological sampling and further oncologic evaluation. Descriptors such as friability, ulceration, and abnormal vascularity are established warning signs of atypical hyperplasia or malignancy.⁴⁵ Additional hysteroscopic

features associated with endometrial neoplasia include irregular endometrial thickening, papillary excrescences, necrotic or haemorrhagic areas, and spontaneous bleeding upon touch. The presence of atypical vascular patterns—such as densely packed, irregular, or chaotic vessels—may further raise the index of suspicion,¹⁵ and when observed in the context of abnormal uterine bleeding, have been correlated with an increased risk of endometrial cancer.⁴⁶ Early recognition of these findings during hysteroscopy, followed by targeted biopsy, significantly improves diagnostic accuracy and enables early oncologic referral. Moreover, in selected cases of early-stage endometrial cancer, particularly in young women with reproductive desire, accurate hysteroscopic assessment and standardised documentation of lesion characteristics may support timely decision-making for fertility-sparing treatment. Recent evidence underscores the importance of detailed endometrial evaluation to guide conservative management strategies.^{47,48}

UAs, commonly resulting from infection or trauma (e.g., post-curettage), are a well-recognised cause of infertility, amenorrhea, and miscarriage due to distortion of the uterine cavity and impairment of endometrial function.^{49,50} Accurate description of IUA location, extent (<1/3, 1/3–2/3, >2/3 of the cavity), and consistency (filmy vs. dense) is essential and reflects the parameters used in established classification systems such as those originally proposed by March and adopted by the American Society for Reproductive Medicine (ASRM),⁵¹ and further supported by international guidelines.¹⁷

Hysteroscopic adhesiolysis remains the gold standard for both diagnosis and treatment of IUA, allowing direct visualisation and targeted lysis of adhesions under vision with restoration of cavity anatomy. Evidence consistently shows that hysteroscopic adhesiolysis can restore normal menstrual function and improve fertility outcomes, with conception rates reported to exceed 40% following effective treatment in infertility cohorts.^{49,52,53}

Recent retrospective analyses also report encouraging pregnancy and live birth rates following adhesiolysis in women with recurrent pregnancy loss and IUA.^{49,54} The severity of adhesions significantly influences success, with mild disease having the most favourable reproductive prognosis.^{49,50,52}

In addition to surgical technique, the use of mechanical barriers and anti-adhesion gels, as well as second-look hysteroscopy, has been advocated to reduce recurrence rates and improve reproductive outcomes.^{50,55}

The growing recognition of isthmocele (uterine niche at the site of caesarean section scar) and its impact on implantation failure, abnormal bleeding, and miscarriage risk justifies its detailed inclusion in hysteroscopic reports. Recent evidence has emphasised its role in reproductive failure and outlined classification systems based on size, residual myometrial thickness, and anatomical complexity.^{18,56–58} Hysteroscopic evaluation allows visualisation of the defect, associated fluid retention, and vascular abnormalities that may interfere with embryo implantation or favour endometritis.⁵⁹

Tubal Ostia

Though hysteroscopy does not directly assess tubal patency, the evaluation of the ostia and surrounding areas can reveal signs of prior salpingitis, occlusion, or peritubal adhesions. Recent studies have proposed that tubal ostial abnormalities may correlate with tubal infertility and reduced IVF success.⁶⁰

Strengths and Limitations

A major strength of this consensus-based template is its ability to bridge the gap between clinical practice and research. By promoting standardised data collection, the structured report enhances not only diagnostic reproducibility but also facilitates the creation of multicentre registries and prospective studies exploring correlations between hysteroscopic findings and reproductive outcomes.

The proposed record may also play a pivotal role in training and certification of hysteroscopists, enabling objective evaluation of procedural completeness and reporting accuracy. Furthermore, its adoption may help reduce inter-operator variability, a known limitation in the interpretation of hysteroscopic images and terminology.⁶

However, several limitations should be acknowledged. First, although the template is grounded in available literature and expert consensus, the clinical significance and prognostic impact of all recorded hysteroscopic findings have not been conclusively established. Some abnormalities included in the structured report—particularly subtle endometrial patterns or minor morphological variations—may not yet have robust evidence demonstrating a direct causal relationship with infertility or adverse reproductive outcomes. Therefore, the inclusion of these items should be interpreted as a comprehensive documentation strategy rather than as confirmation of proven clinical relevance.

Second, the consensus reflects expert opinion and structured discussion rather than prospective validation studies. The ultimate value of the reporting system will depend on its application in real-world settings and on future research assessing interobserver agreement, feasibility, and correlation between specific hysteroscopic findings and reproductive prognosis, particularly in IVF cycles.

Future research should focus on validating the predictive value of individual items, determining which findings carry independent prognostic significance, and refining the template accordingly based on outcome-driven evidence.

Conclusion

This international consensus developed by ESGE, ESHRE, and IFFS provides the first structured framework for reporting diagnostic hysteroscopy in women with reproductive disorders. The final template includes comprehensive clinical, anatomical, and pathological parameters based on literature and expert validation.

The standardised approach promotes consistent data collection across centres to enhance the value of hysteroscopy in fertility evaluation. It represents a pragmatic tool for clinical care, research, and educational purposes, with the potential to inform predictive models and digital health integration. Its adoption is recommended in both routine clinical settings and IVF programmes.

Future work will focus on the implementation of the structured report across diverse healthcare systems, translation into additional languages, and validation through prospective outcome studies.

