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HYSTEROSCOPY ASSESSMENT OF ENDOMETRIAL PATHOLOGY WITH ENDOMETRIAL THICKNESS CUT-OFF VALUE 5mm IN POSTMENOPAUSAL WOMEN WITH VAGINAL BLEEDING

Gati Hayatullah[1*], Song Ji Rong[2] and Mirwais Alizada[3]

[1]*Resident, Department of Gynecology and Obstetrics, First Affiliated Hospital of Jiamusi University, Jiamusi University, 188 xuefu Road Jiamusi, Heilong jiang, China*

[2]*Professor and Head of Department of Gynecology and Obstetrics, Jiamusi University First Affiliated Hospital, Jiamusi, Heilong Jiang, China*

[3]*Resident, Department of Orthopedic-II, Jiamusi University First Affiliated Hospital, Jiamusi, Heilong Jiang, China*

ABSTRACT

Background: Postmenopausal Bleeding (PMB) is a common gynecological problem. Various cut-off values of endometrial thickness (ET) have been proposed to rule out endometrial carcinoma (EC) and avoid unnecessary tests. The object of our study was to assess the accuracy of hysteroscopy in evaluating endometrial lesions of postmenopausal women with vaginal bleeding and to correlate incidence of EC considering ET cut-off value of 5mm.

Materials and method: 102 postmenopausal bleeding women were studied retrospectively. ETs of all subjects were measured by transvaginal ultrasonography (TVU), succeeded by hysteroscopy, and eye-directed biopsies were taken during hysteroscopy. Clinical and demographic characteristics of all patients were correlated with EC. Sensitivity, specificity, PPV, and NPV of hysteroscopy with 95% confidence interval have been determined against histopathological findings, the later being considered the reference standard.

Results: The mean age of participants was 62.2±7.6 years (range 48 to 80). Of the 102 cases, n=34(33.33%) had ET< 5mm, of those 3(8.82%) women had endometrial cancer. The remaining n=68(66.67%) cases had ET

≥ 5 mm, of those 21(30.88%) cases had EC. Histopathology showed normal result in 1(0.98%) case. Histopathology diagnosed hyperplasia in 9(8.82%) cases, polyp in 42(41.18%) cases, myoma in 8(7.84%) cases, EC in 24(23.53%) cases, endometritis in 4(3.92%) cases, and cervical lesions in 14[13(12.75%) benign and 1(0.98%) malignant] cases. Hysteroscopy showed an overall sensitivity of 95.05%, specificity of 100%, PPV of 100, NPV 16.67% and accuracy of 95.1%. Hysteroscopy showed high sensitivity, specificity, PPV, NPV and accuracy for polyp and endometrial carcinoma. But substantially lower sensitivity and PPV for diagnosing hyperplasia.

Conclusion: Endometrial thickness is unreliable for excluding endometrial carcinoma and/or avoiding further invasive investigations in women with PMB. Despite the fact that hysteroscopy is highly accurate in diagnosing intrauterine lesions but direct biopsy in all patients for the diagnosing of postmenopausal uterine bleeding is warranted.

Key words: Postmenopausal Bleeding, endometrial thickness, Hysteroscopy, histopathology, sensitivity, specificity, PPV, and NPV

INTRODUCTION

Uterine bleeding that takes place more than one year after the last day of the last menstrual cycle is defined as PMB. Due to common occurrence of anovulatory “cycles” with multimonth amenorrhea ahead to menopause, no consensus is present in relation to proper interval of amenorrhea prior to an episode of bleeding that can define PMB [4]. PMB is the most common problem that makes the patients to visit gynecologist [8] and 10% of general population has PMB [9]. Benign pathology of the endometrium accounts for almost 90% etiology of PMB with only 10% of the cases having endometrial carcinoma (EC), while in some cases incidence of EC goes up to 60% in this population [1, 2, 3, 7, 9, 10, 12]. 80% to 90% postmenopausal women with EC have vaginal bleeding (VB) as their chief complaint [1, 2, 5, 7, 9, 10]. Immediate and precise diagnosis of endometrial cancer in women with PMW is essential for the survival of the patients [16].

Techniques that are frequently used for the investigation of postmenopausal bleeding women are TVU, saline infusion sonography (SIS), dilatation and curettage (DC), hysteroscopy (HY), and direct endometrial sampling [6].

