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Original article

Ultrasound Findings versus Hysteroscopic Guided Endometrial Histopathological Findings in Women with Postmenopausal Bleeding

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Abstract

Background: Postmenopausal bleeding (PMB) is a common clinical presentation with a broad differential diagnosis, including atrophic endometrium, endometrial hyperplasia, polyps, and carcinoma. Accurate diagnosis is crucial for appropriate management. This prospective study aimed to correlate transvaginal morphological ultrasound findings with histopathological findings from hysteroscopic-guided endometrial biopsies in women with PMB, to assess the diagnostic accuracy of ultrasound compared to the gold standard of histopathology. **Methods:** This prospective study was conducted at the Benha University Hospitals' Obstetrics and Gynecology outpatient clinics, including 59 women with PMB. Detailed patient histories, physical examinations, laboratory investigations, ultrasonography, and hysteroscopic-guided endometrial biopsies were performed. **Results:** The study group had a mean age of 57.77 years and a mean BMI of 30.17 kg/m^2. Histopathology identified atrophic endometrium (37.3%), endometrial hyperplasia (54.2%), endometrial polyps (6.8%), and endometrial carcinoma (1.7%). The mean endometrial thickness measured by ultrasound was 14.42 ± 7.93 mm. Ultrasonography showed high PPV and NPV for endometrial hyperplasia (96.97% PPV, 100% NPV) but lower for endometrial carcinoma (33.33% PPV) and polyps (66.67% PPV). Hysteroscopy yielded higher agreement rates with histopathology than ultrasound, particularly for diagnosing atrophic endometrium, endometrial carcinoma, and polyps, with kappa values indicating substantial to almost perfect agreement. **Conclusion:** Hysteroscopic-guided biopsy, supported by transvaginal ultrasound, offers a reliable approach for diagnosing endometrial pathologies in women with PMB. While ultrasound is valuable for initial assessment, particularly for endometrial hyperplasia, its limitations in detecting carcinoma and polyps suggest that hysteroscopy should be considered when ultrasound findings are inconclusive or indicate potential malignancy.

Keywords: Postmenopausal bleeding; Transvaginal ultrasound; Hysteroscopy; Endometrial biopsy; Histopathology.

Introduction

Postmenopausal bleeding (PMB) is uterine bleeding occurring at least one year after menopause. PMB is a common clinical problem, the incidence of spontaneously occurring PMB in the general population can be as high as 10% after menopause (1).

PMB is often caused by abnormalities of the endometrium, whether they are benign or malignant. Of postmenopausal women with vaginal bleeding, 10%–15% have endometrial carcinoma (2).

The incidence of endometrial polyps in patients with PMB and an increased endometrial thickness measured with transvaginal sonography (TVS) is estimated to be around 40% (3).

Transvaginal sonography can detect subtle changes in the endometrium and it has been observed that endometrial thickness <4 mm is usually associated with normal morphology. In patients with thickened endometrium, a secondary test such as power Doppler could play a role in refining the diagnosis (4).

Dilatation and curettage (D&C) under general anesthesia has long been the most common diagnostic tool in cases of abnormal uterine bleeding. However, this blind procedure often results in unrepresentative biopsies, missing a certain number of endometrial polyps, submucous leiomyomata and focal hyperplastic or neoplastic lesions (5).

Over the years, hysteroscopy with direct biopsy has assumed the gold standard investigation for postmenopausal bleeding because it is an accurate method for the diagnosis and treatment of endometrial abnormalities, but its availability, its high cost and the need for general anesthesia sometimes prevent its use as a primary diagnostic procedure in postmenopausal bleeding patients (6).

Hysteroscopy is the only access route for direct visualization of the uterine cavity; previous publications confirmed that hysteroscopy without an endometrial biopsy has a low positive predictive value in the detection of endometritis. Endometrial biopsy has proven useful for the diagnosis of intrauterine inflammatory states. Hysteroscopy with endometrial biopsy is assumed to be the best method for the detection of intrauterine abnormalities that may interfere with implantation (7).

