Section: Pathology

Original Research Article

POSTMENOPAUSAL BLEEDING AN ALARMING SYMPTOM OF ENDOMETRIAL CARCINOMA- A CLINICOPATHOLOGICAL EVALUATION AND ITS CORRELATION WITH RISK FACTORS

Anam Khan[1], Divya Bajpai[2], Nitesh Mohan[3]

[1]Assistant Professor, Department of Pathology, Rohilkhand Medical College and Hospital Bareilly, India.
[2]Assistant Professor, Department of Pathology, Rohilkhand Medical College and Hospital Bareilly, India.
[3]Professor, Department of Pathology, Rohilkhand Medical College and Hospital Bareilly, India.

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Corresponding Author:
Dr. Anam Khan
Email: dranam08@gmail.com

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Abstract

Background: To evaluate the clinico-pathological significance of postmenopausal bleeding and to identify risk factors associated with future development of endometrial cancer. **Materials and Methods:** Study was performed on forty postmenopausal women who clinically presented with bleeding from genital tract, with their last menstrual period at least one year back. All patients were subjected to transvaginal sonography and samples (endometrial curettage/ biopsy/ hysterectomy specimens) from patients with endometrial thickness > 5mm were sent for histopathological examination. Patient characteristics and endometrial assessment of women with or without endometrial cancer and hyperplasia were compared. Continuous variables were presented as mean ± standard deviation while qualitative data was analysed using Chi-square test. Results were considered significant when $P<0.05$. **Result:** In this study, the mean age at the time of presentation was 51.52 ± 6.29 years. Of these 40 women, most are multiparous (parity >4). About 32.5% (13/40) of the study patients were diabetic, 35% (14/40) were hypertensive, and 40% (16/40) were either obese or overweight. The mean thickness of endometrium was 12.16 ± 7.36 mm. Histological examination revealed the presence of 4 (10%) women with endometrial atrophy, 9 (22.50%) with proliferative endometrium, 3 (7.50%) with secretory endometrium, 4 (10%) with disordered proliferative endometrium, 4 (10%) cases of endometrial polyps, 2 (5%) with chronic endometritis, 7 (17.50%) with endometrial hyperplasia (atypical+ without atypia) and 7 (17.50%) of endometrial carcinoma. **Conclusion:** As clinical characteristics are possible predictors of endometrial carcinoma, these should also be taken into account in risk estimations and in the formulation of management plans. This is beneficial not only in disease detection but also may result in improved efficiency of care.

INTRODUCTION

World Health Organization (WHO) defines menopause as permanent cessation of menstruation, resulting from loss of ovarian activity.[1] Postmenopausal bleeding (PMB) is defined as bleeding that occurs from the genital tract more than 12 months after the last menstrual period in a woman who is not receiving hormone replacement therapy.[2]

About 80-90% of patients presenting with postmenopausal bleeding have benign causes.[3] However, more sinister causes of the bleeding such as atypical endometrial hyperplasia and endometrial carcinoma must first be ruled out. Patients at risk of endometrial carcinoma are those who are obese, diabetic and/or hypertensive, nulliparous, taking exogenous estrogens (including tamoxifen) or those who experience late menopause.[4] Transvaginal sonography (TVS) is an efficient and acceptable noninvasive method for assessing the endometrium. With a threshold of 5 mm for endometrial thickness, the sensitivity for detecting endometrial carcinoma was 96%.[5] Dilatation and curettage and hysteroscopic guided endometrial biopsy are valuable tools to evaluate the underlying etiology.[6] Postmenopausal bleeding demands complete assessment for diagnosis and treatment of high risk patients so as to ensure considerable reduction in societal burden imposed by endometrial cancer.

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Therefore, this study strives to determine clinical significance and to evaluate endometrial pathology in patients with postmenopausal bleeding with an objective to identify risk factors associated with future development of endometrial carcinoma.