Dilatation and curettage (DC), which was considered gold standard diagnostic modality in the assessment of PMW with uterine bleeding, has been used for decades. This modality has a large number of drawbacks mainly due to being a blind procedure and can easily miss certain endometrial lesions such as polyps, submucous leiomyomata, and focal hyperplastic or neoplastic lesions [2,3, 8, 11, 12, 14, 28]. Non-

invasive techniques such as TVU are getting popular due to its high acceptability and feasibility [18].

TVU is first-line modality used for the assessment of PMB, which is non-invasive, cost-effective, having high feasibility and acceptability [8, 13, 15, 16, 17, 18]. However, this modality has a low specificity and sensitivity [8]. Cut off value for endometrial thickness measured by TVU is still controversial and various values have been studied. Endometrial thickness (ET) of 5mm is considered to have high sensitivity and specificity for detecting endometrial carcinoma [1, 16, 17]. Even though endometrium is expressed normal if its thickness <4mm [2,13, 16], but endometrial carcinoma is even reported at ET of 3mm and 4mm [16, 17, 18]. Endometrial thickness of 4mm-5mm is globally accepted as threshold point for assessing EC in women with postmenopausal bleeding. ET< 4mm is hardly related with risk for EC [20]. If endometrial thickness is more than 4mm evaluation by second-line modalities such as HY and endometrial biopsy (EB) is recommended [13, 16, 25].

Hysteroscopy (Hy) is “gold standard” modality, which is accurate, highly sensitive, direct to point, minimal invasive, timesaving, and highly specific technique for assessment of intrauterine lesions of PMW with vaginal bleeding. The test almost has the same accuracy as histopathology of the endometrium [8,3,19,21, 28]. HY allows direct visualization of the uterine cavity. It’s “see-and-treat” potential increased its feasibility and acceptability. Focal and diffuse biopsies of the uterine cavity can be taken accurately and reliably [5,8,13 19, 16, 22, 25]. In addition to being a successful and direct to point diagnostic technique, it is best therapeutic minimal invasive surgical modality for excising benign intrauterine cavity lesions. [5,8,10,13]. The main drawbacks of Hy are its inability to provide information about extra uterine organs of the pelvic cavity, low feasibility due to intolerance by patients, chance of missing the correct point due to intrauterine bleeding and debris, and spreading of cancerous cells if not performed with care and skill [14, 18]. Frequently HY and TVU are used complementarily of each other [18]. Clinical and demographic features such as age, bleeding duration, attaining age of menopause also have role in assessing the chance of endometrial cancer [9].

The aim of this study was to assess the diagnostic accuracy of hysteroscopy with endometrial thickness cut-off value of 5mm in women with PMB, by comparing all hysteroscopic results with histopathological reports of the corresponding patients, and evaluated the correspondence between demographic features and incidence of EC in women presenting with PMB.

METHODS

From January 2015 up to September 2017, medical records of 102 postmenopausal women with vaginal bleeding, who were admitted to first affiliate Hospital of Jiamusi University, were collected from computerized database of department of obstetrics and gynecology. The demographic and clinical data such as age, age of attaining menopause, age since menopause, hypertension, diabetes mellitus, and bleeding

duration of all patients were retrieved from their medical records. Inclusion criteria were all postmenopausal women with vaginal bleeding who were admitted to hospital. Exclusion criteria were subjects who were taking hormone replacement therapy, taking tamoxifen, anticoagulant therapy, whose ultrasound report and/or hysteroscopy and/ or histopathological reports were missing. The patients with conditions that are contraindicated for performing hysteroscopy were also excluded. All patients underwent a thorough physical examination including abdominal, pelvic, vaginal and rectal examinations. Endometrial thickness was measured with TVU followed by hysteroscopy and eye-directed biopsy during hysteroscopic examination.

All ultrasound examinations were performed with a Siemens ACUSON S2000 Ultrasound machine with a 4.0 MHz vaginal transducer. Endometrial thicknesses were measured in the longitudinal plane of uterus as double layer and the thickest point was taken. The results were classified according to thickness of the endometrium as <5 mm and ≥5 mm. Following the TVU examinations patients were directed for diagnostic and/or therapeutic hysteroscopic evaluation.

