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Research Article

Endometrial Study in Postmenopausal Women

Kavya Kota[1]*, B Mani Deepika Reddy[1] and Manchuru Aruna[2]

[1]*Junior Resident, Department of Obstetrics and Gynaecology, JJM Medical College, Davangere, Karnataka, India*

[2]*Senior Resident, Department of Obstetrics and Gynaecology, JJM Medical College, Davangere, Karnataka, India*

***Corresponding Author**: Kavya Kota, Junior Resident, Department of Obstetrics and Gynaecology, JJM Medical College, Davangere, Karnataka, India. **E-mail:** dr.kavya52@gmail.com

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Abstract

Background: Health aspects in postmenopausal women have gained importance in recent years owing to the increased life expectancy. Out of all gynaecological (40%) cancers, Endometrial cancer is currently the most common gynecological malignancy in developed countries. Endometrial carcinoma fortunately when detected early can be cured with less morbidity and mortality. It has much higher cure rates if diagnosed early. In contrast to cervical cancer, there are no routine mass screening programs for the early detection of endometrial abnormalities.

Objective: To evaluate the endometrial pathology by TVS, efficacy of pipelle biopsy and hysteroscopy guided biopsy in postmenopausal women with endometrial thickness of ≥ 4 mm.

Materials and Methods: A total of 60 patients attending gynaecological OPD in JJM Medical College were taken for the study. All postmenopausal women will initially undergo a transvaginal ultrasonography and women with endometrial thickness ≥ 4mm will be further subjected to pipelle biopsy and hysteroscopy guided biopsy.

Results: Majority of postmenopausal women were in the age group of 51 - 60 years and presented with PMB as a leading symptom. 30% of women with endometrial thickness between 4 - 5 mm had atrophic endometrium. Carcinoma endometrium was diagnosed in 5 cases by hysteroscopy guided biopsy whereas by pipelle only 2 cases were detected.

Conclusion: Transvaginal sonography was initially used to evaluate patients with PMB. An endometrial thickness of 4 mm was taken as the cut off and subjected to hysteroscopy guided biopsy

Keywords: *Menopause; Postmenopausal Bleeding; Transvaginal Ultrasound; Hysteroscopy; Endometrial Cancer*

Introduction

Health aspects in postmenopausal women have gained importance in recent years owing to the increased life expectancy. According to WHO, the disability adjusted life expectancy (DALE) exceeds 70 years in about 24 countries, with women living longer than men by an average of 7 to 8 years [1]. The average age at menopause ranges from 45 years in the Indian woman to 51 years in the Western population depending on the hereditary, life style and nutritional factors [2-4]. Thus, a woman spends more than two to three decades of life in her menopause.

The principal gynecological cancers (breast, ovary, uterus, and cervix) account for over 40% of cancers found in women worldwide. However, large differences exist, in both their incidence and geographical distribution. Endometrial cancer is currently the most common gynecological malignancy in developed countries [5]. A number of reports have suggested that the incidence of carcinoma of the endometrium is increasing in the United States and other industrialized countries [6,7]. The incidence of endometrial cancer is 3.7% to 17.9% in

postmenopausal women with abnormal uterine bleeding [8,9]. The incidence of endometrial cancer in asymptomatic women was 0.13% and atypia was seen in 0.63% [10].

Endometrial carcinoma fortunately when detected early can be cured with less morbidity and mortality. It has much higher cure rates if diagnosed early. Localized disease (stage I and II) has a 5 year survival of 87% and 76% respectively, but much poorer for stage III with 5 year survival rate of < 60% [11]. Endometrial polyps often have hyperplastic changes and the risk of premalignant to malignant polyp increases with age, menopausal status and co-morbid conditions [12]. In contrast to cervical cancer, there are no routine mass screening programs for the early detection of endometrial abnormalities.

Traditionally dilatation and curettage has been used for endometrial sampling. Dilation and curettage is invasive, and is associated with a 1 - 2% complication rate, thus less invasive endometrial biopsy techniques are increasingly favoured for evaluating these women [13]. Although many safe techniques are now available for detecting and diagnosing neoplastic lesions of the endometrium, these methods are invasive [14,15]. It might be preferable to first use some non-invasive method, such as ultrasound, to identify women at risk who should undergo endometrial biopsy.

