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A Study on Correlation of Endometrial Thickness and its Histopathological Finding in Women with Postmenopausal Bleeding

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Original Research Article

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Abstract: Postmenopausal bleeding is frequent in gynaecology and accounts approximately 5-10% of postmenopausal women. The incidence of malignancy in postmenopausal period remains sufficiently high so it requires immediate investigation for early diagnosis, vigilant follow up and prompt treatment. The aims and objectives of the study is to correlate histopathology of endometrium with endometrial thickness of women with postmenopausal bleeding, to detect early pre-cancerous lesions (atypia) & endometrial hyperplasia and to confirm benign nature of problem by ruling out carcinoma, so that unnecessary surgery can be avoided. This is a non-randomized longitudinal prospective observational study done at the Department of Obstetrics & Gynaecology, Rangaraya Medical College, Kakinada during the period of December2014 –July2017. All patients having established menopause except those undergone hysterectomy/premature menopause (<40 year)/on Hormone Replacement Therapy/on anticoagulant /having bleeding disorder included. Clinical & histopathological details were collected & analyzed using mean & standard deviation. Total 50 cases were included in the study. The incidence of PMB was found to be 2.1%. Mean age of PMB was 55.96±7.70 years. Mean duration since menopause was 7.62±6.8 years. Majority (70%) were benign causes,20% had pre malignant lesion and 10% had endometrial cancer. Out of 50 women who underwent transvaginal ultrasound 26 women with postmenopausal bleeding had endometrial thickness of less than or equal to 4mm and 24 women had endometrial thickness more than 4mm.Carcinoma of genital tract is one of the most important cause of PMB, so early detection of the cause can be life saving. In the present study of 50 postmenopausal women, only one patient with endometrial thickness less than 4mm had abnormal endometrium on histopathological examination. So, Transvaginal ultrasound can be used as a screening procedure for evaluation of endometrium in postmenopausal women, taking the cut- off value for endometrium as 4mm.

Keywords: Menopause, Postmenopausal bleeding (PMB), Endometrium, Histopathology, Endometrial cancer.

INTRODUCTION

The approximate age of menopause is 49 ± 3.6 years. With increasing life expectancy, the average age of menopause increased to 51 year [1]. Even without amenorrhea or irregularity, menstruation continuing after the age of 55 year should be investigated [2]. Neither normal (functional) bleeding nor dysfunctional bleeding should occur after menopause.

As the women are spending increasing portion of their lives in menopause and thus postmenopausal problems are gaining more importance in gynecological clinical practice. Approximately, 10% of menopausal women suffer from postmenopausal bleeding. The commonest cause for bleeding occurring after menopause is atrophy of vagina and endometrium and the indiscriminate use of estrogens for hormone replacement therapy.

If this is excluded 10% of all patients and (30-50%) of those in whom the bleeding is continuous or occurs more than once, are accounted for by malignant diseases of the cervix or of the body of the uterus [3]. Women on continuous progesterone and estrogen hormone replacement therapy can expect to have irregular vaginal bleeding, especially for the first six months. This bleeding should cease after one year. Any unexpected bleeding or significant change in

withdrawal bleeding should prompt further investigation.

The chances of postmenopausal bleeding decreases with increasing age but the frequency of malignancy is increased with increased age and increased interval between postmenopausal bleeding and menopause. The risk of endometrial cancer in women with postmenopausal bleeding increases with age approximately 1% at the age of 50 years to 25% at 80 years of age[4].

Post- menopausal bleeding accounts for 9-10% of gynecological complaints [5]. 10% of patients presenting with post- menopausal bleeding are diagnosed to have carcinoma endometrium. At the same time 90% of the patients with carcinoma endometrium present with postmenopausal bleeding, therefore it is important to evaluate all patients with post-menopausal bleeding to rule out malignancies of the genital tract.

Traditionally, screening for endometrial carcinoma is achieved by performing uterine curettage. However, new methods of examining the endometrium have been introduced into clinical practice like hysteroscopy and directed endometrial biopsy, sono hysteroscopy, transvaginal ultrasound. Transvaginal ultrasound is relatively cheap, easy, non invasive and needs no an aesthesia. It does not need full bladder, avoiding the discomfort associated with the transabdominal full bladder procedure. It has permitted the use of higher frequency ultrasound at greater proximity to the uterus, leading to superior resolution. It can detect the presence of myometrial invasion of endometrial cancer and concomitant pelvic pathology. The best method of investigating the women with postmenopausal bleeding is still disputed.

