

Postmenopausal Bleeding in Women Utilizing Hormone Replacement Therapy: Not all the patients need to be referred or investigated

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Abstract

Background: Unscheduled bleeding while on Hormone replacement therapy (HRT) is a common concern, and it is one of the most typical reasons for dissatisfaction for women on HRT and a recognized reason for its discontinuation. The primary strategy for managing unscheduled bleeding in women using HRT is, first, to identify the pathology and, secondly, to correct the cause.

Objective: To investigate the occurrence, pattern of referral, and the aetiological factors of postmenopausal bleeding in women using HRT.

Methods: This was a retrospective study involving women referred from primary care with postmenopausal bleeding while using HRT from January 1, 2022, to June 30, 2022. Medical records were reviewed, and relevant data, including demographics, type and duration of HRT, and investigation results, were extracted. Data was entered on an Excel spreadsheet and anonymized. Descriptive statistics were used to calculate the proportion, mean, and standard deviation. The data is presented in charts and text.

Results: A total of 147 patients met the inclusion criteria. The incidence of postmenopausal bleeding (PMB) while on HRT was 12.4%, the mean age was 56 years, and the average duration of use of HRT was 16 months. Most patients were on combined HRT (84%), and the patch was the most typical form of HRT. Among women using continuous HRT, more than half (57.2%) had been using the preparation for less than six months. All the patients had pelvic ultrasound scans for endometrial assessment, and those meeting criteria had Hysteroscopy and endometrial sampling. Most patients had no sinister pathology identified, but one patient who had used HRT for over three years was diagnosed with endometrial cancer. Depending on the clinical situation, most patients were managed conservatively by expectant management, altering the HRT regimen, or surgical treatment.

Conclusion: Diagnostic evaluations, including Hysteroscopy, endometrial sampling, and transvaginal ultrasound, play a pivotal role in determining the underlying pathology associated with PMB in women on HRT. These investigations aid in distinguishing benign causes from potentially more serious conditions, such as endometrial hyperplasia or cancer, as was found in this study. It also highlights the need to ensure referred patients meet the referral criteria.

Keywords: Endometrial cancer; Hormone replacement therapy; Hysteroscopy; Investigation; postmenopausal bleeding

Introduction

Postmenopausal bleeding (PMB) is a distressing condition affecting many women in their postmenopausal phase [1]. Defined as vaginal bleeding that occurs 12 months or more after the cessation of menstruation, PMB can be a cause for concern, as it may indicate underlying pathology [1,2]. Among the various factors contributing to PMB, hormone replacement therapy (HRT) has gained attention as a potential culprit. With the increasing uptake of HRT, this problem is set to persist [3-5]. HRT, a widely prescribed treatment for menopausal symptoms, involves the administration of exogenous hormones to alleviate vasomotor symptoms, prevent bone loss, and reduce the risk of cardiovascular disease. However, the impact of HRT on the occurrence of PMB and its management remains a topic of debate and investigation. Unscheduled bleeding on HRT is a common concern, and it is one of the most typical reasons for dissatisfaction for women on HRT and a recognized reason for its discontinuation [2,3]. The mechanisms underlying PMB in women using HRT are poorly understood [4] and may pose a diagnostic challenge/dilemma for the clinician and cause distressing patient anxiety [1]. Given that the benefit of using the HRT is increasingly becoming more apparent and more women are taking up HRT, a better understanding of the pathophysiology and the aetiological factors for PMB and how to mitigate them will no doubt allay the anxieties and the myths that have been associated with this symptom, thereby benefiting both the provider and the potential user [2-4].

The main reason for investigating PMB is to exclude a sinister endometrial pathology [6]. Abnormal vaginal bleeding is the most frequent presenting symptom in women with endometrial cancer, but most of the aetiological causes of PMB are benign in 90-95% of cases [7-10]. While there are several risk factors for endometrial cancer, HRT, especially unopposed estrogen therapy in un-hysterectomized women, is a significant risk factor that should warrant an assessment regardless of the HRT regimen. The primary strategy for managing unscheduled bleeding in women using HRT is first to identify the pathology and second to correct the cause [1-7]. There remains no ideal approach to managing PMB in women using HRT, but this paper aims to explore the patterns of presentation of PMB in women using HRT. By delving into the available evidence and current guidelines, we describe our experience and present a practical approach to managing PMB in women utilizing HRT. Additionally, we will discuss the diagnostic modalities employed in investigating postmenopausal bleeding, including imaging techniques, Hysteroscopy, and endometrial sampling.