Trans-abdominal sonography can be used to detect many forms of endometrial pathology including cancer. Trans-vaginal sonography yields even more detailed images of the uterus [16,17]. It facilitates the measurement of endometrial thickness and morphology with good patient acceptance. Transvaginal sonographic measurement of endometrial thickness and morphology has been demonstrated to have high accuracy in excluding endometrial polyps, hyperplasia and cancer in women with post-menopausal bleeding [18]. It is minimally invasive and has high cancer detection rates [19,20]. In populations with 31% or less combined prevalence of endometrial carcinoma or atypical adenomatous hyperplasia, algorithms utilizing transvaginal sonography as the initial test are most cost effective when compared to biopsy based algorithms in evaluating perimenopausal and postmenopausal women with abnormal vaginal bleeding [21,22]. The society of Radiologists in Ultrasound sponsored Consensus Conference statement state that in the evaluation of women with PMB either transvaginal sonography or endometrial biopsy could be used safely and effectively as the first diagnostic step [23].

Objective of the Study

- To evaluate endometrial pathology in postmenopausal women with endometrial thickness ≥ 4 mm on transvaginal ultrasound.
- To evaluate the efficacy of pipelle aspiration biopsy and hysteroscopy guided biopsy in women with endometrial thickness ≥ 4 mm by transvaginal scan

Materials and Methods

With a level IV evidence, an observational study was performed from September 2017 to August 2018 in the department of Obstetrics and Gynaecology, Bapuji hospital, Chigateri Government General hospital, Women and Child Health hospital attached to JJM Medical College, Davangere, Karnataka, India. The patients for this study were recruited by convenient sampling technique. A total of 60 postmenopausal women who satisfied the inclusion and exclusion criteria were taken for the study.

Women who reported a period of at least 12 months of amenorrhea after the age of 40 years provided that the amenorrhea was not explained by medication or disease, women with postmenopausal bleeding on HRT and postmenopausal women with breast cancer on anti-estrogen therapy were included in the study. Women with bleeding diathesis and cardiac diseases, women with abnormal pap smear report/grossly abnormal cervix and women with diagnosed genital tract malignancy were excluded from the study.

All postmenopausal women whether symptomatic or asymptomatic who fulfil the inclusion criteria and were willing to participate in the study will be selected on the basis of purposive sampling. A detailed gynaecological history, systemic examination and routine Pap smear were taken. Informed and written consent of all cases for routine transvaginal sonogram were taken after explaining the procedure. All patients underwent trans-abdominal ultrasound followed by trans-vaginal sonogram. Patients with endometrial thickness ≥ 4 mm

were subjected to office pipelle biopsy and diagnostic hysteroscopy directed fractional curettage. Hysteroscopy results were compared with histological findings following endometrial biopsy.

Results

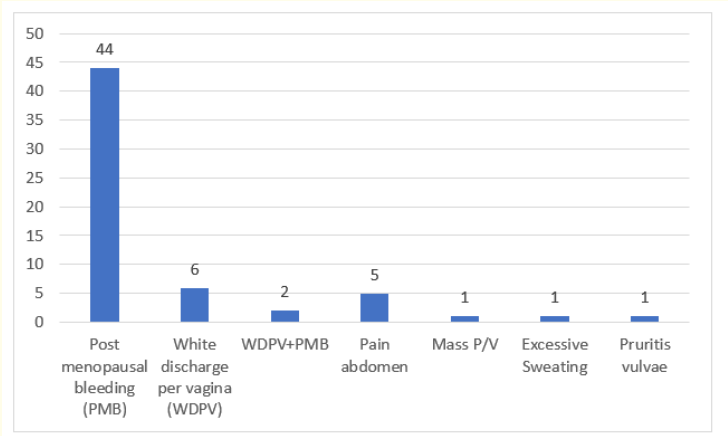
The analytical statistics were evaluated statistically with IBM SPSS Statistics for Windows, Version 24.0, IBM Corp, Chicago, IL. All 200 patients were subjected for statistical analysis. An observational endometrial study with 60 postmenopausal women is undertaken to evaluate the endometrial pathology and to study the efficacy of pipelle aspiration biopsy and its correlation with Hysteroscopy guided biopsy.