Professional doctor performed hysteroscopic procedures and topical oxybuprocain hydrochloride anesthetic gel was applied to cervix before the procedure. Rigid hysteroscopes with 3.5mm to 5mm outer diameter sheath and 30° fore oblique lens were used. 5% mannitol was used as distention media. An automated electronic device (Endo-mat, Karl Storz, Tuttlingen, Germany) was used for regulation of intrauterine pressure of 100-120mmHg. Paracervical block was used for hysteroscopy resection of intrauterine lesions and in patients with difficulty at the level of internal OS. Hysteroscopic findings were classified as hyperplasia, polyp, myoma, endometrial carcinoma, endometritis, cervical lesions (benign and malignant), and normal. Hysteroscopic results were compared with histopathological results of eye-directed biopsy. All cases were categorized according to the endometrial thickness as <5mm and ≥5mm, while under each category the hysteroscopic results were studied against histopathology.

Statistical analyses were performed using SPSS. Data was analyzed using Chi-square test. Fisher's exact test was used if the Chi-square test criteria were not met. Correlations between age and endometrial cancer, age since menopause and endometrial cancer, co-morbidities and endometrial cancer, bleeding duration and endometrial cancer were calculated. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of hysteroscopy were calculated. Incidence of endometrial carcinoma at cut-off value of 5mm was evaluated.

RESULTS

The most alarming symptom in postmenopausal women is vaginal bleeding; even one episode needs to be investigated promptly and cautiously. The study period was selected based on the availability of records of consecutive postmenopausal women who were admitted to hospital for vaginal bleeding and all of whom

underwent diagnostic hysteroscopy, therapeutic hysteroscopy or both.

Total number of subjects in this study was102. The mean age of the participants was (62.2±7.6) years, ranging from 48 to 80 years. The age of attaining menopause ranged from 40 to 59 years with an average of (51.6±3.7) years. The time since menopause ranged from 1 to 39 years with mean of (10.6±8.6) years.

In our study, even though the number of patients in their 50s was relatively higher 28 (27.45%) but the incidence of endometrial carcinoma (EC) was higher in subjects who were in their 60s.i.e. 9 out of 24 (37%) and 6 out of 19 (31.58%) women between the ages of 60 and 70 years had EC. None of the patients under the age of 50 had endometrial carcinoma [Table1].

Age	No. Of Patients	Incidence Of Endometrial Carcinoma (%)
<50	2	0(00.00)
50-54	13	3(23.08)
55-59	28	3(10.71)
60-64	24	9(37.50)
65-69	19	6(31.58)
70-75	8	2(25.00)
>75	8	1(12.50)

Table1: Correlation between age and incidence of EC (Original Table)

Figures in parenthesis are in percentage

The relation between the "years since menopause" and endometrial carcinoma was also evaluated which is shown in Table2. Patients, who were menopausal for a period of 20-24 years, had higher incidence of endometrial carcinoma, i.e. one out of two patients (50%) had EC, but this difference was not significant (p=0.1289)*

Years Since Menopause	No. Of Patients	Endometrial Cancer (%)
<5	33	4(12.12)
5-9	18	5(27.78)
10-14	23	8()34.78
15-19	14	5(35.71)
20-24	2	1(50.00)
≥25	11	1(09.09)

Table2: Correlation between years since menopause and incidence of EC (Original Table)

*Calculating alpha at 95% CI for this post hoc test by bonferroni correction method is (a'=0033), so we reject

null hypothesis if $p<0.00333$.

The correlation between "postmenopausal bleeding duration" and incidence of EC was studied. Subjects, who had postmenopausal bleeding for a period of 11-12 months, were at highest risk of EC i.e. out of 6 patients 4 had EC (66.67%), but this difference was not statistically significant ($p=0.0476$)*. These correlations are listed in Table 3.

Bleeding Duration (month)	No. Of Patients	Incidence Of EC (%)
<1	59(60.18)	10(16.95)
1-2	13(12.75)	4(30.77)
3-4	11(10.78)	5(45.46)
5-6	6(5.88)	0(00.00)
7-8	1(0.98)	0(00.00)
9-10	2(1.96)	0(00.00)
11-12	6(5.88)	4(66.67)
>12	4(3.92)	1(25.00)

Table 3: Correlation between the postmenopausal bleeding duration and endometrium cancer (Original Table)

*Calculating alpha at 95% CI for this post hoc test by bonferroni correction method is (a'=00179), so we reject null hypothesis if $p<0.00179$.

Association of co-morbidities with endometrial cancer was assessed as mentioned in Table4. Patients with both HTN and DM had high incidence of endometrial cancer i.e. 6 out of 10 (60%) patients with DM&HTN had endometrial carcinoma. However this difference was not significant ($p=0.0362$). Six out of 29(20.69) patients with HTN had EC. Subjects with only DM had no EC.