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Supplementary Files 1-2: <https://d2v96fxpocvxx.cloudfront.net/7a593d95-86ec-4d2b-8dd3-26b0d0b79ea4/content-images/76d75108-3cc3-49e3-aafc-14a32e4615b0.pdf>

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Tubo-ovarian abscess in an adolescent with uterine didelphys and prior cloacal repair: case report and literature review

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ABSTRACT

Tubo-ovarian abscess (TOA) is an uncommon complication of pelvic infection, particularly in patients with Müllerian anomalies. We report the case of a 16-year-old girl with uterine didelphys and a history of cloacal repair who presented with fever, abdominal pain, and a large multiloculated left adnexal mass. Laparoscopy revealed a TOA within a severely distorted pelvis, requiring extensive adhesiolysis, excision of the abscess cavity with adherent tubal remnants, and partial cystectomy with ovarian preservation. Histopathology confirmed a purely inflammatory process, excluding malignancy. This case highlights a non-obstructive mechanism for TOA, in which distorted pelvic anatomy and postsurgical adhesions predisposed to infection, underscoring the need for individualised evaluation and fertility-preserving management in this population.

Keywords: Adolescent, cloacal malformation, Müllerian anomalies, Tubo-ovarian abscess, uterine didelphys

Introduction

Müllerian duct anomalies comprise a heterogeneous group of congenital malformations that result from defective formation, fusion, or resorption of the paramesonephric ducts.^{1,2} They are relatively uncommon in the general population, with an estimated prevalence ranging between 6% and 7%, but their incidence is likely underestimated due to the high number of asymptomatic cases.³ Among the various types of anomalies, uterine didelphys is one of the rarest forms and is characterised by the presence of two uterine cavities with independent endometrial

linings, most often associated with a double cervix and sometimes a longitudinal vaginal septum.⁴ The population prevalence of didelphys uterus is reported to be between 0.3% and 5%.⁵

The clinical presentation of uterine didelphys is variable. Many patients remain asymptomatic, while others may present with dysmenorrhea, pelvic pain, dyspareunia, or complications related to pregnancy and fertility.⁴ Importantly, this anomaly frequently coexists with renal malformations, reflecting the close embryological relationship between the Müllerian and Wolffian duct systems.⁶

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This association between Müllerian and urinary tract anomalies is particularly evident in patients born with cloacal malformations, a rare group of congenital defects (estimated incidence 1:50,000 live births) in which the uro-rectal septum fails to divide the cloaca during weeks 6-7 of gestation, resulting in a single perineal channel shared by the urinary, genital, and gastrointestinal tracts.^{7,8} Up to 60% of these patients have a duplicated Müllerian system, and renal anomalies are identified in up to 83% of cases.^{8,9} Surgical reconstruction of cloacal malformations in early childhood is among the most complex procedures in paediatric surgery and typically requires multiple staged interventions, resulting in extensive pelvic adhesions and distorted anatomy that may carry long-lasting gynaecological consequences.^{10,11}

As these patients reach adolescence, the occurrence of adnexal masses poses a significant diagnostic and therapeutic dilemma. The differential diagnosis ranges from functional ovarian cysts to infectious Tubo-ovarian abscesses (TOAs) or, less frequently, neoplastic lesions.¹² The presence of complex features such as septations, thickened walls, or papillary projections on imaging raises the suspicion of malignancy and necessitates surgical intervention.¹³

In most published cases, TOA is described in association with obstructive malformations, such as the obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome, where stasis of menstrual blood predisposes to ascending infection.¹⁴⁻¹⁶ However, patients with a history of cloacal repair represent a distinct population in which non-obstructive mechanisms, namely post-surgical adhesive disease and altered pelvic anatomy, may independently predispose to adnexal infections.¹⁷ This pathophysiological pathway remains poorly characterised in the literature.

Here we describe the case of an adolescent with uterine didelphys and a history of cloacal repair who developed a large multiloculated adnexal mass ultimately diagnosed as a TOA. We also review the literature to explore the relationship between cloacal anomalies, uterine malformations and adnexal infections, highlighting the challenges in diagnosis and fertility-preserving management.

Methods

This case report was prepared in accordance with the CAsE REport guidelines.¹⁸ Written informed consent for publication, including clinical details, imaging, and

surgical video, was obtained from the patient and her legal guardians.

For the literature review component, we adhered to the quality standards for narrative reviews as defined by the Scale for the Quality Assessment of Narrative Review Articles.¹⁹ Relevant publications were identified through a comprehensive search of PubMed, Scopus, Embase and Google Scholar, complemented by cross-checking the reference lists of retrieved articles. We used combinations of the following search terms: "Tubo-ovarian abscess", "Müllerian anomaly", "uterine didelphys", "cloacal malformation", "cloacal repair", "pelvic abscess", and "adolescent". No language restriction was applied. All articles describing Tubo-ovarian or pelvic abscess in the context of Müllerian anomalies or cloacal malformations were considered eligible for inclusion.

Case Presentation

A 16-year-old female presented with fever and acute abdominal pain localized to the left iliac fossa.

Surgical and Medical Background

Her medical history was remarkable for a complex cloacal malformation repair with a 4.5 cm common channel, uterine didelphys, complete longitudinal vaginal septum, normal sacrum, and left vesicoureteral reflux. Neonatal management included loop sigmoidostomy and vesicostomy on the first day of life. On the seventh day of life, emergency laparotomy was performed for jejunal perforation, which was repaired by primary closure; appendectomy was performed concomitantly. At three months of age, surgical revision was required for colostomy prolapse. Definitive cloacal repair was undertaken at ten months of age at a tertiary colorectal referral centre and comprised posterior sagittal anorectovaginourethroplasty (PSARVUP) with laparotomy, extended total urogenital mobilisation, vaginal septum resection, vaginal flap vaginoplasty, and redo vesicostomy. Colostomy and vesicostomy closure were completed at fifteen months. The subsequent course was complicated by obstructive ileus at three years of age, requiring emergency laparotomy with resection of a large segment of small bowel. At five years, endoscopic subureteric injection was performed on the left side to address progressive renal damage secondary to vesicoureteral reflux. At seven years, a neo-appendicostomy with caecal flap (Malone procedure) was fashioned to allow antegrade colonic enemas for the management of faecal incontinence.

