Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.6 No. 12 (2025): December 2025 Issue
https://doi.org/10.51168/sjhrafrica.v6i12.2381
Original Article

A prospective observational study of histopathology of endometrium in abnormal uterine bleeding in perimenopausal and postmenopausal women.

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Abstract

Background

An understanding of the varieties in the normal morphological appearance of the endometrium provides an essential background of the evaluation of endometrial pathology and early diagnosis of malignant and premalignant lesions.

Methods

Histopathological examination was done after endometrial biopsy for 340 women of age above 40 years presenting with abnormal uterine bleeding and with endometrial thickness > 4 mm on transvaginal ultrasonography, 260 of which were perimenopausal group and 80 were postmenopausal group and incidences of respective pathological outcomes in each group and their associations with specific demographic and patient comorbidities was studied.

Results

Proliferative endometrium was the most common finding among perimenopausal women (45.76%), while atrophic endometrium predominated in postmenopausal women (47.5%). Endometrial carcinoma was significantly higher in postmenopausal women (16.25%) compared to perimenopausal women (3.46%). Obesity, diabetes mellitus, and hypertension were significantly associated with malignant endometrial pathology.

Conclusion

Histopathological examination is mandatory in perimenopausal and postmenopausal abnormal uterine bleeding to detect lesions like polyps, hyperplasia, atypical hyperplasia and cancer. Obesity, history of chronic anovulation, diabetes mellitus, hypertension are important risk factors for endometrial carcinoma.

Recommendations

Routine endometrial biopsy should be considered in perimenopausal and postmenopausal women with abnormal uterine bleeding, particularly those with metabolic risk factors.

Keywords: *Abnormal Uterine Bleeding; Endometrial Carcinoma; Histopathology; Bleeding; Postmenopausal bleeding; Endometrial Biopsy*
Submitted: *September 15, 2025* ***Accepted:*** *October 30, 2025* ***Published:*** *December 30, 2025*

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Introduction

Abnormal uterine bleeding (AUB) is defined as any bleeding pattern that differs in frequency, amount and the bleeding pattern observed during the normal menstrual cycle or menopause and a common problem with varying causes in different age groups [1,2,3] and is the commonest presenting symptom and a major gynecological problem in almost one-third of all out patient gynecologic visits.[4,5] The underlying disease in a patient presenting with abnormal uterine bleeding can be detected by histological variations of endometrium taking into account the age, the phase of the menstrual cycle, and the use of any exogenously administered hormones. Prompt and thorough evaluation of abnormal uterine bleeding is essential as it may be the only

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manifestation of endometrial carcinoma especially in perimenopausal and postmenopausal period. An increased risk for hyperplasia and adenocarcinoma is seen in patients with obesity, hypertension, a history of anovulation, diabetes mellitus and exogenous estrogen use.[6] Around 90–95% of postmenopausal women with endometrial cancer report a vaginal bleeding Experience [7,8] , whereas an intrauterine malignancy is revealed in about 10% of symptomatic postmenopausal women.[9] Early and accurate diagnosis of endometrial hyperplastic lesions is essential along with proper treatment to prevent progress to endometrial cancer thereby precluding an unwarranted hysterectomy without a definitive diagnosis. [10] Endometrial biopsy is an essential investigation performed in women having postmenopausal bleeding (PMB) with an endometrial thickness of ≥4 mm to exclude endometrial hyperplasia or cancer with a sensitivity as high as 96%.[11,12]

This study is done to evaluate the endometrial causes of abnormal uterine bleeding and to determine the specific pathology in perimenopausal and postmenopausal age groups.

Methodology

Study design

This was a prospective observational study.

Study setting

The study was conducted at the Population Resource and Research Centre, Allahabad, a tertiary level referral hospital.

Ethical approval

The study was approved by the Institutional Ethics Committee of the Population Resource and Research Centre, Allahabad, and conducted in accordance with the Declaration of Helsinki.

