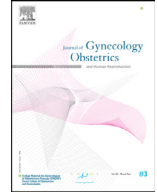




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Review

Endometrial biopsy: Indications, techniques and recommendations. An evidence-based guideline for clinical practice



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ABSTRACT

This practice guideline provides updated evidence for the gynecologist who performs endometrial biopsy (EB) in gynecologic clinical practice.

An international committee of gynecology experts developed the recommendations according to AGREE Reporting Guideline.

An adequate tissue sampling is mandatory when performing an EB. Blind methods should not be first choice in patients with suspected endometrial malignancy. Hysteroscopy is the targeted-biopsy method with highest diagnostic accuracy and cost-effectiveness. Blind suction techniques are not reliable for the diagnosis of endometrial polyps. In low resources settings, and in absence of the capacity to perform office hysteroscopy, blind techniques could be used for EB. Hysteroscopic punch biopsy allows to collect only limited amount of endometrial tissue. grasp biopsy technique should be considered first choice in reproductive aged women, bipolar electrode chip biopsy should be preferred with hypotrophic or atrophic endometrium. EB is required for the final diagnosis of chronic endometritis. There is no consensus regarding which endometrial thickness cut-off should be used for recommending EB in asymptomatic postmenopausal women. EB should be offered to young women with abnormal uterine bleeding and risk factors for endometrial carcinoma. Endometrial pathology should be excluded with EB in nonobese women with unopposed hyperestrogenism. Hysteroscopy with EB is useful in patients with abnormal bleeding even without sonographic evidence of pathology. EB has high sensitivity for detecting intrauterine pathologies. In postmenopausal women with uterine bleeding, EB is recommended. Women with sonographic endometrial thickness > 4 mm using tamoxifen should undergo hysteroscopic EB.

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1. Introduction

Endometrial biopsy (EB) is a common gynecologic procedure frequently performed in clinical practice. There are several equipment and techniques to perform an EB. Over the last years, office-based endometrial sampling has replaced the need for diagnostic dilation and curettage (D&C) or operative hysteroscopy, procedures that are

usually both performed in the operating room with the patient under general anesthesia [1].

There are many different clinical scenarios that require EB, such as patients presenting with thickened endometrium or abnormal uterine bleeding (AUB) [1,2]. Although a very safe and effective procedure for detecting endometrial cancer (EC) or atypical hyperplasia (AH), EB could result in a false-negative test, missing the diagnosis which is mainly due to biopsy technique, non-representative sampling, and variable pathologic interpretation [3].

The aim of this practice guideline is to summarize the most relevant available scientific evidence regarding EB techniques and indications.

1.1. Identification and assessment of evidence

This practice guideline was produced using the following search methodology: electronic databases including MEDLINE, EMBASE, Global Health, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), Health Technology Assessment Database and Web of Science, research registers (such as www.clinicaltrials.gov) were searched from inception to June 2022; we used the medical subject heading (MeSH) term "Endometrium" (MeSH Unique ID: D004717) in combination with "Biopsy" (MeSH Unique ID: D001706). The study search was not restricted to the English language but extended to Spanish, Chinese, French, Italian and Portuguese. Authors who are fluent in languages other than English (Spanish, Chinese, French, Italian and Portuguese) evaluated relevant publications in foreign language and provided, after English translation, related information to the panel. The reference lists of all identified papers were checked to identify studies not captured by electronic searches. All studies were assessed for methodologic rigor and graded according to the United States Preventive Services Task Force classification system (Table 1). Titles and/or abstracts of studies retrieved using the search strategy were screened independently by 2 authors to identify studies that meet the aims of this guideline. The full texts of the eligible articles were retrieved and independently assessed for eligibility by other 2 team members. Any disagreement between them over the eligibility of selected articles was resolved through discussion with a third (external) collaborator. Two authors independently extracted data from articles about study features and included populations, type of intervention and outcomes. Any discrepancies were identified and resolved through discussion (with a third external collaborator where necessary).

1.2. Stakeholders' involvement and applicability

These recommendations are based on professional opinion and are intended to assist gynecologists in treating the average patient. They should not be seen as hard and fast rules, and they were not designed to take the place of clinical judgment.

Recommendations were based on the best available scientific evidence, when practicable, and on the expert panel's consensus when such evidence was not available. They might probably change as we learn more about the condition.