At the time of presentation, bowel continence was maintained through regular antegrade colonic enemas via the appendicostomy, and bladder emptying was achieved by clean intermittent self-catheterisation. Despite subureteric injection, left renal dysplasia with impaired function had developed as a consequence of chronic vesicoureteral reflux, with compensatory hypertrophy of the contralateral kidney. Menarche occurred at 12 years of age, and menstrual cycles had since been regular in frequency (28-30 days) and duration (4-5 days), with moderate flow and no dysmenorrhoea. There was no history of intermenstrual bleeding, cyclical pelvic pain, or symptoms suggestive of haemocoels. The patient did not use vaginal dilators; gynaecological follow-up had not identified vaginal stenosis requiring dilation. A structured safeguarding assessment was performed as part of the multidisciplinary evaluation: the patient confirmed that she had never been sexually active, and no safeguarding concerns were identified. Recurrent urinary tract infections with *Escherichia coli* had been documented over the preceding years.

Clinical Findings and Imaging

The patient presented to the emergency department with an approximately 4-day history of fever and progressively worsening pain in the left iliac fossa. On admission, she was febrile (38.9 °C), with localized tenderness in the left lower quadrant and a palpable adnexal mass. Laboratory tests demonstrated neutrophilic leucocytosis and markedly elevated C-reactive protein (CRP >30 mg/dL), while tumour markers (CEA, CA 19-9, CA 125) remained within normal limits. Urine cultures grew *Escherichia coli*, while vaginal swabs were sterile.

Vaginal examination revealed a patent vaginal introitus without stenosis and adequate vaginal calibre. A longitudinal vaginal septum was identified but was thin, non-obstructing, and allowed free passage to both cervical canals. Two distinct cervixes were visualised, both appearing macroscopically normal, with no purulent cervical discharge.

Approximately one year before admission, a pelvic magnetic resonance imaging (MRI) documented a uterine didelphys with double cervixes and a longitudinal vaginal septum. At that time, a large multiloculated cystic lesion was identified in the left adnexa (about 10 cm in size), helical in configuration, composed of multiple communicating cystic spaces and enclosing the left ovary. No mural nodules or papillary projections were detected.

The differential diagnosis included a markedly distended hydrosalpinx vs. a large inclusion cyst.

Several months later, a contrast-enhanced abdominal computed tomography confirmed persistence of the left adnexal cystic lesion, described as a tubular, helical structure with mild homogeneous wall enhancement, displacing the ovary laterally. No ascites or lymphadenopathy were present.

At the time of hospitalization, a repeat pelvic MRI demonstrated significant interval progression of the adnexal lesion compared with prior imaging. The mass had developed diffuse wall thickening, perilesional inflammatory fat stranding, and a 1.4 cm papillary projection showing intermediate signal intensity on diffusion-weighted imaging (Figures 1, 2). The left ovary, though encapsulated by the cystic structure, remained identifiable with preserved follicular morphology. On coronal T2-weighted sequences (Figure 3), the spatial relationship between the mass and the pelvic organs was clearly depicted: the two separate uterine horns of the didelphys uterus were visible inferiorly, symmetric in size and signal intensity, with no evidence of hematometra or haemocoels. Based on these findings, the lesion was classified as Ovarian-Adnexal Reporting and Data

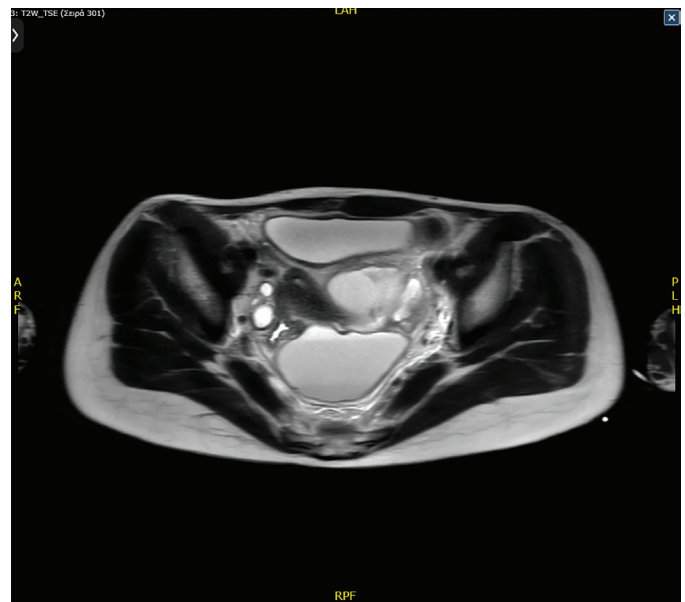


Figure 1. Axial T2-weighted pelvic magnetic resonance imaging obtained at the time of hospitalisation. The large multiloculated left adnexal mass is depicted with thickened walls and heterogeneous content consistent with Tubo-ovarian abscess. The bladder is visible anteriorly. The normal right ovary with preserved follicular morphology is identified in the right hemipelvis (contralateral side), providing comparison with the affected left adnexa.

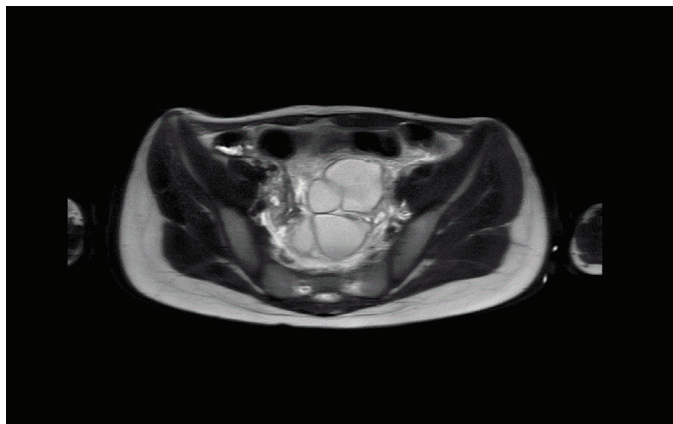


Figure 2. Axial pelvic magnetic resonance imaging (MRI) at the time of hospitalisation. The multiloculated mass demonstrates diffuse wall thickening and perilesional inflammatory changes consistent with Tubo-ovarian abscess formation. The multiple communicating cystic spaces of the lesion are clearly depicted.