Co-morbid Conditions	No. Of Women With PMB	No. Of Women With EC
HTN	29	6(20.69)
DM	6	0(00.00)
HTN &DM	10	6(60.00)
NONE	57	12.(21.05)

Table 4: Correlation between co-morbid conditions and carcinoma of endometrium (Original Table)

*Calculating alpha at 95% CI for this post hoc test by bonferroni correction method is (a'=00179), so we reject null hypothesis if $p<0.0083$

HTN hypertension; DM diabetes mellitus;

Two classes of endometrial thickness were identified. The first class, thickness less than 5mm (n=34, 33.33%), comprised 2(5.88%) cases of hyperplasia, 12(35.29%) cases of polyp, 6(17.65%) cases of myoma, 3(8.81%) cases of endometrial carcinoma, 1(2.94%) cases of endometritis, 8(23.53%) cases of benign cervical lesions, 1 (2.94%) case of cervical carcinoma, and 1(2.94%) case of normal endometrium. The second class, thickness ≥5mm (n=68, 66.67%), comprised 7(10.29%) cases of hyperplasia, 30(44.12%) cases of polyp, 2(2.94%) cases of myoma, 21(30.88) cases of endometrial carcinoma, 3(4.41%) cases of endometritis, and 5(7.35%) cases of benign cervical lesions. Table 5 shows the incidence of normal and pathological endometrial results in relation to endometrial thickness.

Endometrial thickness	Hyperplasia	Polyp	Myoma	EC	Endometritis	Cervical lesions	Normal
<5mm n=34	2	12	6	3**	1	8+1*	1
ET≥5mm N=68	7	30	2	21	3	5	0

Table 5: cross-matched distribution of ultrasound measurement and histopathological classes (Original Table)

One case of cervical cancer; ** p=0.0133

Out of 102(100%) cases studied, 9(8.82%) cases had hyperplasia on histopathology. 42(41.18%) cases had polyp, 8(7.84%) cases had myoma, 24(23.53%) cases had endometrial carcinoma (EC), 4(3.92%) cases had endometritis, 14(13.73%) cases cervical lesions [1(0.98%) cervical cancer and 13(12.75%) cases benign cervical lesions], and 1(0.98%) case had normal endometrium. Table 6 demonstrates hysteroscopy and histopathology findings.

	Hysteroscopy=n (%)	Histopathology =n (%)
Hyperplasia	4(03.92)	9(08.82)
Polyp	43(42.16)	42(41.18)
Myoma	10(09.80)	8(07.84)
EC	22(21.57)	24(23.53)
Endometritis	3(02.94)	4(03.92)
Cervical lesions (Benign & Malignant)	14(13.73)*	14(13.73)*
Normal	6(05.88)	1(00.98)
Total	102	102

Table 6: Hysteroscopic and histopathological findings (Original Table)

*one cervical carcinoma and 13 benign cervical lesions; The figures in parenthesis are in percentage

Hysteroscopy diagnosed 6(5.88%) cases of normal endometrium, of which 1(0.98%) case was confirmed by histopathology, the remaining 3(2.94%) cases had hyperplasia and 2(1.96%) cases had endometritis on histopathology.

Hyperplasia was diagnosed in 4(3.92%) cases by hysteroscopy, of those 2(1.96%) cases were confirmed by histopathology and remaining 2(1.96%) cases were diagnosed endometrial cancer by histopathology. Hysteroscopy showed hyperplasia only in 2(1.96%) cases that had hyperplasia on histopathology. 2(1.96%) cases of polyp, 2(1.96%) cases of myoma, and 3(3.94%) cases of normal endometrium were reported by hysteroscopy that had hyperplasia on histopathology.

Polyp (n=43, 42.16%), being the commonest abnormality diagnosed by hysteroscopy, of which 40(39.22%) cases were confirmed by histopathology and the remaining 2 (1.96%) cases showed hyperplasia and 1(0.98%) case showed myoma on histopathology. 1(0.98%) case was diagnosed myoma and 1(0.96%) case was diagnosed endometritis by hysteroscopy that were shown polyp by histopathology.

Hysteroscopy showed endometrial carcinoma in 22(21.57%) cases and all cases were confirmed by histopathology. Histopathology diagnosed 24(23.53%) cases of endometrial carcinoma, of those 2(1.96%) cases were missed by hysteroscopy, which were diagnosed as hyperplasia.

