EVALUATION OF POSTMENOPAUSAL BLEEDING BY USING PIPELLE CURETTE AND HYSTEROSCOPIC-GUIDED BIOPSY: A COMPARATIVE STUDY

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ABSTRACT

INTRODUCTION

The health aspects in postmenopausal women including postmenopausal bleeding have gained importance in the present days as the life expectancy has increased.

AIMS

To compare the diagnostic accuracy of Pipelle biopsy and hysteroscopic-guided biopsy in the detection of endometrial pathologies in women with postmenopausal bleeding and to calculate sensitivity, specificity, predictive values for Pipelle endometrial sample in comparison to hysteroscopic-guided biopsy.

MATERIALS AND METHODS

This was a prospective comparative study carried out in the Department of Obstetrics and Gynaecology over a period of one year nine months in 100 postmenopausal women attending Gynaecology Outpatient Department and having postmenopausal bleeding as the chief complaint.

RESULTS

In our study, mean age of women presented with postmenopausal bleeding was 54.76±8.02 years. The mean duration of menopause was 7.95±5.40 years. 66% cases were para 4 or above. 62 cases (62%) had one or more risk factors hypertension being the most common present in 22 cases (22%). Majority of women with postmenopausal bleeding had endometrial thickness between 5-8 mm (44%) on TVS. Histopathological findings of Pipelle endometrial biopsy compared with hysteroscopic-guided biopsy in diagnosing polyps showed statistically significant difference with p value 0.0, whereas, for atrophic, proliferative endometrium, hyperplasias, carcinoma, it was statistically insignificant (p value >0.05). Sensitivity of Pipelle for detecting focal endometrial lesions is lesser than hysteroscopic biopsy.

CONCLUSION

Endometrial sampling with Pipelle alone is not effective for diagnosing focal endometrial lesions. Hence, Pipelle can be used as a first line investigation for histopathological evaluation of postmenopausal bleeding. Whenever focal lesions are suspected as on a TVS, a hysteroscopic biopsy is preferable.

KEYWORDS

Postmenopausal Bleeding, Endometrial Biopsy, Pipelle, Hysteroscopic Biopsy.

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INTRODUCTION: The health aspects in postmenopausal women have gained importance in the present days as the life expectancy has increased. In many countries, the life expectancy of women is more than that of men by 7 to 8 years.[1]

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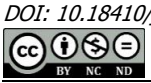

The Indian woman on an average attains menopause around 45 years and in the western population menopausal age is around 51 years.[2] Thus, the postmenopausal years makes up a substantial period of a woman's life. Cancers of breast, ovary, uterus and cervix account over 40% of cancers found in women all over the world. However, the incidence varies based on the geographical distribution. In India, cervical cancer predominates over other gynaecological malignancies and the incidence of endometrial carcinoma is as low as 5-7% of all genital cancers.[3] Patients with Postmenopausal Bleeding (PMB) have 10%-15% chances of having endometrial carcinoma and therefore the diagnostic workup is aimed at excluding malignancy. Endometrial carcinoma has much higher cure rates and less mortality and morbidity if diagnosed early.[4]

In contrast to cervical cancer, there are no routine mass screening programs for the early detection of endometrial abnormalities. Compared with traditional methods such as curettage, hysteroscopy offers the possibility of visualising macroscopic or focal abnormalities and taking directed biopsies.[5] With the development of smaller diameter hysteroscopic systems, patient acceptance has improved considerably and hysteroscopy nowadays can be performed in an outpatient setting without the use of anaesthesia.[6]

AIMS AND OBJECTIVES:

1. To compare the diagnostic accuracy of Pipelle biopsy and hysteroscopic-guided biopsy in the detection of endometrial pathologies in women with postmenopausal bleeding.
2. To calculate sensitivity, specificity, predictive values for Pipelle endometrial sample in comparison to hysteroscopic-guided biopsy.

MATERIALS AND METHODS: This was a prospective comparative study carried out in the Department of Obstetrics and Gynaecology, Modern Government Maternity Hospital, Petlaburj, Hyderabad, over a period of one year nine months from December 2012 to August 2014. The study included 100 postmenopausal women attending Gynaecology Outpatient Department (OPD) with the complaint of per vaginal bleeding with the following criteria.

Inclusion Criteria: Postmenopausal women (at least 1 yr. of amenorrhea) with complaint of per vaginal bleeding provided that the amenorrhea was not explained by medication or disease.

