UPDATES IN DIAGNOSIS AND MANAGEMENT OF POSTMENOPAUSAL BLEEDING AND ITS ASSOCIATED ANXIETY: A SYSTEMATIC REVIEW

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Abstract

Objectives: To review the diagnosis and management of postmenopausal bleeding (PMB).

Methods: We conducted a thorough search of PubMed, SCOPUS, Web of Science, and Google Scholar to find pertinent literature. Rayyan QRCI was utilized during the entire process.

Results: We included twelve studies with a total of 1859 participants. Hysteroscopy is the most acceptable tool to initially manage cases with PMB to stop the bleeding. Endometrial biopsies have been demonstrated to be beneficial in cases when malignancy is suspected. Spiral artery power and velocity addition Doppler flow mapping can help distinguish between benign disease and endometrial cancer in patients with thicker endometrium. TVS with endometrial thickness (ET) assessment is a non-invasive, easily accessible, and cost-effective method of diagnosis, it should be the first line of study in the examination of women with PMB who have suspected endometrial disease. SIS is a well-tolerated, safe, and uncomplicated treatment that yields excellent diagnostic accuracy. Diagnosis of the cause of bleeding and its management will relieve the associated anxiety.

Conclusion: In clinical practice, PMB is an important factor for healthcare professionals. There is an ongoing debate on the best investigative order for patients with PMB. The goal of future studies should be to obtain higher accuracy with less interference. Blind biopsies should be avoided as they have the potential to overlook endometrial disease, particularly when it is localized. To detect intrauterine pathology, hysteroscopy with biopsy under visualization is a more accurate operation and needs to be preferred over blind methods. A common gynecologic problem that is never to be disregarded is PMB.

Keywords: Postmenopausal bleeding; Diagnosis; Management; Systematic review.

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Introduction

The permanent cessation of menstruation following a year of amenorrhea is known as natural menopause. It is a diagnosis made in retrospect. In western nations, the menopause typically occurs at the age of 51.4 [1]. The "perimenopause," which is the period that precedes menopause by four years, is marked by irregular periods, a change in hormone levels, such as elevated follicle stimulating hormone, and clinical symptoms like hot flashes, insomnia, and dry vagina [2, 3].

The synthesis of progesterone, estrogens, and, to a lesser extent, androgens—particularly testosterone, dehydroepiandrosterone sulfate, androstenedione—decreases significantly regardless of the cause(s) of menopause. While vaginal atrophy, osteoporosis, and changes in the metabolic profile that increase the risk of heart attacks are among the long-term repercussions, hot flushes and other vasomotor symptoms play a significant role in the menopausal transition [4]. The reproductive organs atrophy gradually as a result of decreased amounts of progesterone and estrogens [5]. The endometrium experiences progressive atrophy during menopause as well; in the absence of cyclic hormonal stimulation, this atrophy takes place. Exogenous hormone therapy used often during menopause may alter the endometrium, which may multiply in response to hormonal stimulation and result in PMB [6].

A typical gynecologic complaint is PMB [7, 8]. After menopause, the prevalence of PMB declines with time, from about 400/1000 women/year immediately following menopause to 42/1000 women/year three years later [7].

A thorough medical history should be obtained at the patient's initial evaluation, with a focus on PMB risk factors. It is crucial to first establish the menopausal state of patients, particularly those who are younger, by getting information on their most recent menstrual cycle and making sure that a full year has passed since the last amenorrhea. An epidemiological investigation showed that whereas the risk of endometrial cancer rises with the years of menopause, the incidence of PMB falls with age [7].

Other organ symptoms, such as those related to the urinary tract that could indicate urological causes of bleeding or that point to gastrointestinal disorders like bloody stools or painful defecation, should also be investigated. A complete medical history, including family history, should be collected. It is necessary to record risk factors for endometrial cancer, such as obesity, diabetes, hypertension, and some genetic diseases like Lynch syndrome, which causes non-polyposis colorectal cancer. It is important to ask about medications that may contribute to PMB, such as nutritional supplements, hormone therapy, tamoxifen, and anticoagulants [7]. This systematic review investigates the recently published literature on the diagnosis and management of PMB.