The majority of patients belonged to the age group of 51 - 60 years (59.8%) with mean (±SD) age being 54.68 ± 6.79 years. The youngest patient in this group was 40 years and the oldest patient was 68 years. 55% (n = 33) of patients presented within 1 - 5 years of menopause in this study where 15% (n = 9) of patients attained within 6 - 10 years, 18.3% (n = 11) of patients within 11 - 15 years and 11.7% (n = 7) of patients within 16 - 20 years.

Age in years	Number of patients	%
< 50	14	23.3
51 - 55	19	31.7
56 - 60	17	28.3
61 - 65	8	13.3
66 - 70	2	3.3
Total	60	100.0

Table 1: *Age distribution of patients studied.*

The most common symptom occurred in our study were post menopausal bleeding in 73.3% (as mentioned in graph 1). Most of the women in our study were multiparous in 98.4% and uniparous in 1.7%. A total of 24 patients (40%) have no risk factors and 36 patients (60%) have risk factors. The following risk factors were observed in risk factor group namely DM (n = 4, 6.7%), HTN (n = 6, 10%), DM + HTN (n = 6, 10%), obesity (n = 11, 18.3%), hypothyroidism (n = 1, 1.7%), late menopause (n = 5, 8.3%), tamoxifen usage (n = 2, 3.3%) and nulliparity (n = 1, 1.7%).



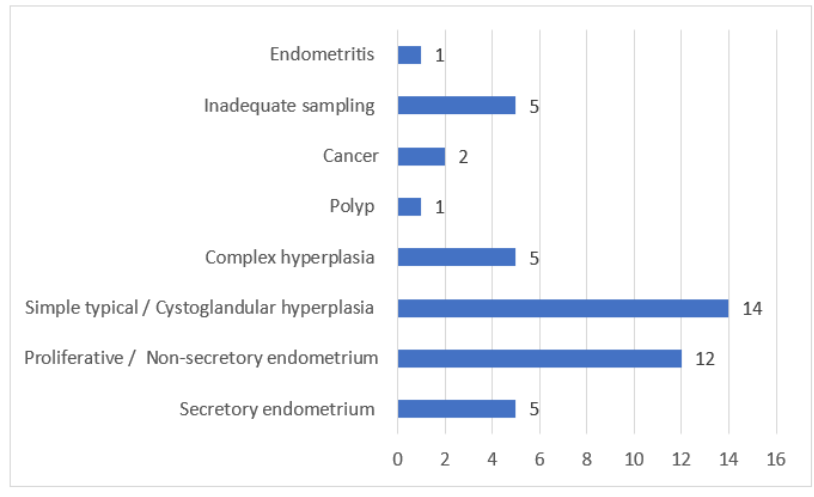
Graph 1: *Symptomatology.*

The majority of women (n=38, 63.33%) had an endometrial thickness between 4 - 8 mm. Out of which 30% has been diagnosed as atrophic endometrium. Two patients with endometrial thickness of 19 - 23 mm had Ca endometrium.

TVS (mm)	Number of patients (n = 60)	%
4 - 8	38	63.3
9 - 13	12	20.0
14 - 18	8	13.3
19 - 23	2	3.3

Table 2: *Distribution of patients according to TVS (mm).*

Pipelling could not be done due to cervical stenosis in 1 case. On MRI it was diagnosed as Ca endometrium (stage 1b) at the isthmus. No sample was obtained in 5 cases and in these patients endometrial thickness was between 4 - 5 mm. Normal endometrium includes atrophy, secretory and proliferative endometrium. In complex hyperplasia, 1 case had typical hyperplasia and 4 cases had atypical hyperplasia.



