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Original Research Article

Study of etiologies of postmenopausal bleeding by cytology and histopathological examination

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ABSTRACT

Background: Postmenopausal bleeding (PMB) is a common gynecologic complaint with a wide range of benign and malignant etiologies. While atrophic changes are the most frequent benign causes, PMB may also be the earliest sign of gynecological malignancies such as cervical and endometrial cancer, particularly in low-resource settings where screening uptake is low. Aim lies to determine the etiologies of PMB using cytological and histopathological evaluation and identify the most common associated factors, particularly those indicating malignant potential.
Methods: A hospital-based cross-sectional study was conducted at Rajendra institute of medical sciences (RIMS), Ranchi, from April 2021 to August 2022. A total of 76 postmenopausal women presenting with vaginal bleeding were included. Detailed histories, clinical examinations, pap smear, transvaginal ultrasonography (TVS), and endometrial or cervical biopsies were performed. Histopathological findings were considered the definitive diagnosis. Data were analyzed using SPSS version 23.0, and associations were tested using chi square test and odds ratios (ORs) with 95% confidence intervals (CIs); a $p<0.05$ was considered significant.
Results: The most common age group affected was 51-60 years (47.4%). Histopathological diagnoses revealed cervical cancer in 30.3% of cases, followed by atrophic endometrium (23.7%), cervical intraepithelial neoplasia (CIN) (23.7%), endometrial hyperplasia (10.5%), and endometrial cancer (6.6%). A significant association was found between low socioeconomic status and cervical cancer ($p=0.03$, OR=4.33). Early childbirth (≤19 years) was significantly associated with CIN ($p=0.03$, OR=3.14). Parity of 0-4 was associated with endometrial hyperplasia ($p=0.03$). Pap smear results correlated well with histopathological findings in high-grade lesions and malignancies.
Conclusions: Cervical cancer remains the leading malignant cause of PMB, especially among women of low socioeconomic background. Atrophy and endometrial hyperplasia are significant benign causes. Cytology and histopathological examination remain essential tools for evaluating PMB, particularly in resource-limited settings.

Keywords: Postmenopausal bleeding, Cervical cancer, Endometrial hyperplasia, Cytology, Histopathology

INTRODUCTION

Postmenopausal bleeding (PMB) is defined as any uterine bleeding occurring after 12 consecutive months of amenorrhea in a woman of menopausal age, and it constitutes one of the most common gynecologic complaints among postmenopausal women.[1] Although PMB can be caused by benign conditions such as endometrial or vaginal atrophy, polyps, or hormone replacement therapy, it remains a key warning sign of malignancy, particularly endometrial and cervical cancers. Studies estimate that approximately 10-15% of women presenting with PMB are found to have an underlying

endometrial carcinoma, making timely investigation vital for early detection and improved prognosis.[2,3]

The global burden of gynecologic malignancies is particularly significant in low-and middle-income countries, including India, where limited access to healthcare services, delayed diagnosis, and inadequate screening programs contribute to poor outcomes.[4] According to the GLOBOCAN 2020 data, cervical cancer remains the second most common cancer among women in India, accounting for over 9% of all female cancer cases, despite being largely preventable through early detection and vaccination.[5] Endometrial cancer, while more common in high-income countries, is also rising in developing nations due to increased life expectancy and prevalence of obesity, diabetes, and hypertension, recognized risk factors associated with unopposed estrogen exposure.[6]

Aging and hormonal changes in postmenopausal women result in structural and functional alterations in the reproductive tract, making them susceptible to various pathological conditions. The endometrial lining thins due to hypoestrogenism, predisposing women to atrophic endometritis or vaginitis, which accounts for a significant proportion of PMB cases.[7] However, distinguishing benign from malignant causes cannot be reliably done through clinical presentation alone; hence, cytological assessment (Pap smear) and histopathological examination of endometrial or cervical tissue remain the gold standards for evaluation.[8]

Recent advancements in diagnostic imaging (e. g., TVS) and molecular testing (e.g., HPV DNA typing) have further enhanced the detection of pre-invasive lesions, especially CIN.[9] Nevertheless, in resource-limited settings, reliance on basic yet effective tools such as cytology and biopsy remain essential. To determine the etiologies of PMB using cytological and histopathological evaluation and identify the most common associated factors, particularly those indicating malignant potential.

