Original Research Report

CLINICOPATHOLOGICAL ANALYSIS OF POSTMENOPAUSAL BLEEDING AND ENDOMETRIUM

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ABSTRACT

Bleeding from the genital organ after a year of menopause is called postmenopausal bleeding. The causes may be either benign or malignant, originating from genital (uterine or extrauterine) and extragenital sites. About 3% of postmenopausal women suffer from uterine cancer. This present study aimed to analyze the clinical significance of postmenopausal bleeding concerning the source, associated risk factors, and various endometrial pathologies, including malignant and premalignant conditions. This retrospective study was conducted over four years and featured postmenopausal bleeding patients who met the inclusion criteria. Different causes of bleeding were noted and managed. Data collection on the history, clinical examination, blood test, and endometrial biopsy was performed on women with endometrial bleeding. The collected data were analyzed using standard descriptive statistics and presented using frequency tables. A total of 88 women were admitted, of whom 73 (82.95%) had endometrial bleeding and 15 (17.05%) experienced bleeding from other sites. The endometrial bleeding group mostly consisted of women aged >50–60 years (45.20%). Hypertension (26.03%), diabetes (21.91%), obesity (43.83%), and nulliparous (5.48%) were the risk factors present among the patients. The majority of the patients (41.10%) were within five years of menopause. The transvaginal ultrasound findings indicated that 56.16% of the women had an endometrial thickness of >10 mm, while 9.59% had an endometrial thickness of ≤4 mm. Upon histological investigation, endometrial hyperplasia (34.24%), atrophy (38.36%), and cancer (4.11%) were detected. Furthermore, a prevalence of 16.44% was identified as proliferative endometrium, whereas polyps were found in 6.84% of cases. In conclusion, postmenopausal bleeding is mostly benign, but it may raise concerns about the possibility of malignancy, which can be distressing for women. Disregarding the amount and frequency, postmenopausal bleeding requires a thorough evaluation, primarily because adequate management can prevent the progression of many premalignant cases to be endometrial cancer.

Keywords: Postmenopausal bleeding; transvaginal scanning; endometrial thickness; histopathology; cancer

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Highlights:
1. Malignancies in postmenopausal bleeding are not very common, yet it is necessary to evaluate the etiology and implement appropriate treatment strategies.
2. The findings of this study highlight the need for early detection of benign, premalignant, or malignant cases to provide more effective management, prevent the development of cancer, and improve the prognosis of the condition.

INTRODUCTION

Postmenopausal bleeding is defined as genital bleeding a year after menopause, which occurs due to the loss of ovarian follicular activity. Menopause is a retrospective diagnosis for a cessation of menstruation for one year at the end of the reproductive period (Kothapally & Bhashyakarla 2013). Any bleeding from the genitals that occurs after menopause is referred to as postmenopausal bleeding. According to Ubeja & Singh (2017), postmenopausal bleeding occurs in 10% of women who have reached menopause. The bleeding may originate from the uterine, extrauterine, genital, or extragenital sites. The possible causes may include benign, premalignant, or malignant lesions in the vulva, vagina, cervix, external urethral meatus, or endometrium. Postmenopausal bleeding may occur due to the use of certain drugs (e.g., anticoagulants, estrogens, or tamoxifen) or as a result of liver cirrhosis. There may be multiple causes and lesions that are present. Nonetheless, endometrial atrophy

is the most common cause of postmenopausal bleeding related to the endometrium, but hyperplasia and polyps are also frequently observed (Gopalakrishna et al. 2022).

According to the American College of Obstetricians and Gynecologists (2018), endometrial carcinoma is present with a symptom of vaginal bleeding in 90% of postmenopausal women. Rathi et al. (2013) and Mallick et al. (2013) observed that endometrial cancer is the most common malignant cause of postmenopausal bleeding. Cases of postmenopausal bleeding resulting from cancer in other parts of the genital tract are less prevalent in comparison to those caused by endometrial cancer. Patients may have a better prognosis when they seek medical consultation for postmenopausal bleeding in the early stages of the pathology (Breijer et al. 2016). Early detection and management of endometrial cancer result in an increased survival rate.