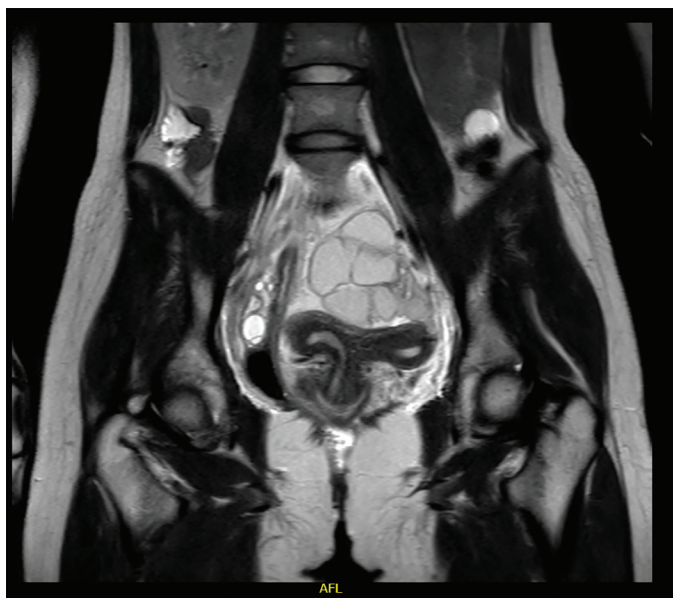


Figure 3. Coronal T2-weighted pelvic magnetic resonance imaging at the time of hospitalisation. The image demonstrates the large multiloculated cystic mass occupying the upper pelvis, with the two separate uterine horns of the didelphic uterus visible in the lower portion of the image. This view illustrates the spatial relationship between the adnexal lesion and the duplicated uterine anatomy and confirms the absence of hematometra in either uterine horn.

System 4 (O-RADS 4), raising concern for possible neoplastic transformation. No ascites or pathologic lymphadenopathy were detected.

Surgical Management

Empirical antimicrobial therapy was initiated with sequential intravenous regimens including cephalosporins

(cefotaxime and ceftriaxone), ciprofloxacin, colistin, piperacillin-tazobactam, and oral doxycycline. Despite 10 days of treatment, the patient remained febrile, prompting surgical intervention. The decision to proceed to surgery rested on two convergent considerations: the failure of the presumed inflammatory process to respond to prolonged, culture-guided antimicrobial therapy, and the O-RADS 4 classification, which could not exclude malignancy and thus mandated surgical exploration with histological characterisation.

On the tenth day of hospitalisation, the patient underwent laparoscopic exploration under general anaesthesia (Supplementary Video). Given her history of cloacal repair and multiple abdominal surgeries, the procedure was technically challenging. Entry was achieved via Palmer's point, followed by placement of additional trocars.

Extensive adhesiolysis was necessary to access the pelvis. During exploration, a large Tubo-ovarian mass was identified, densely adherent to the sigmoid colon and pelvic sidewall. The ureters were carefully identified bilaterally to prevent injury. The sigmoid colon was mobilized to improve exposure of the adnexal region. The Tubo-ovarian complex was opened, releasing thick purulent material and inflammatory debris, which were thoroughly evacuated. Samples of intraperitoneal and cystic fluid were obtained for microbiological examination. Despite the macroscopic appearance, cultures were sterile.

Given the extent of inflammation and tissue destruction, complete anatomical identification of the left fallopian tube as a discrete structure was not achievable. The Tubo-ovarian complex was approached as a single inflammatory mass: the abscess cavity was opened, drained of purulent material and inflammatory debris, and its wall was progressively excised together with the adherent, necrotic tubal remnants that were inseparable from the abscess capsule. Partial cystectomy was then carried out using ultrasonic scissors, excising the majority of the remaining cyst wall while carefully preserving the left ovary and its vascular pedicle. Special care was taken to avoid injury to the ureter and bowel, given the distorted anatomy from previous surgeries. Haemostasis was secured with bipolar diathermy, followed by copious irrigation. A drain was placed in the pouch of Douglas.

The patient tolerated the procedure well, and the immediate postoperative course was uncomplicated.

Postoperative Course

The total hospital stays lasted 15 days. Following surgery and continuation of antimicrobial therapy, laboratory parameters showed progressive improvement. The initial neutrophilic leucocytosis and markedly elevated CRP decreased steadily, with normalisation of leukocyte counts and CRP levels approaching 5 mg/dL by the time of discharge. Haemoglobin levels transiently declined postoperatively to 8-9 g/dL, consistent with mild anaemia, but subsequently stabilised without the need for transfusion. At discharge, the patient was afebrile, asymptomatic, and in good clinical condition.

Histopathological examination of the excised specimen revealed fragments of a fibrous wall devoid of epithelial lining, containing inflammatory tissue with abundant neutrophilic polymorphonuclear leukocytes and foamy histiocytes, as well as haemorrhagic infiltration and dilated vessels. No evidence of malignancy was identified.

Discussion

This case illustrates that TOA can develop in adolescents with Müllerian anomalies through a non-obstructive pathway driven principally by post-surgical adhesive disease and altered pelvic anatomy rather than by menstrual outflow obstruction, thereby expanding the current understanding of the mechanisms linking congenital uterovaginal malformations to adnexal infection.

