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Original Research Article

Fetal Doppler for prediction of adverse perinatal outcome in preeclampsia in a low resource setting

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ABSTRACT

Background: Menopause is defined as the permanent cessation of menstruation resulting from loss of ovarian activity. Menopause normally occurs between the age of 45 to 50 years. The age of menopause varies with geographical, racial and nutritional factors. The objective of this study was to evaluate and to know the incidence of various cause of PMB.
Methods: This was a prospective study of the patient with PMB attending the OPD or admitted for evaluation under Obstetrics and Gynecology department. Hi-Tech Medical College and Hospital, BBSR, Odisha from November 2016 to October 2018 who fulfilled the inclusion criteria with history clinical examination and investigation and informed consent from the patient. Data analyses will be done by appropriate statistical methods.
Results: Maximum number of cases with PMB were found in age group 55-64 (52%). 57% of cases were malignant and rest 43% were benign origin. carcinoma cervix is most common malignant lesion in 80% cases and atrophic endometrium is most common benign lesion (42%).
Conclusions: In the present study the incidence malignancy causing PMB was 57% and benign cases was 43% Universal Screening of all PMB cases for genital tract malignancy is mandatory.

Keywords: Carcinoma cervix, Menopause, Odisha, Postmenopausal bleeding, Universal screening

INTRODUCTION

Menopause is defined by WHO as permanent cessation of menstruation resulting from the loss of ovarian follicular activity.[1] Postmenopausal bleeding is defined as bleeding from genital tract occurring after one year of menopause. Throughout the world, the most common age group for attaining menopause is 45-55 years and the average age is 51 years.[2] Common menopausal age in Indians is 45-50. Postmenopausal women constitute only 1% of female population. Postmenopausal bleeding represents one of the most common reasons for referral to gynaecological services, largely due to suspicion of an underlying endometrial malignancy.[3] A woman not taking hormone replacement therapy (HRT) who bleeds after the menopause has a 10% risk of having genital cancer and a further 10% risk of significant pathology.[4] Therefore, postmenopausal bleeding should always be investigated no matter how minimal or non-persistent.

The period between cessation of regular menses and onset of postmenopausal bleeding is called clear span. Clear span has been found to be longer in malignant cases.[5-7]

Etiology of postmenopausal bleeding includes both gynaecological and non gynaecological causes. The possible causes are:[8]

- Oestrogen therapy
- Benign and malignant neoplasms of vulva, vagina, cervix, corpus, fallopian tubes
- Ovarian tumours: estrogen producing tumors or any tumours of large size affecting the vascularity of the uterus "misfit tumours".
- Infections:
  - Vaginitis: Trichomonas, Candida, Chlamydia, Senile
  - Endometritis: Tuberculous, senile pyometra and hematometra
- Dysfunctional uterine bleeding
  - Anovulatory
  - Ovulatory
- Injuries
- Diseases of the blood and capillaries
- Bleeding from urethra, bladder and rectum
- No cause found

Transvaginal ultrasonography (TVS) is the recommended first line non invasive procedure for assessing the endometrium in women with post menopausal bleeding. In general, the thicker the endometrium, the higher probability of important pathology i.e. endometrial cancer being present. Measurement of endometrial thickness by TVS having a cut off of >4mm yields 98% sensitivity for detection of endometrial carcinoma9.

Hysteroscopy and biopsy (curettage) is the preferred diagnostic technique to detect polyps and other benign lesions. As such there are several investigations available to complement clinical evaluation, including ultrasound, endometrial sampling techniques and hysteroscopy to evaluate the underlying etiology of postmenopausal bleeding. Following such assessment reassurance can be given or further investigations or treatment can be discussed and rearranged.[10] Proper evaluation of PMB will isolate the benign conditions. Treatment of benign conditions and early detection of malignant lesions will help a menopausal lady to lead a healthy life.

A number of studies on clinical evaluation of postmenopausal bleeding have been conducted worldwide, but there are few reports from India and none from rural setup hospital to determine the problem and the risks in the rural population.

Objective of this study was to find out incidence of malignancies and various causes of post-menopausal bleeding among patients coming to Hi-Tech Medical College and Hospital from November, 2016 - October, 2018. To investigate the clinical significance of postmenopausal bleeding in terms of incidence of malignancy and histopathological evaluation.

METHODS

The data was collected from patients with postmenopausal bleeding per vaginum attending the outpatient department or admitted for evaluation under Obstetrics and Gynecology Department, Hi-Tech Medical College, Bhubaneswar, Odisha over a period of two years from November 2016 to October 2018. A total of 100 cases who presented clinically with PMB varying from spotting per vaginum, scanty flow, moderate to profuse bleeding were included.