The preparation of this guideline involves specialists in gynecological ultrasound (US), hysteroscopy, infertility, and oncologic therapy of endometrial pathology, according to AGREE Reporting Guideline standards [4]. Three external reviewers, two gynecologists and a gynecologic histopathologist randomly selected with a computer-based randomization from a list of 200 experts, with expertise in the aforementioned domains extensively assessed these practice recommendations in two rounds of revisions before publication.

Table 1

Assessment of evidence for the practice guideline.

Evidence was reviewed and evaluated for quality using criteria outlined by the U.S. Preventive Services Task Force
- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:
- Level A: Recommendations are based on good and consistent scientific evidence.
- Level B: Recommendations are based on limited or inconsistent scientific evidence.
- Level C: Recommendations are based primarily on consensus and expert opinion.

1.3. Indications to endometrial biopsy

Every year, many women require gynecological visit with symptoms that prompt EB. EC is diagnosed in about 65,000 women every year in the United States. Among the most frequent indications for EB in clinical practice include infertility and subfertility, the assessment of the uterine cavity before assisted reproduction technique (ART); evaluation of premenopausal and postmenopausal patients with AUB among other indications [5]. The etiology of AUB is classified according to the PALM-COEIN classification, developed by Munro et al. [6] and adopted by the International Federation of Gynecology and Obstetrics (FIGO). By classifying abnormal uterine bleeding according to the potential cause, this system distinguishes among polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified cause. The structural reasons of abnormal uterine bleeding are included by the acronym "PALM" section of the PALM-COEIN. Conversely, the non-structural, hormonal, or systemic causes of AUB are denoted under the acronym "COEIN" [1,2].

Before proceeding to perform an EB, questions about the menstrual bleeding pattern (frequency, duration, regularity and quantity), presence of pain, family history of AUB or underlying bleeding disorders, medication or herbal preparation that might affect bleeding generally, such as ginseng, ginkgo, use of hormonal contraceptives, nonsteroidal anti-inflammatory drugs, warfarin or heparin derivatives, should be included in a medical history. Careful analysis of the bleeding pattern will be one of the most crucial components of the medical history. For instance, cancer or even hyperplasia would be unlikely to be the cause of cyclic menstrual bleeding [1,2].

Regardless of the clinical scenario, EC could be performed in multiple ways [7].

1.4. Endometrial biopsy techniques

A plethora of studies have been performed evaluating different techniques for EB. Taraboanta et al. performed a retrospective cross-sectional study on 1677 hysterectomy specimens diagnosed with Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia (AH/EIN) or EC evaluating those with previous negative endometrial biopsy. Of these cases with negative endometrial biopsies before hysterectomy, 172 were classified as inadequate/insufficient since no endometrial tissue was present or had a benign diagnosis. An important limitation of this study was not identifying the procedure that was used to perform the endometrial sampling. In negative

endometrial biopsy result, the post-test probability of EC or AH/EIN diagnosis in the hysterectomy specimen was found to be 0.74%. Results from this study provide evidence about the importance of an adequate endometrial sampling [8,9].

D&C was once recognized as the gold standard for endometrial sampling [10]. Initially, D&C was considered as an accurate method for identifying endometrial cancer tumor grade [11]. More recently, D&C preoperative FIGO grade 1 endometrial cancer diagnosis was found congruent in 85% of cases with EB. However, a higher grade was found in 8.7% of the cases at the time of hysterectomy [12]. Piatek et al. assessed a retrospective cohort analysis considering all the patients who underwent endometrial biopsy using a Pipelle® and D&C. The purpose of this study was to determine the rate of endometrial sampling failure and factors affecting the quality of specimen obtained for histopathological examination. Of the 895 endometrial sampling procedures performed, 339 patients underwent Pipelle® biopsy, and 556 D&C. Inadequate samples were found in 60 and 88 cases, respectively. The study suggested that none of these two methods guarantee adequate specimen sampling [13]. Utida et al. designed a cross sectional study comparing the efficiency of histological endometrial samples collected using Pipelle® aspiration and hysteroscopic biopsies. The main aim of this study was to assess the congruency between these two endometrial sampling techniques. Specifically, the histological diagnosis of malignancy was a priority and, subsequently, the comparison between the costs of both techniques was assessed. The study enrolled 45 women (over 35 years old with AUB or postmenopausal bleeding) who underwent EB using both hysteroscopy and Pipelle®. Interestingly, EBs obtained using Pipelle® had a high accuracy for EC (100% agreement between the two procedures) but a lower accuracy for the diagnosis of polyps. It is important to note that Pipelle® biopsies costed 27 times less than hysteroscopic biopsies [14]. A very important aspect of this study is that it highlights the importance of performing EBs under direct visualization [15]. However, such findings were limited by the reduced sample size of the study.