By consolidating the current knowledge and advancements in the investigation and management of postmenopausal bleeding in women using hormone replacement therapy, this paper aims to contribute to clinical decision-making, enhance patient care, and shed light on future research directions in this important field. Ultimately, the findings of this study will serve as a valuable resource for healthcare providers, empowering them to optimize patient outcomes while effectively addressing the challenges posed

by postmenopausal bleeding in women on HRT. In our unit, women experiencing PMB on HRT are referred from primary care through the '2-week wait' pathway to the one-stop PMB clinic. The one-stop clinic has personnel and facilities for same-visit assessment (pelvic ultrasound scan, Hysteroscopy, endometrial sampling) and may provide on-the-spot treatment if appropriate [8]. The One-stop PMB clinic model is convenient for patients and more cost-effective to the NHS than the traditional outpatient clinic with subsequent inpatient theatre assessment [7,8]. There is a need to make efficient use of the one-stop clinic to attain the objective for which it was set up. To achieve this objective, patients referred to the one-stop clinic should meet the criteria for such a referral according to the British Gynaecological Cancer Society guideline on managing endometrial cancer [8].

Materials and Method

Study Design

This study utilized a retrospective observational design to investigate postmenopausal bleeding (PMB) in women utilizing hormone replacement therapy (HRT). Patient data from electronic medical records were collected and analyzed to explore the relationship between HRT and PMB and the strategies for investigation and management.

Data Collection

A comprehensive review of electronic medical records from a tertiary center was conducted. The study included women aged 40 and older with a documented history of PMB while on HRT. Consecutive data were collected over six months, from January 1, 2022, to June 30, 2022.

Variables

The collected data included a range of variables, including demographic information (age, ethnicity), HRT characteristics (type of hormone regimen, dosage, route of administration), PMB characteristics (frequency, duration, severity), underlying pathology (endometrial hyperplasia, endometrial cancer), diagnostic investigations (endometrial sampling, imaging results), and management strategies (changes in HRT regimen, medical interventions, surgical interventions).

Data Analysis

Data were entered into an Excel spreadsheet, anonymized, and descriptive statistical analysis was performed to summarize the demographic characteristics of the study population, the frequency of PMB, the types of HRT utilized, and the outcomes of the investigation.