Written and informed consent was taken from all the patients enrolled in the study. They were evaluated by history, clinical examination and investigations like abdominal/transvaginal sonography, endometrial biopsy, fractional curettage, Pap smear and hysteroscopic guided biopsy if required was done for all subjects and the specimen collected was sent to the department of pathology for examination and reporting. These data were entered into IBM SPSS statistics 24.0 of SPSS South Asia Pvt Ltd. Permission from the Institutional Ethics Committee at Hitech Medical College and Hospital, Bhubaneswar was taken for the study.

Inclusion criteria

- The Postmenopausal women with complaints of per vaginal bleeding.

Exclusion criteria

- Presence Premature menopause (<40 years)
- Surgical menopause
- Radiation menopause
- Chemotherapy induced menopause
- HRT
- Anticoagulant therapy
- Coagulation disorders
- Injuries to genital tract.

Full assessment was done by detailed history, physical examination and investigations including histopathological evaluation.

Statistical analysis

Calculation of mean was done by method described by J E Park According to the method individual observation are added together and divided by number of observations, Process of adding together is Known as summation and is donated by or 'S', individual observation donated by sign 'X' and arithmetic mean donated by sign x (x bar). Total number of observations is denoted by the sign "n".

So, mean:

$$\overline{X} = \frac{\Sigma x}{N}$$

Standard deviation: it is calculated by formula

$$\sigma = \frac{\sqrt{\sum(x-\bar{x})^2}}{N}$$

OR

Standard deviation equation for a sample or a population, if sample size is 30 or less.

$$s = \frac{\sqrt{\sum(x-\bar{x})^2}}{N-1}$$

Where,

- s = the standard deviation
- x = each value in the sample
- x = the mean of the values.
- N = the number of values (the sample size)

It is calculated in the following steps:

Calculated the mean:

$$\overline{X} = \frac{\sum x}{N}$$

Calculated $\overline{x} - x$ for each value in the sample

Calculate $\sum(x-x)^2$

Calculate the standard deviation.

$$s = \frac{\sqrt{\sum(x-\bar{x})^2}}{N-1}$$

Sampling technique

Simple random sampling
The number of Sample size was taken as 100

RESULTS

Maximum numbers of cases with postmenopausal bleeding were found in the age group of 55 - 64 years (52%) (Table 1).

Table 1: Distribution of cases according to age of the patients.

Age group	No. of cases	Percentage (%)
40 - 44 years	2	2
45 - 54 years	33	33
55 - 64 years	52	52
65 - 74 years	1	11
≥ 75 years	2	2

61% of the patients were multipara and 29% of patients were grand multipara (parity >=5) whereas only 5% of cases were nullipara and primipara each.

57% of cases were malignant origin and rests 43% of cases were benign (Table 2).

Table 2: Distribution of cases according to pathological types.

Etilogy	No. of cases	Percentage (%)
Malignant	57	57
Benign	43	43

Carcinoma cervix is most common 55-64 years of age (57%) and is most common among multiparous and grand multiparous women accounting for almost 98% in total. Carcinoma endometrium is also most common in 55-64 years of age and is more commonly seen in nulliparous women (43%).

Table 3: Distribution of various malignant cases according to etiology.

Etiological facts	Total cases	Ca cervix (%)	Ca endometrium (%)	Ca vagina (%)	Ca ovary (%)
Age groups (years)					
40 - 44	-	-	-	-	-
45 - 54	18	14 (30%)	2 (29%)	1 (33%)	1 (100%)
55 - 64	32	26 (57%)	4 (57%)	2 (67%)	-
65 - 74	5	5 (11%)	-	-	-
≥ 75	2	1 (2%)	1 (14%)	-	-
Total	57	46	7	3	1

Carcinoma vagina has maximum incidence 55-64 years (67%) and is more commonly seen in grand multiparous women (67%); whereas carcinoma ovary seen in multiparous women and in 45-54 years of age (Table 3).

Most commonly benign cases were seen between 45-64 years of age 81% and maximum cases were seen in multiparous women constituting 70% and grand multiparous 19%.

Table 4: Distribution of various bening cases according to the etiology.