Exclusion Criteria:

- Women with bleeding diathesis.
- Obvious cause of bleeding from cervix and vagina.
- Women with diagnosed genital tract malignancy.
- Women on anticoagulant therapy.
- Surgical menopause.
- Women taking Hormone Replacement Therapy (HRT).
- Women with postmenopausal bleeding with genital prolapse.
- Transvaginal Sonogram (TVS) showing adnexal pathology.
- Women with postmenopausal bleeding who fulfilled the inclusion criteria and were willing to participate in the study were selected.
- All the patients with postmenopausal bleeding were worked up according to the following procedure.
- For each patient, detailed history was taken, which included severity and duration of Postmenopausal Bleeding (PMB), duration of menopause, menstrual and obstetric history, general medical history, history of gynaecologic operations, drug intake and associated symptoms. A thorough general and systemic examination was done along with abdominal, vaginal and rectal examinations.
- Pap smear was done.
- Endometrial Thickness (ET) was measured in the longitudinal plane on TVS. The adnexal region was also covered in the ultrasonic examination to exclude extrauterine pelvic masses.
- Clinical and sonographic evaluation was followed by Pipelle biopsy and hysteroscopic-guided biopsy.

Informed and written consent was taken from all the subjects after explaining the procedure.

Technique for Pipelle Biopsy and Hysteroscopy-Guided Biopsy: The patient was advised to take a nonsteroidal anti-inflammatory drug one hour before the procedure to decrease uterine cramping. Initially, a pelvic examination was performed to determine whether the uterus was anteverted or retroverted. The cervix was swabbed with iodine. Uterine sound was passed to know the uterocervical length. Then, the Pipelle was inserted through the cervical os. When persistent resistance to the Pipelle is felt, the procedure should be abandoned because of the danger of creating a false passage through the cervical os and risk of perforation. Once the Pipelle is in the uterine cavity, suction is created by withdrawing the piston. While moving the Pipelle in and out, the cannula is slowly rotated 360° so that the sample is taken from a wide area of the uterine cavity. To increase the area of sampling, the cannula can be advanced again into the cavity before it is withdrawn entirely. Once the Pipelle is full, another Pipelle can be used if there is a lot more tissue in the cavity. The tissue is then placed in a container of formalin fixative and submitted for histopathological examination.

For hysteroscopy, ideally the best time is during the early proliferative phase in reproductive age. This allows for best visualisation of the endometrial surface and any intrauterine pathologic condition. In luteal phase, the endometrium is much thicker and may cause difficulty in visualisation. In postmenopausal bleeding women, it can be done at any time except during the bleeding episode because it obscures the view. Paracervical blockade with the local anaesthetic agent 20 mL of 1% lidocaine mixed with 5U of vasopressin was used. In addition, intravenous sedation was also used in a few patients. Hysteroscopy was carried out with the patient in the dorsal lithotomy position.

Assembling the Equipment: The basic diagnostic set up included a speculum, swab holder, single-toothed tenaculum, hysteroscope and outer sheath, illumination system, distension medium and video equipment. A set of cervical dilators should be available though they were rarely used during diagnostic hysteroscopy. Hysteroscope was inserted into the sheath and the lock ring closed.

The distension system was connected to the inflow stopcock and the sheath flushed thoroughly to demonstrate easy passage of the medium. The light cable was attached to the light post of telescope and cold light was switched on. Once the scope was inserted through the external os, it was advanced and withdrawn slightly to allow direct visualisation of the internal os, which appeared as a dark circle.

The area that represented the internal os was at 12 o'clock position at the edge of the field of vision when the scope was upright and at 6 o'clock position when the scope was inverted. Endocervical canal and endometrium should not be disturbed as far as possible so as to ensure better visualisation.

The hysteroscopy findings were recorded as below:

1. Normal.
2. Atrophic.
3. Endometrial hyperplasia.
4. Endometrial carcinoma - obvious intrauterine growth with necrotic tissue was seen.
    - Endometrial biopsy with curette was taken in all the cases.
    - Histopathological findings of Pipelle biopsy were compared to hysteroscopic-guided biopsy.