In a study by Mahdy et al. (2024), it was found that the lifetime risk of endometrial cancer among American women is 2.8%. Out of 100 American women, 2.8 individuals are susceptible to developing this pathology during their lives. Though this is a disease of perimenopausal and postmenopausal age, about 5% of cases occur in individuals under the age of 40. Type I endometrial cancer is associated with various risk factors, including nulliparity, late menopause (occurring after the age of 52), obesity, diabetes mellitus, hypertension, unopposed estrogenic stimulation of the endometrium, a history of tamoxifen therapy, atypical endometrial hyperplasia, and Lynch syndrome II (American Cancer Society 2019). In the absence of appropriate, acceptable, and cost-effective screening procedures, surveillance and preventive treatment may be useful in reducing the incidence of the disease.

Approximately 10% of patients with type II endometrial cancer do not exhibit the typical risk factors. However, the cancer manifests with increased aggressiveness and primarily affects post-menopausal individuals within the older age group. Abnormal per vagina (PV) bleeding in postmenopausal women is the prevailing symptom of endometrial cancer. The symptoms also include blood-stained or watery discharge, abdominal pain, and abdominal mass (Potikul et al. 2016). These symptoms are particularly prevalent in patients diagnosed with type II endometrial cancer who also have pyometra and an enlarged uterus due to cervical stenosis and pyometra. Therefore, risk assessment and thorough investigation are required to reduce the burden of common genital cancer in women. Transvaginal ultrasound and biopsy are necessary to analyze the histopathology of the endometrial lining and determine the appropriate management of postmenopausal bleeding.

Transvaginal ultrasound is a non-invasive method for measuring endometrial thickness. An endometrial thickness of ≤4 mm reduces the risk of developing endometrial cancer to 2.4%. Similarly, an endometrial thickness of ≤5 mm suggests a risk of 5% (Begum & Samal 2019). An elevated endometrial thickness is associated with an increased risk of endometrial cancer. A biopsy for histopathological analysis of the endometrium, despite being an invasive procedure, can accurately identify any abnormalities in the endometrial tissue, such as malignancy, as well as its specific type and degree of severity. Biopsy is considered the gold standard for diagnosing endometrial cancer (Otify et al. 2015).

Not all type II endometrial cancer patients exhibit an increased thickness of the endometrium. Therefore, it is recommended that women who experience repeated episodes of postmenopausal bleeding, despite having a thin endometrium, should undergo an endometrial biopsy (Goldstein 2018). A biopsy is the definitive diagnostic method, regardless of the thickness of the endometrium. Endometrial biopsy has a sensitivity of up to 98%. In cases where the patients are sensitive or have cervical stenosis, the procedure may be performed under anesthesia and with diagnostic curettage. A hysteroscopy-guided biopsy is the more preferable procedure to prevent the possibility of overlooking endometrial polyps due to the focal pathology of endometrial cancer. Irrespective of the amount or episodes of postmenopausal bleeding, it is crucial to conduct a transvaginal ultrasound, followed by an endometrial biopsy (Smith et al. 2014). This study aimed to examine the clinical significance of postmenopausal bleeding, including the bleeding source, prevailing risk factors, cancer prevalence, and different endometrial pathological findings.

MATERIALS AND METHODS

This retrospective study was carried out in the Department of Obstetrics and Gynecology of Mamata Medical College Hospital in Khammam, India, from January 2019 to December 2022. Post-menopausal women who were admitted to the hospital with complaints of per vagina bleeding were assessed with a thorough history and clinical examination to be included in the study. The inclusion criteria consisted of postmenopausal women with complaints of per vagina bleeding. The exclusion criteria involved women with premature menopause (occurred before the age of 40) or menopause induced by surgery, radiation, or

chemotherapy. This study also excluded individuals who were on hormone replacement therapy (HRT) or anticoagulant therapy, had a coagulation disorder or genital tract injuries, and refused to undergo hysteroscopy or hysterectomy despite an inadequate endometrial sample obtained from dilation and curettage (D & C) (Talari & Goyal 2020).