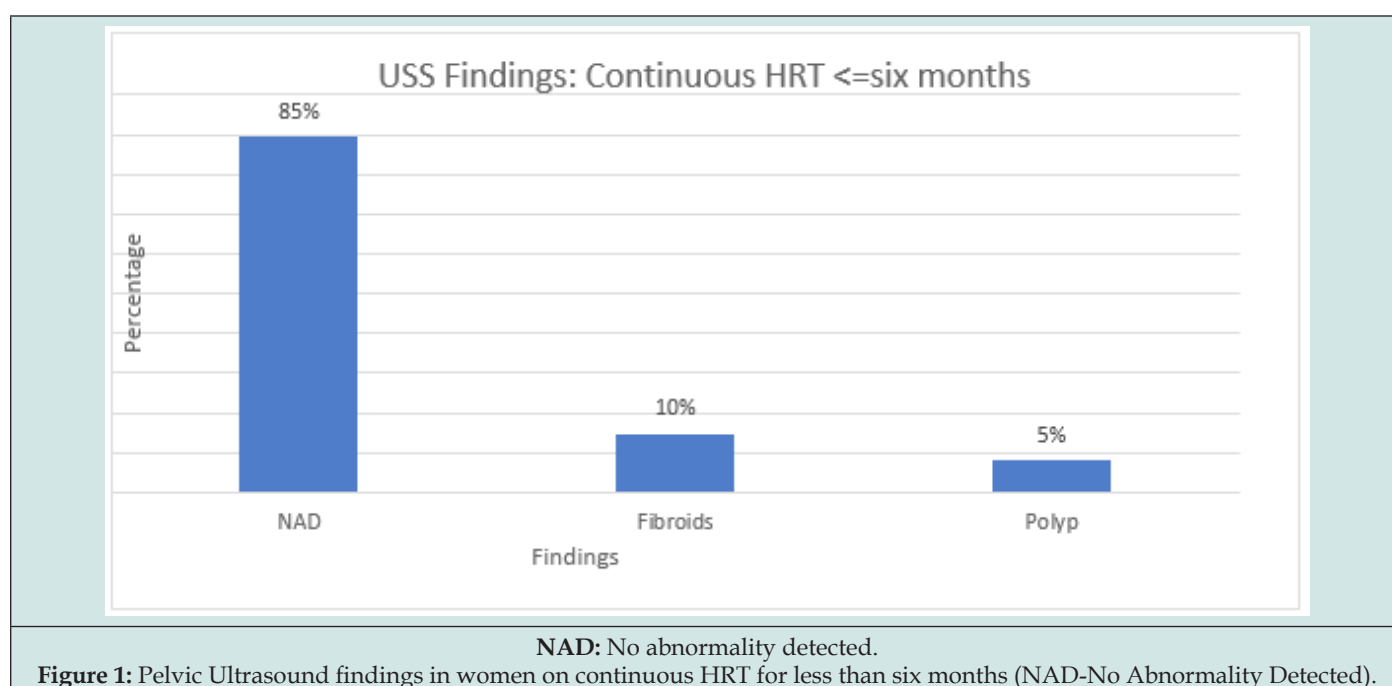
Ethical Considerations

Ethical approval was not required, given that the study was retrospective, but permission was obtained from the clinical outcome unit of the hospital. All patient data were de-identified and handled confidentially, ensuring compliance with privacy regulations and ethical guidelines.

Results

The total number referred for PMB was 1185, Total number on HRT was 147 (12.4% of the total referred). Women on Sequential HRT comprised 11% (16), and Continuous HRT, 89% (131). The number of patients referred after six months of continuous HRT was 42.8% (56), and while the majority (57.2%) had been on HRT for less than six months at the time of their referral, the mean duration of HRT use among the study population was one year and four months. The mean age of the patients on HRT referred for PMB was 56 years, ranging from (41-80). Regarding the types of HRT utilized, 84% of the women on continuous HRT were on the combined therapy, with 62% of these patients using the patch preparation, while for women using the estrogen-only therapy, 72% used the patch. Both cases were followed by oral therapy

as the next most common form of preparation. About 10% of the patients used Oestrogen combined with an intrauterine system. When stratified by HRT type, women on combined estrogen-progestogen therapy had a higher frequency of PMB (95.0%) than those on estrogen-only therapy (5.0%). Diagnostic investigations were performed in all cases of PMB. All the patients referred for PMB on HRT had pelvic ultrasound scans. The endometrial thickness was also measured, and the mean thickness was 13.8 mm. Women with five millimeters or more dometrial thicknesses were offered Hysteroscopic endometrial assessment and biopsy where applicable. In Figure 1, Eighty-five percent of the women on continuous HRT had no abnormality when pelvic ultrasound was performed. In comparison, ten percent and five percent had uterine fibroid and polyp, respectively.

