

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20233821>

Original Research Article

## Outcome of office hysteroscopy in postmenopausal women with red flag signs: a single centre-based study from Northern Ireland

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**Received:** 21 October 2023

**Accepted:** 29 November 2023

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### ABSTRACT

**Background:** Assessment of postmenopausal women with red flag signs like postmenopausal bleeding/ endometrial thickness  $\geq 5$  mm is needed for early detection of any pathology. Early-stage endometrial cancer detection through office hysteroscopy is one of crucial modality for effective management. Objective was to assess the outcome of office hysteroscopy in postmenopausal women with red flag sign and correlated with histopathology findings.

**Methods:** A prospective observational study at a single facility in Northern Ireland involving 122 post-menopausal women aged  $\geq 45$  years subjected to AUB/increased endometrial thickness. Advance diagnostic examination by office hysteroscopy followed by histopathology to detect and rule out endometrial cancer and related ailments.

**Results:** The mean age of the study population was  $63.07 \pm 10.317$  SD years and 91.8% were over-weight. 71.3% women had endometrial thickness  $< 5$  mm. Hysteroscopic reported for 8.2% (10 cases) endometrial cancers having diagnostic accuracy of 98.36%. The histological and hysteroscopic diagnoses were having significantly similar outcomes. Office hysteroscopy has 100% specificity and positive predictive value in detecting normal endometrium whereas 98.25% specificity and 100% negative predictive value in case for cancer detection.

**Conclusions:** In Irish women, office hysteroscopy proved helpful in determining the pathologies that cause postmenopausal bleeding. Correlating hysteroscopic and histological findings with red flag indications should be the focus of future explorations.

**Keywords:** Abnormal uterine bleeding, Postmenopausal bleeding, Cancer endometrium, Red flag sign, Hysteroscopy, Histopathology

### INTRODUCTION

Abnormal uterine bleeding (AUB) affects women of all ages, including premenopausal and postmenopausal women. Post-menopausal bleeding is the most prevalent symptom of endometrial cancer (EC) and EC affects 4% of women who visit their health care provider with PMB.<sup>1,2</sup> EC is the sixth most frequent gynaecologic malignancy responsible for a projected 382,069 new cases and 89,929

deaths globally in 2018 with its highest incidence found in developed nations.<sup>3</sup> EC is the fourth most frequent cancer in the United Kingdom among females and is considered to have a lifetime risk of between 1.7 and 2% in European women, translating to a lifetime risk of about 1/80.<sup>4,5</sup> Annually over 550 women in Ireland are diagnosed with endometrial cancer.<sup>6</sup> In Northern Ireland, there were 278 cases of uterine cancer with 69 deaths in 2018. During the years 1994 to 2018, there were 2,787 females diagnosed

with uterine cancer, with 52.9 percent of them being above the age of 70.<sup>7</sup> Postmenopausal bleeding (PMB), endometrial thickness (ET)  $\geq$  5mm, any abnormal uterine bleeding post six-month HRT treatment were considered as a red flag signs. However, PMB was most common presenting red flag sign and indicates the presence of an undetected endometrial pathology found in up to 90% of hospital-based cases.<sup>8,9</sup> EC is detected in around 75% of postmenopausal women at an early stage, which improves the odds of a successful therapy and outcome.<sup>10</sup> Although most women with PMB will not develop severe pathology, the wisdom that PMB is cancer unless proven otherwise continues to exist. The primary goal of PMB investigation is to diagnose or rule out EC. The current standard of care in UK for postmenopausal women who present with PMB for the first time is to perform a gynaecological pelvic examination along with a transvaginal sonography (TVS) as the initial test further hysteroscopy and biopsy until a diagnosis has been made.<sup>11,12</sup> Evidence advocates intrauterine diseases can be identified and treated in a "see and treat approach" due to the advances in technology leading to availability of high-definition mini-hysteroscopic endoscopes and the vaginoscopic approach of hysteroscopy along with feasibility of using saline as a distending medium. The patients prefers office hysteroscopy since it eliminates difficulties, allows for a faster recovery period, and minimises costs.<sup>13</sup> At present there is no routine screening method is used to detect EC among the general population in the UK.<sup>14</sup> The association between inadequate patient awareness of red flag sign and delayed presentation/delays in health-seeking behaviour exists even in today.<sup>15</sup> Early diagnosis improves the chances of survival since the disease is more likely to be diagnosed at an earlier stage, when curative therapy is more likely.<sup>9</sup> Hysteroscopy appears to be a valuable tool in the identification of endometrial pathology in postmenopausal women with red flag signs. The aim and objective of the study to see the clinical and pathological outcome of office hysteroscopy among postmenopausal women.