The purpose of this study was to correlate transvaginal morphological ultrasound findings with histopathological findings of hysteroscopic guided patients with PMB.

Patients and methods

Patients:

Patient Population:

This was a prospective study conducted to correlate transvaginal morphological ultrasound findings with histopathological findings of hysteroscopic guided

endometrial biopsies in patients with postmenopausal bleeding.

The study included 59 (sample size) female patients with post-menopausal bleeding presented at Obstetrics and Gynecology outpatient clinics at Benha University Hospitals, during the period from December 2022 to June 2023.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University **Approval code:** Ms 27-11-2022

Inclusion criteria were female patients experiencing postmenopausal uterine bleeding.

Exclusion criteria were patients with any associated local gross abnormality, acute, chronic cervicitis or PID, associated medical/ systemic cause of postmenopausal bleeding and patients on hormonal replacement therapy.

Methodology:

The methodology of the study was carefully designed to address the complexities of investigating PMB, employing a structured approach to collect, analyze, and interpret data from participants. This comprehensive methodology was divided into several distinct phases, each targeting different aspects of the participant's health and medical history to ensure a holistic assessment.

Detailed History Taking:

The initial phase involved taking a detailed history from all participants. This crucial step aimed to gather baseline data, including the participant's age at enrollment, their reproductive history encapsulated by gravida and parity, the severity of their bleeding episodes categorized as mild, moderate, or severe, and the duration of their postmenopausal bleeding.

General and Local Examination:

Following the collection of detailed histories, a general examination was conducted focusing on two primary indicators of health: blood pressure and Body Mass Index (BMI), with BMI data reiterated from the history phase. This was followed by a meticulous abdominal and pelvic examination, aiming to identify any potential physical signs of underlying conditions, including tenderness, masses, or abnormalities within the abdomen and the pelvic region.

Laboratory Investigations:

The study also included a comprehensive suite of laboratory investigations. These tests were pivotal in providing a broader understanding of each participant's health status, encompassing a complete blood count, blood sugar level assessment, kidney and liver function tests, and a detailed bleeding profile.

Ultrasonography and Diagnostic Procedures:

Ultrasonography, performed using advanced equipment, played a crucial role in evaluating the reproductive health aspects of participants. This included measuring uterine dimensions, assessing endometrial thickness, detecting focal lesions, and examining the adnexal regions. Additionally, diagnostic hysteroscopy and endometrial biopsy were conducted without anesthesia, utilizing a sophisticated hysteroscope to visually examine the uterine cavity, identify abnormalities, and collect tissue samples for further analysis.

Histopathological Examination:

The final phase of the methodology involved a histopathological examination of the biopsied material. This examination was critical for confirming the diagnosis of endometrial pathologies, serving as the gold standard against which the effectiveness of ultrasonography and hysteroscopy in identifying endometrial abnormalities was assessed.

Statistical analysis

The statistical analysis of the collected data was conducted using the Statistical Package for Social Science (SPSS), Version 25.0, by IBM Corp. Data was carefully revised, coded, and tabulated for analysis, which was tailored to the nature of the data collected for each parameter. The Shapiro-Wilk test was utilized to assess the normality of data distribution. For normally distributed numerical data, descriptive statistics were presented as mean and standard deviation (± SD), while for data not normally distributed, median and range were used. Non-numerical data were analyzed in terms of frequency and percentage. Analytical statistics involved the use of the Student T Test and Mann Whitney Test (U test) to evaluate the statistical significance of differences between two groups, along with the Chi-Square test to explore relationships between two qualitative variables. Correlation analysis assessed the association strength between two quantitative variables. The ROC Curve analysis determined the sensitivity and specificity for quantitative diagnostic measures, defining the optimum cut-off point through the maximum AUC value, indicating the accuracy level of the test. Logistic regression analysis predicted risk factors when the dependent variable was categorical, using odds ratios (OR) to measure the association between exposures and outcomes. Results were deemed significant with a p-value <0.05 at a 95% confidence interval, ensuring a robust statistical foundation for interpreting the study's findings.