To date, blind endometrial sampling alone are not considered effective for diagnosing focal lesions of the uterine cavity such as polyps or submucosal myoma [16].

Endometrial sampling could also be performed using ultrasound (US)-assisted guidance. However, US has a lower capacity to detect endometrial lesions compared to hysteroscopy [17,18]. Indeed, a prospective study performed by Reznak et al. showed that US abnormal findings need to be confirmed by hysteroscopic visualization with targeted biopsy and histological examination to avoid low accuracy [19].

Cheng et al. performed a retrospective cohort study evaluating the use of Lin's biopsy grasper for endometrial biopsy. Lin's biopsy grasper is one device specifically designed to work in conjunction with a flexible hysteroscope to perform intrauterine biopsy under transabdominal ultrasound guidance. This targeted biopsy method allows to perform endometrial biopsies in an office setting. They performed 126 targeted endometrial biopsies achieving a high diagnostic rate (92.1%, with 116 cases confirmed histologically) and adequate tissue quality (77.8%, with 98 cases obtaining optimal specimen volume) [20].

Bryant et al. performed a retrospective analysis on 141 hysterectomies performed in patients with a preoperative or incidental diagnosis of AH/EIN. Their data provided evidence about the value of selective rather than complete specimens sampling for the detection of AH/EIN and EC, showing that a selective approach could be extensively useful for the diagnosis [21].

Regarding the office hysteroscopy EB technique, different studies have provided results regarding the use of operative grasping forceps introduced through a 5 Fr operative channel of the hysteroscope [22]. The standard technique to perform hysteroscopic guided EB was proposed in 2002 by Bettocchi et al. Briefly, the forceps is placed, with its jaws opened, against the endometrium. The jaws are pushed into the tissue for 0.5 to 1 cm. Once a large portion of mucosa has been tangentially detached, the jaws are closed and the entire hysteroscope is

removed from the uterine cavity, without pulling the tip of the instrument back into the channel. This method allows to collect a larger amount of tissue [23].

One of the most recent advantages in EB technique relies on the study of the tumor material present in bodily fluids. Liquid biopsies also provide advantages for monitoring cancer progress and the response to therapy. The diagnostic procedure consists of an endometrial biopsy, which is obtained by a minimally invasive aspiration from the uterine cavity using a Pipelle®. Abnormal cells present in the aspirate are analyzed [24]. Hirai et al. performed a multicenter study comparing the clinical performance of liquid based endometrial cytology using Sure-Path™ to classic suction endometrial tissue biopsy. They suggested that liquid-based endometrial cytology was not inferior to suction endometrial tissue biopsy for the detection of endometrial cancer [25].

1.5. Recommended guidelines for the endometrial biopsy

Based on the available evidence, we promote the following recommendations:

- An appropriate sampling is mandatory when performing an EB (Level A).
- When performing diagnostic hysteroscopy and EB, the EB should be performed after the hysteroscopic procedure (Level C).
- D&C and Pipelle® should not be the first choice for EB method in patients with suspected endometrial malignancy (Level B).
- The use of VA, Pipelle® for outpatient EB is not efficient and lacks sensitivity when diagnosing endometrial polyps (level C).
- Office hysteroscopy is the targeted-biopsy method with the highest diagnostic accuracy (Level A).
- Liquid based biopsy is a promising method for endometrial markers detection (Level B).
- Suction techniques are not reliable for the diagnosis of endometrial polyps (Level A).
- In low-resources settings without the capacity to perform office hysteroscopy, blind techniques could be used for EB (Level B).

1.6. Hysteroscopic techniques for endometrial biopsy

The punch biopsy was the first type of technique commonly used for hysteroscopic biopsy. It utilized the spoon forceps and were regarded the standard biopsy instrument for several years. According to this technique, the biopsy forceps' jaws are held opened in close contact with the endometrium before being closed [26]. The hysteroscope is left in the uterine cavity while the closed forceps are retracted through the working channel. However, because the jaw extension is relatively limited compared to other biopsy forceps (2.5 vs. 5 mm for alligator forceps), the obtained tissue volume is sometimes insufficient for a satisfactory histological diagnosis [27,28].