The literature on TOA in the context of Müllerian anomalies has been dominated by reports associated with the OHVIRA syndrome, also known as Herlyn-Werner-Wunderlich syndrome.^{14-16,20-29} In this condition, the combination of an obstructed hemi-vagina and functional endometrium creates a closed cavity where menstrual blood accumulates, leading to haemocoels, retrograde menstruation, and a stagnant environment that facilitates ascending bacterial colonisation, with potential progression to pyocolpos, pyosalpinx, and ultimately TOA.^{14,30,31} Retrospective paediatric and young adult series demonstrated that between 14% and 17% of OHVIRA patients presented with pelvic or intra-abdominal abscesses requiring surgical intervention.^{27,32} A significant proportion of patients are diagnosed only years after menarche or even in adulthood, when complications such as TOA or pyometra become clinically evident.^{15,33,34}

This obstructive model, however, does not apply to our patient and offers only a limited framework for

understanding TOA that arises in the absence of menstrual outflow obstruction. Our patient shared some phenotypic features with OHVIRA, such as uterine didelphys, double cervix, and ipsilateral renal anomaly, yet the pathophysiology was entirely distinct. Menses were regular, and serial imaging consistently excluded hematometra, haemocoels, or any evidence of outflow obstruction. Rather, the development of TOA in this case must be understood in the context of her cloacal malformation and its surgical consequences.

Reconstruction of cloacal malformations is among the most complex undertakings in paediatric surgery, typically requiring PSARVUP, often with vaginal replacement, followed by staged procedures such as stoma reversal, bladder augmentation, and creation of catheterisable conduits.^{7,11} In a review of 490 cases, Levitt and Peña³⁵ reported that 19% of patients required reoperation for complications including vaginal stricture or atresia, urethrovaginal fistula, and rectal prolapse. These multiple interventions inevitably result in extensive pelvic adhesive disease, which is a well-recognised cause of infertility, dyspareunia, bowel obstruction, and increased surgical complexity at subsequent operations.^{36,37} In our patient, the dense adhesions between the Tubo-ovarian complex, sigmoid colon, and pelvic sidewall, encountered at laparoscopy, are entirely consistent with this pattern and likely contributed to the formation of a confined, poorly vascularised pelvic compartment, favouring abscess development.

Infectious complications, including pelvic abscess and pyometrocolpos, are in fact recognised sequelae of cloacal reconstruction. Fumino et al.¹⁷ described a remarkably similar case of TOA developing after colonic vaginoplasty for a high cloacal anomaly in a 13-year-old sexually inactive girl and Sharma and Gupta³⁸ reported pelvic abscess among the complications of early vaginal replacement in cloacal malformations.

An anatomically sequestered compartment, however, still requires a source of infection, and here the urinary tract is the most likely candidate. Although our patient was not sexually active and no evidence of ascending genital tract infection was identified, she presented with a concurrent urinary tract infection caused by *Escherichia coli*. This finding is clinically relevant because patients with cloacal anomalies are particularly susceptible to recurrent urinary infections as a consequence of vesicoureteral reflux, incomplete bladder emptying, and the need for clean intermittent catheterisation,^{8,9} all of which were

present in our patient. The direct anatomical proximity of the dysplastic left urinary tract to the confined adnexal space, together with the disruption of normal fascial planes from prior reconstructive surgery, likely facilitated local extension of urinary infection to the entrapped Tubo-ovarian complex.¹² It should be emphasised, however, that this contiguous urinary-to-adnexal route remains a plausible hypothesis rather than a proven mechanism. Urine cultures grew *Escherichia coli*, whereas the intraoperative peritoneal and cystic-fluid cultures were sterile, a finding most plausibly attributable to the prolonged multidrug antibiotic therapy administered preoperatively.³⁹ Direct microbiological continuity between the urinary and adnexal compartments could therefore not be established.

Beyond the obstructive paradigm, a distinct and growing body of literature documents TOA in non-sexually active adolescents in whom menstrual outflow is unobstructed.⁴⁰⁻⁴³ In the largest series to date, Hakim et al.⁴⁰ described sixteen non-sexually active adolescents with TOA (mean age 14.6 years), the majority of whom had an underlying comorbidity, including genitourinary tract anomalies, obstructed hemi-vagina, ipsilateral renal agenesis, or recent appendicitis, with *Escherichia coli* the organism most frequently recovered. Comparable non-obstructive mechanisms have been reported in individual cases, including contiguous spread from appendiceal inflammation with bacterial translocation to the adnexa,⁴¹ while a recent systematic review of pelvic inflammatory disease in sexually inactive paediatric patients identified urinary tract infection, congenital anomalies and prior appendicitis as the most frequent associated conditions.⁴² Contemporary reviews of paediatric and adolescent TOA similarly emphasise that the aetiological spectrum in this population differs substantially from that of sexually active adults, with contiguous and haematogenous routes predominating over ascending sexually transmitted infection.⁴³ Our patient conforms to this non-obstructive, comorbidity-driven profile: a repaired cloacal malformation with distorted pelvic anatomy, recurrent *Escherichia coli* urinary tract infections, and no evidence of menstrual outflow obstruction.

The management of TOA in patients with prior cloacal reconstruction poses specific challenges that differ from both OHVIRA-associated cases and de novo TOA in the general population. In classical OHVIRA, the cornerstone of treatment is vaginal septectomy with marsupialisation, which restores drainage, relieves pain, and prevents re-accumulation and infection,^{15,16,23,25,27,30} with hemi-

hysterectomy or salpingectomy reserved for delayed or refractory disease at the cost of future fertility.^{21-23,28,30,32} In patients with post-surgical adhesive disease, the goal was to eradicate the infection while preserving adnexal structures, a priority of paramount importance given the already compromised reproductive anatomy. Options include laparoscopic drainage or partial cystectomy of multiloculated adnexal collections with adnexal preservation, reserving organ-removing procedures for necrotic or unsalvageable tissue.