Methodology

Study Design and Duration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in this systematic review [9]. In April 2024, the systematic review got started.

Search strategy

To find relevant material, a comprehensive search was conducted using four key databases: PubMed, SCOPUS, Web of Science, and Google Scholar. We searched through databases that contained only English content, paying attention to the unique requirements of each. To find the relevant papers, we converted the following keywords to PubMed Mesh terms; "Postmenopausal bleeding," "Abnormal uterine bleeding," "Diagnosis," and "Management." "OR," "AND," and "NOT," three boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Any study design that discussed the diagnosis and management of PMB.
- Studies conducted within the last five years (2019-2024).
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

Two output verifications of the search method were conducted using Rayyan (QCRI) [10]. By using inclusion/exclusion criteria, the researchers evaluated how relevant the abstracts and titles were to the combined search results. The reviewers carefully considered every manuscript that met the inclusion

requirements. The authors talked about ways to resolve conflicts. A pre-made data extraction form was used to upload the approved study. The authors extracted data on the study title, authors, study year, country, participants, age, parity, state of hormonal therapy, diagnostic tools, management, and the main outcomes.

Strategy for data synthesis

Summary tables using information from relevant studies were compiled to provide a qualitative assessment of the research's findings and components. The best technique for using the data from the included study articles was chosen after the data for the systematic review was gathered.

Results

Search results

The systematic search produced 1005 study articles in total, of which 499 duplicates were eliminated. After 506 studies had their titles and abstracts screened, 412 were not included. After 94 reports were requested to be retrieved, 4 articles were not found. After screening 90 studies for full-text assessment, 54 were rejected due to incorrect study results, 19 were rejected due to incorrect population type, 3 articles were editor's letters, and 2 were abstracts. This systematic review included twelve eligible study articles. A synopsis of the procedure for choosing studies is provided in (Figure 1).

Characteristics of the included studies

Table (1) shows the sociodemographic details of the research articles that are included. Our results included twelve studies with a total of 1859 participants. Eight studies were prospective in nature [11, 13, 16, 18-22] and only two were retrospective in nature [12, 15]. Five studies were conducted in india [13, 18, 19, 20, 22], two in Egypt [16, 21], two in Vietnam [11, 14], one in the USA [12], one in Saudi Arabia [15], and one in the UK [17].

Clinical characteristics

Management

Table (2) reveals the clinical characteristics including the diagnosis and management of women with PMB. As PMB is a pathological condition that represents a symptom of other major pathology that could be benign or malignant, there are few studies that discuss the management of our condition. One study stated that hysteroscopy is the most acceptable tool to initially manage cases with PMB to stop the bleeding. Experienced surgeons can safely and effectively perform hysteroscopic endometrial resection in conjunction with resection of intrauterine pathology in women with PMB [15].

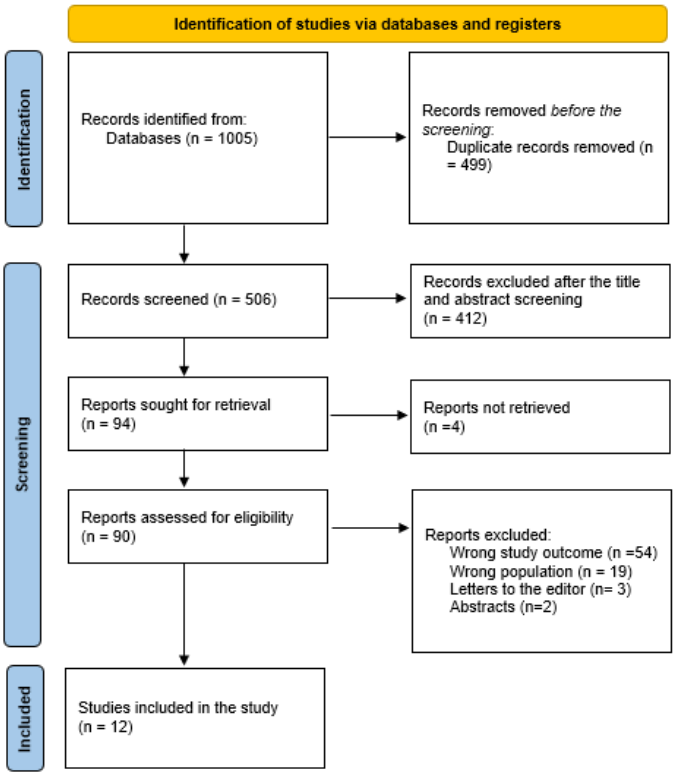

Figure 1. Study selection is summed up in a PRISMA flowchart.