## METHODS

A prospective observational study on postmenopausal women presenting with red flag signs and attending Gynaecology and Obstetrics Clinical Unit of a social care trust hospital in Northern Ireland for office hysteroscopy between June 2020 to November 2020. The research was carried out in compliance with the Helsinki Declaration. Institutional ethical committee approval was received prior to the initiation of the study. Since all of the procedures are routinely implemented at the clinical setup, acquiring informed written consent is a basic norm. All patients gave written informed consent prior to the procedures, agreeing to share clinical procedure data for scientific purposes in accordance with European privacy law. A detailed explanation of all procedures involved was provided in the informed consent, allowing all patients understand the purpose of the study in which they will be going to participate.

Convenient sampling was done and a total of 122 participants experiencing red flag signs above the age of 45 years with history of natural menopause, and none of them had positive personal history of cancer of the genital tract were included in the study. The exclusion criteria for the study were the cases of vaginal bleeding in lady with post hysterectomy status. Menopause is interpreted as the cessation of menstruation for at least twelve months in a row after the age of 45 years that is not induced by medicines, operative procedure or illness. Postmenopausal bleeding (PMB), endometrial thickness (ET)  $\geq$  5 mm mm, any abnormal uterine bleeding post six-month HRT treatment were considered as a red flag sign for the inclusion in the study. According to BMI values, patients were considered as normal-weight (BMI between 18-24.9 kg/m<sup>2</sup>), over-weight (BMI between 25-29.9 kg/m<sup>2</sup>) or obese (BMI >30 kg/m<sup>2</sup>).

The optimum anterior-posterior thickness of the endometrial echo on a long-axis transvaginal image of the uterus was assessed using TVUS. A maximal thickness of  $\geq$ 5 mm was chosen as a cut-off for suspecting endometrial disease and such subset of patients were recommended to undergo office hysteroscopy. Hysteroscopy were performed as per RCOG guidelines using a vaginal approach.<sup>16</sup> Miniature hysteroscope (2.7mm with a 3-3.5mm sheath) with a 30° view. Saline solution (0.9% sodium chloride, pH 5.5) was utilised as a distension medium with a pressure of 50-70 mmHg. The uterine cavity was explored by obtaining a panoramic image of the cavity and then evaluating the endometrial pattern in detail. The endometrial pattern was carefully assessed using a standard form and labelled as either normal hysteroscopy or a problem identified. Each patient had an endometrial biopsy following hysteroscopy. For histological tests, the endometrial materials were delivered to the pathologist. The pathologist was informed of the ultra-sonographic and hysteroscopy results in each case. The definition of normal and atrophic endometrium on hysteroscopy and histopathology were accorded as per the description of the study by Elkholi et al.<sup>17</sup> SPSS 26.0 was used to analyse the data (SPSS Inc, Chigaco, IL). Qualitative data were given as actual frequencies and percentages, while continuous data were calculated as mean $\pm$ SD. Multinomial logistic regression was used to calculate categorical variables on a dependent variable based on multiple independent variables. Statistical significance was determined by the significance level at  $p < 0.05$ .