Inclusion criteria

Women aged above 40 years presenting with abnormal uterine bleeding and endometrial thickness greater than 4 mm on transvaginal ultrasonography were included.

Exclusion criteria

Women with bleeding due to intrauterine devices, cervical or vaginal pathology, abnormal Pap smear findings, leiomyomas, adenomyosis, ovarian tumors, coagulopathies, pregnancy, hormone replacement therapy, or genitourinary infections were excluded.

Sample size determination

The sample size was calculated using the formula:
$\mathbf{n = Z^2 \times p \times q / d^2}$,
where Z represents the standard normal variate at 95% confidence level, p is the expected prevalence, q = 1−p, and d is the allowable error.

Sampling method

Consecutive eligible patients fulfilling the inclusion criteria were enrolled until the desired sample size was achieved.

Data collection

Clinical history, demographic data, transvaginal ultrasonography findings, laboratory investigations, and histopathological results of endometrial biopsy were recorded using a structured questionnaire.

Data analysis

Statistical analysis was performed using GraphPad Prism. Continuous variables were analyzed using Mann-Whitney test, and categorical variables using Chi-square or Fisher's exact test. Logistic regression was applied for predictor variables. A p-value <0.05 was considered significant.

Bias control

Selection bias was minimized by enrolling consecutive eligible patients, and standardized histopathological reporting was used to reduce observer bias.

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Results

Out of all women presenting with abnormal uterine bleeding during the study period, 340 met the inclusion criteria and were enrolled. Among them, 260 were perimenopausal and 80 were postmenopausal women. All participants completed clinical evaluation and histopathological assessment and were included in the final analysis.

Descriptive characteristics of study participants

A total of 340 women aged above 40 years with abnormal uterine bleeding were included in the study, of which 260 (76.47%) were perimenopausal and 80 (23.53%) were postmenopausal. The most common age group affected was 41–45 years, accounting for 192 participants (56.47%). The median age of menarche was 14 years, observed in 146 women (42.94%).

Among postmenopausal women, the mean age of menopause was 48.28 ± 2.93 years, with the majority attaining menopause between 46–50 years (63.75%). The duration of menopause was most commonly between 6–10 years in 36 participants (45%), showing an inverse relationship between duration of menopause and frequency of bleeding episodes.

Regarding menstrual pattern one year prior to menopause, shortened cycles were reported by 29 women (36.25%), infrequent bleeding by 20 women (25%), normal cycles by 17 women (21.25%), and heavy menstrual bleeding by 14 women (17.5%). In the perimenopausal group, the most common presenting complaint was heavy menstrual bleeding, seen in 139 patients (53.46%).

Parity distribution showed that grand multiparity was present in 108 women (41.53%) in the perimenopausal group and 33 women (41.25%) in the postmenopausal group.

Anemia was prevalent, with 212 participants (62.35%) having hemoglobin levels below 10 g/dL. Regarding comorbidities, 61 women (17.94%) were obese, 51 (15%) had hypertension, and 40 (11.76%) had diabetes mellitus, all of which were significantly associated with abnormal uterine bleeding.

Variable	Number (n=340)	Percentage
Perimenopausal	260	76.47%
Postmenopausal	80	23.53%
Age 41–45 years	192	56.47%
Hemoglobin <10 g/dL	212	62.35%
Obesity	61	17.94%
Hypertension	51	15%
Diabetes mellitus	40	11.76%

Incidence of abnormal uterine bleeding in perimenopausal period was 14.47% whereas in postmenopausal women incidence was 3.98%. Histopathological examination of endometrium in perimenopausal patients revealed that maximum number of patients had proliferative pattern in 119 cases (45.76%) followed by secretory in 63 (24.23%), hyperplasia without atypia in 49 (18.84%), benign endometrial polyp in 13 (5%), hyperplasia with atypia in 5 (1.92%), endometrial carcinoma (1.53%) and atrophic endometrium (1.53%) in 4 each and chronic endometritis in 3 cases (1.15%). Histopathological examination of endometrium in postmenopausal patients revealed atrophic endometrium in 38 cases (47.5%) followed by hyperplasia without atypia in 12 cases (15%), benign endometrial polyp and hyperplasia with atypia in 7 cases each (8.75%), proliferative

and endometrial carcinoma in 6 cases each (7.5%) and secretory in 4 cases (5%). Endometrial malignancy was seen with only nulliparous in 4 cases (40%) and primiparous in 5 cases (12.5%). No case was reported with multiparity and