In our case, surgery was technically challenging, necessitating laparoscopic adhesiolysis, meticulous dissection to preserve ureter and bowel integrity, and partial cystectomy with ovarian preservation. This level of surgical complexity is well documented in the cloacal anomaly literature, where pelvic adhesions from prior reconstructive surgery significantly increase operative difficulty and the risk of iatrogenic injury to adjacent structures.¹¹ Fertility preservation was particularly important in light of the limited reproductive potential documented in this population. In a literature review, Vilanova-Sanchez et al.³⁶ reported that pregnancy is achievable in women with prior cloacal or complex anorectal malformation repair, with 24 pregnancies documented in 16 patients; the majority conceived spontaneously. However, these pregnancies carried significant risks: 5 ended in spontaneous miscarriage and 2 in ectopic pregnancy. Among the 19 live births, two thirds were delivered prematurely and nearly all required caesarean section.³⁶

In conclusion, this case demonstrates that post-surgical adhesive disease, potentially compounded by recurrent urinary tract infections, represents a distinct and under-recognised risk factor for TOA in patients with repaired cloacal malformations. We advocate for proactive gynaecological surveillance in all adolescents with prior cloacal repair, with particular attention to both obstructive and non-obstructive complications as these patients reach reproductive age. Multidisciplinary, fertility-preserving approaches remain critical to optimising both short-term clinical outcomes and long-term reproductive potential in these complex patients.

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Ethical approval: This study is an observational case report based on data collected during routine clinical practice. This type of study does not require approval by an Ethics Committee.

Informed consent: Written informed consent for publication, including clinical details, imaging, and surgical video, was obtained from the patient and her legal guardians.

Data sharing: Data sharing is not applicable to this article as no datasets were generated or analysed during this study.

Transparency: The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.



Supplementary Video: <https://youtu.be/xWtWUYJRrSQ>

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A stepwise approach to the hysteroscopic management of cystic adenomyosis

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ABSTRACT

Background: Adenomyosis may alter the functional architecture of the inner myometrium and has been associated with impaired reproductive outcomes. Focal cystic adenomyotic lesions can persist despite hormonal suppression and may be challenging to identify and treat hysteroscopically.

Objectives: To demonstrate a reproducible, stepwise, hysteroscopic technique for the identification and management of focal cystic adenomyosis of the inner myometrium.

Participant: Women with infertility and recurrent implantation failure, defined as failure to achieve a clinical pregnancy after repeated embryo transfers, diagnosed with focal cystic adenomyosis of the inner myometrium based on transvaginal ultrasound and hysteroscopic assessment.

Intervention: Procedures were performed in an ambulatory digital hysteroscopy setting at the Life Expert Centre (Leuven, Belgium) under conscious sedation. The approach combined hysteroscopy and transvaginal ultrasound throughout diagnosis, treatment, and follow-up. Preoperative hormonal suppression was used to identify lesions persisting despite medical therapy. Key steps were: (1) lesion mapping using ultrasound-hysteroscopic correlation, including bipolar-marker topographic correlation of lesions not directly visible during hysteroscopy; (2) meticulous dissection and resection using 5Fr mechanical instruments and / or a bipolar loop within a 15Fr mini-resectoscope; (3) application of a crosslinked hyaluronic acid anti-adhesion barrier; and (4) structured postoperative follow-up, including second-look hysteroscopy when indicated.

Conclusions: Combination of hysteroscopy and transvaginal ultrasound enables minimally invasive management of focal cystic adenomyosis of the inner myometrium. This video demonstrates a reproducible approach based on precise lesion identification, targeted treatment, and structured postoperative assessment.

What is New? This video introduces a novel technique of topographic ultrasound-hysteroscopic correlation using bipolar-marker localisation, facilitating the identification and treatment of adenomyotic cysts not directly visible during hysteroscopy.

Keywords: Adenomyosis, hysteroscopy, ultrasonography, infertility, reproduction, technique

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Transparency: The authors affirm that this video article is an accurate and transparent account of the work presented, and that no important aspects have been omitted.



Video 1. A stepwise approach to the hysteroscopic management of cystic adenomyosis:
<https://youtu.be/1Bu-W40SIMY>

Laparoscopic-guided TVT placement after prior colpo-suspension

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ABSTRACT

Background: Previous retropubic surgery, such as laparoscopic Burch colpo-suspension, can significantly alter the anatomy of the space of Retzius due to fibrosis and scarring. These changes increase the technical difficulty and risk of complications during subsequent retropubic procedures, particularly midurethral sling placement.

Objectives: To demonstrate the feasibility and safety of laparoscopic-assisted tension-free vaginal tape (TVT) placement in a patient with recurrent stress urinary incontinence (SUI) following prior colpo-suspension.

Participant: A 74-year-old woman with recurrent SUI following laparoscopic Burch colpo-suspension performed five years previously.

Intervention: Retropubic TVT placement was performed under simultaneous laparoscopic guidance at a tertiary gynaecological centre. Intraoperative laparoscopy enabled visualisation of the retropubic space, revealing significant fibrosis and distorted anatomy. Needle passage and sling positioning were performed under direct visualisation. Because extensive retropubic dissection reduced the usual tissue support of the tape, it was temporarily secured with a rapidly absorbable suture to maintain its position without increasing suburethral tension.

Conclusions: Laparoscopic-assisted TVT placement is a feasible and safe approach in patients with prior retropubic surgery. Direct visualisation allows identification of altered anatomical planes, facilitating controlled needle passage and potentially reducing the risk of complications.

What is New? This video demonstrates the importance of avoiding blind needle insertion in patients with prior colpo-suspension and highlights laparoscopic guidance as a valuable strategy to improve safety during retropubic sling procedures.