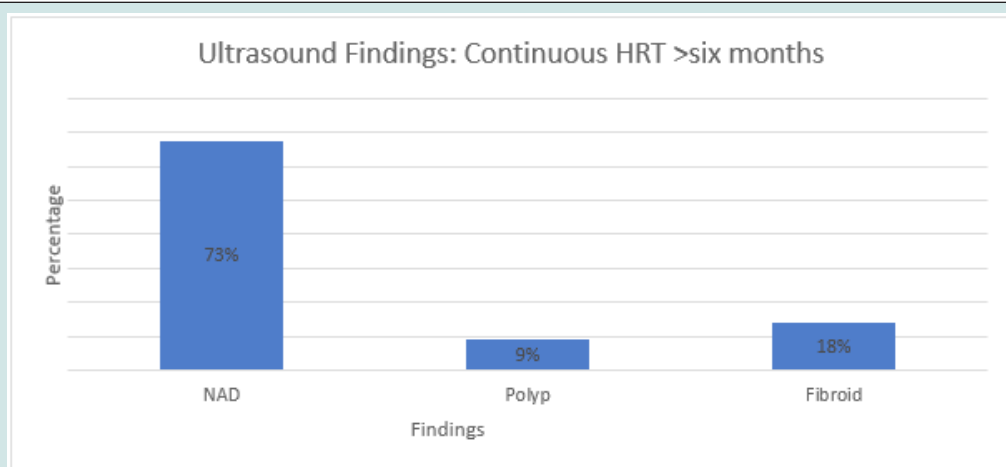


Like the report in Figure 1, 73% of women on continuous HRT for more than six months had no pathology on pelvic ultrasound scan, while nine and eighteen percent had polyp and fibroid, respectively. When Hysteroscopy was done, many of the patients had normal endometria (Figure 2). Hysteroscopy was not done for cases with normal pelvic ultrasound scan findings, regardless of the duration of use of HRT. In Figure 3, for Women on HRT for six months or less, Hysteroscopy was not done for 41% of the patients due to normal ultrasound reports. Forty-one percent of the patients with Hysteroscopy had no abnormality detected (NAD). In comparison, the rest had polyps at ten percent, fibroid at one percent, and thickened endometrium described at four percent. Figure 4 four

depicts the Hysteroscopy findings in women on HRT for over six months. It was not done in 39% of them, and it was normal findings in 39%. Polyp comprised 19% of the pathologies identified, with thickened endometrium contributing three percent. In Figure 5, Endometrial sampling with Pipelle was done in women with suspicious endometrial cavities on Hysteroscopy, and the tissues were sent for histological analysis. Histology was normal in 48% of the patients, but the sample was reported as insufficient in two percent. In Figure 6, among the cases where endometrial sampling was performed, one patient (one percent) on continuous HRT for more than six months was diagnosed with endometrial cancer. The report was normal in 59% of the samples. Regarding management

strategies, 90% of women with PMB had their HRT regimen adjusted by changing the type of hormone, altering the dosage, switching from sequential to continuous, or switching the route of administration. Surgical interventions, such as hysteroscopic

endometrial ablation, Polypectomy, or Myosure treatment, were performed in the rest of the patients due to persistent bleeding or significant risk factors for endometrial pathology.



NAD: No abnormality detected.

Figure 2: Pelvic Ultrasound report in women on continuous HRT for more than six months (NAD-No Abnormality Detected).