All the selected patients underwent several examinations, including a blood sugar test, a Papanicolaou (pap) smear, a biopsy of any genital lesions, as well as a transvaginal ultrasound. This ultrasound assessed endometrial thickness, uterine condition, and adnexal pathology. These examinations were conducted in addition to routine and relevant investigations. A biopsy was performed on the extra-endometrial lesions to detect the bleeding source and determine the necessary management to be administered. The final study population consisted of individuals experiencing endometrial bleeding who were selected for analytical purposes. The subjects were assessed based on their historical data, including age during the initial presentation of postmenopausal bleeding, age at menopause, duration since menopause, and high-risk factors for endometrial cancer (Xu et al. 2023). Relevant investigations and endometrial biopsy by dilatation and curettage were performed regardless of the endometrial thickness observed in transvaginal ultrasound.

Patients with nil or inadequate endometrial retrieval from dilatation and curettage were subjected to abdominal hysterectomy. Histopathological reports were obtained from the analysis of the examination results. The data were collected from medical records and subsequently compiled and analyzed using Microsoft Excel for Windows, version 16.0 (Microsoft Inc., Redmont, WA, USA). Standard descriptive statistics were presented using tables displaying the frequency and percentages of categorical variables (Vetter 2017). The observations and findings were critically discussed and compared with similar studies.

RESULTS

There were 88 patients admitted with postmenopausal bleeding. Among these patients, 73 women (82.95%) experienced endometrial bleeding, while 15 women (17.05%) suffered from bleeding due to extra-endometrial lesions. Among these 15 cases, eight had bleeding from a decubitus ulcer in genital prolapse, one had primary carcinoma of the vagina, four had a cervical polyp, and two had carcinoma of the cervix. Figure 1 shows the distribution of postmenopausal bleeding sources among the entire group of 88 participants.

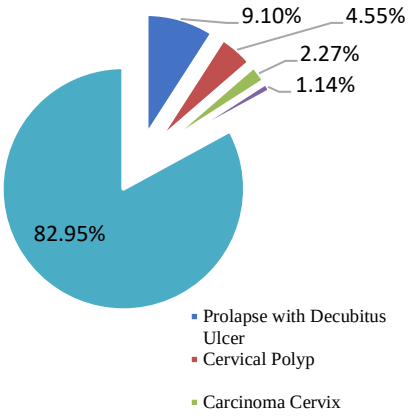

Figure 1. Sources of bleeding in postmenopausal women.

The study population consisted of women who experienced endometrial bleeding, and they were subjected to a comprehensive analysis. Table 1 presents their characteristics, including age distribution, duration after menopause, parity, and risk factors. Among the participants, 15 women (20.55%) were above 60 years of age. The age group of >50–60 years constituted the highest proportion (45.20%) across all age groups. The earliest and latest age at which menopause occurred were 41 and 56 years, respectively. The first episode of bleeding appeared within five years of menopause in 30 women (41.10%) and within 10 years of menopause in 54 women (73.98%). Only 2.73% of the participants developed postmenopausal bleeding beyond 20 years of menopause. Nulliparity was observed in 4 women (5.48%). Meanwhile, 25 women (34.25%) fell beyond the category of para 2. None of the patients had a family history of related malignancies.

Table 1. Distribution of postmenopausal patient characteristics.

Characteristics	n (n=73)	%
Age		
>40–50	25	34.25%
>50–60	33	45.20%
>60	15	20.55%
Parity		
Nulliparous	4	5.48%
≤2	44	60.27%
>2	25	34.25%
Duration after menopause (years)		
≤ 5	30	41.10%
>5–10	24	32.88%
>10–20	17	23.29%
>20	2	2.73%
Risk factors		
Hypertension	19	26.03%
Diabetes mellitus	16	21.91%
Obesity/overweight	32	43.83%

Table 2 presents the distribution of endometrial thickness among the postmenopausal patients according to the transvaginal ultrasound. An endometrial thickness of ≤4 mm was found in 7 women (9.59%), while an endometrial thickness of >10 mm was observed in 41 women (56.16%).

Table 2. Distribution of endometrial thickness among postmenopausal women.