In the present study, non invasive TVS and endometrial biopsy obtained by dilatation and fractional curettage are correlated for the evaluation of endometrial pathology in women with postmenopausal bleeding. Subsequently, an attempt has been made to effectively and promptly evaluate a woman with postmenopausal bleeding as early as possible.
The aims and objectives of the study is to

- To correlate histopathology of endometrium with endometrial thickness of women with postmenopausal bleeding.
- To detect early pre-cancerous lesions (atypia) & endometrial hyperplasia.
- To confirm benign nature of problem by ruling out carcinoma, so that medical treatment or conservative surgery can be offered and unnecessary radical surgery can be avoided.

MATERIALS AND METHODS

This non-randomized longitudinal prospective observational study, carried out on 50 women at the Department of Obstetrics & Gynaecology, Rangaraya Medical College, from December 2014-July 2016.

All postmenopausal women presenting through emergency or outpatient department, with complaint of bleeding per vaginum, with their last menstrual period 1 year back were considered eligible for participation after informed consent, irrespective of their parity, social background, and previous medical, surgical or gynaecological history. Patients having premature menopause (before 40 year age), surgical induced menopause, and radiation induced menopause and chemotherapy induced menopause, those on HRT were excluded from the study.

A full history of the patients was obtained. The name, age, parity, marital status, address of the patients was noted. Details regarding vaginal bleeding were recorded. These included the timing of its onset, duration, colour and whether or not associated with passage of clots. History of associated symptoms included presence of any vaginal discharge, abdominal masses or distension, any accompanying abdominal pain or backache or a feeling of heaviness or something coming out of vagina. A note is made regarding recent weight loss or anorexia, presence of any accompanying bowel or urinary symptoms and any treatment taken. Drug history especially that of HRT, tamoxifen was also noted.

Obstetric history was obtained. Gynaecological history included details about age at menarche and menopause, menstrual cycle, contraception, coitus in particular; post coital bleeding and details regarding cervical smears were recorded. Family history of any carcinomas of breast, endometrium, ovary, colon. Past Medical and Surgical History was checked.

A thorough general physical examination was performed with special attention to pallor, lymph nodes and breasts. Specific clinical examination including abdominal, speculum and bimanual pelvic examination was performed. Vaginal Swabs were taken of any vaginal discharge and cervical smear was taken. Bimanual examination was performed to assess the size, position and mobility of the uterus and any adnexal mass is noted.

All patients had their blood group, haemoglobin, random blood sugar estimation, urine routine examination done. Transvaginal ultrasonography to note the size, position and contours of the uterus and endometrial thickness. Endometrium obtained by Dilatation &Fractional Curettage was subjected for histopathological examination. Biopsy from any suspicious areas was taken. Endometrial

polyps if present were avulsed and sent for histopathological examination. Incidentally causes of postmenopausal bleeding were also evaluated. Correlation of endometrial histopathological report was done with endometrial thickness, with other pathologies and other external factors like oral contraceptive pill use, obesity, effect of systemic diseases like hypertension and diabetes was done. The final diagnosis of each woman was made on the curettage specimen and resected material or hysterectomy specimen when present.

STATISTICAL METHODS

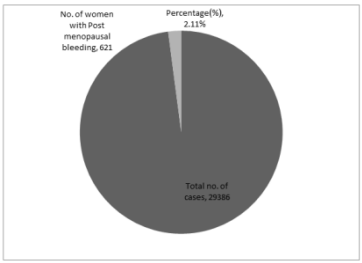
The statistical methods used in the study were

- Sensitivity and Specificity
- Positive Predictive Value (PPV) and
- Negative Predictive Value (NPV)
- Mean
- Standard Deviation(SD)

RESULTS AND DISCUSSION

Incidence

Incidence of postmenopausal bleeding among women attending Gynaec OPD in G.G.H., Kakinada during a 20 month period from December 2014 to July 2016



The figures in the above table show that out of 29386 patients attending the Gynaec OPD in G.G.H., Kakinada, during December 2014 to July 2015, 621 patients presented with postmenopausal bleeding. Hence, the incidence of postmenopausal bleeding is 2.11

Table-1: **Age incidence**

Age in years	No. of cases	Percentage
41-45	7	14%
46-50	11	22%
51-55	8	16%
56-60	14	28%
61-65	4	8%
>65	6	12%

Most of the women (28%) who presented with postmenopausal women were in 56-60years age group.