Hysteroscopy diagnosed 13(12.75%) cases of benign cervical lesions and 1(0.98%) case of cervical carcinoma. All cases of cervical lesions (benign and malignant) were confirmed by hysteroscopy. Table 7 shows comparison of hysteroscopy findings and histopathology diagnosis.

	Histopathological results							
Hysteroscopy	Hyperplasia	Polyp	Myoma	EC	Endometritis	Cervical lesions (Benign & Malignant)	Normal	Total
Hyperplasia	2	0	0	2	0	0	0	4
Polyp	2	40	1	0	0	0	0	43
Myoma	2	1	7	0	0	0	0	10
EC	0	0	0	22	0	0	0	22
Endometritis	0	1	0	0	2	0	0	3
Cervical lesions (Benign & Malignant)	0	0	0	0	0	14*	0	14
Normal	3	0	0	0	2	0	1	6
Total	9	42	8	24	4	14	1	102

Table 7: Hysteroscopy versus histopathological results (Original Table)

*One case of cervical carcinoma

DISCUSSION

Postmenopausal uterine bleeding is an alarming symptom in women who are not on HRT. Postmenopausal bleeding can be caused either by benign or malignant endometrial lesions [9]. Therefore this symptom should be evaluated precisely in order to differentiate between these two conditions and mainly exclude endometrial malignant pathology. Many modalities are available for assessing cervical abnormalities but those regarding examining endometria lesions are still controversial.

D&C was considered the most common modality for obtaining endometrial sample, while this technique has serious assessment failure (2-6%), being invasive, blind, and high cost procedure [2,3,8,11,22]. There are also other blind techniques for obtaining histological sample, which bear the same drawbacks [3]. However, TVU became largely used modality for investigating endometrial pathologies in postmenopausal bleeding women, particularly over the last two decades [9, 29]. TVU carries a false negative rate of 3%, which may be explained by the fact that the presence of subendometrial edema makes it difficult to get an accurate measurement of the true endometrial thickness [35].

Due to high incidence of endometrial carcinoma in postmenopausal women with vaginal bleeding [1, 3] the selection of a simple and accurate diagnostic modality is a prompt necessity. In this regard, many studies have suggested threshold of 5 mm for pursuing endometrial sampling reasonably excludes malignant endometrial pathology and can avoid unnecessary diagnostic procedures [1,3].

Granberg *et al* studied 1110 women with postmenopausal bleeding prospectively, endometrial pathology was most common among the patients with endometrial thickness more than 8mm, while there was no endometrial cancer in subjects with endometrial less than 4mm [30]. Similarly, Nasri and Coast, taking cutoff value of 5mm of endometrial thickness over the entire uterine cavity, reported that there is no likelihood of endometrial cancer in postmenopausal bleeding women [31]. Although, it is proposed that further investigations are essential if the endometrial thickness is beyond 5mm [7], but endometrial carcinoma is reported even below this cut-of value. Bakour *et el* concluded that a threshold of 4 mm or less can reliably exclude malignancy in women with PMB [32], with an approximately one case of carcinoma missed for every 250 cases evaluated with endometrial thickness of less than 5 mm [33].

It should be emphasized that postmenopausal women with vaginal bleeding have been diagnosed with endometrial carcinoma with endometrial thickness as thin as 3mm [34]. It is reported in a study that three of nine cases of carcinoma had a thickness of 3 mm [33]. Some authors have proposed taking endometrial thickness of 3mm as a threshold to reduce the chance of missing cases of carcinoma [1]. It is also debated that there is no endometrial cutoff point that provides good diagnostic accuracy and/or reliably to

exclude the presence of endometrial cancer in patients with PMB [42].

Although the globally accepted threshold cut-off value of ET in postmenopausal bleeding women for assessing of endometrial carcinoma is from 4mm to 5mm [20], but endometrial thickness alone cannot exclude endometrial carcinoma and it is due to the fact that metrorrhagia and endometrial shedding could reduce endometrial thickness even in the presence of a malignancy [3].

Invasive modalities such as office endometrial sampling, sonohysterography, hysteroscopy or D&C are recommended in PMW with vaginal bleeding if endometrial thickness is above 4mm and/or endometrial thickness cannot be visualised adequately [36, 37]. Individual characteristics, including age, time since menopause, body mass index, endometrial thickness, presence of hormone therapy, history of recurrent bleeding, and history of diabetes may have high influence on the probability of endometrial cancer in women with postmenopausal women [36, 38, 39,40, 41].

All subjects of our study underwent hysteroscopy examination after measuring their endometrial thickness by TVU. In recent years, hysteroscopy is considered as first line and potential minimally invasive technique for assessment of postmenopausal bleeding women [35].