## RESULTS

The data analysed from 122 participants showed their mean age (years) 63.07 $\pm$ 10.317 SD, median age-60 years, (range 47-89 years), majority 42 (34.4%) and 35 (28.7%) belonged to the age group of 50-59 and 60-69 years respectively (Figure 1). Participants' parity showed 102 (83.6%) were multiparous and the rest 20 (16.4%) were nulliparous. The mean BMI (kg/m<sup>2</sup>) of the participants were 31.6525 $\pm$ 5.61838 SD (range 19.7-45.5 kg/m<sup>2</sup>),

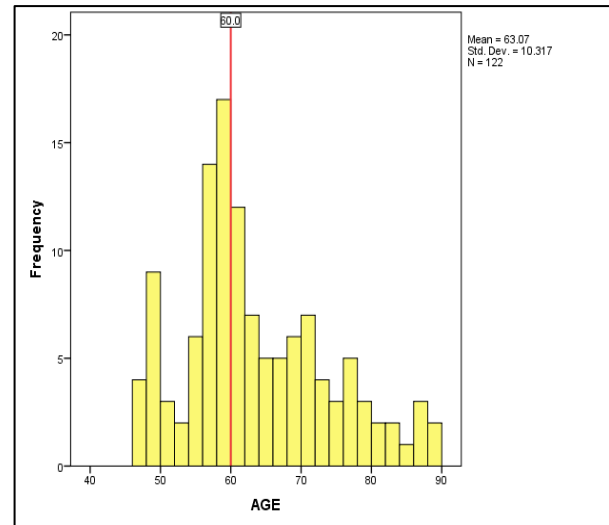
where mostly 54 (44.3%) and 58 (47.5%) participants were overweight and obese in that order.

**Table 1: Frequency distribution of Age subgroup, parity, BMI, endometrial thickness, hysteroscopy finding and histopathology.**

Nomenclature	Subgroup	N	%
Age (years)	≤49	13	10.7
	50-59	42	34.4
	60-69	35	28.7
	70-79	22	18.0
	≥80	10	8.2
Parity	Multiparous	102	83.6
	Nulliparous	20	16.4
BMI	Normal (18-24.9 kg/m <sup>2</sup> )	10	8.2
	Over-weight (25-29.9 kg/m <sup>2</sup> )	54	44.3
	Obese (more than 30 kg/m <sup>2</sup> )	58	47.5
Endometrium thickness	<5 mm	87	71.3
	≥5 mm	35	28.7
Hysteroscopy finding	Normal	37	30.3
	Atrophic	56	45.9
	Polyp	15	12.3
	Hyperplasia	4	3.3
Histopathology result	Cancer	10	8.2
	Normal	50	41.0
	Atrophic	37	30.3
	Polyp	17	13.9
	Hyperplasia	10	8.2
	Cancer	8	6.6

More than one red flag signs were also observed in some participants of study population. The distribution of study population according to any one of red flag sign was as follows. Majority have 97/122 (79.51%) PMB. Endometrial Thickness ≥5 mm was found in 28.7% cases (35/122) and only 5.74% (07/122) cases presented with bleeding post six months of HRT. TVS showed 35 (28.7%) participants having ≥5 mm incidental endometrium thickness among them 15 were obese. On the other hand, endometrial thickness (<5 mm) was found to be normal among the majority 87 (71.3%) participants. Detailed frequency distribution is shown in (Table 1). Histopathology confirmed 50 (40.98%) normal and 37 (30.3%) atrophic cases. Whereas Hysteroscopy showed cases as 37 (30.3%) normal and 56 (45.9%) atrophic cases. Histology confirmed 17 (13.93 %) and 10 (8.197%) as polyps and hyperplasia respectively. Incidents of endometrial cancer was presumed in 10 (8.197%) cases after hysteroscopy. Eight (6.6%) of them were confirmed as cancer by histopathology. For histological diagnosis, each sample was sufficient. The (Table 2) shows a detailed comparison of hysteroscopic and histological findings in relation to age, parity, BMI, and endometrium thickness in study participants. Cohen's kappa was 0.723 (p < 0.001),

indicating that histological diagnosis and hysteroscopy were almost identical.