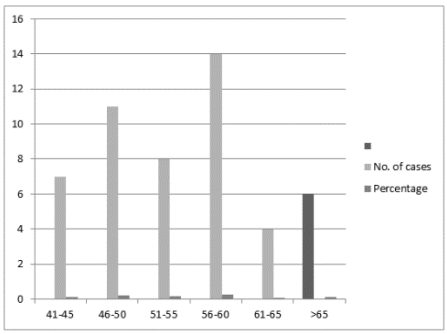


Table-2: **Socioeconomic status**

SES	No.of cases	Percentage
Low	43	86%
Middle	7	14%

The figures in the above table show that 86% of women were in the low socioeconomic status group and 14% in the middle socioeconomic status group.

Table-3: **Parity**

Parity	No. of cases	Percentage
Multiparous	47	94%
Nulliparous	3	6%

94% of women were multiparous and 6% of women were nulliparous.

Table-4: **Risk factors**

Risk factors	No. of cases	Percentage
Recurrent bleeding	5	10%
Obesity	17	34%
Hypertension	8	16%
Diabetes	2	4%

Table-5: **Endometrial thickness**

Endometrial thickness	No. of cases	Percentage
4 or less than 4mm	26	52%
More than 4mm	24	48%

The figures in the above table show that out of 50 women who underwent transvaginal ultrasound 26 women with postmenopausal bleeding had endometrial thickness of less than or equal to 4mm and 24 women had endometrial thickness more than 4mm.

Table-6: **Ultrasound and hpe report in 50 postmenopausal women**

ET	No.of cases	HPE report	No.of cases
4 or less than 4	26	Atrophic	6
		Non-secretory	10
		Proliferative	3
		No material	4
		Hyperplasia Simple Complex	 2 Nil
		Carcinoma	1
More than 4mm	24	Atrophic	1
		Non-secretory	7
		Proliferative	2
		Polyp	2
		Hyperplasia Simple Complex	 6 2
		Carcinoma	4

Of the 26 women who had ET less than or equal to 4mm,6 women had atrophic endometrium,10 had non-secretory endometrium,3 had proliferative endometrium,2 had hyperplasia,1 women had endometrial carcinoma and no material was obtained in 4 cases for histopathological examination.

Of the 24 women who had ET more than 4mm,1 women had atrophic endometrium,7 had non-secretory endometrium, 2 had proliferative endometrium, 8 had hyperplasia, 2 women had glandular polyp and 4 women had endometrial carcinoma.

Table-7

No.of cases	**TVS ET**	**HPE Report**	
		Normal	Abnormal
26	<4mm	23(a)	3(b)
24	>4mm	12(c)	12(d)
Total: 50		35	15

a = True positives, b = False positives, c = False negatives, d = True negatives

Sensitivity = $\frac{a}{a+b} \times 100 = \frac{23}{35} \times 100 = 65.71\%$

Specificity = $\frac{d}{b+d} \times 100 = \frac{12}{15} \times 100 = 80\%$

Positive Predictive Value = $\frac{a}{a+b} \times 100 = \frac{23}{25} \times 100 = 92\%$

Negative Predictive Value = $\frac{d}{c+d} \times 100 = \frac{12}{24} \times 100 = 50\%$

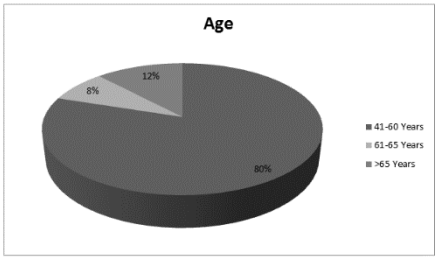
DISCUSSION

Postmenopausal bleeding is frequent in gynecology and accounts approximately 3% of postmenopausal women [6].This symptom can reveal benign causes as well as cancers. The primary aim is to identify and exclude atypical hyperplasia and endometrial carcinoma. The risk of endometrial carcinoma in women with postmenopausal bleeding rises with age from 1% at the age of 50 years to approximately 25% at the age of 80 years [7].