Endometrial thickness (mm)	n (n=73)	%
≤4	7	9.59
>4–8	11	15.07
>8–10	14	19.18
>10	41	56.16

Patients who did not experience uterine bleeding and reported no intraepithelial lesions or malignancies were subjected to a pap smear. The histopathological examination of endometrium in 73 patients with post-menopausal bleeding is shown in Table 3. The results revealed that endometrial atrophy was the most common pathology, as observed in 28 women (38.36%). Endometrial hyperplasia was the second-most common pathology, occurring in 25 women (34.24%). While the prevalence of endometrial cancer was only 4.11%, as many as 12.33% of the patients exhibited complex hyperplasia, with 5.48% of the cases also accompanied by atypia.

Table 3. Endometrial histopathological reports.

Endometrial pathology	n (n=73)	%
Simple hyperplasia without atypia	16	21.91
Complex hyperplasia without atypia	5	6.85
Complex hyperplasia with atypia	4	5.48
Endometrial atrophy	28	38.36
Proliferative endometrium	12	16.44
Polyp	5	6.84
Carcinoma	3	4.11

DISCUSSION

Postmenopausal bleeding in patients who are not on hormone replacement therapy, regardless of the amount and frequency, should be considered abnormal and thoroughly evaluated to rule out any possible presence of malignancy. Postmenopausal bleeding becomes less common as a person gets older, although the risk of developing malignancy increases with older age and a longer duration since menopause. The incidence of endometrial cancer in individuals experiencing postmenopausal bleeding was estimated to range from 1% at the age of 50 years to 25% at the age of 80 years (Singh et al. 2016). The risk of cancer increases as the age of women experiencing postmenopausal bleeding advances.

The present study found that postmenopausal bleeding was most common in the age group of >50–60 years, with a prevalence rate of 45.20%. Furthermore, the prevalence rate of post-menopausal bleeding among individuals aged over 60 years was found to be 20.55%. The findings of this study aligned with the results of prior studies by Agrawal et al. (2018) and Rita et al. (2016). In the two studies, the prevalence rates of postmenopausal bleeding in women aged >50–60 years were found to vary between 48% and 67%. Meanwhile, among women over 60, the estimated prevalence rates ranged from 16% to 24%. The majority (41.1%) of the patients who reported postmenopausal bleeding in this study were women who had been menopausal for 5 years or less. In prior research, the same group was identified as constituting the largest proportion of postmenopausal bleeding cases, with prevalence rates of 55.33% and 68.75% (Agrawal et al. 2018, Sharma & Yerrapragada 2022).

In this study, the percentage of nulliparous women was 5.48%, whereas women with a parity of more than two accounted for 34.25% of the total cases. These findings aligned with a previous investigation that demonstrated a prevalence of 2.24% of nulliparous women among the research subjects (Gopalakrishna et al. 2022). Previous studies by Kothapally & Bhashyakarla (2013) and Sravanthi (2020) reported higher prevalence rates of nulliparous women of 6.7% and 11%, respectively. These two studies further showed that women with a parity of more than two constituted 90% and 66% of the overall research subjects, respectively.

The transvaginal ultrasound in this study revealed that 9.59% of the participants had an endometrial thickness of ≤4 mm. Although they were at a lesser risk of developing malignancies, the possibility could not be ruled out completely as the participants with endometrial cancer exhibited a thin endometrium. A majority (56.16%) of the participants had an endometrial thickness of >10 mm, indicating a higher risk of malignancy. The investigations conducted by Agrawal et al. (2018) and Rita et al. (2016) reported prevalence rates of endometrial thickness of ≤5 mm as 44.87% and 52%, respectively. Furthermore, the two studies found that the prevalence rates of endometrial thickness exceeding 10 mm were 30.77% and 90%, respectively.

The present study found that diabetes mellitus, hypertension, and obesity were present as risk factors for endometrial cancer in 21.91%, 26.03%, and 43.84% of the cases, respectively. In a prior

study, it was found that the three risk factors were observed in 21.34%, 40.44%, and 22.47% of the cases, respectively (Gopalakrishna et al. 2022). Similarly, a study conducted by Muzaffar & Maraj-ud-din (2020) showed the prevalence rates for the three risk factors were 16%, 34.6%, and 39.9%, respectively. Asymptomatic women with any risk factor for endometrial cancer require a rigorous examination. This is corroborated by the findings of a systematic review and meta-analysis conducted by Su et al. (2021).