Etiological factor	Total cases (%)	Atrophic endo+cervicitis	Atrophic endo+cin	Leiomyoma/ adenomyosis	Polyp (cervical and endometrial)	Endometrial hyperplasia	Hsil	Others (sec / proli / anovu endo)	Ovarian tumour	No tissue
Age groups (years)										
40 - 44	2 (5)			1	1					
45 - 54	17 (40)	7		4		2	1	3		
55 - 64	18 (41)	5	2	2	2	3		1	1	2
65 - 74	6 (14)	3	1		1	1				
≥ 75										
Total	**43**	**15 (35)**	**3 (7)**	**7 (16)**	**4 (9)**	**6 (14)**	**1 (2)**	**4(10)**	**1 (2)**	**2 (5)**

Atrophic endometrium (42%) was the most common histological finding associated with CIN and cervicitis in some cases. Endometrial Hyperplasia was found in 14% of cases and leiomyoma and adenomyosis was seen in 16% of cases. Polyps seen in 9% of cases (Table 4).

Table 5: Incidence of different malignant causes of postmenopausal bleeding.

Malignancy	No. of cases	Percentage (%)
Ca Endometrium	7	12 %
Ca Cervix	46	81 %
Ca Vagina	3	5 %
Ca Ovary	1	2 %
Ca Vulva	0	-

Table 6: Incidence of different bening lession of postmenopausal bleeding.

Malignancy	No. of cases	Percentage (%)
Atrophic endometrium	18	42
+Cerviciteis	7	
+Dysplasia	3	
Endometrial hyperplasia	6	14
Leiomyoma / adenomyosis	7	16
Endometrial polyp	3	7
Endocervical polyp	1	2.3
HSIL	1	2.3
Other endometrial pathology	4	9.4
Secretary	1	
Proliferative	2	
Anovulatory	1	
Benign ovarian tumor	1	2.3
No tissue	2	5
Total	**43**	**100**

Carcinoma cervix was found to be the most common cancer amongst the patients presenting with postmenopausal bleeding in this study accounting 81% of the total causes. Carcinoma endometrium was seen in 12% of cases followed by carcinoma vagina (5%) and carcinoma ovary (2%) (Table 5).

Table 7: Endometrial histology in postmenopausal bleeding.

Endometrial histology	No. of cases	Percentage (%)
Atrophic	25	49
Proliferative	3	6
Secretory	1	2
Anovulatory	1	2
Cystic glandular hyperplasia	4	7.8
Complex hyperplasia	4	7.8
Adenomatous hyperplasia	1	2
Ca Endometrium	6	11.7
Insufficient tissue	6	11.7
Total	**51**	**100**

Table 8: Causes of postmenopausal bleeding.

Types	No. of cases	Percentage (%)
Ca cervix	46	46
Atrophic endometrium	18	18
Ca endometrium	7	7
Leiomyoma/adenomyosis	7	7
Endometrial hyperplasia	6	6
Polyps	4	4
Ca vagina	3	3
Ovarian pathology	2	2
Others	5	5
Inconclusive	2	2
Total	**100**	**100**

Most common benign lesion associated with postmenopausal bleeding was atrophic endometrium (42%) followed by Leiomyoma / adenomyosis (16%) and endometrial hyperplasia 14% (Table 6). Maximum benign cases presented within first 2 years after menopause. Incidence of malignancy increased as the

clear span increased. 73% of the total cases had postmenopausal bleeding after two years of clear span out of which 66% were malignant (Table 7).

The most common cause of postmenopausal bleeding was found to be carcinoma cervix (46%) followed by atrophic endometrium (18%). Carcinoma endometrium accounted for 7% of the total causes. Here, the other causes include HSIL, proliferative, secretory and anovulatory endometrium (Table 8).

DISCUSSION

Malignant causes of bleeding

In our study we found carcinoma cervix to be the most common malignancy causing postmenopausal bleeding representing 46% of total causes and 81% of total malignancies.

Carcinoma endometrium found in 12% cases amount total malignancies, resulting in carcinoma endometrium: carcinoma cervix ratio to be 1:7 which is in contrast to that found in other studies. The low incidence of cervical cancer in Western studies could be due to effective methods for screening and diagnosis of cervical carcinoma and its precursor lesion that has reduced the incidence of cervical carcinoma as a cause of postmenopausal bleeding in development countries. On the other hand, in countries where effective cervical screening programme is not in place, especially in a developing country, cervical carcinoma still accounts for a majority of cases with postmenopausal bleeding.

In all the studies carcinoma endometrium and carcinoma cervix were the commonest malignant causes. In Postmenopausal women the anticipated ratio between endometrial and cervical carcinoma is 1:1 Most of the studies from other countries gave almost similar ration. Norries in 1935 noted that "after the menopause has been established the relative incidence of corpus carcinoma increases and practically parallels that of the cervix".[12]

Pacheco and Kempers found the ratio of 16:1 between endometrial carcinoma and cervical carcinoma in their study.[13] They explained it by lowered incidence of advanced cancer of cervix through widespread and thorough use of cervical smear. Also they selected cases only after 2 years of menopause. They suggested that since the cervical cancer develops at an early age than dose endometrial cancer, they found small number of cervical cancers.