MATERIALS AND METHODS

The indexed prospective study was commenced after due clearance from institutional ethics committee. The study was performed on postmenopausal women who clinically presented with bleeding from genital tract, with their last menstrual period at least one year back and details regarding age, parity, body mass index, history of hypertension and diabetes were obtained. Excluded all symptomatic postmenopausal women with bleeding arising from cervical or vaginal or vulvar disease, women with bleeding diathesis, on anticoagulants therapy or on menopausal hormone therapy (MHT). All patients were subjected to transvaginal sonography and endometrial thickness (double layered) was recorded. Samples (endometrial curettage/ biopsy/ hysterectomy specimens) from patients with endometrial thickness >5mm were sent for histopathological examination. Specimens were fixed in 10% formalin, processed, embedded in paraffin, 3-4 micron thick sections were cut and stained with hematoxylin & eosin (H&E).

Sample size estimation: 40 subjects

Formula used: N = 4pq/L2

Where, N= sample size, p(prevalence) = 2.6%, q= 97.4 (100-p), L = 5% (allowable error).

Calculation

N= 4x2.6x97.4/25 =40.51≅ 40.

Statistical analysis was done using Microsoft excel. Data was imported in SPSS (Statistical Package for the Social Sciences) version 23.0 where means and standard deviations were calculated. Depending on the distribution and type of data, the data was analyzed by Chi-square test. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

The study included forty admitted and OPD patients who clinically presented with postmenopausal bleeding. The mean age at the time of presentation was 51.52 ± 6.29 years. Of these 40 women, most were multiparous (parity >4). About 32.5% (13/40) of the study patients were diabetic, 35% (14/40) were hypertensive, and 40% (16/40) were either obese or overweight. In this study, the mean thickness of endometrium was 12.16 ± 7.36 mm [TABLE 1]

Table 1: Basic Characteristic of Women with Postmenopausal Bleeding

Basic Characteristic Parameters (n=40)	Mean/ SD (Range) or n (%) (which ever applicable for data)
Age at presentation	51.52± 6.29 (44-70)
Parity	5± 2.13 (0-8)
BMI (obesity/ overweight)	16 (40%)
Hypertension	14 (35%)
Diabetes	13 (32.5%)
Endometrial thickness (ET)	12.16± 7.36 (8- 17)

Histological examination revealed the presence of 4 (10%) women with endometrial atrophy, 9 (22.50%) with proliferative endometrium, 3 (7.50%) with secretory endometrium, 4 (10%) with disordered proliferative endometrium, 4 (10%) cases of endometrial polyps, 2 (5%) with chronic endometritis, 7 (17.50%) with endometrial hyperplasia (atypical+ without atypia) and 7 (17.50%) of endometrial carcinoma [TABLE 2]. The final sample consisted of 9 cases (malignant) and 31 controls (benign), of total 40 patients. The 9 cases included 7 women with endometrial carcinoma and 2 with atypical hyperplasia. In 31 controls, 26 had benign pathology and 5 with simple hyperplasia.

Table 2: Histopathology of Endometrium

Histopathology Of Endometrium		Cases (9)	Control (31)	Total (40)
Atrophic Endometrium		-	4 (12.90%)	4 (10%)
Proliferative Phase		-	9 (29.03%)	9 (22.50%)
Secretory Phase		-	3 (9.68%)	3 (7.50%)
Disordered Proliferative Phase		-	4 (12.90%)	4 (10%)
Polyp		-	4 (12.90%)	4 (10%)
Chronic Endometritis		-	2 (6.45%)	2 (5%)
Hyperplasia	Without Atypia	-	5 (16.14%)	7 (17.50%)
	With Atypia	2 (22.22%)	-	
Endometrial Carcinoma		7 (77.78%)	-	7 (17.50%)

Chi-square test was used to know the association between individual clinical characteristics and the development of endometrial carcinoma was performed. Patient characteristics, such as, diabetes, presence of obesity/overweight and endometrial thickness had highly significant association with malignancy [TABLE 3].