Diagnosis

Hysteroscopy and biopsy

Endometrial biopsies have been demonstrated to be beneficial in cases when malignancy is suspected [12]. Hysteroscopic viewing is essential and has been linked to greater sensitivity in diagnosing intrauterine disease in women with symptomatic uterine hemorrhage [12, 15, 16, 19, 22]. Another study repoted that hysteroscopy should only be used in instances with poorly defined endometrial lining, recurrent or chronic bleeding, and endometrial thickness greater than 5 mm, regardless of endometrial echotexture, in low-resource settings [18]. Saad et al. reported that hysteroscopy's diagnostic accuracy in identifying submucosal myoma was superior to that of SIS and TVS [21].

Doppler

Spiral artery power and velocity addition Doppler flow mapping can help distinguish between benign disease and endometrial cancer in patients with thicker endometrium [13, 14].

Non-invasive methods (US, TVS, SIS)

Ultrasound has good inter-rater reliability when used to diagnose benign endometrial polyps, endometrial cancer, and uniformly thickened endometrium in women with PMB [11, 17]. Other studies reported that because TVS with endometrial thickness (ET) assessment is a non-invasive, easily accessible, and cost-effective method of diagnosis, it should be the first line of study in the examination of women with PMB who have suspected endometrial disease [18, 22]. Another found that SIS is a well-tolerated, safe, and uncomplicated treatment that yields excellent diagnostic accuracy [20] (Table 1, Table 2).

Discussion

For the menopausal woman with vaginal tract pathology to receive an effective course of treatment, precise diagnostic procedures are necessary. One typical gynecologic ailment is PMB. As up to 10% of bleeding cases are caused by cancer or premalignant diseases, the doctor needs to look into the source of the bleeding. In the past, dilatation and curettage (D&C) performed under general anesthesia was the gold-standard diagnostic technique for PMB, but novel, less invasive, office-based methods of examination have arisen [23].

As PMB is a pathological condition that represents a symptom of other major pathology that could be benign or malignant, few studies discuss the management of our condition in this review. One study stated that hysteroscopy is the most acceptable tool to initially manage cases with PMB to stop the bleeding. Experienced surgeons can safely and effectively perform hysteroscopic endometrial resection in conjunction with resection of intrauterine pathology in women with PMB [15].

We also found that endometrial biopsies have been demonstrated to be beneficial in cases when malignancy is suspected [12]. Hysteroscopic viewing is essential and has been linked to greater sensitivity in diagnosing intrauterine disease in women with PMB [12, 15, 16, 19, 22]; however, another study reported that hysteroscopy should only be used in instances with poorly defined endometrial lining, recurrent or chronic bleeding, and endometrial thickness greater than 5 mm, regardless of endometrial echotexture, in low-resource settings [18]. Wortman, reported that when compared to hysteroscopy with target eye biopsy, diagnostic hysteroscopy is the gold standard technique because it can subjectively assess the size and characteristics of the lesion with a reported sensitivity of 58–99%, specificity of 87–100%, positive predictive value (PPV) of 21–100%, and NPV of 66–99% [24]. Despite the excellent accuracy of visual hysteroscopy, a guided biopsy is always necessary to rule out the existence of malignant diseases. Compared to alternative blind sampling techniques like D&C) and pipelle, which may fail to sample a sizable amount of the endometrial cavity, office hysteroscopy-guided biopsies have higher accuracy. Consequently, while examining endometrial polyps, blind biopsy should not be performed as a diagnostic technique, per the guidelines [25].