To improve the quantity of retrieved tissue enough for a correct histological investigation, in 2002 Bettocchi et al. proposed a novel biopsy technique named "grasp biopsy". They used a toothed grasp forceps, known as alligator forceps. Because of the double length of the softly toothed jaws, the alligator forceps can collect a larger volume of tissue. Briefly, the alligator forceps is placed in close contact with the target location where the endometrial sample has to be taken with the jaws wide open. The forceps is then moved forward, "plowing" together with the tissue for roughly 0.5–1 cm, aiming to avoid contacting the underlying myometrium, in order to prevent stimulating myometrial nerve fibers and minimize pain. The jaws are then closed, grabbing the segment of endometrial tissue to be removed, which is subsequently retrieved from the uterine cavity alongside the hysteroscope [23,29].

In case of perimenopausal and postmenopausal women with hypotrophic or atrophic endometrium, it is more difficult to clench an appropriate quantity of tissue. In this case, performing the chip biopsy, cutting a “chip” of endometrium with a 5 Fr bipolar electrode inserted into the operating channel of the hysteroscope, is particularly effective. “Chipping” the endometrium may make the technique easier than others and may also be useful when sampling the superficial myometrial surface (i.e., in women with suspected premalignant or malignant endometrial pathology) [30–32].

An alternative approach to retrieve endometrium from an hypotrophic or atrophic surface is the pick-up biopsy technique. It consists of picking up tissue using the tip of the hysteroscope as a plow or the tip of dedicated mechanical tools to collect more sampling material. A recently patented tool for this purpose is the biopsy snake forceps sec. VITALE (Centrel Srl, Ponte San Nicolò, Padua, Italy). It is characterized by a flat pointed tip with serrated edges which can help to expose the hypotrophic or atrophic endometrium to be resected avoiding at the same time to loose fragments of the specimen [33]. Another crucial aspect to be remarked is the pain experienced during hysteroscopic endometrial sampling. Class I evidence reported an increased pain perception with the punch biopsy relative to the grasp and pick-up technique [31].

1.7. Recommended guidelines for the appropriate hysteroscopic biopsy technique

- Punch biopsy allows to collect a limited amount of endometrium to be sampled. (Level B).
- Grasp biopsy should be considered the most appropriate technique in reproductive aged women. (Level A).
- Chip biopsy is effective in collecting more endometrium compared with other techniques in perimenopausal and postmenopausal women. (Level B).
- In perimenopausal and postmenopausal women, the pick-up biopsy technique is more effective in collecting endometrial tissue compared with punch biopsy. (Level A).

1.8. Clinical scenarios

Generally, hysteroscopy aims to diagnose precancerous or cancerous lesions, to see and treat endocavitary benign pathology, such as leiomyomas or endometrial polyps previously identified by US scan, and to assess subclinical conditions that can lead to infertility (such as Asherman’s syndrome or endometritis) [34,35]. Currently, the only absolute contraindication to hysteroscopy is active uterine or pelvic infection. In addition, women diagnosed with primary infertility, recurrent pregnancy loss or subfertility have a clinical indication to undergo evaluation of endometrial pathology and uterine morphology [36]. On this purpose, we subclassified the clinical scenarios according to the patient’s age and symptomatology. For the purpose of this review, asymptomatic women were considered those without an AUB, regardless of their menopausal status, conversely symptomatic women are those presenting with symptoms (commonly AUB).

1.9. Asymptomatic women

1.9.1. Asymptomatic patients of reproductive age

In this group of patients, paucity of specific population studies affects our guideline results. One of the main reasons requiring EB in asymptomatic women is infertility [37]. Specifically, chronic endometritis has been recognized as one of the uterine factors that impair embryo implantation and immunohistochemical (IHC) diagnosis on endometrial specimens is mandatory [38]. In this regard, Zargar et al. performed a cross-sectional study with the aim of compare the

prevalence of chronic endometritis in patients with recurrent implantation failure (RIF) and recurrent pregnancy lost (RPL) using hysteroscopy and immunohistochemistry. Results showed that hysteroscopic visual inspection (searching for micro polyps or red spots) is a reliable tool in patients with RIF and RPL in order to diagnose chronic endometritis, however its accuracy is not sufficient to be considered as an alternative to IHC [39]. Other studies confirmed the need of combined diagnostic hysteroscopy and EB in women complaining of reproductive issues [40–42]. Especially in situations of repeated ART failure, there is a substantial chance of undiagnosed uterine abnormalities during regular US scan in infertile individuals. Higher rates of effective ARTs and non-inferior pregnancy rates have been observed when patients are routinely screened using in-office hysteroscopy and EB [43–49].