Keywords: Feasibility, laparoscopy, midurethral sling, scarring, stress urinary incontinence, suture

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Video 1. Laparoscopic-guided TVT placement after prior colpo-suspension: <https://youtu.be/Dn743EUYjE8>

Letter to the Editor: Research and audit are essential to improving women's experience of outpatient hysteroscopy

 Valerie Humphreys

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Keywords: Hysteroscopy, pain

Dear Editor,

It is pleasing to see the authors¹ acknowledging the significant concern expressed in the Department of Health and Social Care (DHSC) Renewed Women's Health Strategy² in which pain suffered during gynaecological procedures, in particular outpatient hysteroscopy (OPH), is highlighted and drives two of its action points:

"Action 7: We will co-develop with women a standard of care for the delivery of gynaecological procedures such as hysteroscopy, ensuring women have informed consent and choice of pain relief"

"Action 4: We will test patient power payments-prioritising some gynaecological services...-which would vary the amount Trusts are reimbursed depending on women's feedback on their experiences, including pain management"

The authors also make reference to the RCOG Green Top Guideline (GTG) on OPH³ stating that the Guideline contains "evidence of interventions to minimise pain and recommendations for implementation".

In fact, the only intervention routinely recommended in the Guideline is pre-medication with NSAIDs. Local anaesthesia is considered unnecessary unless cervical dilatation is planned and sedation in an outpatient setting is deemed to provide little additional pain relief and to be inadvisable on safety grounds. So-called "vocal local" is mentioned but without evidence that it has any effect on pain. However, the paper "Music and Oral Premedication for Pain Management during Outpatient Hysteroscopy: Results from a Randomised Controlled Trial"⁴ indicates that such premedication has no effect on pain, as acknowledged in the editorial.

There is therefore something of an incongruity here. As premedication has no effect, the GTG therefore has nothing to offer women, one third of whom suffer severe pain, in terms of routine pain relief. It is difficult to reconcile this with the view that, if the GTG were fully implemented, this would improve women's experience.

It is notable that ACOG guidance⁵ contains a list of options for pain management in OPH, including

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benzodiazepine, opiates, topical anaesthetic, intracervical and paracervical blocks and that the Faculty of Sexual and Reproductive Healthcare Guideline⁶ on intrauterine contraception lists several pain management options.

Whilst it is encouraging to see that Pentrox is becoming more widely used, I am at a loss to understand why the GTG has not been amended to reflect what is becoming apparent, viz that OPH will, for ethical, financial and patient satisfaction reasons, be acceptable to women and, importantly, to the DHSC only if a full range of pain management options is routinely offered.

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Transparency: I affirm that the manuscript is an honest, accurate and transparent response.

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Authors' reply to: "Research and audit are essential to improving women's experience of outpatient hysteroscopy"

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Keywords: Ambulatory care, outpatient hysteroscopy, pain, patient experience, patient preferences, women

Dear Editor,

We thank the authors for their letter responding to our editorial and for highlighting some important points. However, we consider it disingenuous to suggest that the Royal College of Obstetricians and Gynaecologists Green-top Guideline (GTG 59) on outpatient hysteroscopy¹ "has nothing to offer women... in terms of routine pain relief", and fundamentally disagree with the assertion that "it is difficult to reconcile this with the view that, if the GTG were fully implemented, this would improve women's experience."

GTG 59 was developed to minimise pain and optimise the overall experience of women undergoing outpatient hysteroscopy. Although approximately one-third of women report severe pain, acceptability remains high, with 97% rating their overall care positively.² This apparent disconnect highlights the importance of measuring pain and patient experience as distinct outcomes. The guideline evaluates not only pharmacological pain relief but also infrastructure, staffing, equipment and procedural technique. Drawing on evidence published since the 2011

guideline, it makes numerous recommendations, including promoting best practice (e.g., vaginoscopy) and discouraging interventions that may negatively affect patient experience (e.g., routine cervical preparation).

Unlike most Green-top Guidelines, GTG 59 is underpinned by eight independently conducted systematic reviews, with meta-analyses where appropriate-the highest levels of evidence. Seven of these reviews have been published in peer-reviewed journals. Where evidence was lacking, recommendations were informed by consensus from approximately 120 expert hysteroscopists within the British Society for Gynaecological Endoscopy Ambulatory Care Network.

The American College of Obstetricians and Gynecologists guidance³ cited by the authors is an opinion document and cannot be considered equivalent to the evidence-based methodology supporting GTG 59. The cited Faculty of Sexual and Reproductive Healthcare guidance⁴ relates specifically to intrauterine contraception insertion and cannot

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be directly extrapolated to outpatient hysteroscopy, although it remains a valuable resource for clinicians performing these procedures.

Penthrox offers a promising additional analgesic option. Although a small randomised controlled trial demonstrated reduced pain during hysteroscopy compared with placebo,⁵ robust evidence of its efficacy, safety, acceptability, feasibility, and cost-effectiveness from a large multicentre National Health Service trial is required before widespread adoption can be recommended. We have recently secured approximately £2 million from the National Institute for Health and Care Research to undertake such a study. If shown to be effective, Penthrox should complement, not compensate for, excellent technique, modern equipment, and appropriate infrastructure.

Ultimately, minimising pain and optimising the patient experience are inseparable goals. Achieving both requires a multimodal approach encompassing infrastructure, equipment, clinician training, procedural technique, patient preferences, and pharmacological and non-pharmacological interventions, including music and virtual reality.