Diagnosis	Hysteroscopy							
	Specificity% (95%CI)	Sensitivity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Prevalence %	Accuracy (95%CI)	LR (+)	LR(-)
Overall	100 (2.50-100)	95.05 (88.82-98.37)	100	16.67 (7.84-31.98)	99.02 (94.66-99.98)	95.10 (88.93-98.39)	.	0.05 (0.02-0.12)
Hyperplasia	97.85 (92.45-99.74)	22.22 (02.81-60.01)	50.00 (13.74-86.26)	92.86 (90.15-94.86)	8.82 (04.11-16.09)	91.18 (83.91-95.89)	10.33 (1.65-64.85)	0.79 (0.56-1.13)
Polyp	95.00 (86.08-98.96)	95.24 (83.84-99.42)	93.02 (81.54-97.58)	96.61 (88.04-99.10)	41.18 (31.52-51.36)	95.10 (88.93-98.39)	19.05 (6.31-57.51)	0.05 (0.01-0.19)
Myoma	96.81 (90.96-99.34)	87.50 (47.35-99.68)	70.00 (42.64-87.99)	98.91 (93.57-99.82)	7.84 (3.45-14.87)	96.08 (90.26-98.92)	27.42 (8.74-86.05)	0.13 (0.02-0.81)
EC	100 (95.38-100)	91.67 (73.00-98.97)	100.00	97.50 (91.19-99.32)	23.53 (15.69-32.96)	98.04 (93.10-99.76)		0.08 (0.02-0.31)
Endometritis	98.98 (94.45-99.97)	50.00 (6.76-93.24)	66.67 (18.40-94.66)	97.98 (94.79-99.23)	3.92 (1.08-9.74)	97.06 (91.64-99.39)	49.00 (5.53-434.50)	0.51 (0.19-1.35)
Cervical lesions (Benign & Malignant)	100 (95.89-100)	100 (76.84-100)	100	100	13.73 (7.71-21.96)	100 (96.45-100)	.	0.00
Normal	95.05 (88.82-98.37)	100 (2.50-100)	16.67 (7.84-31.98)	100	0.98 (0.02 -5.34)	95.10 (88.93-98.39)	20.20 (8.59-47.48)	0.00

Table 8: Specificity, sensitivity, prevalence, and accuracy of hysteroscopy for diagnosing endometrial pathologies casing PMB (Original Table)

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio

Sensitivity	95.59%(95% CI, 87.64-99.08)
Specificity	.
Positive predictive value	100
Negative predictive value	0
Likelihood ratio for positive test	0.96
Likelihood ratio for negative test	0.06 (95% CI, 0.02-0.23)
Prevalence	100%(95% CI, 94.72-100)
Accuracy	95.59%(95% CI, 87.64-99.08)

Table 9: Accuracy of hysteroscopy for detection of intrauterine pathology in postmenopausal bleeding women with endometrial thickness ≥5mm (Original Table)

Sensitivity	93.94%(95% CI, 79.77-99.26)
Specificity	100%(95% CI, 2.50-100)
Positive predictive value	100
Negative predictive value	33.33(95% CI, 11.54-65.70)
Likelihood ratio for positive test	.
Likelihood ratio for negative test	0.06 (95% CI, 0.02-0.23)
Prevalence	97.06%(95% CI, 84.67-99.93)
Accuracy	94.12%(95% CI, 80.23-99.28)

Table 10: Accuracy of hysteroscopy for detection of intrauterine pathology in postmenopausal bleeding women with endometrial thickness less than 5mm (Original Table)

We found that endometrial cancer occurs at any age over 50 years, but more commonly in ages above 60 years. 75% of the endometrial cancer cases occurred in patients above 60 years. This is consistent with Phillip *et al* [14], who showed the highest incidence of endometrial cancer in patients of this age group.

The years since menopause is related to endometrial cancer, with 50% of the cases had cancer after a period of 20-24 years of menopause. This agrees with Phillip *et al* [14], who indicated that 50% of endometria cancer occurs in women with postmenopausal who had 22 years postmenopause.

We also studied the relation between postmenopausal bleeding duration and endometrial cancer, with 4 out of 6 women (i.e. 66.67%), whose postmenopausal bleeding duration was 11-12 months, had endometrial cancer. We found the association between co-morbidities and endometrial cancer, with six out of ten (i.e. 60%) women with DM&HTN had endometrial cancer, while none of the women with only DM had endometrial carcinoma.