Sur & Chakravorty (2016) emphasized the importance of a comprehensive investigation to rule out the possibility of endometrial cancer and hyperplasia as the precursors of lesions that cause postmenopausal bleeding. This study revealed that 38.36% of the cases exhibited endometrial atrophy in the histopathological examination. The examination also identified various forms of hyperplasia in 34.24% of the cases, including simple hyperplasia without atypia (21.1%), complex hyperplasia with atypia (5.48%), and complex hyperplasia without atypia (6.85%).

Table 4 demonstrates the consistent identification of endometrial atrophy as the primary cause of postmenopausal bleeding originating from the endometrium across numerous studies. The present study excluded cases without definitive endometrial histopathological examination reports, as noted in the research methodology, unlike numerous other studies that presented inconclusive findings. This study observed a prevalence of 4.11% for endometrial cancer. According to a study conducted by Muzaffar & Maraj-ud-din (2020), endometrial hyperplasia was identified as the most common pathology, with a prevalence rate of 4%. Table 4 presents a comparison between the findings of the present study and those of various prior studies conducted using histopathological examination reports. The outcomes of various studies exhibited variations resulting from different degrees of data availability regarding patient characteristics and risk factors. However, both the present and prior studies have established either endometrial atrophy or hyperplasia as the major contributing factors to postmenopausal bleeding.

Table 4. Comparison of research findings from numerous studies on endometrial histology.

Studies	Endometrial hyperplasia (%)	Endometrial atrophy (%)	Polyp (%)	Proliferative endometrium (%)	Endometrial cancer (%)
Present study	34.24	38.36	6.84	16.44	4.11
Gopalakrishna et al. (2022)	23.52	35.95	11.2	16.8	6.7
Rita et al. (2016)	40	31	5	13	6
Sharma & Yerrapragada (2022)	47.5	33.75	3.75	11.95	2.5
Sravanthi (2020)	19	13	04	22	11
Nirupama et al. (2013)	18	11	8	14	12
Singh et al. (2017)	6	18	3	2	7
Walke et al. (2020)	12.49	37.5	06.25	16.07	5.35

Strength and limitations

This study successfully detected numerous premalignant cases during the evaluation and effectively prevented the occurrence of endometrial cancer with appropriate management in post-menopausal women. However, this study had a limited number of cases as it was conducted during a time period when the COVID-19 pandemic happened. In addition, multiple cases were managed on an outpatient basis, which could potentially be overlooked when collecting data from the medical records. Inadequate data on the risk factors might also result in an inability to analyze the correlation between premalignant and malignant cases. A prospective study with a larger sample size would be a more optimal approach to accomplishing the objective.

CONCLUSION

Most cases of postmenopausal bleeding result from benign causes. However, premalignant cases, particularly in the presence of atypical endometrial hyperplasia, possibly exist due to the potential development of endometrial cancer in one-third of cases. The population of post-menopausal women grows with increasing life expectancy, which leads to an increase in the incidence of postmenopausal bleeding and its underlying causes. This becomes an inconvenience for women, and the most horrific part is the fear of developing cancer. Therefore, it is imperative to conduct a comprehensive evaluation and swiftly manage postmenopausal bleeding to ensure an optimal prognosis. Women with a high risk for postmenopausal bleeding, regardless of the endometrial thickness, should undergo endometrial biopsy. It is recommended that this procedure be performed along with a hysteroscopy. A careful follow-up is crucial for investigating negative endometrial samples. If

recurrent or persistent bleeding occurs, it is recommended to perform a hysterectomy and histopathological examination to stop the bleeding and prevent the possibility of malignancy.

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Conflict of interest

None.

Ethical consideration

The Institutional Ethics Committee of Mamata Medical College, Khammam, India, affiliated with Kaloji Narayana Rao (KNR) University of Health Sciences, Warangal, India, issued the approval for this study (No. MMC/IEC/2022/2945/111/2023 dated 30/09/2023).

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Author contribution

BMH contributed to the conception and design, analysis and interpretation of the data, and drafting of the article. KB carried out a critical revision of the article for important intellectual content. GL contributed to the provision of study materials and statistical expertise. NM provided administrative and technical support along with the collection and assembly of the data. Both BMH and KB approved of the final version of the article.

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