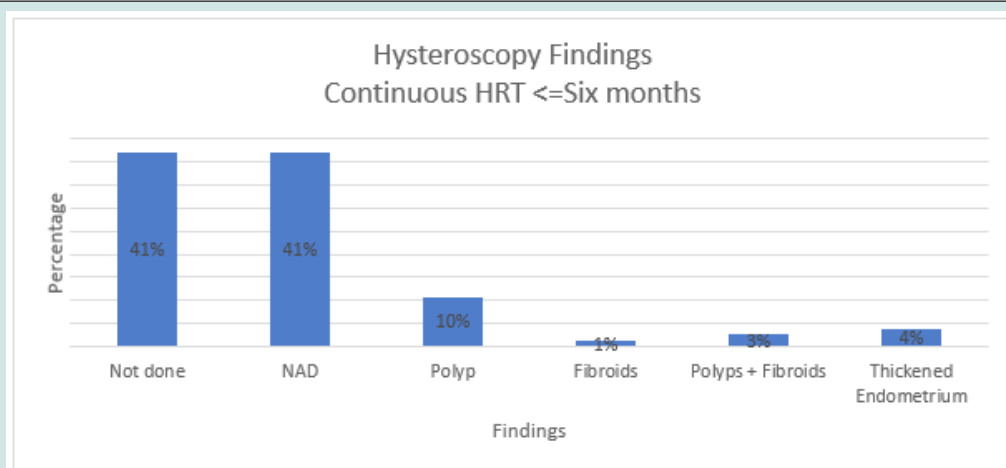
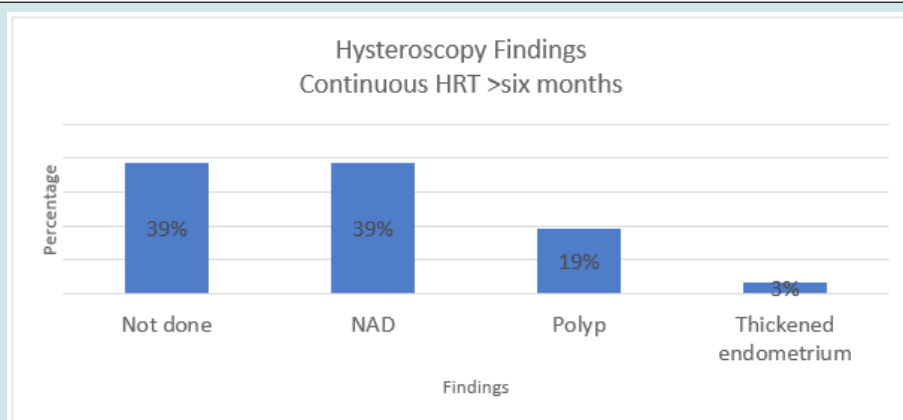
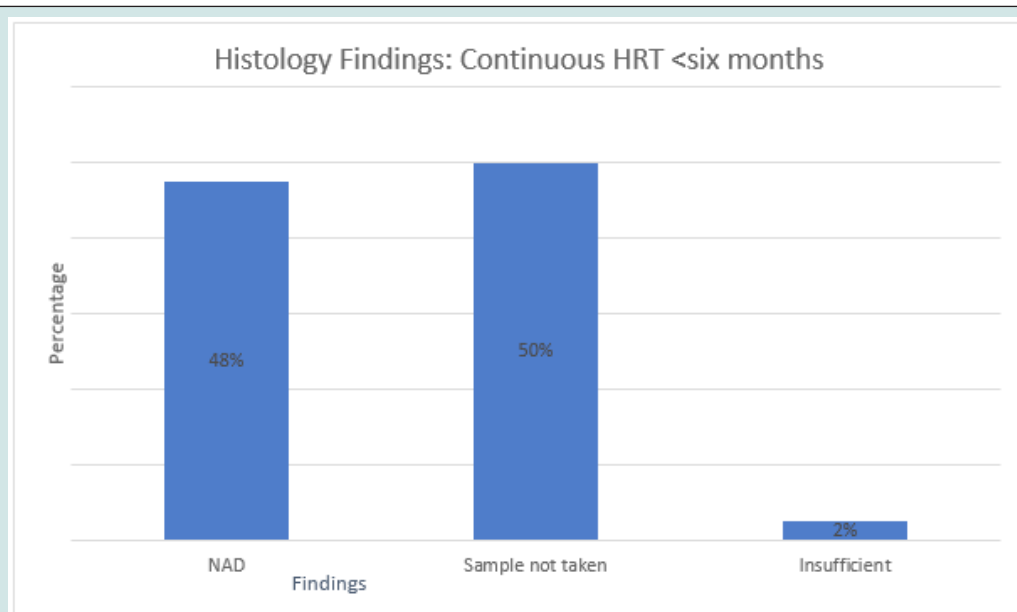


Figure 3: Hysteroscopy finding for women on HRT for six months or less.



NAD: No abnormality detected.

Figure 4: Hysteroscopy findings in women on continuous hormone replacement therapy for more than six months.



NAD: No abnormality detected.

Figure 5: Histology reports in women on continuous HRT for six months or less.