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Letter to the Editor: “Music and oral premedication for pain management during outpatient hysteroscopy: results from a randomised controlled trial”

 Areeba Murtaza

Department of Medicine, Khyber Girls Medical College, Peshawar, Pakistan

Keywords: Outpatient hysteroscopy, pain management, post-randomization exclusion, randomised controlled trial

Dear Editor,

I have read with keen interest the article, “Music and oral premedication for pain management during outpatient hysteroscopy: results from a randomised controlled trial” written by Alessandro Loddo et al.¹ This study addresses the clinically significant issue of pain associated with outpatient hysteroscopy and compares the effects of music and oral premedication for its management. The authors have done a great job in describing the strengths and limitations of their study. However, I would like to draw their attention to an important methodological consideration that might be helpful in the interpretation of their results. The authors state that those patients whose hysteroscopy could not be completed because of severe pain due to cervical stenosis requiring mechanical dilatation under general anesthesia were excluded from statistical analysis. As the main objective of the study was to evaluate the efficacy of strategies for pain management during hysteroscopy, I wonder whether exclusion of these participants might have influenced the analysis of interventions. One previous methodological research study has suggested that

the treatment effects might be influenced by the exclusion of randomised participants from analysis and can introduce bias in randomised controlled trials.² Therefore, it would be valuable to report the number of failed procedures in each randomised group and clarify whether their exclusion had any potential impact on the observed treatment effects. Considering procedural failure alongside pain scores in an appropriate analysis may also provide a more comprehensive assessment of the clinical effectiveness of music and oral analgesia.

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Authors' reply to: "Music and oral premedication for pain management during outpatient hysteroscopy: results from a randomised controlled trial"

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Keywords: Hysteroscopy, outpatient, pain, music therapy, patient experience, premedication

Dear Editor,

We thank the correspondent for the careful reading of our article¹ and for raising the question of post-randomisation exclusion, which gives us a welcome opportunity to clarify our methods and to add context that we believe strengthens confidence in our conclusions.

First, regarding the request to report the number of failed procedures in each randomised group: these data are already presented in our study flow diagram (Figure 1). Procedural failure occurred in three participants overall, none in the music group, one in the oral premedication group, and two in the control group. Procedural failure was therefore uncommon, and, importantly, no failure occurred in either of the active intervention arms.

Second, regarding the concern that excluding these participants may have biased the estimated treatment effects, we agree in principle. Post-randomisation exclusion can distort effect estimates, as elegantly demonstrated by Nüesch et al.² in the meta-epidemiological study the correspondent cites.

However, several features of our data make a clinically meaningful bias unlikely in the present case. The failures were few and were not concentrated in any single arm. In all three instances the cause of failure was severe cervical stenosis requiring mechanical dilatation under general anaesthesia, an anatomical factor unrelated to the intervention being tested (music vs. oral analgesia vs. control), rather than a consequence of the allocated treatment. Most importantly, the bias described by Nüesch et al.² operates chiefly by exaggerating an apparent treatment benefit; our trial found no significant difference between groups in either the primary outcome (intra- and post-procedural pain) or the secondary outcomes. Reinstating three stenosis-related failures, distributed, if anything, away from the intervention arms, could not plausibly convert these null findings into a treatment effect, and would not alter our conclusion that neither intraoperative music nor oral ibuprofen–paracetamol premedication reduces pain compared with standard care.

Third, we fully agree with the correspondent that procedural failure is itself a clinically meaningful endpoint that merits consideration alongside pain

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intensity. Our study did report procedure completion as a secondary outcome, and completion rates did not differ significantly between the three groups ($P=0.62$), with pain and severe cervical stenosis being the principal causes of failure. We concur that future, adequately powered trials would benefit from pre-specified composite endpoints that integrate pain intensity with procedural success and, ideally, patient-reported acceptability, providing a more comprehensive assessment of clinical effectiveness. We are grateful for this constructive suggestion.

We thank the correspondent once again for the thoughtful comments and the opportunity to clarify these points.

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Letter to the Editor: “Conventional laparoscopic segmental bowel resection with mini-laparotomy specimen extraction compared with Natural Orifice Specimen Extraction (NOSE) procedures in patients with colorectal endometriosis”

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Keywords: Colorectal endometriosis, natural orifice specimen extraction (NOSE), laparoscopic surgery

Dear Editor,

The paper “Conventional laparoscopic segmental bowel resection with mini-laparotomy specimen extraction compared with Natural Orifice Specimen Extraction (NOSE) procedures in patients with colorectal endometriosis” by Popov et al.¹ caught our attention. The authors deserve praise for tackling a significant and clinically difficult facet of managing colorectal endometriosis. The study provides important information about the safety, effectiveness, postoperative results, and quality of life related to various surgical techniques by contrasting the new NOSE technique with the traditional laparoscopic approach. Additionally, adding patient-centered outcomes like pain scores and KESS quality-of-life evaluations improves the data therapeutic relevance and gives surgeons managing deep infiltrating endometriosis helpful information.

While acknowledging these significant advantages and the work's contribution to the current conversation about the best way to treat colorectal endometriosis, we would want to draw attention to a few methodological issues with the study.

First, the retrospective design inherently limits causal inference and increases susceptibility to selection bias.² More importantly, the conventional laparoscopic surgery (CLS) cohort and NOSE cohort were not treated contemporaneously. The authors reported that CLS was routinely performed between 2015-2020, whereas NOSE was introduced later as an alternative technique. Such temporal separation raises the possibility of historical and proficiency bias, as improvements in surgical expertise, perioperative care pathways, and institutional experience over time may independently affect outcomes.³ Therefore, observed similarities or differences may partly reflect

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evolution in practice rather than the surgical technique itself.

Second, a number of potentially significant confounding factors, such as lesion complexity, disease severity, prior surgical history, and concomitant pelvic involvement, were not taken into account even though baseline data including age, body mass index, and symptom levels were compared. Additionally, neither multivariable regression analysis nor propensity score matching were used to reduce baseline imbalance across groups. Thus, residual confusion is still a possibility.⁴

Despite these considerations, we commend the authors for their valuable contribution to the growing body of literature on surgical management of colorectal endometriosis. Their study provides important insights into the feasibility and safety of NOSE techniques and highlights an evolving area of minimally invasive surgery. We appreciate the authors' efforts in addressing this clinically relevant topic and believe their findings will stimulate further research. We concur that larger prospective, multicenter randomized studies are warranted to further clarify the comparative effectiveness and long-term outcomes of these surgical approaches.

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