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ASSOCIATION OF ENDOMETRIAL CANCER RISK WITH POSTMENOPAUSAL BLEEDING IN WOMEN- A SYSTEMATIC META-ANALYSIS.

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ABSTRACT **BACKGROUND:** Globally, cancer of the corpus uteri (typically referred to as endometrial carcinoma, EC) ranked as the 6th most common type of cancer and 14th main cause of cancer death in women. **AIMS AND OBJECTIVE:** To provide a reference of the prevalence of PMB in endometrial cancers and the risk of endometrial cancer in women with post menstrual bleeding (PMB) **METHODS AND MATERIALS:** A prospective cohort study was conducted in the Department of Obstetrics and Gynaecology at Madhubani Medical College and Hospital, Madhubani, Bihar. Data from consecutive selected patients were collected between September 2021 to February 2022, reporting the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer in women with PMB in unselected populations were selected. Patient demographics, vital signs, and laboratory and ultrasound results, were selected in the final analysis. **RESULT:** A total of 900 unique studies (patients) with PMB were analyzed. The pooled prevalence of PMB among women with endometrial cancer was 5.33% (95%CI, 87%-93%), irrespective of tumor stage. The pooled risk of endometrial cancer among women with PMB was 9%(95%CI,8%-11%), with estimates varying by use of hormone therapy (range, 7%[95%CI, 6%-9%] to 12%[95%CI, 9%-15%]; P < .001 for heterogeneity) and geographic region (range, 5%[95% CI, 3%-11%] **CONCLUSION:** Early detection strategies focused on women with PMB have the potential to capture as many as 90% of endometrial cancers; however, most women with PMB will not be diagnosed with endometrial cancer.

KEYWORDS : Postmenopausal vaginal bleeding; Endometrial carcinoma, risk and prediction.

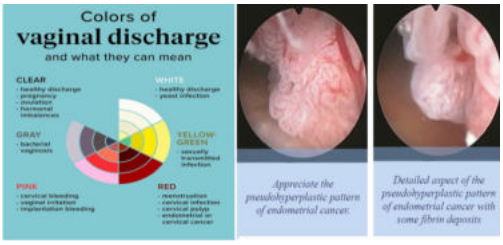
INTRODUCTION:

Postmenopausal bleeding (PMB) can be defined as uterine bleeding occurring at least one year after menopause. Postmenopausal bleeding refers to any genital tract bleeding in a postmenopausal woman, other than the expected bleeding that occurs in women taking sequential hormone replacement therapy (HRT). Because postmenopausal bleeding is the most common symptom of endometrial cancer, when postmenopausal bleeding occurs, clinical evaluation is indicated (Goldstein et al, 2001).PMB is a common clinical problem in both general and hospital settings [1, 2]. The incidence of spontaneously occurring PMB in the general population can be as high as 10% immediately after menopause [3]. Endometrial atrophy, endometrial hyperplasia and polyps are the most common cause of genital tract bleeding among postmenopausal women. PMB is often caused by abnormalities of the endometrium, whether they are benign or malignant. Postmenopausal women with vaginal bleeding, 10%–15% have endometrial carcinoma [4–8]. In contrast, the prevalence of endometrial polyps in patients with PMB and an increased endometrial thickness measured with transvaginal sonography (TVS) is estimated to be around 40% [9, 10]. Endometrial cancer is the most common malignancy of the female genital tract in developed countries [11]. Unlike other malignancies, endometrial cancer often presents at an early stage when there is a possibility of curative treatment by hysterectomy. Survival decreases with increased staging and lower histological differentiation, thus accurate and timely diagnosis is important and should preferably be carried out by a safe, simple and minimally invasive method. Guidelines addressing PMB are therefore aimed at excluding cervical cancer, endometrial carcinoma or precancerous lesions of the endometrium [12–15]. Several risk factors such as obesity, tamoxifen use, increasing age, hypertension, diabetes, and unopposed use of exogenous estrogens are strongly associated with increased risk of type-I endometrial cancer. Early menarche and late menopause have also been implicated due to prolonged estrogen stimulation of the endometrium. Currently, controversy exists as to whether transvaginal ultrasonography or endometrial biopsy should be used as the initial diagnostic step for clinical evaluation of women presenting with postmenopausal bleeding.

AIMS AND OBJECTIVE:

The aim of our study was to use routinely collected clinical data from history and ultrasound evaluation of the endometrium to develop an algorithm to predict the risk of endometrial carcinoma in women presenting with postmenopausal vaginal bleeding.

To provide a reference of the prevalence of PMB in endometrial cancers and the risk of endometrial cancer in women with PMB.



MATERIAL AND METHODS:

Participants

This is a prospective cohort study, was conducted in the Department of Obstetrics and Gynecology at Madhubani Medical College and Hospital, Madhubani, Bihar. Data from consecutive selected patients were collected between September 2021 to March 2022. All postmenopausal women presenting with vaginal bleeding were included. Menopause was defined as at least 12 months of spontaneous amenorrhea. Premenopausal women were not included in the study as there is no standard threshold for endometrial thickness in this group that is considered abnormal. Asymptomatic women with an incidental finding of increased endometrial thickness on imaging and asymptomatic women with abnormal endometrial cytology found on cervical smear.