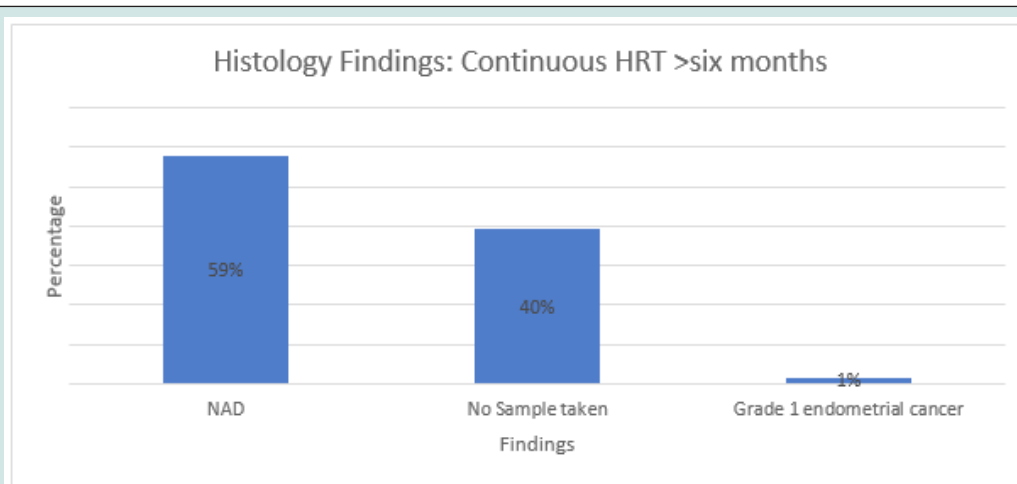


Figure 6: Histology report in women on continuous HRT for more than six months.

Discussion

Investigating and managing postmenopausal bleeding (PMB) in women using hormone replacement therapy (HRT) is a topic of considerable clinical interest and significance. This study aimed to explore the pattern of referral of women on HRT with PMB and discuss the various strategies for Investigation and management in this specific patient population. About 12.4% of all the women referred for PMB were using one form of HRT or another. This proportion suggests that many women experiencing PMB are on HRT, which indicates increasing acceptance and use of HRT [5]. While HRT may lead to harmless breakthrough bleeding or spotting caused by hormonal variations in the body, such women must be evaluated as this might be a red herring concerning endometrial pathology, including cancer and endometrial hyperplasia [1-3].

This prevalence also highlights the need for good communication between the patient and the healthcare provider. It is crucial to make the patient aware of the increased risk of unscheduled bleeding while initiating the HRT and encourage them to seek help.

The mean age from our study was 56 years, slightly higher than the 54 years reported by Hickey et al. [10]; however, it was less than 57 years of presentation reported by Lalchandani et al. [9] which is likely because the average age of menopause in the United Kingdom is 51 years. However, it ranges from 45 to 55 years [11]. The risk of developing PMB increases with age, even in women using HRT. Older women are more likely to experience malignant and premalignant endometrial pathologies, which may be independent of the HRT usage but likely associated with age-related endometrial changes, including changes in metalloproteinases which are thought to

be contributory to the pathogenesis of PMB [10,12]. Women on Sequential HRT made up 11% (16) and Continuous HRT 89% (131) but only 42.8% of patients on continuous HRT were referred after six months, while the majority (57.2%) had been on HRT for less than six months at the time of their referral. This referral pattern does not comply with the national guidance according to the National Institute of Health and care excellence, which advises that continuous HRT commonly produces irregular breakthrough bleeding or spotting in the first four to six months of treatment, and women with bleeding persisting more than six months or becoming heavier or occurring after a spell of amenorrhoea should be referred for endometrial assessment [8,13]. This is also supported by the British and Australian menopause society [5,14]. Also, most patients on continuous HRT achieve amenorrhoea within six months of use [2]. We found that a significant proportion of the referred women did not meet the threshold for such referral as defined by the guidance referred. This situation is problematic as a significant proportion of women are referred for investigations and potential treatments that they do not need, and it also leads to wastage of scarce resources. The One-stop PMB clinic (also called rapid access clinic) was designed to bridge the delays associated with the outpatient assessment of women with PMB and subsequent inpatient endometrial assessment with Hysteroscopy, and populating the clinic with inappropriate referrals defeats the essential purpose of the clinic [8]. The mean duration of HRT use among the study population was 16 months, almost half the mean reported by Hickey et al. [10] and significantly less than the 39 months reported in the series by Lanchadnia et al. [9].