Before starting ART, the gynecologist should thoroughly examine the uterine cavity and document (with appropriate biopsy or excision) any abnormal endometrial findings.

1.10. Recommended guidelines for asymptomatic patients of reproductive age

- In asymptomatic premenopausal women, the EB is a useful tool for chronic endometritis diagnosis (Level A).
- Hysteroscopy with or without EB is useful in the infertility workup (Level A).
- In case of ART failure, hysteroscopic EB is crucial to avoid misdiagnoses and improve reproductive outcomes (Level B).

1.11. Asymptomatic postmenopausal patients

The incidental finding of a thickened endometrium at US in asymptomatic women is a common clinical scenario [50–53].

Several experts advocate adopting an US cut-off value of 4.0 or 5.0 mm in patients with postmenopausal bleeding (PMB) to recommend additional endometrial investigation [50,54–58]. The risk of EC is estimated to be less than 1% when the endometrial thickness (ET) is below 4.0 mm [50,54–58]. Some women with uterine premalignant or malignant conditions are asymptomatic [51]. There is no clear consensus on when to screen for EC in asymptomatic women with thickened endometrium, in contrast to the guidelines on the management of PMB. To improve diagnostic accuracy, it is necessary to investigate the ideal cut off value to warrant further endometrial investigation in asymptomatic postmenopausal women [59–61].

1.12. Recommended guidelines for asymptomatic postmenopausal patients

- There is no clear consensus regarding which ET cut-off should be used for recommending endometrial sampling in asymptomatic postmenopausal patients (Level B).

1.13. Symptomatic women

1.13.1. Symptomatic patients of reproductive age

In women of reproductive age, it is extremely important to perform EB in obese patients with AUB, and in those heterogeneous and/or hypervascularized endometrium on US, due to increased risk of malignancy [62–65]. In nonobese patients, several trials suggest performing EB in patients with AUB and/or in the presence of one of the following conditions: chronic anovulatory dysfunction, unopposed estrogen stimulation, those not responding to medical management, or patients with genetic high risk of endometrial cancer (e.g., Lynch syndrome, Cowden syndrome) [37,64,66–71]. In addition,

endometrial neoplasia should be suspected in premenopausal patients who are anovulatory and have prolonged periods of amenorrhea [72,73].

Similarly, EB is recommended if bleeding is frequent (interval between the onset of bleeding episodes is <21 days), heavy, or prolonged (>8 days). In patients who are ovulatory, this includes intermenstrual bleeding [37].

1.13.2. Recommended guidelines for symptomatic patients of reproductive age

- Young women with increased risk for endometrial malignancies and endometrial heterogeneity should undergo EB (Level A)
- Premalignant conditions or malignancy should be ruled out in nonobese women with unopposed hyperestrogenism (Level B)
- Hysteroscopy with EB is useful in women with heavy, prolonged or intermenstrual bleeding even in those without sonographic evidence of pathology (Level B).

1.13.3. Symptomatic perimenopausal patients

Several trials showed that hysteroscopy with directed biopsy is more sensitive than D&C for the diagnosis of uterine pathology in patients with AUB [11,15,26,74–77].

Nicholls-Dempsey et al. reviewed the indications for EB at their center. After analysis of 371 patients, they concluded that in women under the age of 41 there was no indication for biopsy in 23% of the biopsies, suggesting a significant over-investigation. Similarly, the value of EB in patients between 41 and 45 years old with menorrhagia and no additional risk factor should be further investigated [78].