We also found that Ultrasound has good inter-rater reliability when used to diagnose benign endometrial polyps, endometrial cancer, and uniformly thickened endometrium in women with PMB [11, 17]. A systematic review and meta-analysis by Vroom et al. demonstrated that women with PMB can be categorized for additional therapy with hysteroscopy or expectant management using saline contrast sonohysterography. All women who are managing their pregnancy should be advised to visit their gynecologist again for additional diagnostic testing if they experience recurrent bleeding [26].

Other studies in this review reported that because TVS with ET assessment is a non-invasive, easily accessible, and cost-effective method of diagnosis, it should be the first line of study in the examination of women with PMB who have suspected endometrial disease [18, 22]. For a preliminary assessment of a patient with PMB, transvaginal ultrasonography is thought to be appropriate [27]. Often seen as the "endometrial lining," the endometrial echo complex

Table 1. Sociodemographic characteristics of the included participants.

Study	Study design	City	Participants	Age range
Nguyen & Nguyen, 2023 [11]	Prospective interventional	Vietnam	150	>40
Ferrando et al., 2023 [12]	Retrospective cohort	USA	689	49
Nasheeha et al., 2021 [13]	Prospective observational	India	50	41-60
Nguyen et al., 2022 [14]	Cross-sectional	Vietnam	60	45-80
Vilos et al., 2020 [15]	Retrospective cohort	Saudi Arabia	151	50-87
Abdel Hameed et al., 2022 [16]	Prospective cohort	Egypt	237	48-80
Wong et al., 2021 [17]	Cross-sectional	UK	52	57-69
Vasudeva et al., 2022 [18]	Prospective cohort	India	82	50-65
Nisha & Sunitha, 2019 [19]	Prospective cohort	India	100	51.5
Bharti & Dewan, 2020 [20]	Prospective cross-sectional	India	138	56.7
Saad et al., 2020 [21]	Prospective interventional	Egypt	50	45-63
Devabhaktuni et al., 2020 [22]	Prospective cohort	India	100	45-79

*NM=Not-mentioned

Table 2. Clinical characteristics and outcomes of the included studies.