In our study (n=34, 33.33%) had endometrial thickness less than 5mm, with endometrial cancer of 3(8.82%) cases. This is consistent with literature. Dørum *et el* [51] reported endometrial thickness of 6.67% in postmenopausal bleeding patients with endometrial thickness less than 5mm. Of the (n=68, 66.67%) cases with endometrial thickness of ≥ 5 mm, 21(30.88%) cases had endometrial carcinoma. These findings are

comparable with Gull *et el* [43].

Hysteroscopy has high diagnostic value in evaluating endometrial pathology in women with postmenopausal bleeding. Directly visualization of the endometrial cavity by hysteroscopy plays important rule for high sensitivity and specificity in diagnosing of endometrial pathology. In this study the overall sensitivity, specificity, PPV, NPV, and accuracy were 95.05 %, 100%, 100%, 16.67%, and 95.1% respectively. This is comparable with literature. In a prospective study of 106 women with postmenopausal bleeding who were not on hormonal therapy conducted by Loverro *et al* [3] showed the pooled sensitivity and specificity of hysteroscopy were 97.5% and 100% respectively. Tinelli et el [10] reported an overall sensitivity of 98%, specificity of 91%, a positive predictive value of 88%, a negative predictive value of 98%, and diagnostic accuracy of 94% for hysteroscopy. Ceci et al [50] reported a sensitivity of 98% and a specificity of 95%. However, NPV in our study was considerably lower than theirs. This may be explained by the high rate of pathologic findings in our study (99.02%) that led to a relatively small number of patients without pathology. Therefore, despite the fact that the total number of false-negative cases in the whole sample was low (5/102, 4.92%), false-negative cases constituted a significant proportion of the subjects who were diagnosed hysteroscopically as normal (5/6, 83.33%), leading to a decrease in NPV. Statistical values of hysteroscopy in diagnosing of various endometrial lesions, which were obtained in our study are shown in Table8.As such, the utility of a test, including PPV and NPV, should be interpreted in the context of the prevalence of pathology, a factor expressed by the likelihood ratio.

In our study hysteroscopy showed an accuracy of 95.1% in diagnosing a normal endometrium, which is higher than that of reported by Patil et al. [44], which showed 85.93% diagnostic accuracy of hysteroscopy for normal endometrium.

The commonest endometrial pathology in this study was polyp (41.18%, n=42). Hysteroscopy showed a high sensitivity and specificity for polyps in our study, which is comparable with the literature. We found that sensitivity, specificity, PPV, NPV and accuracy of hysteroscopy for diagnosing polyp were 95.24%, 95%, 93.02%, 96.61%, and 95.10 respectively. In a meta-analysis Gkrozou et al. [45] were able to show a sensitivity and specificity of 95.4% and 96.4% respectively. In a prospective study conducted by Patil et al [44] reported a sensitivity, specificity, PPV and NPV of 100% each for endometrial polyps. Non-pedunculated polyps may sometimes be confused as submucous fibroids on hysteroscopy.

We were able to find that hysteroscopy had 91.67% sensitive and 100% specific in diagnosing endometrial carcinoma, with PPV, NPV and accuracy of 100%, 97.5% and 98.04% respectively. Gkrozou et al. [44] in their systemic review and meta-analysis reported sensitivity of 82.6% and specificity of 99.7% of hysteroscopy in diagnosing endometrial carcinoma. Hysteroscopy missed two cases of endometrial carcinoma in this study. Hysteroscopy is significantly effective in excluding endometrial cancer in

postmenopausal women with uterine bleeding.

We found a sensitivity of 22.22%, a specificity of 97.85%, a PPV of 50%, a NPV of 92.86%, and accuracy of 91.18% of hysteroscopy in diagnosing hyperplasia. This is consistent with present literature. Bar-On et al. [49] showed a sensitivity of 25%, specificity of 96.6%. The visual accuracy of outpatient hysteroscopy seems to be inaccurate in diagnosing or exclusion of endometrial hyperplasia. The low prevalence of hyperplasia among our study cohort (9/102, 8.82%) and the proportionally high false-negative rate of the women who were histologically diagnosed with hyperplasia (7/9, 77.78%) are reflected in low sensitivity. Furthermore, in spite of the small proportion of false-positive cases (2/102, 1.96%), those cases had a significant negative effect on the PPV because of the low prevalence of hyperplasia. This is consistent with the findings of low sensitivity rates in other studies [7,47], and may indicate the importance of obtaining endometrial biopsies during those procedures to increase accuracy. The variation in the results of different studies could be due to the presence of lack of uniformity in the diagnostic criteria of hyperplasia [47].