Rai reported the ratio of endometrial carcinoma to carcinoma cervix to be 1:10 in India.[14] In 1977 by Panda et al carcinoma cervix as a cause of postmenopausal bleeding in 53% of patients comparable to its incidence of 46% in our study.[15] This high frequency is attributed to the high incidence of undiagnosed cancer of cervix in this underdeveloped country. Effective methods for screening and diagnosis of cervical neoplasia and its precursor lesion have effectively eliminated it as a significant cause of postmenopausal bleeding in developed countries, but we are still far from that situation. Recent study by Epstein (2006), calculated ratio of carcinoma cervix to carcinoma endometrium to be 2:1.

We found Ca endometrium in 7% of cases and Ca ovary in 1% of case which is similar to observed by Arati et al Ca endometrium was 9.28% and Ca ovary 3.57%.

We found adenocarcinoma endometrium in 5% of cases and SCC and malignant epithelial carcinoma of endometrium each in 1% of cases. Lidor et al, found it in 7% and Gredmark et al, found it in 8% of the cases.[16] Carcinoma cervix was most common in age group 55-64 years accounting for 56.5% cases among total carcinoma cervix cases.

Benign causes of postmenopausal bleeding

Atrophic endometrium, leiomyomas / adenomysosis, endometrial hyperplasia and polyps were the most commonly found benign conditions, each constituting 18%, 6%, 7% and 4% respectively. Benizie also found polyps (endometrial and endcervical) in 12% of cases as the most common benign cause. Procope reported the incidence as 17.2% and Karagas et al found it to be 11.7%.[17,18]

In the present study 2 cases of adenomyosis were observed but one of them was associated with leiomyoma uterus and the other one with carcinoma cervix. Arati et al, found 17.85% of atrophic endometrium, leiomyoma in 5.71%, adenomyosis in 1.43%, endometrial hyperplasia in 10% and polyps in 5% of cases.[11] Atrophic endometrium was the most common benign cause in this study, associated with CIN and chronic cervicitis in some cases. Procope reported atrophic endometrium as the most frequent cause in non-malignant group (20.5%).[17] In the present study atrophic endometrium was found in 18% of total cases and 42% of benign causes.

Brewer and Miller, found atrophic endometrium in approximately 17% of their group and in addition they had a large number in whom no endometrium was found but they did not ascribe the bleeding specifically to atrophic endometrium.[19] Other authors have also reported large percentage of women in whom either atrophic or insufficient endometrium was obtained, but in contrast to Brewer and Miller, they attributed to atrophic endometrium.[19] It was reported 20% by Pacheco and Kempers, 20.5% by Procope and 11.9% nu Karagas et al.[13,16,18] With increased life span the incidence of postmenopausal bleeding is on rise. Since the incidence of malignancy is quite high, any bleeding in that age group should be evaluated in the line of malignancy unless otherwise proved. Patient characteristics like nulliparity, hypertension, diabetes mellitus, obesity etc. should be taken into account in the diagnostic workup

along with increased endometrial thickness >4mm by transvaginal sonography (TVS) while considering further investigations like endometrial sampling.

High cervical cancer preponderance stresses on need for better patient education for screening and early diagnosis. Although routine Pap smears are easily available and widely encouraged, our system depends on opportunistic screening of women who seek medical care and misses out on many women, especially the elderly and those in high risk groups, who may not be aware of serious implication of postmenopausal bleeding and significance of routine Pap smears. Hence, there is need to intensify cytology screening programmes and to increase the awareness in general population about the value of periodic gynaecological examination and adoption of healthy and hygienic practices.

CONCLUSION

With increased life span the incidence of postmenopausal bleeding is on rise. Since the incidence of malignancy is quite high, any bleeding in that age group should be evaluated in the line of malignancy unless otherwise proved. Patient characteristics like nulliparity, hypertension, diabetes mellitus, obesity etc. should be taken into account in the diagnostic workup along with increased endometrial thickness >4mm by transvaginal sonography (TVS) while considering further investigations like endometrial sampling. High cervical cancer preponderance stresses on need for better patient education for screening and early diagnosis. Although routine Pap smears are easily available and widely encouraged, our system depends on opportunistic screening of women who seek medical care and misses out on many women, especially the elderly and those in high risk groups, who may not be aware of serious implication of postmenopausal bleeding and significance of routine Pap smears. Hence, there is need to intensify cytology screening programmes and to increase the awareness in general population about the value of periodic gynaecological examination and adoption of healthy and hygienic practices.

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