Table-8: **Comparison of mean age of patients with post-menopausal bleeding**

S.No	Study group	Mean age
1	Manjusha *et al.*	55.5 years
2	AratiMallick *et al.*	57.12years
3	Present study	55.9years

Ages of patients with postmenopausal bleeding in the current study ranged between 45 years and 70 years with a mean age of 55.96 ± 7.70 years. This age is much nearer to the mean age 57.12 year by Arati Mallick *et al*.[8].



It has been reported that the incidence of PMB decreases with increasing age[9]. This study also proved the same. 40 (80%) cases of postmenopausal bleeding were between 41 and 60 years of age, while only 6 cases (12%) were above 65 years of age.

Table-9: **Comparisionof incidence of cancer in women with post-menopausal bleeding**

S.No	Study group	Percentage of endometrial cancer
1	Myrveta et al	5%
2	Manjusha et al	10%
3	Sadia et al	9%
4	M.C.Breijer et al	9%
5	Present study	10%

In a study conductedby IBani- Irshaid *et al*, it was reported that post-menopausal women with vaginal bleeding have a probability of endometrial carcinoma of approximately 9%[10]. SadiaZulfiquar Cheema *et al*. [11] Breijer MC *et al*.[12] reported the incidence of endometrial cancer to be 10% in cases of PMB. Here this probability was 10% (5 cases out of 50).

Nulliparity, early menarche, chronic anovulation, late menopause, unopposed endogenous and exogenous oestrogens and Tamoxifen therapy have all been proven to be risk factors for the development of endometrial hyperplasia and carcinoma[12].

Table-10:**Comparision of age at menopause**

S.No	Study group	Mean age
1	Manjusha et al	49.5yrs
2	Present study	48.44yrs

The current study reveals that the age at menopause ranged from 44 years to 55 years. Mean age of menopause was 48.44 ± 3.4 years. The maximum number of patients 39 (78%) had menopause between 46-50 years. According to Manjusha *et al*. the mean age of menopause is 49.5yrs.

The period between menopause and onset of postmenopausal bleeding ranged from 1 year to 25 years. Majority of patients 16 (32%) had >3-10 years period between menopause and onset of symptom. The mean duration since menopause was 7.62 ± 6.8years. Here out of the total 5 cases of endometrial carcinoma 2 cases had low parity (P_1-P_2).3 cases had early menarche (before 12 years of age) and 1 case had late menopause (after 51 years of age).

Likewise obesity, diabetes mellitus and hypertension have been associated with endometrial carcinoma. In the present study, out of 5cases of endometrial carcinoma 4 cases had obesity, hypertension in 3 cases and recurrent bleeding in 1 case. Tamoxifen therapy in the treatment or prevention of breast cancer increases the risk of endometrial cancer 3-6 fold [14].In the present study, no case was having breast cancer.

Table-11: **Comparision of ppv, npv and specificity of d&c**

S.No	Study group	PPV	NPV	Specificity
1	Sadia et al	100%	93.1%	100%
2	Present study	100%	98.95%	100%

The specificity of D&C was 100%, positive predictive value was 100% and negative predictive value was 98.95%. It is consistent with study by AizaSaadia *et al*.[15] ,where the positive predictive value and specificity of endometrial curettage in diagnosing endometrial cancer found was 100% and negative predictive value was 93.1%.

Endometrial hyperplasia is an oestrogen dependent condition and has the same risk factors as for endometrial carcinoma. The complex atypical

hyperplasia has 25-30% incidence of progression to invasive carcinoma while simple hyperplasia has only 1% incidence of progression. Women with simple hyperplasia respond to hormonal treatment like levonorgestrol IUS[16] but with atypical hyperplasia should be offered total hysterectomy[17].