**Figure 1: Age distribution of study population.**

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy for endometrial cancer were 100%, 98.25%, 80%, 100% and 98.36% respectively (Table 3). A multinomial logistic regression model was fitted to know the effects of Histopathology, Age, parity BMI and Endometrium thickness on Hysteroscopy (table -4). Pearson chi-square statistic 18.709 (p=1.000) indicates that the model does fit the data well. The Chi-squared ratio test on the fitted model information yielded a value of 258.189 (p=0.000), indicating a good model fit. Satisfactory values were also obtained for the pseudo R-squared (Cox and Snell: 0.880, Nagelkerke: 0.951). The likelihood ratio tests for the effects of the model and the partials analysis yields that the independent variables age and histopathology are statistically significant. Whereas, parity, BMI and endometrial thickness were non-significant.

**DISCUSSION**

AUB is a Red Flag sign for approximately 4 to 11 percent of postmenopausal women that could indicate either benign or malignant uterine disorder.<sup>18-20</sup> The majority of women with endometrial cancer have vaginal bleeding or discharge at the time of diagnosis.<sup>1</sup> In developed countries, endometrial cancer is the most prevalent cancer of the female reproductive tract.<sup>3</sup> Endometrial disorder evaluation and assessment includes a variety of techniques. Evidence centred therapeutics is increasingly emphasising the importance of hysteroscopic endometrial assessment. In addition, AUB is the most common reason for diagnostic hysteroscopy.<sup>21</sup> In cases of PMB among women in Ireland on hysteroscopy, the current study establishes patterns for various endometrial variants and pathologies.

**Table 2: Comparative breakdown of hysteroscopic and histological findings with age, parity, BMI and endometrium thickness among women participants (n=122).**

Nomenclature	Subgroup	Hysteroscopy	Histopathology				
			Normal	Atrophic	Polyp	Hyperplasia	Cancer
Age group (years)	≤49	Normal	7	0	0	0	0
		Atrophic	2	4	0	0	0
	50-59	Normal	10	0	0	0	0
		Atrophic	4	18	0	1	0
		Polyp	0	0	5	0	0
		Cancer	0	0	0	0	4
	60-69	Normal	10	0	0	0	0
		Atrophic	5	8	0	4	0
		Polyp	0	0	4	0	0
		Cancer	0	0	0	1	3
	70-79	Normal	8	0	0	0	0
		Atrophic	1	2	2	1	0
		Polyp	0	0	4	0	0
		Hyperplasia	1	1	0	2	0
	≥80	Normal	2	0	0	0	0
		Atrophic	0	4	0	0	0
Polyp		0	0	2	0	0	
Cancer		0	0	0	1	1	
BMI (kg/m <sup>2</sup> )	Normal (18-24.9)	Normal	5	0	0	0	0
		Atrophic	2	2	0	0	0
		Polyp	0	0	1	0	0
	Over-weight (25-29.9)	Normal	22	0	0	0	0
		Atrophic	2	14	0	2	0
		Polyp	0	0	4	0	0
		Hyperplasia	1	1	0	0	0
	Obese (≥30)	Cancer	0	0	0	2	6
		Normal	10	0	0	0	0
		Atrophic	8	20	2	4	0
		Polyp	0	0	10	0	0
	Parity	Multiparous	Hyperplasia	0	0	0	2
Cancer			0	0	0	2	8
Normal			29	0	0	0	0
Atrophic			11	28	1	6	0
Polyp			0	0	13	0	0
Nulliparous		Normal	8	0	0	0	0
		Atrophic	1	8	1	0	0
		Polyp	0	0	2	0	0
		Hyperplasia	1	1	0	0	0
		Cancer	0	0	0	2	8
Endometrium thickness	< 5mm	Normal	35	0	0	0	0
		Atrophic	12	29	0	2	0
		Polyp	0	0	7	0	0
		Hyperplasia	1	1	0	0	0
	≥ 5mm	Normal	2	0	0	0	0
		Atrophic	0	7	2	4	0
		Polyp	0	0	8	0	0
		Hyperplasia	0	0	0	2	0
Cancer	0	0	0	2	8		