METHODS

Study design

This study was a cross-sectional, observational, hospital-based original research investigation.

Study setting

The research was conducted at the department of obstetrics and gynecology, Rajendra institute of medical sciences (RIMS), Ranchi, Jharkhand, India. The study duration extended from April 2021 to August 2022.

Study participants

A total of 76 postmenopausal women who presented with vaginal bleeding were included in this study. All patients were selected consecutively from those attending the gynecology outpatient department (GOPD) of RIMS during the study period.

Inclusion and exclusion criteria

Women who were amenorrheic for at least 12 consecutive months, signifying natural menopause, and those presenting with PMB who provided informed written consent for participation and follow-up investigations were included. Women with surgical menopause (e. g., bilateral oophorectomy or hysterectomy), those who experienced premature menopause before age 40, women presenting with perimenopausal or irregular bleeding not qualifying as PMB, and those unwilling or unable to provide consent were excluded.

Bias and minimization strategy

To reduce selection bias, random sampling was employed among eligible patients presenting during the study period. Diagnostic bias was minimized by using standardized protocols for cytology (PAP smear) and histopathological examination (endometrial biopsy or curettage), with all specimens interpreted by experienced pathologists. Inter-observer bias was reduced by double-blind analysis where feasible.

Data collection

Data were collected through a structured proforma including demographic variables (age, religion, socioeconomic status), reproductive history (parity, age at marriage and childbirth, age at menarche and menopause), medical history (hypertension, diabetes, thyroid disorders), and use of oral contraceptives. Each participant underwent clinical examination, followed by relevant investigations including Pap smear, transvaginal sonography (TVS), and endometrial sampling for histopathology.

Procedure

After obtaining informed consent, participants underwent a detailed general, systemic, and gynecological examination.

Cytology: Pap smear was performed using a spatula and endocervical brush technique, and slides were fixed and stained using the papanicolaou method.

Histopathology: Endometrial sampling was done via curettage or biopsy depending on clinical indications. Samples were fixed in 10% formalin and processed for routine histopathological examination.

Diagnostic confirmation: Histopathological examination (HPE) findings were considered the gold standard for final diagnosis.

Statistical analysis

Data were compiled and analyzed using IBM SPSS statistics software, version 23.0. Descriptive statistics such as mean, standard deviation, frequency, and percentage were calculated. The chi-square test was used to determine associations between categorical variables. OR with 95% CI were computed to estimate the strength of associations. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 76 postmenopausal women presenting with bleeding per vaginum were enrolled in the study conducted between April 2021 and August 2022 at RIMS, Ranchi.

Sociodemographic characteristics

The majority of patients were in the age group of 51-60 years, accounting for nearly half of the study population. This observation indicates that PMB is more commonly encountered in early postmenopausal years, as reflected in Table 1. In terms of parity distribution, most patients were multiparous, with a large proportion having three or more children. Specifically, women with para 3-4 and para ≥5 represented an equal and dominant share of the cohort. This high parity rate is noteworthy given its established association with increased risk for certain gynecologic malignancies, especially cervical cancer (Table 2).

Table 1: Age distribution of patients.

Age group (in years)	N	Percentage (%)
41-50	21	27.6
51-60	36	47.4
61-70	17	22.4
71-80	2	2.6
Total	76	100

Table 2: Parity of patients.

Parity	N	Percentage (%)
Para 1-2	8	10.5
Para 3-4	34	44.8
Para ≥5	34	44.8

Etiological distribution based on histopathological examination

Cervical cancer emerged as the most frequent cause of PMB in this study, accounting for 30.3% of all cases. This was closely followed by atrophic changes of the endometrium or vagina and CIN, each contributing 23.7% of the cases. Endometrial carcinoma and hyperplasia, although less frequent, still constituted notable etiologies. Other benign causes such as polyps and fibroids were relatively rare. These findings are detailed in Table 3. Overall, malignant lesions, when combining cervical and endometrial cancer, accounted for 36.9% of the cases.