Study	Parity (range)	Hormonal therapy (%)	Diagnostic tool	Management	Main outcomes
Nguyen & Nguyen, 2023 [11]	NM	NM	Sonography and CBC	NM	While assessing intrauterine anomalies in women experiencing perimenopausal and PMB, hemoglobin concentration and fundamental sonographic characteristics should be taken into consideration. In uterine intracavitary diseases, the prognosis of anemia can be ascertained using ultrasonic indices of uterine size.
Ferrando et al., 2023 [12]	0-10	69 (10%)	Hysteroscopy and endometrial biopsy	NM	Endometrial biopsies have been demonstrated to be beneficial in cases when malignancy is suspected; nevertheless, blind evaluation of the endometrial cavity for a conclusive diagnosis should be abandoned when benign localized pathology is detected. Hysteroscopic viewing has been linked to greater sensitivity in diagnosing intrauterine disease in women with symptomatic uterine hemorrhage.
Nasheeha et al., 2021 [13]	NM	NM	Uterine and spiral artery Doppler	NM	Spiral artery power and velocity addition Doppler flow mapping can help distinguish between benign disease and endometrial cancer in patients with thicker endometrium.
Nguyen et al., 2022 [14]	NM	NM	ET and uterine artery Doppler parameters	NM	The Doppler indices of uterine artery endometrial thickness, resistance index, pulsatility index, and peak systolic velocity may be useful in distinguishing between benign and malignant endometrial alterations. There appears to be a correlation between the higher stages of endometrial cancer and pulsed ultrasonic Doppler velocimetry.
Vilos et al., 2020 [15]	0-7	83 (54.9%)	Hysteroscopy	Hysteroscopy	For the majority of intrauterine pathology, including nonatypical endometrial hyperplasia and some cases of atypical hyperplasia and endometrial cancer, as well as for the diagnosis of all cases, experienced surgeons can safely and effectively perform hysteroscopic endometrial resection in conjunction with resection of intrauterine pathology in women with PMB.
AbdelHameed et al., 2022 [16]	NM	NM	Hysteroscopy	NM	The essential instrument for accurately identifying a range of endouterine disorders in women with PMB is hysteroscopy.
Wong et al., 2021 [17]	NM	NM	US	NM	The findings demonstrate that subjective pattern recognition has good inter-rater reliability when used to diagnose benign endometrial polyps, EC, and uniformly thickened endometrium in women with PMB by ultrasound.
Vasudeva et al., 2022 [18]	89% are multipara	NM	TVS and Hysteroscopy	NM	Because TVS with ET assessment is a non-invasive, easily accessible, and cost-effective method of diagnosis, it should be the first line of study in the examination of women with PMB who have suspected endometrial disease. Despite being more sensitive and specific, hysteroscopy should only be used in instances with poorly defined endometrial lining, recurrent or chronic bleeding, and endometrial thickness greater than 5 mm, regardless of endometrial echotexture, in low-resource settings.
Nisha & Sunitha, 2019 [19]	NM	NM	TVS and Hysteroscopy	NM	For the assessment of post-menopausal bleeding, hysteroscopy, and transvaginal ultrasonography are both options. When comparing transvaginal ultrasonography and histology, hysteroscopy has a stronger correlation. When a woman experiences bleeding after menopause, hysteroscopy is the most effective method for identifying endometrial abnormalities.
Bharti & Dewan, 2020 [20]	NM	NM	SIS, TVU, and hysteroscopy	NM	SIS is a well-tolerated, safe, and uncomplicated treatment that yields excellent diagnostic accuracy. For endometrial examination, SIS appears to be similar to hysteroscopy.
Saad et al., 2020 [21]	0-7	NM	SIS and hysteroscopy	NM	Regarding pathological diagnosis, hysteroscopy's diagnostic accuracy in identifying submucosal myoma was superior to that of SIS and TVS. When it came to the diagnosis of polypoid lesions in the uterine cavity, SIS and hysteroscopy agreed 100% of the time, making them more accurate than TVS. When it came to pathological diagnosis, SIS's diagnostic accuracy was superior to both hysteroscopy and TVS in the detection of endometrial hyperplasia.
Devabhaktuni et al., 2020 [22]	NM	NM	Hysteroscopy	NM	ET measurement TVS, US, and ideally endometrial echo complex is required for women experiencing PMB.

*NM=Not-mentioned

(ECC) is a double layer with homogeneous sonolucency. It ought to be measured with the uterus seen in a sagittal perspective at its thickest point. Regarding the threshold value for a normal ECC in a postmenopausal woman, there is no agreement. According to multiple investigations, patients with PMB who have a homogenous ECC of less than 4 mm have a larger than 99% negative predictive value for endometrial cancer [27-29]. To firmly rule out endometrial cancer in patients with PMB, various endometrial thickness cutoff values have been suggested as a non-invasive method.

Another study in this review found that SIS is a well-tolerated, safe, and uncomplicated treatment that yields excellent diagnostic accuracy [20]. In order to improve the assessment of intracavitary lesions, SIS entails the intrauterine injection of normal saline solution. According to a recent systematic review and meta-analysis, SIS has a sensitivity of 86.5% (95% CI 63.6–100%) and a specificity of 91.1% (95% CI 63.2–100%) when it comes to diagnosing endometrial disease in patients with PMB [30]. Ultimately, the authors estimated a sensitivity of 95% and a specificity of 88% utilizing pooled data from systematic reviews conducted to assess the diagnostic accuracy of SIS in the examination of women with irregular uterine bleeding. However, postmenopausal women's (87%) total SIS success rate for endometrial disease diagnosis was substantially lower than that of premenopausal women ($p < 0.01$) [31].

Conclusion

In clinical practice, PMB is an important factor for healthcare professionals. There is an ongoing debate on the best investigative order for patients with PMB. The goal of future studies should be to obtain higher accuracy with less interference. Blind biopsies should be avoided as they have the potential to overlook endometrial disease, particularly when it is localized. In order to detect intrauterine pathology, hysteroscopy with biopsy under visualization is a more accurate operation and need to be preferred over blind methods. A common gynecologic problem that is never to be disregarded is PMB.

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