With good accuracy, hysteroscopic pattern recognition was used to detect secretory endometrium, polyps, and malignancy. Hysteroscopic findings in this study showed

37 (30.3%) subjects having absence of any pathology. Atrophic endometrium was found among 45.9% cases in the present study. Some previous studies, assert that

normal hysteroscopic findings are insufficient to rule out endometrial pathology, and recommend a biopsy in women with increased endometrial thickness, whether or not they have AUB.<sup>20,22,23</sup> Data in the literature with regard to the identification of endometrial polyps as the most frequent disease in patients with AUB.<sup>20,22,24</sup> However, this

study revealed much lesser incidence of endometrial polyps, hysteroscopic impressions noticed 12.3% in total, with histopathological affirmation in 13.9% of cases with similar results from study with incidence of endometrial polyps.<sup>25</sup>

**Table 3: Distribution of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, disease prevalence, positive predictive value, negative predictive value and accuracy for hysteroscopic finding.**

Parameters	Normal		Atrophic		Polyp		Hyperplasia		Cancer	
	Value	CI	Value	CI	Value	CI	Value	CI	Value	CI
<b>Sensitivity</b>	74.00	59.66-85.37	97.30	85.84-99.93	88.24	63.56-98.54	20.00	2.52-55.61	100.00	63.06-100.00
<b>Specificity</b>	100.00	95.01-100.00	76.47	66.03-85.00	100.00	96.55-100.00	98.21	93.70-99.78	98.25	93.81-99.79
<b>Positive likelihood ratio</b>	-	-	4.14	2.81-6.09	-	-	11.20	1.76-71.24	57.00	14.43-225.15
<b>Negative likelihood ratio</b>	0.26	0.16 - 0.42	0.04	0.01-0.25	0.12	0.03-0.43	0.81	0.60-1.11	0.00	-
<b>Disease prevalence</b>	40.98	32.17-50.25	30.33	22.33-39.30	13.93	8.33-21.37	8.20	4.00-14.56	6.56	2.87-12.51
<b>Positive predictive value</b>	100.00	-	64.29	55.00-72.61	100.00	-	50.00	13.59-86.41	80.00	50.31-94.05
<b>Negative predictive value</b>	84.71	77.63-89.84	98.48	90.36-99.78	98.13	93.46-99.48	93.22	90.97-94.94	100.00	-
<b>Accuracy</b>	89.34	82.47-94.20	82.79	74.90-89.02	98.36	94.20-99.80	91.80	85.44-96.00	98.36	94.20-99.80

**Table 4: Multinomial logistic regression (n=122).**

Effect	Model fitting criteria -2 Log likelihood of reduced model	Likelihood ratio tests		
		Chi-Square	df	Sig.
<b>Intercept</b>	32.769	.000	0	.
<b>Age (group)</b>	59.706	26.937	16	.042
<b>Parity</b>	40.098	7.329	4	.119
<b>BMI (group)</b>	46.139	13.371	8	.100
<b>Endometrium thickness</b>	33.555	.787	4	.940
<b>Histopathology</b>	196.747	163.978	16	.000