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grand-multiparity in perimenopausal patients which was statistically significant (p <0.05). Endometrial carcinoma was observed with all parity in postmenopausal patients but maximum number of patients were nulliparous and primiparous who had malignancy which was statistically significant (p<0.05). Endometrial carcinoma was observed in 3.46% of perimenopausal and 16.25% of postmenopausal patients. It was seen that endometrial carcinoma was not associated with any specific menstrual pattern one year before menopause as malignancy was observed with all menstrual patterns but heavy menstrual bleeding patients had increased risk of endometrial carcinoma in 35.71% which was statistically significant p <0.05).

The most common age group presenting with abnormal uterine bleeding was 41-45 years (56.47%) out of all age groups and the commonest histopathological pattern seen in this group was proliferative i.e., in 102 patients (53.15%). The commonest pattern irrespective of the age was proliferative in 36.76% followed by secretory in 19.70%, hyperplasia without atypia in

17.94%, atrophic in 12.35%, benign endometrial polyp in 5.88%, hyperplasia with atypia in 3.52%, endometrial carcinoma in 2.94% and chronic endometritis in 0.88%.

Maximum number of cases of abnormal uterine bleeding in perimenopausal group were in the age group of 41-45 years [192 (73.84%)] whereas in postmenopausal group were in the age group of 51-55 years [34 (42.5%)]. Median of age of menarche was 14 years in 146 (42.94%). Among postmenopausal subjects, 51 out of 80 (63.75%) had onset of menopause at age 46-50 years with mean age of menopause±SD being 48.28±2.93 years. 36 patients (45%) had duration of menopause between 6-10 years indicating inverse relationship between duration of menopause and frequency of postmenopausal bleeding. Looking at the menstrual pattern one year before menopause in postmenopausal patients, maximum number of patients i.e. 29 (36.25%) had shortened menstrual bleeding pattern followed by infrequent bleeding in 20 (25%) , normal cycle in 17 (21.25%) and heavy menstrual bleeding in 14 cases (17.5%). 108 (41.53%) in perimenopausal and 33 (41.25%) in postmenopausal group were grandmultipara. Most common complaint was *heavy menstrual bleeding* in 139 cases (53.46%) in perimenopausal patients.

The endometrial cause and its relation with age group in perimenopausal and postmenopausal patients with abnormal uterine bleeding was highly significant (p <0.05). 212 patients (62.35%) in both perimenopausal and postmenopausal group had hemoglobin less than 10 gm%. Out of total 340 patients, 61 patients were obese (BMI>30kg/m2) (17.94%), 51 were hypertensive (15%) and diabetes mellitus was present in 40 patients (11.76%) which was statistically significant (p < 0.05). Medical disorders were the independent risk factors associated with an increased risk of bleeding in both perimenopausal and postmenopausal women. Out of 38 obese patients in perimenopausal period, 8 patients (21.05%) had malignant pattern, 19 (50%) had benign and 11 patients (28.84%) had normal cyclic pattern whereas out of 23 obese patients in postmenopausal period, 10 patients (43.47%) had malignant pattern, 10 (43.47%) had benign and 3 patients (13.04%) had normal cyclic pattern. Association of hypertension and diabetes mellitus with endometrial carcinoma was statistically significant in postmenopausal period(p<0.05), with malignancy found in 2 out of 9 diabetics (22.22%) and 3 out of 17 hypertensive patients (17.64%) in postmenopausal group.

