

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

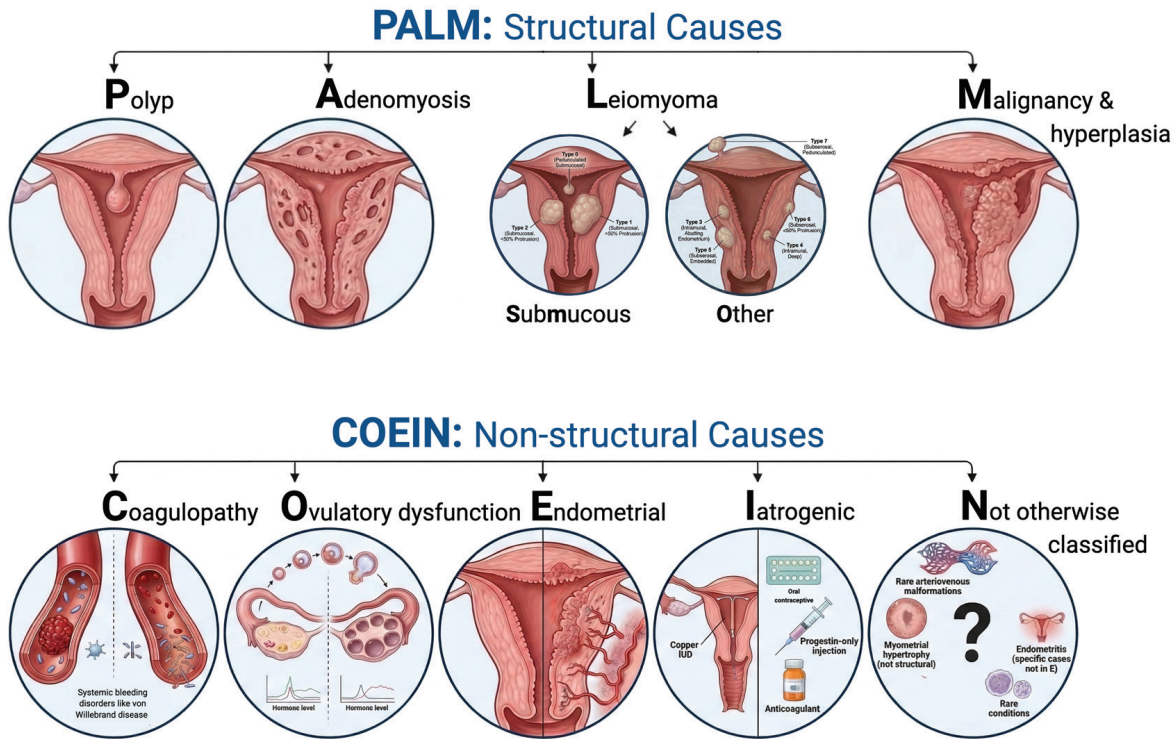


Figure 1. The International Federation of Gynecology and Obstetrics (FIGO) PALM–COEIN classification system for causes of abnormal uterine bleeding in reproductive-aged individuals and postmenopausal bleeding. Structural etiologies are summarised by the acronym PALM and include polyp, adenomyosis, leiomyoma, 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.

practice.