OBSERVATIONS AND RESULTS:

Age in Years	Number of Patients	%
<50	36	36
51-55	26	26
56-60	24	24
61-65	6	6
66-70	4	4
71-75	2	2
76-80	-	-
81-85	2	2
Total	**100**	**100**

Table 1: Age Distribution of Patients Studied

In our study, mean age of women presented with postmenopausal bleeding was 54.76±8.02 years. Youngest patient presenting with PMB was 43 years and the oldest patient was 85 years. The mean duration of menopause for the 100 subjects was observed to be 7.95±5.40 years. Out of 100 individuals, only 4 cases (4%) were nulliparous, 30 cases (30%) were para 1 to 3 and 66 cases (66%) were para 4 and above. Out of 100 subjects, 38 cases (38%) had no risk factors, whereas, 62 cases (62%) had one or more risk factors.

Hypertension was present in 22 cases (22%), diabetes mellitus in 6 cases (6%), obesity in 4 cases (4%) and a combination of these risk factors along with others such as hypothyroidism, nulliparity were seen in 30 cases (30%). The Endometrial Thickness (ET) by TVS was noted for all the cases. The ET was less than 4 mm in 22 cases (22%), 5-8 mm in 44 cases (44%), 9-13 mm in 20 cases (20%), 14-18 mm in 12 cases (12%) and 19-23 mm in 4 cases (4%).

Majority of women with postmenopausal bleeding had endometrial thickness between 5-8 mm (44%).

Histopathology	Pipelle Biopsy (n=98)	Hysteroscopic-Guided Biopsy (n=98)	p value
Atrophic endometrium	20	20	1
Proliferative endometrium	20	20	1
Simple hyperplasia	24	24	1
Complex hyperplasia	22	14	0.092
Polyp	2	8	0.045
Carcinoma	4	6	0.502
Inadequate	6	6	

Table 2: Correlation of Pipelle Biopsy and Hysteroscopic-Guided Biopsy

Pipelling and hysteroscopic biopsy could not be done in 2 cases due to cervical stenosis. Inadequate/No sample obtained in 6 cases and in these patients endometrial thickness was $\leq$4 mm on TVS. By Pipelling technique, complex hyperplasia cases were 14 out of which Typical were 14 and Atypical were 8 cases. Out of 8 cases which were detected as complex hyperplasia by Pipelle biopsy, 6 were diagnosed as polyps and 2 cases were diagnosed as endometrial carcinoma with hysteroscopy. Histopathological findings of Pipelle endometrial biopsy compared with hysteroscopic-guided biopsy in diagnosing polyps showed statistically significant difference with p value 0.04. Histopathological findings of Pipelle endometrial biopsy for atrophic, proliferative endometrium, hyperplasias, carcinoma were statistically insignificant with histopathological findings of hysteroscopy (p value >0.05).

Findings	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Atrophic Endometrium	100.00	100.00	100.00	100.00	100.00
Proliferative Endometrium	100.00	100.00	100.00	100.00	100.00
Simple Hyperplasia	100.00	100.00	100.00	100.00	100.00
Complex Hyperplasia	100.00	89.74	63.44	100.00	91.30
Polyp	25.00	100.00	100.00	93.33	93.48
Carcinoma	66.67	100.00	100.00	97.72	97.82

Table 3: Pipelle Biopsy Results in Comparison to Hysteroscopic-Guided Biopsy

The sensitivity of Pipelle in diagnosing atrophic endometrium, hyperplasia, proliferative endometrium was 100% and diagnostic accuracy was 100% except for complex hyperplasia (91.3%). The sensitivity of Pipelle device in diagnosing carcinoma was 66.67%, specificity was 100% and accuracy was 97.82% whereas in diagnosing polyps, sensitivity was 25%, specificity was 100% and accuracy was 93.48%.

DISCUSSION: Menopause, the permanent cessation of menstruation is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhea. Postmenopause describes the period following the final menses.[2] Vaginal bleeding occurring any time after 6 months of amenorrhea in a menopausal age should be considered as postmenopausal bleeding. Any woman above 52 years irrespective of the menopausal status needs investigations to find the cause for the PMB.[3] There are various causes for PMB as follows.[3] Senile endometritis, tubercular endometritis, endometrial hyperplasia, polyp, endometrial carcinoma and sarcoma, mixed mesodermal tumours, benign and malignant lesions of vulva, foreign body such as ring pessary for prolapse, senile vaginitis, vaginal tumours (benign as well as malignant) and post radiation vaginitis, cervical polyps, decubitus ulcers in prolapse and the more common causes like cervical malignancy. Tubal and ovarian malignancies can also cause PMB. Other nongenital causes include urethral caruncle, papilloma and carcinoma of the bladder that maybe mistaken for genital tract bleeding. The less common systemic causes include hypertension and blood dyscrasias, drugs such as tamoxifen, which can cause endometrial hyperplasia and cancers. Indiscriminate or prolonged use of oestrogen unopposed by progestogens and HRT when applied cyclically and use of anticoagulants can also give rise to PMB.