Procedures

All women presenting with vaginal bleeding underwent transvaginal ultrasound scanning to evaluate the endometrium. The double-wall endometrial thickness was measured in an anteroposterior dimension from one basalis layer to the other. In keeping with departmental guidelines, when endometrial thickness was measured to be less than 5mm no further investigations were performed as evidence suggests a low probability of cancer below this threshold (Karlsson et al, 1995; Smith-Bindman et al, 1998). For the purpose of the study, we considered all women with endometrial thickness less than 5mm as negative for endometrial cancer. Women with endometrial thickness equal to or greater than 5mm had endometrial sampling performed using an endometrial Papillae device. Hysteroscopic evaluation of the endometrium with biopsy under a general anaesthetic was performed if Papillae biopsy was not possible or did not yield sufficient tissue for

histological diagnosis. A hysteroscopy was also performed for any woman reappearing at the OPD for a second time with a recurrent episode of bleeding.

Our retrospective research Inclusion criteria included women undergoing endometrial biopsy, dilation and curettage, or hysterectomy. Exclusion criteria Women with endometrial atypical hyperplasia, any prior malignancy, current pregnancy, or severe infectious disease were excluded. This study was approved by the Medical Ethics Committee of the college.

According to the endometrial pathology diagnoses, patients were classified into two categories: the case group with EC and the control group without EC (referred as benign group). The benign group consisted of women with a normal endometrium, endometrial polyps, hyperplasia without atypical or submucosal uterine fibroids. The case group included women with endometrial adenocarcinoma or other types such as clear cell carcinoma of the endometrium, endometrial stromal sarcoma, serous carcinoma, carcinosarcoma, or large- or small cell neuroendocrine carcinoma. A total of 48 patients with EC or benign gynecological disease were enrolled. Patients were removed if the incomplete data accounted. Features relating to clinical characteristics, laboratory test results, and ultrasound data were extracted. About 23% of cases were deleted because of missing data Utility of predictive mean matching was conducted. Patient demographics, vital signs, and laboratory and ultrasound results, were selected in the final analysis.

Data collection

The collection of routine data and presence of risk factors for endometrial cancer using a pre-designed proforma. Data extracted from these forms for this study were age of the patient at presentation, body mass index (BMI), use of HRT, presence of hypertension and diabetes, previous history of breast cancer, and use of tamoxifen. Endometrial thickness measured on ultrasound scan and results of histology when performed were also recorded. We excluded data regarding parity as we consider that it is the frequency of an ovulatory cycle that increases the risk of endometrial cancer and not nulliparity per se. Data from 90% of the patients were collected prospectively and only in 10% of the cases was it collected retrospectively.

We also attempted to assess whether the bleeding pattern of women had any predictive value in the histological outcome. The amount of bleeding was characterised as spotting, light (¼ less than a period), and heavy (¼ like a period or worse). Any event lasting less than 7 days was defined as a single bleeding episode.

STATISTICALANALYSIS:

The distributions of continuous variables were not symmetric. Binomial exact methods were used to calculate 95% confidence intervals (CIs) of the proportions and to test any differences in the proportions observed. W2-test was used after checking the expected assumptions. All analyses were performed using STATA software, version 10.1 SE (Stata Corporation, College Station, TX, USA).

RESULT:

Demographics

A total of 900 unique studies (patients) with PMB with endometrial cancer, were analyzed. During 7 months interval, women were investigated for postmenopausal vaginal bleeding. Age distribution ranged from 35 to 77 years with a median of 59 years. A total of 48 women (5.33% of total) were diagnosed with endometrial carcinoma. Women with all types of endometrial cancer were included in this group. The remaining 852 women (94.67%) were included in the non-cancer group for the purposes of the study. The pooled prevalence of PMB among women with endometrial cancer was 5.33% (95%CI, 87%-93%), irrespective of tumor stage. The pooled risk of endometrial cancer among women with PMB was 9%(95%CI,8%-11%), with estimates varying by use of hormone therapy (range, 7%[95%CI, 6%-9%] to 12%[95%CI, 9%-15%]; P < .001 for heterogeneity) and geographic region (range, 5%[95% CI, 3%-11%].