Results

Baseline criteria:

The current study included 59 women with PMB, their mean age was 57.77 years. Mean BMI was 30.17 km/m^2. According to parity, 24.4% were nullipara, 32.2% were primipara and 42.4% were multipara. Table 1

Histopathological findings:

According to histopathological results, 1.7% of the studied subjects had endometrial carcinoma. Atrophic endometrium took place in 37.3% of cases, endometrial hyperplasia was in 54.2% and endometrial polyps in 6.8%. Figure 1

According to hysteroscopic findings in the studied subjects, endometrial polyps were observed in 6.8% of the subjects, while atrophic endometrium was found in 39% of the subjects. Endometrial hyperplasia was found in 52.5% of the subjects and endometrial carcinoma was suspected in 1.7% of the subjects. Figure 2

The mean endometrial thickness in the studied subjects was 14.42 ± 7.93 mm. Associated ultrasound findings included ovarian cysts in 10.2% of the subjects, a globular uterus in 18.6% of the subjects, adenomyosis in 3.4% of the subjects, and uterine fibroids in 10.2% of the subjects. Table 2

The association between ultrasound endometrial thickness and histopathological diagnosis was examined for different conditions. A significant higher endometrial thickness in endometrial carcinoma compared to the of histopathological diagnosis ($p<0.001$). Table 3

Ultrasound results compared to histopathology in each finding as true positive, false positive, true negative and false negative to calculate positive predictive and negative predictive values for each finding. Ultrasound results showed high positive prediction and negative prediction in all findings except endometrial carcinoma (PPV =33.33%) and endometrial polyp (66.67%). Table 4

Hysteroscope results compared to histopathology in each finding as true positive, false positive, true negative and false negative to calculate positive predictive and negative predictive values for each finding. Hysteroscope results showed high positive prediction and negative prediction in all findings. Table 5

Ultrasonography vs hysteroscopy:

According to Kappa agreement between hysteroscope and ultrasound findings compared to histopathological diagnosis, hysteroscopy showed higher agreement in atrophic endometrium, endometrial carcinoma, and endometrial polyp. Hysteroscopy showed similar agreement with ultrasound in endometrial hyperplasia. Table 6

Table 1: Baseline criteria of the studied subjects

Variable	n=59
Demographic and clinical data	
Age (years)	57.77±4.44
BMI (kg/m^2)	30.17±4.16
SBP (mmHg)	112.64±9.12
DBP (mmHg)	72.89±8.09
Laboratory investigations	
WBC (x10^3/mL)	6.24±1.94
HGB g/dl	10.27±1.28
Platelets (x10^9/mL)	160.81±17.99
FBS (mg/dL)	90±8
RBS (mg/dL)	91.88±12.12
Creatinine mg/dL	1±,09
INR	1.07±0.1
ALT U/L	30.52±13.24
AST U/L	30.5±10.71
Parity	
Nullipara	15(25.4%)
Primipara	19(32.2%)
Multipara	25(42.4%)
Duration of PMB, years	7.15±2.32

BMI = Body Mass Index, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, WBC = White Blood Cell, HGB = Hemoglobin, FBS = Fasting Blood Sugar, RBS = Random Blood Sugar, INR = International Normalized Ratio, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, PMB = Postmenopausal Bleeding.

Table 2: Ultrasound findings in the studied subjects

Variable		Total subjects (59)
Endometrial thickness (mm)	Mean ± SD	14.42±7.93
	Median (Range)	17.40 (3.01-33.88)
Associated ultrasound findings (%)	Ovarian cyst	6(10.2%)
	Globular uterus	11(18.6%)
	Adenomyosis	2(3.4%)
	Uterine fibroid	6(10.2%)

Table 3: Association between ultrasound endometrial thickness and histopathological diagnosis

Variable	Atrophic endometrium	Endometrial carcinoma	Endometrial hyperplasia	Endometrial polyp	Test	p
Endometrial thickness (mm)	3.16±0.56	25.06	18.19±1.56	22.67±1.63	3.938	<0.001*

Test= Kruskal Wallis test; * =p<0.05.