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Table 3: Distribution of Association of Clinical Characteristics with Development of Malignancy

Variables		Cases (9)	Control (31)	P Value
Diabetes(%)	YES	7 (77.78%)	6 (19.35%)	<0.002*
	NO	2 (22.22%)	25 (80.65%)	
Hypertension(%)	YES	6 (66.67%)	8 (25.81%)	<0.023*
	NO	3 (33.33%)	23 (74.19%)	
Obesity/ Overweight (%)	YES	7 (77.78%)	9 (29.03%)	<0.006*
	NO	2 (22.22%)	22 (70.97%)	
Endometrial Thickness (Mm)		12.91± 2.11	7.82± 3.02	<0.0001*

*Statistically Significant

DISCUSSION

Post-menopausal bleeding represents one of the most common reasons for referral to medical services, mainly due to the suspicion of an underlying endometrial malignancy[8], as approximately 90% of women with endometrial carcinoma presents with postmenopausal bleeding as the only presenting complaint[9]. In this study, the mean age at presentation was 51.52 ± 6.29 (44- 70) years. Literature reveals the mean age of presentation ranged from 40- 81 years in one[10] and 41- 70 years in other.[11] The peak incidence of endometrial carcinoma was observed in the age group of 58-70 years (mean 61.2 years), which was in concordance with several published literature.[12,13] Most of the patients (75%) were multiparous (parity >4). Literature shows that the risk of endometrial carcinoma is inversely related to parity.[14] Nulliparity, however by itself does not appear to increase the risk; instead, the association probably lies with the high frequency of anovulatory cycles in infertile women.[15,16] However, an Indian literature showed that most of the women presented with postmenopausal bleeding were multiparous.[17] The most frequently observed medical co-morbidity was obesity/ overweight, as 87.5% of the patients diagnosed with atypical hyperplasia and carcinoma endometrium were obese. Several published literature confirmed the strong association between obesity and carcinoma endometrium.[18,19] One explanation for this association is that obese women have high levels of endogenous estrogens due to conversion of androstenedione to estrone and the aromatization of androgens to estradiol, both of which occur in peripheral adipose tissue.[20,21] Furthermore, obese women can also have lower circulating levels of sex hormone binding globulins, alterations in the concentration of insulin like growth factor and its binding proteins, and insulin resistance all of which may contribute to the increased risk of endometrial carcinoma in these women.[22] Out of 9 cases diagnosed with atypical hyperplasia and endometrial carcinoma, 77.78% were diabetic, while 66.67% were hypertensive. Several literature show that women with diabetes and hypertension are at increased risk of endometrial carcinoma.[23,24,25,26,27] Diet high in carbohydrates and associated hyperinsulinemia, insulin resistance and elevated levels of insulin like growth factor may play a role in endometrial proliferation and development of endometrial carcinoma.[24,28,29] A 5mm endometrial thickness cut-off value for investigating asymptomatic postmenopausal women was used for following:

- The risk of endometrial cancer in symptomatic postmenopausal women with endometrial thickness <5mm is very low (0.1- 1%).
- Almost all women with endometrial cancer have an endometrial thickness >5mm.
- When a cut-off value of 5mm is used, the sensitivity of detecting endometrial cancer using transvaginal sonography is comparable with that of the endometrial biopsy .[30]

With a threshold of 5 mm for endometrial thickness, the sensitivity for detecting any endometrial disease was 92%, and the sensitivity for detecting endometrial cancer was 96% [5]. Smith Bindman et al. found that lowering the endometrial thickness cut-off to 4mm causes only a little decrease in the sensitivity, but a substantial decrease in the specificity (which means more false positive results), for cancer detection.[31]

CONCLUSION

This study was undertaken to determine the clinical significance, to identify the risk factors and to study the endometrial pathology in postmenopausal bleeding. We intended to evaluate each risk predictor in women with postmenopausal bleeding for cancer diagnosis and prognostication at an earliest. The most important finding of this study was identifying clinical factors significantly associated with the risk of endometrial carcinoma in univariate analysis. The results of multivariate logistic regression analysis showed the significant predictive variables associated with development of endometrial carcinoma were ET, recurrent episode of bleeding, diabetes with moderate ability to identify endometrial hyperplasia or cancer in women with PMB. The above mentioned clinical and imaging risk factors warrants further diagnostic workup as these women with postmenopausal bleeding are at increased risk for endometrial hyperplasia or carcinoma. As mentioned in published literature, even without amenorrhea or irregularity, menstruation continuing after the age of 55 years should be investigated[11]. Keeping in view, the diagnostic workup should not be withheld in postmenopausal women without these characteristics.

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Conflict of Interest

The authors declare no conflicts of interest.

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