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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.

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

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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 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 trough 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 SurePath™ 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 Franciscis 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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Review

Short review on adverse childhood experiences, pelvic pain and endometriosis

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ABSTRACT

The exposure to adverse childhood experiences has been associated with the subsequent development of several chronic health conditions, including pelvic pain. Endometriosis is a chronic disease characterized by the growth of endometrial-like tissue outside of the uterus, and is considered a common cause of chronic pelvic pain and infertility in reproductive-age women. However, the topic of pelvic pain and endometriosis is fraught with many challenges. This applies not just to clinical practice but also to research where many inconsistencies relating to pelvic pain and endometriosis definitions are encountered. A review was carried out for articles exploring the association of adverse childhood experiences and endometriosis. Studies addressing self-reported endometriosis suggested a relationship with childhood adversity, whilst papers relying on surgically diagnosed lesions of endometriosis irrespective of clinical presentation did not. This highlights the potential bias associated with the inconsistent use of the expression "endometriosis" in research.

Introduction

Endometriosis is classically defined as the presence of endometrial glands and stroma outside the uterine cavity and has been associated with pelvic pain and infertility in reproductive-age women [1]. The prevalence of endometriosis is estimated at approximately 10% of reproductive-age women [2], and 40–60% of women with chronic pelvic pain [3–5]. Although the gold-standard for diagnosing endometriosis still relies on laparoscopy, some authors have recently argued for diagnosis based on pain and clinical symptoms [6]. However, the association between endometriosis lesions and pelvic pain is unclear, with growing evidence that the presence and extent of endometriosis lesions correlate poorly with disease symptoms, and that endometriosis lesions can be found incidentally in up to 45% of asymptomatic women [7]. Moreover, endometriosis pathophysiology and contributive factors to pelvic pain are poorly understood [8].

Adverse childhood experiences (ACEs) refer to potentially traumatic events, including exposure to physical, sexual and emotional abuse, neglect and household dysfunction before the age of 18 [9]. Numerous studies have documented a relationship between childhood adversity and the development of poor health outcomes in adulthood [10], including chronic pain [11] and pelvic pain [12,13]. Recent work has shown that early life stressors can result in neurobiological alterations, modifying nociceptive processing and increasing vulnerability to pain sensitivity [14].

An association has been reported between the exposure to ACEs and the development of endometriosis in some studies, however there has been no systematic review aiming at summarizing this topic. The aim of this review was to investigate the association between the exposure to ACEs and the development of endometriosis in adulthood.

Material and methods

We reviewed the literature for articles investigating the exposure to ACEs and the risk of endometriosis. PubMed, Embase and PsycInfo were searched in September 2021 with no date restriction. The search strategy is detailed in the online supplementary material. Observational studies exploring the association between childhood adversity and endometriosis were included. Papers reporting non-original research, case reports and articles not written in English were excluded. Data including design study, number and age of participants, type of

Abbreviations: ACEs, adverse childhood experiences; CTQ, childhood trauma questionnaire

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Table 1
Summary of characteristics and key results of included studies.