Table 3: Causes of PMB.

Etiology	N	Percentage (%)
Atrophic endometrium/ vagina	18	23.7
Endometrial hyperplasia	8	10.5
Endometrial carcinoma	5	6.6
CIN	18	23.7
Cervical cancer	23	30.3
Endometrial polyp	2	2.6
Others (fibroid and benign)	2	2.6
Total	76	100

Statistical associations with key variables

A statistically significant association was identified between low socioeconomic status and the occurrence of cervical cancer. Patients from lower socioeconomic backgrounds were found to be over four times more likely to develop cervical cancer compared to their counterparts from middle or high socioeconomic strata, as indicated in Table 4. Similarly, a significant correlation was found between early age at first childbirth (≤19 years) and the incidence of CIN. This reinforces established understanding of early sexual and reproductive activity as risk factor for cervical dysplasia and malignancy (Table 5).

Table 4: Association of socioeconomic status with cervical cancer.

Socioeconomic status	Cervical cancer, (n=23)	Percentage (%)
Low	18	78.3
Middle and high	5	21.7
P=0.03	OR=4.33	95% CI=1.59-11.7

Table 5: Association of age at first childbirth with CIN.

Age at first childbirth, (in years)	CIN, (n=18)	Percentage (%)
≤19	9	50
≥20	9	50
P=0.03	OR=3.14	95% CI=1.04-9.46

Cytological findings and correlation with histopathology

Pap smear cytology was evaluated for 60 of the 76 patients, with a strong correlation observed between cytological findings and final histopathological diagnosis. Inflammatory smears generally corresponded with benign or atrophic changes, whereas high-grade lesions such as HSIL and smears suggestive of malignancy correlated well with confirmed diagnoses of CIN or carcinoma. These findings validate the utility of pap smear as an effective initial screening tool for high-grade cervical lesions, as demonstrated in Table 6.

Table 6: Pap smear cytology versus histopathological correlation.

Pap smear result	Corresponding histopathological diagnosis	Cases
Inflammatory	Benign/atrophic	20
ASCUS/ LSIL	CIN	12
HSIL	CIN/ carcinoma	10
Suggestive of malignancy	Carcinoma	18
Total		60

Comorbidities among study participants

Hypertension was the most prevalent comorbidity, affecting approximately one-third of the patients. This was followed by coexistent diabetes and hypertension, and hypothyroidism. A similar proportion of patients had no comorbidities. The presence of such comorbid conditions, particularly hypertension, is of interest due to its known links with endometrial pathology. The distribution of comorbidities is outlined in Table 7.

Table 7: Distribution of comorbidities.

Comorbidity	N	Percentage (%)
Hypertension	25	32.9
Diabetes mellitus + HTN	8	10.5
Hypothyroidism	8	10.5
No comorbidity	25	32.9
Others	10	13.2

Summary of key statistical outcomes

A summary analysis revealed several significant associations. Low socioeconomic status was strongly linked to cervical cancer (p=0.03, OR=4.33). Endometrial hyperplasia showed a notable association with lower parity (para 0-4), although OR was close to 1 (OR=0.88). Early age at first childbirth (≤19 years) was significantly associated with CIN (p=0.03, OR=3.14). Other factors such as age, religion, and use of oral contraceptive pills did not demonstrate any significant correlation with disease outcomes. These results are summarized in Table 8.

Table 8: Summary of key statistical results.

Variables	Outcome	Significance
Low socioeconomic status	Cervical cancer	P=0.03, OR=4.33
Parity 0-4	Endometrial hyperplasia	P=0.03, OR=0.88
First childbirth ≤19 years	CIN	P=0.03, OR=3.14
Age, religion, OCP use	No significant associations	P>0.05

DISCUSSION

The study analyzed 76 cases of PMB to identify underlying causes using cytological and histopathological methods. The majority of participants (47.4%) were between 51–60 years of age, with a mean age of 56 years, indicating that PMB is most common in the early postmenopausal period. Most women (81.6%) were of Hindu religion, and over half (53.9%) belonged to the low socioeconomic class. High parity was prevalent, with 44.8% of women having five or more children, suggesting a link between multiparity and certain gynecologic pathologies.