Table 4: Validity of ultrasound in predicting accurate diagnosis compared to histopathology

	TP	FP	FN	TN	PPV%	NPV%
Atrophic endometrium	17	0	5	37	100.00%	88.10%
Endometrial carcinoma	1	2	0	56	33.33%	100.00%
Endometrial hyperplasia	32	1	0	26	96.97%	100.00%
Endometrial polyp	4	2	0	53	66.67%	100.00%

TP true positive, FP false positive, FN false negative, TN true negative.

Table 5: Validity of hysteroscope in predicting accurate diagnosis compared to histopathology

	TP	FP	FN	TN	PPV%	NPV%
Atrophic endometrium	22	1	0	36	95.65%	100.00%
Endometrial carcinoma	1	0	0	58	100.00%	100.00%
Endometrial hyperplasia	31	0	1	27	100.00%	96.43%
Endometrial polyp	4	0	0	55	100.00%	100.00%

TP true positive, FP false positive, FN false negative, TN true negative

Table 6: Agreement between hysteroscope, ultrasound and histopathology

	Hysteroscope agreement (Kappa)	Ultrasound agreement (Kappa)
Atrophic endometrium	0.964	0.810
Endometrial carcinoma	1.000	0.487
Endometrial hyperplasia	0.966	0.966
Endometrial polyp	1.000	0.780