Citation	Country	Study group	Age range and/or mean age, yr	Type of adversity	Outcome	Study design	Key results
Harris et al. 2018	USA	60′595 nurses	Premenopausal	CTQ short form	Self-reported diagnosis of endometriosis	Cross-sectional	Association between CTQ score and severity of physical and sexual abuse and self-reported endometriosis.
Tietjen et al. 2009	USA	1187 women with migraine	41 +/- 0.4	CTQ short form	Self-reported diagnosis of endometriosis	Cross-sectional	Association between CTQ score and self-reported endometriosis.
Liebermann et al. 2018	Switzerland, Germany and Austria	842 women	37.3 for the endometriosis group and 36.6 for the control group	CTQ short form	Surgically confirmed diagnosis of endometriosis among women with symptoms	Matched case-control study	Association between CTQ score, sexual abuse, emotional abuse, neglect and self-reported endometriosis. No association found for physical abuse and household challenges.
Hawks et al. 2019	USA	13,310 women	18–44	Forced sexual initiation (75% occuring before the age of 18)	Self-reported diagnosis of endometriosis	Cross-sectional	Association between forced sexual initiation (75% of these occuring before the age of 18) and self-reported endometriosis.
Schliep et al. 2016	USA	471 women undergoing laparoscopy for various reasons	18–44	Childhood physical abuse (< 14yo)	Surgically visible lesions of endometriosis	Cross-sectional	No association between childhood physical abuse and visible lesions of endometriosis at surgery.
Harrop-Griffiths et al. 1988	USA	55 women undergoing laparoscopy for various reasons	27 for the pelvic pain group and 31.9 for the control group	Childhood sexual abuse (< 14yo)	Surgically visible lesions of endometriosis	Cross-sectional	No association between childhood sexual abuse and visible lesions of endometriosis at surgery, but association when comparing women with chronic pelvic pain and without.

Abbreviation: CTQ, Childhood Trauma Questionnaire.

adversity and how the diagnosis of endometriosis was made, were extracted and included in a summary diagram (Table 1).

Results

Of 1001 unique articles, 878 were excluded after title and abstract screening. The 123 remaining records were assessed for eligibility by full-text reading. Finally, 6 studies were identified and selected for inclusion (Table 1). All of them had been conducted in industrialised countries (USA or European countries).

Data obtained from more than 60 000 women as part of the Nurses' Health Study II cohort showed that the Childhood Trauma Scale Score and the severity of physical and sexual abuse were associated with the incidence of reported endometriosis in a dose-response manner [15]. Similarly, a cross-sectional study among a headache clinic population showed a higher prevalence of reported endometriosis among women who also reported childhood maltreatment [16]. A multicentre case-control study including 421 matched pairs showed that women with self-reported endometriosis had a higher ACEs score and significantly more often reported a history of sexual abuse, emotional abuse and neglect than control women [17]. No statistically differences could be demonstrated for physical abuse and household challenges. Hawks et al. reported that forced sexual initiation (75% of these occurring before the age of 18) was associated with a 1.6 increased odds ratio of self-reported endometriosis among a population-based sample of more than 13 000 women [18].

In contrast, Schliep et al. did not find an association between childhood maltreatment, (identified in a standardized abuse questionnaire as childhood physical abuse prior to 14 years of age) and visible lesions of endometriosis among 471 women undergoing laparoscopy or laparotomy for a variety of reasons [19]. Similarly, in an earlier study comparing 25 women undergoing laparoscopy for chronic pelvic pain and 30 asymptomatic women undergoing laparoscopy for another indication, there was no association between the presence of visually diagnosed endometriosis at surgery and childhood sexual abuse before the age of 14, identified in structured psychiatric and sexual abuse interviews [20]. However, when the authors compared the groups according to the indication of laparoscopy irrespective of the operative findings, they found a higher proportion of childhood sexual abuse in women with chronic pelvic pain than in women without pain.

Discussion

In summary, of the six studies exploring the relationship between ACEs and endometriosis, four of them found an association and two did not. The important feature of note is that three of the four positive studies assessed "self-reported diagnosis of endometriosis", with the fourth including women with a diagnosis of endometriosis as noted in a medical office (although without data on whether this was a confirmed operative or histological diagnosis). In contrast, the two negative studies used visually confirmed endometriosis lesions, regardless of indication for surgery or symptoms.

Thus, our findings suggest that childhood adversity is associated with pelvic pain where there is an associated but mostly unproven diagnosis or label of endometriosis (that is, women reporting pelvic pain symptoms and a doctor mentioning the diagnosis and/or a surgical confirmation). In contrast, there was no association between ACEs and surgically visible lesions of endometriosis irrespective of clinical presentation. Thus, the reported association appears to be driven by pain, rather than by visible lesions of endometriosis. This is consistent with the findings in other pain conditions where ACEs are associated with chronic pain [11].