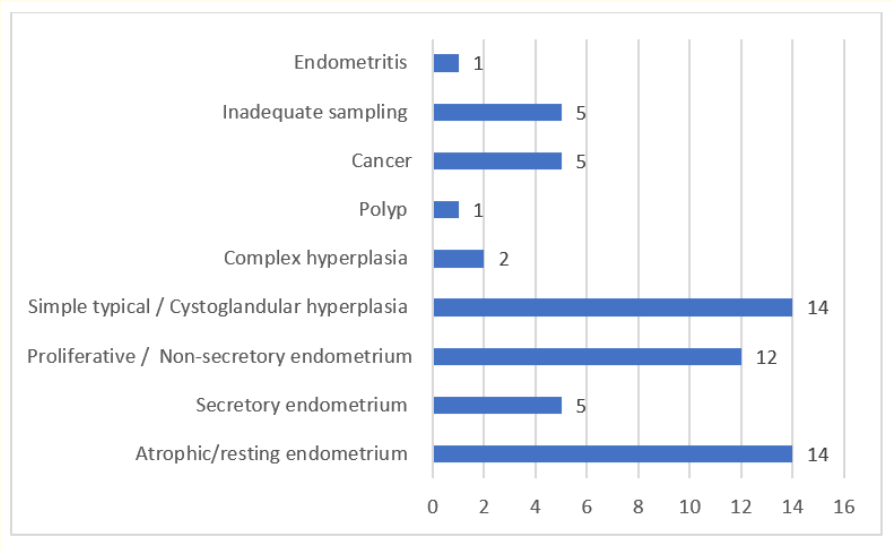
Graph 2: *Distribution of patients according to Pipelle biopsy.*

With pipelle biopsy, only 2 out of 5 cases were diagnosed as Ca endometrium. As endometrial thickness increased more pathological endometrium could be diagnosed with pipelle biopsy (as mentioned in table 3).

Pipelle biopsy	Endometrial thickness by TVS (mm)			
	4 - 8	9 - 13	14 - 18	19 - 23
Atrophy	1	4		
Secretory	2	1	2	
Proliferative	8	3	1	
Simple hyperplasia	7	5	2	
Complex hyperplasia	2	2		1
Polyp			1	
Carcinoma			1	1
Inadequate sample	4	1		
Endometritis			1	

Table 3: *Correlation of pipelle biopsy with endometrial thickness by TVS.*

Hysteroscopy could not be done in one case due to cervical stenosis where MRI diagnosed as Ca endometrium. Hysteroscopy could diagnose Ca endometrium in all 5 cases. No sample was obtained in 5 cases and most of them had an endometrial thickness between 4 - 5 mm.



Graph 3: *Distribution of patients according to Hysteroscopy directed biopsy.*

Pathological findings	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
Atrophic/resting endometrium	100.00	100.00	100.00	100.00	100.00	< 0.001**
Secretory endometrium	100.00	100.00	100.00	100.00	100.00	< 0.001**
Proliferative endometrium	100.00	100.00	100.00	100.00	100.00	< 0.001**
Simple hyperplasia	100.00	100.00	100.00	100.00	100.00	< 0.001**
Complex hyperplasia	100.00	94.74	40.00	100.00	94.92	< 0.001**
Polyp	100.00	100.00	100.00	100.00	100.00	< 0.001**
Carcinoma	40.00	100.00	100.00	94.74	94.92	< 0.001**
Inadequate sample	100.00	100.00	100.00	100.00	100.00	< 0.001**
Endometritis	100.00	100.00	100.00	100.00	100.00	< 0.001**
Overall inference	94.9% cases the Pipelle biopsy is correlating with hysteroscopy directed biopsy with P < 0.001**					

Table 4: *Correlation of pipelle biopsy and hysteroscopy directed biopsy.*

In pipelle biopsy, 3 cases reported as complex atypical hyperplasia were diagnosed as adenocarcinoma by hysteroscopy directed biopsy. Hysteroscopy is the gold standard for the diagnosis of endometrial pathology especially in women with PMB as pipelle biopsy can miss focal lesions.

Discussion

The most frequent symptom suggesting an endometrial pathology is uterine bleeding. Each postmenopausal bleeding requires to be investigated. Although the incidence of carcinoma among these women is higher, other benign causes of postmenopausal bleeding such as normal proliferative or atrophic endometrium are much more common.

In cases of postmenopausal bleeding, for many years the most widely used technique for obtaining a sample of endometrium for histological evaluation was dilatation and curettage. However, this procedure has numerous limitations with a false negative rate between 2 - 6%. Such figures also hold true for other methods of obtaining endometrial sample such as pipelle biopsy as a single curettage will not remove all the surface of endometrium completely from the uterine cavity.

It seems clear therefore that the use of D and C/pipelle biopsy as the gold standard technique for the assessment of endometrial pathology has serious limitations. Hence a non-invasive diagnostic modality has to be used as a screening method. Transvaginal ultrasonography is a good method for the evaluation of endometrial pathology in postmenopausal women.