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

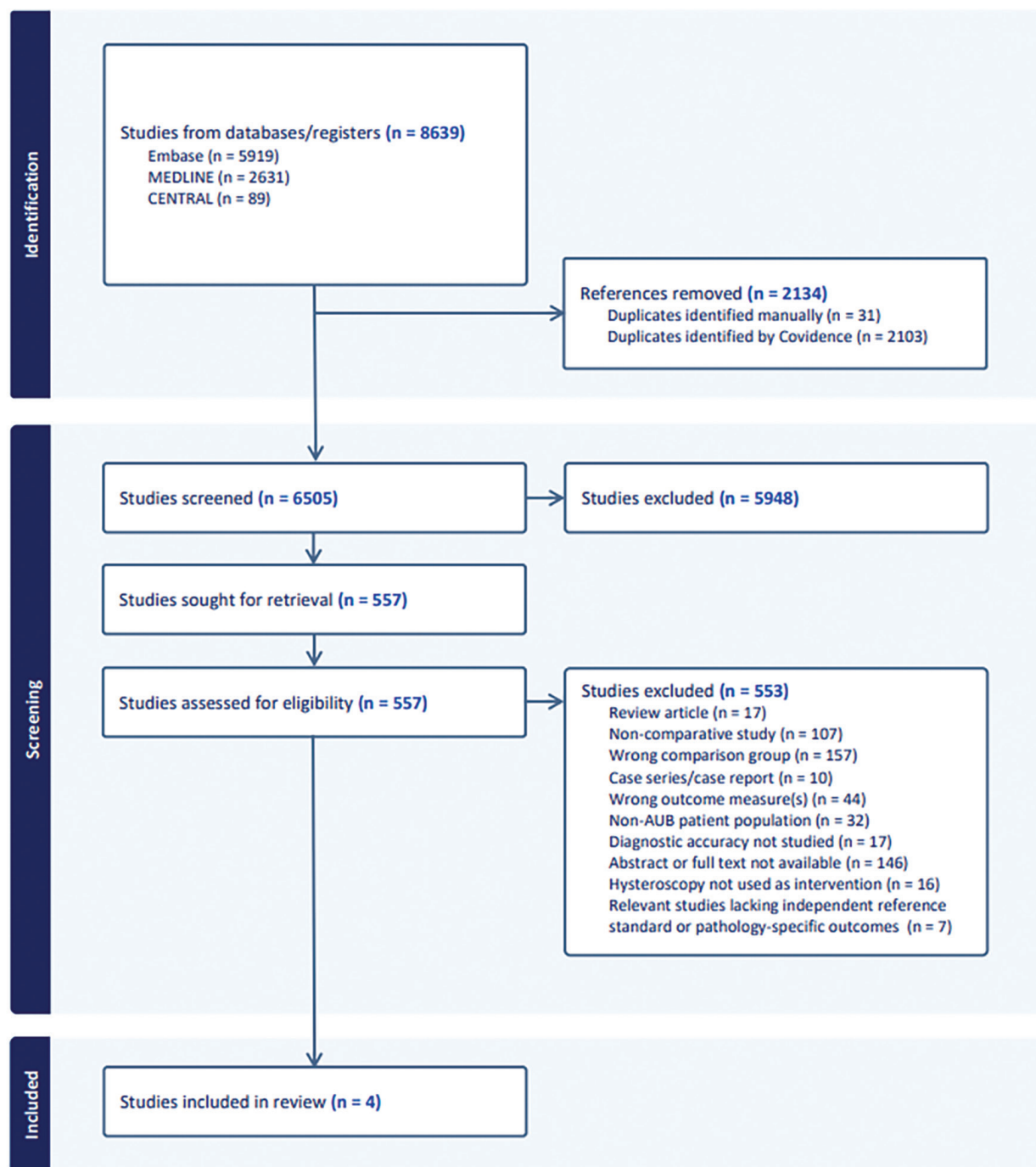


Figure 2. Flow diagram of study selection. AUB: Abnormal uterine bleeding.

the reference standard.

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

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

insufficient detail about patient selection.

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

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.

hyperplasia without atypia and hysterectomy for EIN/AEH. Diagnostic discordance was noted in several 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

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.

diagnostic accuracy of endometrial evaluation techniques for the detection of endometrial polyps, comparing blind endometrial sampling 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

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.

during blind curettage were subsequently identified on hysteroscopic-directed biopsy.

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

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% (72.2, 97.5)	95.5% (78.2, 99.2)	62.5% (30.6, 86.3)	88.9% (56.5, 98.0)
Specificity	100% (96.5, 100)	100% (96.5, 100)	100% (95.0, 100)	98.9% (93.8, 99.8)
PPV	100% (83.9, 100)	100% (84.5, 100)	100% (56.6, 100)	88.9% (56.5, 98.0)
NPV	98.2% (93.5, 99.5)	99.1% (94.9, 99.8)	96.1% (89.0, 98.7)	98.9% (93.8, 99.8)
LR+	NC -	NC -	NC -	77.3 (10.9, 550.3)
LR-	0.09 (0.03, 0.35)	0.05 (0.01, 0.31)	0.38 (0.17, 0.89)	0.11 (0.02, 0.71)
Diagnostic Odds Ratio	1747 NC-	3053 NC	231 NC	688 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	
Sensitivity	11.3%	88.7%		60.0%	95.2%		34.8%	100%	
	7.0, 17.8	(82.2, 93.1)		(35.8, 80.2)	(77.3, 99.2)		(18.8, 55.1)	(85.7, 100)	
Specificity	93.0%	93.0%		98.5%	96.0%		92.3 %	69.2 %	
	88.4, 95.9	(88.4, 95.9)		(91.9, 99.7)	(88.9, 98.6)		(66.7, 98.6)	(42.4, 87.3)	
PPV	53.6%	90.1%		90.0%	87.0%		88.9%	85.2%	
	(35.8, 70.5)	(83.8, 94.1)		(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%		44.4%	100%	
	(53.7, 64.9)	(87.3, 95.1)		(82.8, 96.1)	(92.6, 99.8)		(27.6, 62.7)	(70.1, 100)	
LR+	1.61	12.7		39.6	23.8		4.52	3.25	
	(0.79, 3.28)	(7.48, 21.5)		(5.43, 288.9)	(7.83, 72.4)		(0.63, 32.3)	(1.52, 6.97)	
LR-	0.95	0.12		0.41	0.05		0.71	0.03	
	(0.89, 1.03)	(0.08, 0.20)		(0.22, 0.76)	(0.01, 0.34)		(0.50, 0.99)	(0.00, 0.49)	
Diagnostic odds ratio	1.69	104.7		97.5	480.0		6.40	99.2	
	(0.78, 3.69)	(48.1, 228.1)		NC	NC		(0.70, 58.5)	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.

biopsy were not detected on blind curettage because of insufficient tissue sampling, and one case 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⁻

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.

³³ Evaluation of diagnostic accuracy is further complicated by the use of imperfect reference 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.

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.

Conclusion

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