Since the possibility of bleeding caused by a polyp, Ngo et al. performed a retrospective analysis evaluating differences in hysteroscopic findings between benign endometrial polyps and EC. The study included hysteroscopic findings of endometrial polyps ($n = 214$) on 3066 women who underwent hysteroscopy for abnormal vaginal bleeding, intrauterine cavity lesions suspected on US, recurrent spontaneous abortion, or infertility assessment. Clinical characteristics such as hyper-vascularity of the surface, ulcers, histopathological and hysteroscopic findings were evaluated retrospectively. The analysis showed that women with hysteroscopic findings of endometrial polyps with hyper-vascular, ulcerative, and polyps with irregular surfaces had a higher likelihood of EC. In this specific population, a target biopsy of the polyps with these specific characteristics should be performed to exclude malignancy [79].

In-office hysteroscopy is accurate for the detection of endometrial hyperplasia and cancer, according to Clarke et al. [84] and De Francis et al. [85]. However, in order to increase diagnostic accuracy, the sampling must be performed on the endometrial areas that seem abnormal [80,81].

1.13.4. Recommended guidelines for symptomatic premenopausal patients

- EB has high sensitivity for detecting benign, premalignant and malignant intrauterine pathologies (Level A).
- Hysteroscopic guided EB has higher accuracy than blind techniques in symptomatic women, regardless of their age (Level A).

1.13.5. Symptomatic postmenopausal patients

This population accounts for the major number of EB performed, due to the highest incidence of EC and AH/EIN. Bar-On et al. performed a retrospective cohort study including all women who underwent outpatient hysteroscopy for the following indications: PMB,

suspected polyp, and/or increased ET. Histological accuracy was evaluated by comparing specimens obtained in hysteroscopy with those obtained by hysterectomy, and visual accuracy was evaluated by comparing visual findings with those obtained by blind biopsies. Office hysteroscopy has been confirmed an adequate and reliable tool for the evaluation of benign pathology in the uterine cavity [82].

Several trials also reported that for women presenting with PMB, the use of transvaginal US is not indicated as a screening tool in evaluating women who have a history as tamoxifen use, due to poor diagnostic accuracy [83–86]. On the contrary, hysteroscopy and EB are the most reliable diagnostic method [30]. A recent study noted that there is no increased risk for EC in these group of patients relative to women taking aromatase inhibitors or without treatment [87]. Weighted sensitivities of endometrial sample for the diagnosis of EC, AH, and endometrial pathologies were 90%, 82%, and 39%, respectively, when hysteroscopy was used as a reference. Specificity was 98–100% for all diagnoses investigated and the reference test utilized. Endometrial sampling failed 11% of the time, with inadequate samples recovered in 31% of the time. Endometrial (pre) cancer was discovered in 7% of the women with inadequate or failed samples. Endometrial sampling's sensitivity to identify endometrial cancer, particularly AH and endometrial pathologies, including endometrial polyps, is lower than previously assumed in women with PMB. After a benign endometrial biopsy result, additional diagnostic work-up for localized pathology is indicated [88]. When compared to the assessment of recurrent bleeding, EC risk variables such as age can give considerable risk stratification [89].

1.13.6. Recommended guidelines for symptomatic postmenopausal patients

In postmenopausal women with any kind of AUB or PMB, EB is indicated (Level A).

Hysteroscopic guided EB should be the first choice due to the highest accuracy and cost-effectiveness (Level B).

1.13.7. Recommendations for future research

These guidelines were developed to provide a concise and updated reference for practicing clinicians facing with EB according to the most common clinical scenarios. However, they should not be intended as strict guidelines and must be adapted to the available facilities in every setting.

AUB, PMB and other intrauterine-related conditions are frequent gynecologic complaints encountered in daily clinical practice. There are some areas that require additional high-quality data to improve their diagnostic accuracy and management.

We propose the following considerations of future research:

- To conduct randomized trials to evaluate the impact of the presence of endometrial polyps on endometrial receptivity in infertile women diagnosed with asymptomatic endometrial polyps.
- To compare different mechanical hysteroscopic tools for performing EB (i.e. tissue retrieval systems, 5Fr forceps)
- To perform large studies evaluating the ET cut-off to recommend further endometrial evaluation in asymptomatic postmenopausal women.

Author contributions

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G.B.: Conceptualization; Methodology Formal analysis; Writing - original draft

G.R.: Conceptualization; Methodology Formal analysis; Writing - original draft

L.A.P.: Formal analysis; Writing - review & editing

A.D.S.S.: Formal analysis; Writing - review & editing
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 S.A.: Data curation; Writing - review & editing
 A.S.L.: Conceptualization; Methodology; Formal analysis; Writing - original draft
 All the authors edited the article for agreement in its final form.

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