In our study sensitivity, specificity, PPV, NPV and accuracy of hysteroscopy for myoma was 87.5%, 96.81%, 70%, 98.91% and 96.08% respectively. Gkrozou et al. [45] reported sensitivity of 97% and specificity of 98.8%. Patil et al. [44] showed sensitivity, specificity, PPV and NPV of 100% each. Chaudhari et al. [48] reported 91% sensitivity, 95% specificity, 78% PPV, 98% NPV and 94% accuracy for myoma.

Considering endometrial thickness the only parameter, using a cut-off value of 5 mm for endometrial pathology, hysteroscopy showed a sensitivity of 95.59%, PPV of 100%, and accuracy of 95.59%. The statistical values of hysteroscopy in this study are shown in Table9.

In our study hysteroscopy showed significant visual accuracy for detection and exclusion of intrauterine malignant lesions of postmenopausal bleeding women who had endometrial thicknesses less than 5mm. The sensitivity, specificity, PPV, NPV, and accuracy were 93.94%, 100%, 100, 33.33%, and 94.12% respectively.

Through this study we came to know that hysteroscopy has a high sensitivity and specificity for diagnosing endometrial and cervical lesions. It is reported in literature that modern day hysteroscopy, which is day care office procedure and can be done without using anesthesia, has a low failure rate, is less painful, has a very low rate of complications, and the “See and treat “ approach possible in it allows one stop management of intra uterine lesions [8,3,19,21, 28]·. We also found that hysteroscopy has a low accuracy in diagnosing hyperplasia. Hyperplasia can be present even when hysteroscopy shows a normal endometrium or often coexist with more benign endometrial lesions. Hyperplasia if not treated can progress to adenocarcinoma [52]. We also evaluated the aetiology of postmenopausal bleeding and looked for possible risk factors. Double-layer transvaginal ultrasonographic measurement of the endometrial thickness was

followed by hysteroscopy and histopathological confirmation. Correlation between imaging and pathology was not reliable. One eighth of the cases with endometrial cancer had an endometrial thickness of less than 5mm. Seventy percent of the women with endometrial thickness of greater than 5 mm had benign pathology. Additionally, the following characteristics were found to be associated with women with endometrial cancer: age over 60 years, time period of 20-24 years since menopause, postmenopausal bleeding duration of 11-12 months, and concomitant presence of DM&HTN.

Our study has several limitations. 1. Small sample size due to low prevalence of our study cohort in general population. 2. Because of lack of experience in operative outpatient hysteroscopy, there was no a standard protocol for the amount of tissue to be obtained for biopsy, thus the obtained amount in this study may have been too small for precise diagnosis. We recommend further larger prospective studies with large sample sizes to address the above-mentioned problems. Despite the limitations of this study we believe that present study provides important information on the accuracy of accuracy of hysteroscopy.

CONCLUSIONS

1. Although majority of the cases were at the age range of 50 to 59 (42.2%) years but the incidence of carcinoma was highest in those above 60 years of age (i.e. 75%), while none of the postmenopausal patients up to 49 years of age had endometrial carcinoma.
2. Factors such as the concomitant presence of diabetes mellitus and hypertension (60%), and hypertension alone (20.69%) were associated with the incidence of endometrial carcinoma.
3. Endometrial polyp was the most common cause of postmenopausal bleeding (41.18%), followed by endometrial carcinoma (23.53%).
4. Outpatient hysteroscopy is a reliable, safe, effective and first-line gold standard method for the assessment of the postmenopausal women with vaginal bleeding.
5. Even though hysteroscopy has sensitivity and specificity in diagnosing endometrial pathology, but endometrial biopsy is compulsory in all cases of postmenopausal uterine bleeding.
6. There is no specific endometrial echo cut-off value, which can successfully exclude the presence of endometrial cancer or exclude the need for further invasive investigations.
7. Outpatient hysteroscopy has better diagnostic accuracy for the detection of benign pathology than for the detection of endometrial hyperplasia

We recommend a larger prospective study with a bigger sample size to better determine the accuracy of outpatient hysteroscopy in diagnosing malignant endometrial pathology. We strongly recommend hysteroscopy in combination direct biopsy in all postmenopausal women presenting with uterine bleeding for the diagnosing and management of postmenopausal uterine bleeding.

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