Postmenopausal bleeding is a common problem representing 5% of all gynaecology outpatient attendances. It is not always possible to assign pathologic cause with certainty in Postmenopausal Bleeding (PMB) given the wide range of diseases that can cause it. It is an alarming symptom and requires immediate and thorough evaluation for the possibility of malignancy.[7] In earlier days, Dilatation and Curettage (D and C) was the method of choice for investigating patients with postmenopausal bleeding. However, this procedure has to be performed under general anaesthesia in an inpatient setting and in approximately 60% of the cases the entire uterine cavity fails to be sampled.[8] It is now considered as an outdated practice and has been replaced by less invasive techniques, which use better endometrial sample collecting devices. At present, many patients undergo hysteroscopic-guided biopsies as a routine OPD procedure.[9] In our study, majority of the patients belonged to the age group of <50 years (36%). Patients in the higher age group (71-85 years) were less (4%). Out of 6 cases diagnosed with carcinoma, 4 cases belonged to the age group of 70-85 years.

These findings are similar to the study by Gredmark et al[10] where they found decreased incidence of postmenopausal bleeding with increasing age while the probability of cancer as the underlying cause increased with increasing age. In the present study, women of all parity were present. Risk factors were present in 62% cases. The most common risk factor observed in our study was hypertension, which was present in 22% cases. Four cases of endometrial carcinoma had multiple risk factors such as diabetes mellitus, hypertension and obesity. The study by Gull et al[11] also reported that several risk factors including hypertension and diabetes are associated with increased endometrial thickness and abnormality. Weiderpass et al[12] have reported that recent overweight/obesity and diabetes mellitus (types 1 and 2) are associated with increased risk for endometrial cancer. Hypertension increases risk all the more in obese women. Increased endometrial thickness correlates well with presence of endometrial pathology such as hyperplasia and carcinoma in women with PMB. Granberg et al[13] reported 9.7±2.5 mm ET for hyperplasia and 18.2±6.2 mm for endometrial carcinoma. This compares well with our study where endometrial hyperplasia and carcinoma had 9.5±3.7 mm and 18.33±1.86 mm ET, respectively. The endometrial thickness related to the histopathological diagnosis of atrophy also in women with PMB. Granberg et al[13] reported the ET as 3.4±2.5 mm and Karlsson et al[14] found it to be 3.9±2.5 mm for atrophic endometrium. This compares well with our present study where the atrophic endometrium had a thickness of 3.9±1.4 mm.

In our study, endometrial biopsy had a negative result of 26% and positive result of 74%, which correlates with the study by Guner et al[15] where they found negatives result in 25.1% cases and positive result in 74.8% cases. (Negative report includes atrophic endometrium and inadequate sample and positive report includes proliferative endometrium, hyperplasia, polyp, carcinoma endometrium). In this study, Pipelle biopsy had shown a sensitivity of 66.67%, specificity of 100%, PPV 100% and NPV 97.72%, accuracy of 97.72% for diagnosing endometrial carcinoma.

The sensitivity of aspiration sampling in detecting uterine cancer varies in studies from 67% to 100%. The overall specificity is around 100%. In studies by Guido et al[16] and Ferry et al,[17] the lower sensitivities (83% and 67%, respectively) are explained by various factors in the study population. In Guido et al[16] study, 5 of the 11 false negative results were patients in whom the malignancy was confined to a polyp. When there is a small focus of malignancy, the Pipelle is more likely to miss it, because it samples a small percentage of the endometrial area. The low sensitivity found in Ferry et al's[17] study can be explained by the fact that all of the patients had undergone a prior dilatation and curettage procedure thereby losing most of the diagnostic tissue. Their observations compare well with the present study where we found 66.67% sensitivity by the Pipelle technique.