In our prospective analysis, the majority of patients belonged to the age group of 51 - 60 years (59.8%). Women of all parity were represented in the study. 55% of patients presented within five years of menopause in this study. 60% had associated co-morbid diseases. The leading symptom was postmenopausal bleeding accounting for 76.5%. Negative result (atrophic endometrium and inadequate sample) was obtained in 30% of patients and most of them had an endometrial thickness between 4 - 5 mm. The positive result was obtained in 70% of patients. Ca endometrium was diagnosed in 6 patients. Hysteroscopy guided biopsy could diagnose 5 cases whereas pipelle biopsy could diagnose only 2 cases of Ca endometrium. In one patient endometrial biopsy could not be done in whom MRI diagnosed stage 1b Ca endometrium at the isthmus.

Thomas Gredmark., *et al.* [24] reported that the occurrence of PMB decreased with increasing age but the probability of cancer as the underlying cause increased with age. Gull B., *et al.* [25] reported that several risk factors including hypertension and diabetes were associated with increased endometrial thickness and abnormality. Our experience with TVS suggests that it may be possible to exclude endometrial carcinoma or those at risk for endometrial hyperplasia with TVS and women with endometrial thickness of 5mm or less do not need pipelle biopsy/endometrial curettage. This would be beneficial especially to this group of patients who are quite often old and frail.

A measured thickness of at least 5 mm should be considered as an indication for further endometrial biopsy. Wikland., *et al.* [26] has shown that an endometrial thickness of < 4 mm indicates low risk for endometrial carcinoma and other major endometrial pathology in women with PMB and suggested that TVS should be the primary method for excluding any endometrial abnormality in women with PMB. Granberg., *et al.* [27] and Nasri., *et al.* [28] transvaginally scanned PMB patients and had chosen a thickness of 5 mm as a cut off point. Lerner JP., *et al.* [29] (Nordic trial) showed that if endometrial thickness of 4mm or less was the cut off point, then 50% of curettages could be avoided.

The endometrial thickness related to the histopathological diagnosis of atrophy in women with PMB was reported to 3.4 ± 1.2 mm in Granberg., *et al.* [27] study, 3.9 ± 2.5 mm in Karlsson., *et al.* [30] study and 4.6 ± 1.5 mm in the current study.

In the current study, the endometrial biopsy had a negative result of 31.6% and positive result of 69.4% which correlate with the study conducted by Guner., *et al.* [31] and the pipelle biopsy had 40% sensitivity, 100% specificity, 100% PPV and 94.7% NPV. Vandenbosch., *et al.* [32] conducted a study in which pipelle endometrial sampling had a sensitivity of 40% and specificity of 98.5% for endometrial disease.

O Ben Baruch., *et al.* [33] and O Critchley HO., *et al.* [34] and reported that sufficient endometrial sample was obtained in more than 85% (on average) women which was similar to our study where sufficient sample was obtained in 91.7%.

O Guido., *et al.* [35] did Pipelle biopsies in 65 patients and found that adequate tissue for analysis was obtained in 97%. O Guido and associates found that Pipelle missed 3 of the 5 polyps and a sub mucous fibroid and hence concluded "Pipelle is excellent for detecting global processes of the endometrium than focal lesions."

In our study endometrial carcinoma was missed in 3.33% cases when pipelle biopsy technique was used which correlates with the study done by Bunyavejchevin S., *et al.* [36] where 1 of 3 cases of adenocarcinoma could not be detected by pipelle. Even though pipelle is simple and easy method for endometrial sampling, the use of pipelle in the management of PMB should be done with caution. False negative could occur in the focal disease of malignancy of the endometrium.

In our study all 5 cases of endometrial carcinoma was detected by hysteroscopy directed biopsy whereas by pipelle biopsy only 2 cases were diagnosed. Tinelli R., *et al.* [37] concluded that hysteroscopy is a significantly more accurate diagnostic method for the detection of endometrial pathology than TVS, has better specificity, and should be considered for all patients with an endometrial thickness of >4mm with PMB.

Conclusion

Hence, from our reports, we suggest that hysteroscopy is a gold standard especially in high risk patients to investigate postmenopausal women with a thickened endometrium found on TVS. Hysteroscopy guided biopsy in postmenopausal women with uterine bleeding reduces the risk of false negative histopathological report which serves the useful method of visualizing the uterine cavity.

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Nil.

Conflict of Interest

Nil.

Acknowledgement

Nil.

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