This observation may be due to differences in population and geography regarding information available to the users. In the UK, the Medical and Health Regulatory Agency warns of the possible adverse effects (including cardiovascular events and increased risk of breast cancer that persists even after discontinuation) of the HRT and advice that HRT preparations should be used if necessary and for the shortest possible period to achieve symptom control. Anecdotal observation suggests a tendency for early discontinuation of HRT in the UK [15]. The findings of this study provide valuable insight into several key aspects related to PMB in women on HRT. Firstly, it is essential to acknowledge that HRT can contribute to the occurrence of PMB, especially during the initial stages of treatment. The exogenous hormones introduced through HRT can influence the endometrium, potentially causing breakthrough bleeding or even endometrial hyperplasia. Therefore, women undergoing HRT should be informed about the possibility of PMB and the need for prompt evaluation if such bleeding occurs. In terms of Investigation, our study underscores the importance of a comprehensive diagnostic approach when evaluating PMB in women using HRT. However, the ideal approach remains an issue of intense debate [6-8]. Endometrial sampling, such as Hysteroscopy and curettage or Pipelle biopsy, remains the gold standard for assessing the endometrium and ruling out endometrial cancer. Imaging techniques, such as transvaginal ultrasound, can aid in evaluating endometrial thickness and detecting structural

abnormalities. In our practice, an endometrial thickness cut of five millimeters or more is generally accepted as significant and will trigger a Hysteroscopy and endometrial biopsy [1-8].

Interestingly, most of the patients evaluated in our population had benign pathologies. The only patient diagnosed with endometrial cancer had used HRT for over three years, underscoring the need to defer the referral of women with minimal PMB within the first six months of initiating the therapy, as the cause is not usually due to a sinister pathology. The management of PMB in women on HRT necessitates a tailored approach, considering individual patient characteristics, symptoms, risk factors, and underlying pathology. For women with breakthrough or short-term irregular bleeding, reassurance and continuation of HRT with close monitoring may be appropriate, as these symptoms often subside with time. The NICE guidance, however, recommends stopping the HRT for six weeks [13]. However, persistent or heavy bleeding requires further intervention. In such cases, adjusting the HRT regimen, such as altering the hormone dose, route of administration, or type of hormone, may help alleviate symptoms and reduce bleeding [2,5,13]. Surgical interventions, such as hysteroscopic endometrial ablation or hysterectomy, may be necessary for women with refractory PMB or those with significant risk factors for endometrial disease, such as endometrial hyperplasia or cancer. The decision for surgical intervention should be made individually, considering the patient's desire, overall health, and available resources. It is essential to acknowledge the limitations of this study. The findings are based on retrospective data and small sample size. Additionally, the study focused on general recommendations. It did not delve into specific patient scenarios or address the impact of other factors, such as comorbidities or concurrent medication use, which may influence the management approach.

Conclusion

In conclusion, the study revealed that PMB occurs in a significant proportion of women on HRT, with a higher frequency observed in those receiving combined estrogen-progestogen therapy compared to estrogen-only therapy. The findings of this study contribute to the existing knowledge base and provide valuable insights for healthcare providers. By understanding the relationship between HRT and PMB, employing appropriate diagnostic investigations, and adopting tailored management strategies, clinicians can effectively address PMB in women on HRT, ensuring personalized care and optimal use of scarce resources.

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Conflict of Interest

There is no conflict of interest.

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Data Sharing Statement

Anonymized data sets used and analyzed during the current study are available upon reasonable request.

Contribution to authorship

JM, WO, MM, MA Conceived the study and collected data. JM, WO, OA, OC, UD, NE, OCB, GU, MA, MM, and OC reviewed the literature, and wrote the manuscript. JM, WO, OCB, GU, OA, OC, UD, NE, MM, MA and OC reviewed the literature, contributed to the manuscript writing, and reviewed the final draft. All the authors reviewed the final manuscript, approved it and consented to publication.

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