The assessment and investigations of cases of PMB is moving away from the operation theatre and ward environment into the outpatient department. The primary assessment in all cases of postmenopausal bleeding should be with transvaginal ultrasound scanning (TVS), as the thickening of the endometrium may indicate the presence of significant pathology (e.g. endometrial cancer)[18]. Endometrial evaluation among postmenopausal women is a topic of ongoing debate in the literature. There is a trend towards investigating intracavitary uterine lesions only with postmenopausal bleeding when the endometrial thickness, as measured by ultrasound is > 4 mm[19]. Other authors have recommended systemic collection of biopsies from symptomatic patients[20] regardless of endometrial thickness, because of reports of cancer in patients presenting ultrasound-measured endometrial thickness ≤ 5 mm [21].

The incidence of malignancy in postmenopausal period remains sufficiently high so it requires immediate investigation for early diagnosis, vigilant follow up and prompt treatment. It is difficult to predict the population changes in future, but it is certain that we are going to see an ever-increasing number of postmenopausal women day by day. In real terms there are more women who are spending a greater proportion of their lives in the postmenopausal years. The famous dictum that "Postmenopausal bleeding must be considered as indicative of malignant disease until proven otherwise" still holds true in our circumstances. Malignancy was the major cause indicating an alarming sign for the Gynecologists to evaluate the postmenopausal bleeding cases more thoroughly and promptly. Endometrial biopsy should be undertaken in all post-menopausal women with endometrial thickness (E.T) greater than 4mm or persistent bleeding despite a normal ET[22].

The reason for high rate of malignancy as a cause of PMB in developing countries compared to developed world might be lack of accessibility for modern health care, the absence of screening method such as Pap smear for detection of precursor lesion of cervical cancer in the former countries. Among the malignant lesions, the incidence of carcinoma cervix and carcinoma endometrium varied in different studies. Studies from India show high incidence of carcinoma cervix than carcinoma endometrium in PMB cases.

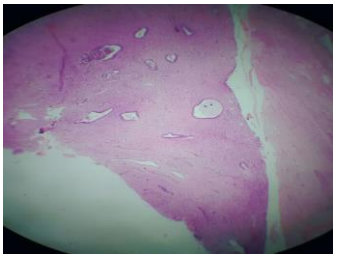


Fig-1: Atrophic endometrium

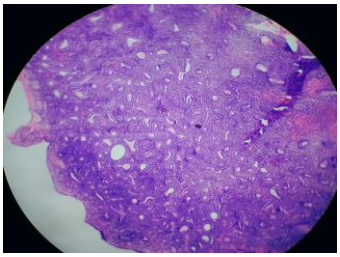


Fig-2: **Simple hyperplasia without atypia**

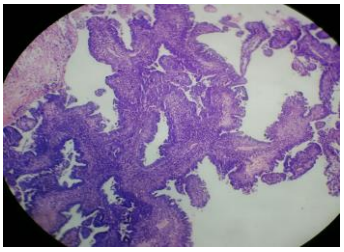


Fig-3: **Moderately differentiated adenocarcinoma**

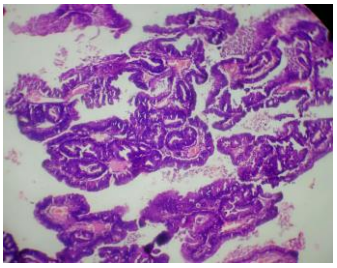


Fig-4: Papillary adenocarcinoma of endometrium

CONCLUSIONS

The ideal screening method should be safe, less or non invasive, less costly and giving rapid result. Dilatation and fractional curettage is a blind and invasive procedure and provides adequate tissue for histological analysis in only a few cases. It is associated with significant complications like perforation, infection, haemorrhage and any of these three complications could result in an unplanned laparotomy and even hysterectomy.

Transvaginal ultrasound is relatively cheap, easy, non invasive and needs no anaesthesia. It does not need a full bladder, avoiding discomfort with the transabdominal full bladder procedure. It also detects the concomitant pelvic pathology. It is not associated with any complications. It is readily acceptable by most of the patients. But, the diagnostic accuracy of the

transvaginal ultrasound depends on the experience and skill of the operator.

In the present study of 50 postmenopausal women, only one patient with endometrial thickness less than 4mm had abnormal endometrium on histopathological examination.

So, Transvaginal ultrasound can be used as a screening procedure for evaluation of endometrium in postmenopausal women, taking the cut- off value for endometrium as 4mm.

Limitations of the study

- Small sample of 50 cases
- Hysteroscopy could not be done due to non availability

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