Histopathological examination revealed that cervical cancer was the most common cause of PMB, present in 30.3% of cases, followed by atrophic endometrium or vaginal mucosa (23.7%) and CIN (23.7%). Other notable causes included endometrial hyperplasia (10.5%) and endometrial carcinoma (6.6%). Collectively, malignant lesions (cervical and endometrial cancers) accounted for over a third of all PMB cases, emphasizing the critical need for thorough evaluation in this demographic.

Statistical analysis highlighted a significant association between low socioeconomic status and cervical cancer (p=0.03; OR=4.33; 95% CI: 1.59-11.7), underlining the impact of social determinants on cancer risk. Additionally, early childbirth (≤19 years) was significantly associated with CIN (p=0.03; OR=3.14), suggesting a reproductive factor influencing premalignant cervical conditions. A significant relationship also found between parity 0-4 and endometrial hyperplasia (p=0.03), suggesting that women with fewer pregnancies may be more prone to unopposed estrogen exposure, contributing to hyperplastic changes.

Pap smear results demonstrated good correlation with histopathological findings, especially in high-grade lesions and malignancies, confirming its utility as a first-line screening tool. Most inflammatory and low-grade smears corresponded to benign pathology, while abnormal cytology such as HSIL or malignant changes aligned with histologically confirmed CIN and cervical carcinoma. In terms of comorbidities, hypertension was the most common, affecting nearly one-third of patients. Coexistent conditions such as diabetes and thyroid disorders were also noted, which may have implications for the pathophysiology or management of PMB.

Recent studies underscore the diagnostic value of combining cytological and histopathological approaches in evaluating PMB. Endometrial aspiration cytology, when correlated with histopathology, provides a reliable and minimally invasive method for screening. In a 2021 study, Ajmera et al. found that endometrial aspiration cytology achieved 100% specificity in identifying malignant lesions and 85% sensitivity in detecting benign ones, with high diagnostic accuracy.[10]

O'Flynn et al demonstrated that non-invasive cytology using urine and vaginal samples could detect endometrial

and other gynecologic cancers with a sensitivity of 91.7% and specificity of 88.8%, suggesting potential use as a triage test to reduce the need for invasive procedures.[11] Supporting this, Yang et al evaluated 570 postmenopausal women and reported that combining TVS with endometrial cytology yielded a sensitivity of 97.4% and specificity of 88.4% for diagnosing precancerous or malignant lesions.[12]

Histopathological analysis continues to be critical. Lakhey et al examined 270 biopsy samples and found endometrial hyperplasia to be the most common lesion (24.8%), while endometrial and cervical cancers were detected in 11.5% of cases, underlining the need for routine biopsy in symptomatic women.[13] Similarly, Kılıççı et al applied liquid-based cytology and reported 100% sensitivity and 96.67% specificity in postmenopausal women, showing strong reliability for cancer detection when combined with TVS.[14]

This study has certain limitations. It was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings to broader populations. Additionally, the cross-sectional design restricts the ability to establish causality between risk factors and outcomes. Selection bias might have occurred due to the hospital-based recruitment of participants. Future multi-center studies with larger sample sizes and longitudinal follow-up are recommended to validate and extend these results. The study emphasizes the necessity of a comprehensive diagnostic approach for PMB. Cervical cancer remains a leading cause, particularly in women of lower socioeconomic status.[15] Early screening, particularly through cytology and histopathological confirmation, is crucial to differentiate between benign and malignant causes and initiate timely intervention.

CONCLUSION

In this hospital-based study, cervical cancer emerged as the most common malignant cause of PMB, particularly among women from lower socioeconomic backgrounds, while atrophic changes and endometrial hyperplasia were significant benign causes. The strong correlation between cytological and histopathological findings underscores the importance of integrating both approaches for accurate diagnosis and timely intervention. By highlighting the role of key risk factors such as low socioeconomic status, high parity, and early childbirth, this study contributes valuable insights into the epidemiology of PMB in resource-limited settings. These findings emphasize the need for enhanced screening programs, patient education, and targeted preventive strategies to improve early detection and reduce the burden of gynecological malignancies among postmenopausal women.

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