The postmenopausal women were included in the study is the probable reason for such finding. Hysteroscopically hyperplasia cases were 4 (3.3%) and suspected endometrial cancer cases were 10 (8.2%). Histologically confirmed among the cases of the endometrium pathology revealed a total of 8 (6.6%) proven cases of endometrial cancer. In 10 (8.2%) cases, endometrial hyperplasia was diagnosed. The histological and hysteroscopy diagnoses were mostly similar ( $\chi^2 = 282.98$ ,  $p < 0.001$ ). The most prevalence of cancer was found in the age group between 50-59 followed by 60-69 and least was found in age group above 80 years which varied too with other studies.<sup>26</sup> Office hysteroscopy is a simple and useful diagnostic procedure that is safe, with a low incidence of clinically significant complications that can provide a good visualization of the uterus. In terms of the rate of detection of various abnormal pathologies, the current study found no significant difference between hysteroscopic and

histopathological findings for nearly all hysteroscopic findings. The diagnostic efficacy of hysteroscopy for different abnormal pathologies was separately evaluated in this study. Hysteroscopy gives evidence of a high diagnostic accuracy. Earlier published studies reported hysteroscopy has sensitivity >90% along with specificity > 80% in predicting normal or abnormal histopathology of endometrium.<sup>21</sup> The diagnostic accuracy of hysteroscopy in detecting serious endometrial disease was investigated in a meta-analysis study, showed the overall sensitivity of hysteroscopy was 86.4 % and the specificity was 99.2 % in cancer.<sup>27</sup> The hysteroscopic correctness were in par with the outcomes obtained in this study in spotting endometrial carcinoma (sensitivity 100%, specificity 98.25%, PPV 80%, NPV 100%).

Hysteroscopic outcome data are very scarce from Ireland in the recent past. The use of blind endometrial sampling

to evaluate the uterine cavity, as was already suggested, seems to be an ineffective method for diagnosing pathologies frequently found with AUB.<sup>28</sup> Directed biopsy of the area with major alterations can enhance the diagnostic yield in pathologies that cause uterine bleeding. Hysteroscopic-guided biopsy also allows for more accurate diagnosis, causes less discomfort, and can be repeated until an adequate amount of tissue is obtained for histologic assessment. The importance of systematically correlating hysteroscopic findings to histopathology is brought into consideration. Considering the fact that there is a considerable difference in nature of different abnormal pathologies, most of the studies have concentrated on evaluating the sensitivity and specificity of hysteroscopy for different abnormal pathologies on histopathology. In present study, attempt was made to evaluate the diagnostic efficacy of office hysteroscopy for different abnormal pathologies separately. The main explanations for the accuracy of histopathological diagnoses in our collection are that hysteroscopic visualisation provided us with better accuracy in pinpointing on the most unusual presentation and better visualisation of small lesions, especially in situations where secretions or tiny amounts of blood would have distorted visibility when using the fluid distension medium. One of the study's constraints was its limited sample size. The sensitivity and specificity of hysteroscopy may have been compromised as a result of small representative sample. The study did, however, explain really, why hysteroscopy is useful in evaluating pathologies that cause PMB/increased ET in Irish women. The study also fulfils the need for evaluation and early detection of uterine abnormality if any, through office hysteroscopy setting.

## CONCLUSION

Postmenopausal women with any of red flag signs should be thoroughly evaluated and investigated. In case of PMB, most common red flag sign among postmenopausal women - early diagnosis is critical for successful treatment of endometrial hyperplasia and cancer. Prior to performing a therapeutic movement, endometrial sampling is required. The current study adds significant and intriguing perspectives into the risk assessment for endometrial cancer in connection to the early indicator for diagnostic office hysteroscopy plus histopathology in postmenopausal women with red flag signs. Nevertheless, a larger sample of Irish populations should be studied for office hysteroscopic outcomes using such a novel concept of Red Flag signs.

## ACKNOWLEDGMENTS

Authors are thankful to all patient consented and participated in this study.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Aggarwal S, Rahim M, Maji D, Debnath P. Outcome of office hysteroscopy in postmenopausal women with red flag signs: a single centre-based study from Northern Ireland. *Int J Reprod Contracept Obstet Gynecol* 2024;13:47-53.