Different mechanisms have been suggested to explain the association between childhood adversity and the development of chronic pain, including not only psychological and social factors, but also biological factors, such as neuroendocrine alteration, immune dysregulation,

genetic damage and nociceptive processing modifications, leading to an increased vulnerability to pain sensitivity [14,21,22].

The prevalence of ACEs in the general population is significant, with more than half of adults having been exposed to at least one ACE in the United States [23]. A better understanding of the impact of ACEs on health is of major importance, in order to highlight the long-lasting consequences of child abuse and support advocacy for prevention programs, to protect and reduce the risk of negative outcomes among already vulnerable children.

There are some limitations associated with our review. Firstly, although the studies' designs were similar (5 cross-sectional and 1 case-control), participant numbers were different, with substantially larger numbers in the positive studies (including two cohorts with thousands of participants) than in the negative studies. This could affect the interpretation of the results, since a smaller difference would have been more difficult to detect in the negative studies. Second, three of the four positive studies looked broadly at ACEs through a validated score, whilst the two negative studies focused more selectively on under 14 year-old sexual abuse and physical abuse respectively, without the use of a standardized tool. However, it should be mentioned that ACEs may not always been reported or confessed by individuals, even in studies using validated scores.

Current guidelines still focus on reducing the diagnostic delay for endometriosis [24]. Efforts to develop models or algorithms based on a combination of patient history, symptoms and ultrasound findings to identify endometriosis in clinical practice without a laparoscopy have shown only limited success in allowing reliable identification of deep infiltrating endometriosis, but not superficial and peritoneal lesions [25,26]. There is however a movement towards a clinical or symptom-based approach to labeling pelvic pain as endometriosis [6,26] despite growing evidence showing the lack of relationship between the severity of symptoms and the severity of endometriosis, that endometriosis lesions are found in women without pain, the lack of relationship between the location of reported pain and site of identified endometriosis lesions and the lack of identifiable symptoms or symptom clusters that predict the presence of endometriosis [7,25,26].

We argue that this review reveals yet another example of inconsistencies and bias in the medical literature regarding endometriosis. It highlights the problem with inconsistent use of the expression "endometriosis" without attention to its definition in the research setting, and the resultant potential bias in papers which also fail to consider the limitations and lack of proposed mechanisms to support their findings. The risk of selection bias is high since not all women with pain symptoms undergo a laparoscopy, the finding of endometriosis does not confirm that this is the origin of the pain and endometriosis lesions may be found in women without pain. In research it is vital that there is clarity in which condition is being investigated so that findings can appropriately inform investigation into underlying pathophysiology of associations found.

Future studies investigating symptoms attributed to endometriosis should specify clearly what definition is used for endometriosis and how the control group is chosen. Ideally four categories of patients should be distinguished: women with symptoms and with lesions, without symptoms and without lesions, with symptoms but no lesions, and without symptoms but with lesions. Asymptomatic women, who have not undergone a laparoscopy, should not be used as controls since a number are likely to have asymptomatic endometriosis lesions.

Conclusion

In conclusion, we found an association between ACEs and "self-reported endometriosis" but not with surgically visible lesions of endometriosis, suggesting that the reported association may be more likely driven by pain than by histological lesions. This finding is consistent with other reported associations between chronic pain conditions and childhood adversity.

In addition to providing further insight into the lack of association between pelvic pain and endometriosis, this review highlights the problematic and inconsistent use of the expression "endometriosis" without attention to its definition in the research setting, and the resultant potential bias in papers failing to consider the limitations and lack of unifying consistent theory to support their findings. Future research should be more specific about the definition used for endometriosis and mindful when selecting controls. Moreover, ongoing research is needed in the field of child abuse and adversity, to improve the understanding of their long-term consequences on health and support advocacy for prevention programs.

Declaration of Competing Interest

The authors report no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jogoh.2023.102603.

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