The diagnostic accuracy of Pipelle in detecting endometrial carcinoma in this study was 97.82%, which correlates well with the study of Dijkhuizen et al[18] a meta-analysis, in which the detection rate for endometrial carcinoma in postmenopausal bleeding women was found to be 99.6%. Baruch et al[19] observed in their study that sufficient endometrial sample was obtained in 90.6% of women and the discomfort caused was only very slight, which is similar to our study where sufficient sample was obtained in 94%. Guido et al[16] did Pipelle biopsies in 65 patients and found that adequate tissue for analysis was obtained in 97%.

Study	Year	%
Guido et al[16]	1995	97%
Baruch et al[19]	1994	90.6%
Present Study	2014	94%

Table 4: Adequacy of Tissue Sample by Pipelle Biopsy in Different Studies

In this study, 6 out of 8 polyps were missed by Pipelle biopsy, i.e. sensitivity was 25% whereas all 8 cases of polyps were diagnosed with hysteroscopic-guided biopsy. The study conducted by Angioni et al[20] as blind biopsy showed a sensitivity of 11%, a specificity of 93% with an accuracy of 59% in detecting endometrial polyps and they concluded that blind biopsy demonstrates very low sensitivity and accuracy in the diagnosis of benign focal intracavitary lesions. Hysteroscopy is thought of as the gold standard in the assessment of abnormal uterine bleeding in menopause. This procedure allows direct visualisation and targeted biopsy of lesions within the endometrial cavity thereby reducing the false negatives. In this study, endometrial carcinoma was missed in 2 of 6 cases (33.3%) of adenocarcinoma when Pipelle biopsy technique was used. Similar findings were noted in a study conducted by Bunyavejchevin S et al[21] where 1 of 3 cases (33.3%) of adenocarcinoma could not be detected by Pipelle. Even though, the Pipelle device is simple and easy for endometrial sampling, it should be used with caution in the management of PMB. It fails to sample focal lesions like polyps and malignancies of the endometrium.

In our study, hysteroscopic-guided biopsy diagnosed all 8 cases of polyps and 6 cases of endometrial carcinoma, whereas, the Pipelle biopsy could not pick up 6 cases of polyps and 2 cases of endometrial carcinoma. Hysteroscopic-guided biopsy in postmenopausal women with uterine bleeding reduces the risk of false negative histopathological report. This is a useful method of visualising the uterine cavity. Tinelli et al[22] concluded hysteroscopy as more accurate diagnostic method for the detection of endometrial pathology than TVS and has better specificity and should be considered for all patients with an endometrial thickness of >4 mm with PMB. Tandulwadkar et al[23] observed that hysteroscopy provides precise diagnosis of various endouterine pathologies with sensitivity of 97% and specificity 98.6%. For obvious benign lesions, it also provides treatment in the same setting.

SUMMARY: Postmenopausal bleeding is a symptom not to be underestimated. Malignancy cannot be ruled out until proved otherwise and justifies a thorough evaluation of patients with this symptom along with histopathological confirmation.

In this Study:

- Mean age of women presenting with postmenopausal bleeding was 54.76±8.02 years and most of them were multiparous.
- Mean duration of menopause was 7.95±5.40 years.
- 62% of patients had risk factors.
- Histopathological findings of Pipelle endometrial biopsy compared with hysteroscopic-guided biopsy in diagnosing polyps and showed statistically significant difference with p value 0.04, whereas, for atrophic, proliferative endometrium, endometrial hyperplasia, endometrial carcinoma, it was statistically insignificant (p value >0.05).
- The sensitivity of Pipelle in diagnosing atrophic endometrium, hyperplasias, proliferative endometrium was 100% and diagnostic accuracy was 100% except for the complex hyperplasias where it was 91.3%.
- The sensitivity of Pipelle device in diagnosing carcinoma was 66.67%, specificity was 100% and accuracy was 97.82% whereas in diagnosing polyps sensitivity was 25%, specificity was 100% and accuracy was 93.48%.

CONCLUSION: Pipelle gives near equal percentage of correct diagnosis when correlated with hysteroscopic-guided biopsy. Random endometrial sampling with Pipelle alone is not effective for diagnosing focal endometrial lesions. Hence, Pipelle can be used as a first line investigation for histopathological evaluation of postmenopausal bleeding. Whenever, focal lesions are suspected as on a TVS, then a hysteroscopic biopsy is preferable.

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