Clinical risk factors:

Women in the endometrial cancer group were significantly older (median 64 vs 59 years) and had higher BMI (31 vs 28 kgm 2) than women without cancer. The duration of use of HRT did not appear to increase the risk of endometrial cancer. The women in the endometrial cancer group were significantly more likely to have a previous history of breast cancer. However, the duration of use of tamoxifen in the breast cancer group did not appear to increase the risk of endometrial cancer (P¼0.091). The amount of vaginal bleeding did not appear to be associated with increased risk of endometrial cancer (P¼0.289). Recurrent episodes of vaginal bleeding were significantly more likely to be associated with endometrial cancer than a single bleeding event (Po0.0001). Endometrial thickness on ultrasound scan was significantly higher in women with endometrial cancer (14.9 vs 4.6 mm)

DISCUSSION:

Our systematic review and meta-analysis demonstrates that PMB is very sensitive for endometrial cancer detection, occurring in approximately 90%of cases. However, our findings indicate that among women with PMB, only approximately 9% will be diagnosed with endometrial cancer, with estimates varying substantially by HT use, geographic region, and the presence of endometrial polyps. Current practice guidelines recommend workup to rule out endometrial cancer among all women with PMB. Our findings support this recommendation by providing reassurance that targeting this high-risk group of women for early detection and prevention strategies will capture most endometrial cancers. However, the low PPV of PMB emphasizes the need for additional triage tests with high specificity to improve management of PMB and avoid unnecessary biopsies in low-risk women. The prevalence of PMB in endometrial cancer and the risk of endometrial cancer in women with PMB were higher before 2000 compared with after 2000. When interpreting these results, it is important to distinguish population risk, which has generally increased over time, from the risk in women with PMB. The number of endometrial cancers without PMB and the number of women with PMB with benign conditions may both have increased over time. This increase could be influenced by factors such as changes in HT use, changes in prevalence of obesity, or changes in clinical management thresholds for abnormal bleeding. The risk of endometrial cancer among women with PMB was notably lower in studies that included HT users compared with those that excluded these women. Use of HT may affect this association at multiple levels. Certain combined formulations of estrogen plus progestin therapy are established to have a protective effect on the endometrium [16]

Furthermore, irregular uterine bleeding is a common adverse effect of HT, particularly within the first 6 months of use. [17] The underlying cause of HT-induced bleeding is thought to involve changes in the size of endometrial blood vessels and regulation of vascular growth and integrity. [18] Because this type of bleeding is generally not associated with abnormal endometrial histologic findings, most guidelines recommend against clinical workup of women using HT who experience irregular uterine bleeding within the first 6 months. However, little consensus exists about how to best treat these women if bleeding persists, and a considerable number of women with HT-associated bleeding will undergo procedures to rule out endometrial cancer.[18] Our data emphasize the importance of considering a woman's HT status to inform clinical decision making, potentially supporting a less aggressive management approach in HT users. We noted striking geographic differences in endometrial cancer risk among women with PMB, ranging from 13% in Western Europe to 5% in North America and 7%in Northern Europe. At present, consensus regarding the optimal approach for evaluating PMB is lacking. Practice may vary depending on resources, clinical expertise and judgment, and patient preferences. The threshold for evaluating PMB may be lower in North American countries compared with other countries in Europe and elsewhere. In many European countries, guidelines recommend TVUS as the first-line test, with histologic assessment indicated for women with a thickened endometrium based on cutoffs ranging from 3 to 5mm.[19,20] In the United States, guidelines recommend TVUS or endometrial biopsy as the first step in evaluating PMB . In sensitivity analyses, we observed a lower risk of endometrial cancer in studies with partial disease verification (i e, not all women received a biopsy) compared with studies with complete diagnostic verification, suggesting that disease may have been missed in women with negative findings for the first-line test (eg, TVUS). However, we cannot exclude that in some settings, women only received a first-line test such as TVUS if they had a lower risk of endometrial cancer. In the subset of studies included in our meta-analysis that included women with PMB and a minimum endometrial thickness, the pooled risk of endometrial cancer was 19%, more than double the risk observed in our main analysis. Our findings also suggest substantial variation in the risk of endometrial cancer

depending on the underlying cause of PMB. Endometrial polyps are one of the most common causes of PMB. Although polyps have been associated with risk of endometrial cancer in women with PMB, [21]other studies have suggested that this association is more likely attributed to detection bias, resulting from incidental findings during the diagnostic workup of PMB caused by endometrial polyps.[22] Our meta-analysis confirms a lower risk of endometrial cancer among women with PMB and polyps.

CONCLUSION:

Early detection strategies focused on women with PMB have the potential to capture as many as 90% of endometrial cancers; however, most women with PMB will not be diagnosed with endometrial cancer. These results can aid in the assessment of the potential clinical value of new early detection markers and clinical management strategies for endometrial cancer and will help to inform clinical and epidemiologic risk prediction models to support decision making. Our study represents an important and timely evaluation of the risk of endometrial cancer in women with PMB and can serve as a reliable reference for the prevalence of PMB in women with endometrial cancer and the risk of endometrial cancer in women with PMB, 2 requisite prior probabilities for prediction of endometrial cancer risk and secondary and tertiary prevention. As new markers are discovered or new clinical management strategies are evaluated, our results can aid in the assessment of their potential clinical value and will help to inform clinical and epidemiologic risk prediction models to support clinical decision making.

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