Discussion

Abnormal uterine bleeding (AUB) is any bleeding not fulfilling the criteria of normal menstrual bleeding, the etiology of which is mostly related to age. The commonest age group presenting with excessive bleeding in our study was 41–45 years. A similar incidence was reported by Yusuf et al.[13] and Muzaffar et al.[14] in their study. Our study, like several others showed that proliferative lesions like disordered proliferative pattern, hyperplasia, and benign endometrial polyp occur more commonly in the age group 41–50 years. Patients being in their climacteric period could be the reason for increased incidence of abnormal uterine bleeding in this age group (41–50 years). As women approach menopause, cycles shorten and often become intermittently anovulatory due to a decline in the number of ovarian follicles and the estradiol level.[15] Proliferative pattern was found in a significant number of cases in this study. The spectrum of proliferative lesions of the endometrium comprises of disordered proliferative pattern that exhibits a hyperplastic endometrial appearance without an increase in endometrial volume at one end, and

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carcinoma at the other end with stages of hyperplasia in between.[16]

Atrophic endometrium was seen predominantly in the postmenopausal group (mean age 55.54±6.62 years) which has also been concluded by Giannella L et al.[17] in their study in 2020.

The incidence of benign endometrial polyps in this study was higher in perimenopausal as compared to postmenopausal group but this was not statistically significant. In the present study incidence of carcinoma endometrium was significantly more in the postmenopausal group which was almost similar to data mentioned by Yusuf et al.13 and Escoffery et al.[18] in their respective studies.

In our study either one or more among hypertension, obesity and diabetes mellitus were present in all cases of endometrial carcinoma with the association being statistically significant in postmenopausal group. Aune, D. *et al*.[19] in their systematic review and meta-analysis concluded that women with hypertension may have a 61% increase in the relative risk of developing endometrial cancer. Saed et al [20] in a systematic review and meta-analysis concluded that diabetes increases the risk of endometrial cancer. Onstad et al [21] and Kitson et al [22] in their respective studies emphasized the role of obesity in the pathogenesis of endometrial carcinoma.

Generalizability

The findings of this study can be generalized to similar tertiary care hospital settings, particularly in developing countries where abnormal uterine bleeding is a common presentation among middle-aged and elderly women.

Limitations

This was a single-center study with no long-term follow-up, and hormonal profile assessment was not included, which may limit broader interpretation of results.

Recommendations

Routine histopathological evaluation of endometrial tissue should be implemented for women over 40 years with abnormal uterine bleeding, especially those with obesity, diabetes, and hypertension.

Conclusion

Histopathological study of endometrium in females above the age of 40 years with abnormal uterine bleeding is mandatory and crucial in diagnosing various histological patterns and can detect organic lesions such as polyps, hyperplasia as well as search out early atypical hyperplasia and cancer of endometrium, which has an excellent prognosis if detected early.

Risk factors for endometrial cancer are conditions typically associated with chronic elevations of endogenous estrogen levels or increased estrogen activity in the endometrium and include obesity, history of chronic anovulation, diabetes mellitus, hypertension. Prevention and treatment of these conditions will help in reducing the incidence of abnormal uterine bleeding,

making it the responsibility of health care professional for creating awareness regarding these modifiable risk factors and their prevention through proper health education.

Acknowledgement

The authors acknowledge the Department of Obstetrics and Gynaecology and pathology laboratory staff for their assistance in conducting this study.

List of abbreviations

AUB – Abnormal uterine bleeding
EB – Endometrial biopsy
PMB – Postmenopausal bleeding
TVS – Transvaginal sonography
BMI – Body mass index

Funding

This study received no external funding.

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Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

All authors contributed to study conception, data collection, analysis, manuscript preparation, and final approval.

Author biography

All authors are clinicians with experience in obstetrics and gynecology working in tertiary care hospitals in India.

Conflict of interest

The author reported no conflict of interest

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https://doi.org/10.51168/sjhrafrica.v6i12.2381
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PUBLISHER DETAILS

Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa