Student's Journal of Health Research Africa
Vol. 4 No. 9 (2023): September 2023 Issue
https://doi.org/10.51168/sjhrafrica.v4i9.702
Original article

DOES POSTMENOPAUSAL BLEEDING ALMOST ALWAYS POINT TOWARDS A SINISTER CAUSE: CLINICAL SCENARIO IN THE "CANCER BELT OF NORTH INDIA" – A PROSPECTIVE HOSPITAL-BASED STUDY.

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Abstract.

Background:

Bleeding after menopause can be an early sign of malignancy in the cervix and the inner layer of the uterus. Detecting the malignancy earlier can make such malignancy manageable. This study aims to determine the occurrence of bleeding after menopause in North Indian women.

Methods:

This was a survey-based prospective study carried out over two years (January 2017 to December 2018) in the Department of Obstetrics & Gynaecology at Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, a government hospital of tertiary care. The remaining 262 women were considered as the subjects for this study.

Results:

Abnormal mass was detected in the abdomen and the pelvic region of 21 women. When a speculum was inserted a mass was observed in the cervical region in 116 women, most of these masses were due to malignancy. Erosion in the cervix was observed in 42 women. A relatively small number of women had growth in their vagina and vulva region. 43.5 % of the women had heavy cervical mass, 2.3% of the women had abnormal growth in the myometrium of the uterus, 6.9% of women had malignancy in the inner layer of the uterus, 5.3% of the women had abnormal growth in the endometrium and 0.4% had cancer in the ovary. Endometrium was thicker than 10mm in 3.4% of the women.

Conclusion:

The bleeding after menopause is generally ignored as it seems harmless. However, it can be an indication of malignancy of the endometrial and cervical tissues.

Recommendation:

Diagnosis and evaluation of the cause can reduce the mortality and morbidity rates.

Keywords: Bleeding after menopause, carcinoma, histopathology, Submitted: 2023-09-26, Accepted: 2023-09-28

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1. BACKGROUND.

World Health Organization states that when the women are not menstruating for more than 12 months then menopause is said to occur. When women who have undergone menopause experience bleeding from their vagina it is said to be postmenopausal bleeding [1]. Bleeding from the vagina after menopause. Recently there has been an increase in the number of cases of bleeding after menopause because women have been using hormonal pills as contraceptives without any supervision, previously women considered bleeding as a taboo and not something that requires medical attention, and now due to increased awareness, they report such condition to a gynecologist. Although malignancy is suspected it cannot be confirmed until a proper diagnosis is done because there can be other causes of bleeding too.

Previously it has been reported that only one-third of the cases of bleeding after menopause turn out to be carcinoma. The other cause of bleeding after menopause can be due to abnormal growth, fibroids, polyps, and erosion of the cervical and endometrial tissue. The cases of malignancy of the female reproductive system have been on the rise and bleeding from the vagina after menopause is one of the symptoms of the malignancy. Hence early and accurate diagnosis of this can only prevent morbidity.

Since this tertiary care hospital caters to the Malwa belt in Punjab, also known as the "Cancer belt of North India, this study aimed to assess the cause of the bleeding from the vagina after menopause and study the prognosis of this particular symptom.

2. MATERIALS AND METHODS.

2.1. Study Design.

It was a prospective study for two years (January 2017-December 2018), conducted in the Department of Obstetrics & Gynaecology at Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, a tertiary care government hospital.

2.2. Inclusion and exclusion criteria.

After ethical board approval, patients attending outpatient and emergency in the Department of Obstetrics and Gynaecology with postmenopausal bleeding (bleeding per vaginum one year after the last menstrual period) during the study period were included. Patients with bleeding disorders, on anticoagulants, receiving radiation or chemotherapy those with trauma to the genital tract, those not consenting to be part of the study, and those on Hormone Replacement Therapy were excluded.

2.3. Data Collection and Analysis.

Detailed patient history taken, and clinical examination done. Complete hemogram, renal & liver function tests, coagulation profile (BT, CT, PTI, INR), viral markers (HBsAg, Anti HAV IgM, Anti HCVab, Anti HEV IgM), Electrocardiogram (ECG), and Chest X-ray were done. Ultrasonography (USG) pelvis to evaluate endometrial thickness (ET), and detection of leiomyoma, polyp, or ovarian mass was done. Per speculum and vaginal examination was done for all patients and findings were recorded. PAP Smear was done in patients with no obvious cervical growth. Based on clinical examination, patients were accordingly planned for cervical biopsy (in cases of a cervical mass or a suspicious-looking cervix); fractional curettage or endometrial biopsy; vulval or vaginal biopsy in case a lesion was identified.

2.4. Statistical Analysis.

The specimen was sent for histo-pathological examination and the findings documented data was analyzed using SPSS 20.0 statistical software. Descriptive statistics were applied and the data was analyzed using percentages and a chi-square test.

3. RESULTS.

A total of 306 patients presented with PMB during the study. Out of these 14.4 % (44) were either lost to follow-up or had to be excluded as the tissue sent for histopathology was not processable, and they refused repeat testing. So, 262 patients

participated in the study. The mean age was 54.22 years (S.D.: 9.551; Range: 42-100 years). The majority (89.3%) were multigravida. Rural patients comprised 76.7 % of the study population as the hospital caters mainly to rural areas in the belt. Thirteen percent of patients had a history of intake of oral contraceptive pills at least once in their lifetime. The majority (53.1 %) of patients were presented with symptoms of discharge per vaginum. Hypertension (21.8%), obesity (15.3%), and Diabetes (5.3%) were the most common medical co-morbidities encountered (Table 1).

3.1. Clinical & Radiological findings.

At clinical examination, 8.1% (n=21) were found to have an abdominopelvic lump. Per speculum examination revealed cervical growth in 116 patients (44.3%), out of which 35.9% had adnexal involvement. Cervical erosion was present in 42 cases (16%). Vulvar or vaginal growth was revealed in 3.1% and 0.8 % respectively. Ultra-sonography findings observed were bulky cervix (43.5%), leiomyoma/adenomyosis (2.3%), endometrial carcinoma (6.9%), endometrial polyp (5.3%) & ovarian tumor (0.4%). Endometrial thickness (ET) > 10 mm was observed in 3.4% of patients (Table 2).

3.2. Histopathology findings.

Cervical biopsy of 164 patients (62.6%) with clinically suspicious cervix revealed: Squamous cell carcinoma (117; 44.7%), CIN (14; 5.3%), and chronic Cervicitis (29; 11.1%). In the endometrial biopsy of 85 patients (32.4%), adenocarcinoma (5.7%); endometrial hyperplasia(5%); atrophic endometrium (11.5%), and clear cell carcinoma (0.8 %) were observed. Fractional curettage revealed adenocarcinoma (0.4 %) & atrophic endometrium (1.5%). Vulvar biopsy of eight patients with vulvar growth revealed vulvar cancer of squamous cell type in 7 patients. Two cases of vaginal squamous cell carcinoma were diagnosed. (Table 3).

3.3. Distribution of various underlying genital tract benign lesions, premalignant and malignant conditions.

Overall, 147 (56.48%) patients with PMB had frank genital tract malignancy: carcinoma cervix (117; 44.7%), endometrial carcinoma (21; 8%); vulvar cancer (7; 2.7%) & vaginal cancer (2; 0.8%). Pre–malignant lesions (27; 10.3%) observed were CIN (14;5.3%) and endometrial hyperplasia (13; 5%). The majority of patients diagnosed with carcinoma cervix were aged between 41-50 years (55; 21%) and the majority were multiparous (71; 27.1%). Grand multiparity was observed to be associated more with cervical cancer. Vulvo-vaginal malignancies were observed in patients aged over 60 years. Atrophic endometrium (34; 13 %) and chronic cervicitis (29; 11.1%) were the commonest observed benign causes of PMB. (Table 4).

Table 5 depicts the correlation between the risk factors and histopathology. The results showed that there is a statistically significant strong to moderate positive association between the area of residence, discharge in between bleeding, and obesity with benign, pre-malignant, and malignant conditions of the genital tract. Strong negative correlations were also seen between socioeconomic status, parity, vulvul biopsy, and hypertension with genital tract pre-malignant and malignant conditions but not statistically significant.

Table 6 shows a correlation between clinico-radiological findings and histo-pathological findings and results showed that all variables had a statistically significant positive correlation between benign, pre-malignant, and malignant conditions of the genital tract except USG uterine with endometrial lesions which had a statistically significant negative correlation.

Risk factors associated with endometrial carcinoma in the present study were Nulliparity, Diabetes, Hypertension, and obesity. Multiparity and oral contraceptive use were associated risk factors in cervical cancer in the present study.

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Table 1: **Demographicparameters of the study population.**

S No	Demographic parameters	n	%age
	Area of residence		
1	Rural	201	76.7
	Urban	61	23.3
	Socioeconomic status		
2	KS 1	50	19.1
	KS 2	189	72.1
	KS 3	23	8.78
	Parity		
	Nullipara	4	1.5
3	Single child	24	9.2
	Two children	146	55.7
	Three or more children	88	33.6
	Use of prior OCP		
4	No	228	87
	Yes	34	13
	Discharge per vaginum		
5	No	123	46.9
	Yes	139	53.1
	Hypertension		
6	No	205	78.2
	Yes	57	21.8
	Diabetes		
7	No	248	94.7
	Yes	14	5.3
	Obesity		
8	No	222	84.7
	Yes	40	15.3

4. DISCUSSION.

India is a largely populated country, and, with increasing life expectancy (average 71 years), presently, post-menopausal women constitute a huge chunk of the population

(around 43 million). Women spend around a third of their lives in menopause. They present with a magnitude of Postmenopausal symptoms, out of which, Post Menopausal Bleeding (PMB) is the most sinister owing to its association with genital tract malignancy. In India, the Malwa region of Punjab is considered the "Cancer belt of North India", where the background risk of malignancies is 107.4 cancer afflictions per lakh as compared to the national figure of 80 per lakh. [2] To study the etiology of PMB, in this cancer-prone zone, the present study was conducted in this hospital as it is the only government tertiary care center providing onco surgery, radiotherapy, and nuclear medicine services in the Malwa region of Punjab, and, receives referrals from a large catchment area.

The mean age of presentation in the present study was 54.22 years (55 years, Sonia et al [3]; 55.4 years, SD:6.4 years, Vishwanathan M [4]. In the present study, women with PMB constituted 5.7% of total patients attending gynecology OPD, higher than the reported incidence of 4.1 % and

Table 2: **Clinical & Radiological ftndings among patients presenting with PMB.**

S.no	Parameters		n	%age
1	Hemoglobin	Hb>10 g/dl	26	9.92
		Hb 6-10 g/dl	198	75.57
		Hb< 6 g/dl	38	14.50
2	Per abdomen examination	NAD	241	91.98
		Pelvic mass	8	3.05
		Uterus enlarged	13	4.96
3	Per speculum examination	NAD	104	39.69
		Cervical erosion	42	16.03
		Cervical mass	116	44.27
4	Per vaginal examination	NAD	137	52.30
		Cervical mass, adnexa free	22	8.40
		Cervical mass, adnexa involved	94	35.88
		Vulval growth	9	3.44
5	Ultrasonographic endometrial thickness	Less than 5 mm	146	55.73
		5-10 mm	107	40.84
		> 10 mm	9	3.44
6	USG uterine size	Menopausal	146	55.73
		Bulky	10	3.82
		Multiparous	106	40.46
7	USG uterine abnormality	NAD	113	43.13
		Endometrial polyp	16	6.11
		CA endometrium	18	6.87
		Cervix bulky	114	43.51
		Ovarian malignancy	1	0.38

5% in studies by Samartzis [5] and Guruwadayarhalli [6] & Moodley.[7] The present study observed a highly significant correlation between advancing age with endometrial carcinoma (p-value <0.01). Low socio–economic status was observed to be associated with carcinoma cervix (p-value < 0.01). 1.5 % nulliparous, 9.2 % primiparous & 89.3% multiparous was observed, contrary to studies by Sonia [3] (65% grand multipara, 32% multipara) & Jilliani [8] (18 % nulliparous, 24% with parity 1-3 and 66 % grand multipara).

This difference in parity in the present study can correlate to the socio-demographic characteristics of the communities. A significant association between high parity and endometrial carcinoma was observed in this study (p-value < 0.05). Literature reports that Oral Contraceptive Pills (OCP) may promote or initiate tumors of the breast or cervix.[9] The use of OCPs had a highly significant correlation with carcinoma cervix in this study. In 46.9% of patients with PMB, discharge per vaginum was the chief presenting symptom. The present study observed a positive association of discharge per vaginum with carcinoma cervix and endometrium (p-value <0.01). Literature shows the close association of genital malignancies with metabolic syndrome. The present study observed 21.8 % hypertensives, 15.3% with BMI > 30 Kg/m2 & 5.3% diabetics. In this study, genital malignancy was reported in % of patients, which is, contrary to, other studies where the majority of cases were benign (Pragati

Table 3: **Histopathology ftndings among patients with PMB.**

S.no.	Histo-path specimen	Findings	n	%age
1	**Cervical biopsy**			
		NAD	4	1.5
		Chronic cervicitis	29	11.1
		CIN	14	5.3
		SCC	117	44.7
	Total cervical samples		164	62.6
	Not done		98	37.4
2	**Fractional Curettage**			
		Atrophic	4	1.5
		Adeno CA	1	0.4
	Total Fractional curettage		5	1.9
	Not done		257	98.1
3	**Endometrial Biopsy**			
		Normal descriptive findings	21	8
		Endometrial hyperplasia	13	5
		Adeno carcinoma	15	5.7
		Clear cell carcinoma	2	0.8
		Adenosquamous carcinoma	4	1.5
		Atrophic endometrium	30	11.5
	Not done		177	67.6
4	**Vulval biopsy**			
		Atrophic	1	0.4
		Squamous cell carcinoma	7	2.7
	Not done		259	98.9
5	**Vaginal biopsy**			
		Squamous cell carcinoma	2	0.8
	Not done		255	97.3

[10] et al; 82.4% benign & 17.6% malignant). In 46.9% of patients, the presenting symptom was discharge per vaginum. In the present study discharge per vaginum and its association with carcinoma cervix and carcinoma endometrium was highly significant with a p-value of <0.01.

In totality, 66.9 % of cases of PMB pointed towards a sinister cause (pre-malignant 10.3% /malignant 56.6%, underlying pathology in PMB) in the present study. Though in literature, vaginal or endometrial atrophy is documented as the most common cause of PMB, however in the present study, this was found to be untrue. This was in contrast to a study by Pragati et al (82.4% had benign lesions) [10]. A few uncommon causes of PMB in the present study included urethral caruncle, decubitus ulcer, and one patient with forgotten impacted vaginal pessary. The staggeringly high percentage of malignancy in patients presenting with PMB in this setup could be attributed to the fact that this being a referral tertiary care centre, receives referrals from a large catchment area. Secondly, this institute caters to all the radiotherapy and nuclear medicine needs of the patients. Also, facilities for all the onco surgeries are provided here which is why almost all the peripheral patients get referred to this hospital, also the background risk of this Malwa belt is

Table 4: **Correlation between risk factors and Histo-pathologic ftndings.**

Variables	Cervical biopsy	Fractional curettage	Endometrial biopsy	Vulval Biopsy
Age	0	0	0	0
Menopause age	0	0	0	0
Area of residence	-.16*	1.00**	0	-
Socioeconomic status	0	1	0	-1
Parity	0	-1	0	-1
Use of OCP prior	-.21**	-	0	1
Discharge in between bleeding	.54**	1	.33**	1.00**
Hypertension	0	-1	0	1
Diabetes	0	0	0	-
Obesity	0	1.00**	0	-

Note: n-262, *p<0.05, **p<0.01

Table 5: **Correlation between clinico-radiological ftndings and histo-pathological ftndings.**

Variables	Cervical biopsy	Fractional curettage	Endometrial biopsy	Vulval Biopsy
Hemoglobin	.30**	1	0	-
Per abdomen exam	0	-	.33**	-
Per speculum exam	.91**	-	-	-
Per Vaginal exam	0	-	-	1.00**
Ultrasonographic endometrial thickness	0	1.00**	0	1
USG uterine size	0	1.00**	-.33**	1
USG uterine abnormality	.90**	1.00**	.36**	-

Note: n-262, *p<0.05, **p<0.01

higher at 107.4 cancer afflictions per lakh, as compared to the national figure of 80 per lakh [5]. On follow-up, out of 117 patients with squamous cell carcinoma cervix,10 patients with staging <2b were planned for Wertheim's hysterectomy out of which 2 were lost to follow up and the rest of the 8 patients underwent the surgery. 22 patients with different histological types of endometrial carcinoma, all underwent successful Extra fascial TAH with BSO with B/L lymphadenectomy. Out of 7 patients with SCC vulva, 5 underwent radical vulvectomy and 2 were lost to follow up. Out of 2 patients with SCC vagina 1 consented to surgery on whom surgeons assisted with abdominoperineal resection with posterior vaginectomy while the other was sent to the department of radiotherapy for further management. One patient with PMB, having undergone laparotomy reported with histology of Theca Cell ovarian tumour. All the operated patients were sent to the department of radiotherapy after 3 weeks of surgery for counseling regarding the need for chemotherapy or chemoradiation.

5. CONCLUSION.

The bleeding after menopause is generally ignored as it seems harmless. However, it can be an indication of malignancy of the endometrial and cervical tissues. With a projected 1.1 billion postmenopausal women in the world by the year

2025, awareness regarding PMB along with early and prompt diagnostic evaluation is of utmost importance Though attributed largely to benign lesions, in this part of the world, PMB seems to be ominous unless proven otherwise.

6. LIMITATIONS.

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population.

7. RECOMMENDATION.

Diagnosis and evaluation of the cause can reduce the mortality and morbidity rates.

8. ACKNOWLEDGEMENT.

We are thankful to the patients; without them, the study could not have been done. We are thankful to the supporting staff of our hospital who were involved in the patient care of the study group.

9. LIST OF ABBREVIATIONS.

BT- Bleeding time
CT- Clotting time
PTI- Prothrombin Index
INR- International Normalized Ratio
HbsAg- Hepatitis B surface antigen
HAV- Hepatitis A virus
HCV- Hepatitis C virus
HEV- Hepatitis E virus
ECG- Electrocardiogram
USG- Ultrasonography
ET- endometrial thickness
SPSS- Statistical Package for Social Sciences
PMB- Postmenopausal bleeding
Hb- Haemoglobin
NAD- Nicotinamide adenine dinucleotide
CIN- Cervical intraepithelial neoplasia
SCC- Squamous cell carcinoma

10. SOURCE OF FUNDING

The study had no funding.

11. CONFLICT OF INTEREST.

The authors report no conflicts of interest in this work.

12. PUBLISHER DETAILS.

Publisher: Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256775434261
Location: Wisdom Centre, P.O.BOX. 148, Uganda, East Africa.

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