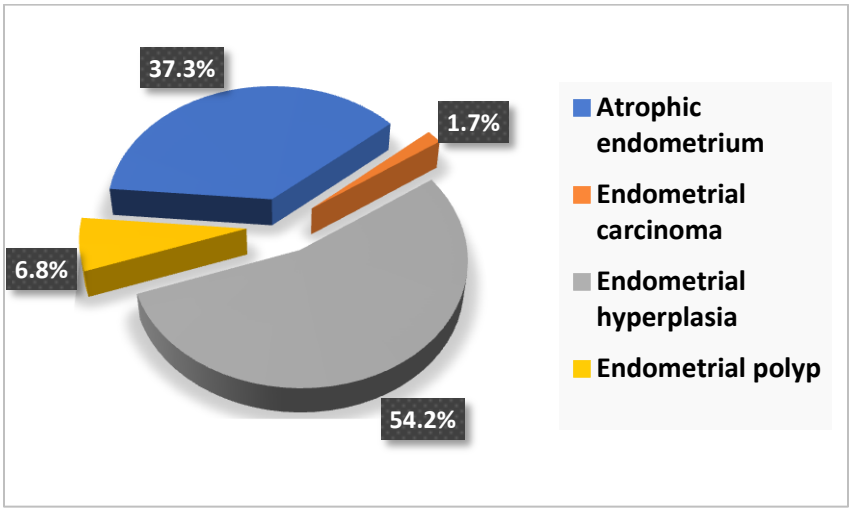

Figure 1: Histopathological results frequencies in the studied subjects

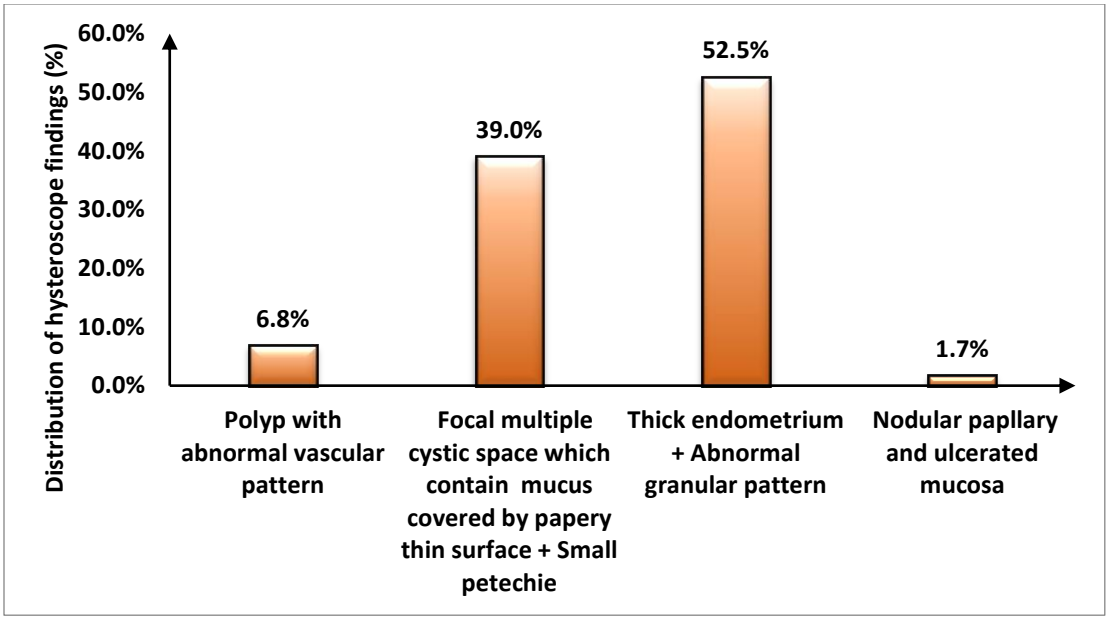

Figure 2: Hysteroscope finding distribution in the studied subjects

Discussion

The current study included 59 subjects with postmenopausal bleeding, their mean age was 57.77 years. Mean BMI was 30.17 km/m^2.

Regarding parity, the current study found that 24.4% of the subjects were nullipara, 32.2% were primipara and 42.4% were multipara. These results are in line with previous studies that have reported a higher incidence of endometrial cancer in nulliparous women and a protective effect of parity against endometrial cancer (8).

The current study found that the mean age of the subjects with postmenopausal bleeding was 57.77 years, which is consistent with previous studies that have reported the mean age to be between 55 and 60 years (9, 10).

The mean BMI of 30.17 km/m^2 observed in our study agrees with studies that have found a higher incidence of endometrial abnormalities in women with obesity (11).

The histopathological results of the current study revealed that 1.7% of the subjects had malignant histopathological criteria, while 98.3% had benign results. Normal and atrophic endometrium was observed in 37.3% of cases, while endometrial hyperplasia was observed in 54.2% and endometrial polyps in 6.8%. These results are in line with previous studies that have reported a higher incidence of benign results in women with postmenopausal bleeding (12-14).

The present study found that endometrial hyperplasia was the most common histopathological result 54.2%, followed

by atrophic endometrium 37.3 %, endometrial polyps 6.8% and endometrial carcinoma 1.7%. Our study disagreed with a study which includes 75 patients with postmenopausal bleeding and reported that the most common cause of bleeding was endometrial cancer 36%, followed by endometrial hyperplasia 34.6%, atrophic endometrium 18.7 % and endometrial polyp 10.7 %. This difference may be due to the mean age of subjects was 67.77 years **(15).**

Another study included 132 women with postmenopausal bleeding and reported that the sensitivity of transvaginal ultrasound in diagnosing endometrial pathology was 89.5%, which is similar to the sensitivity found in the current study for diagnosing benign pathology (87.5%). However, ultrasound results showed high positive prediction and negative prediction in all findings except endometrial carcinoma (PPV =33.33%) and endometrial polyp (66.67%), unlike in (shokouhi,2015) study which show (ppv=100%) in endometrial carcinoma and (ppv=96%) in endometrial polyp (16).

There are several studies that have investigated similar factors in relation to postmenopausal bleeding and endometrial pathology. One study included women with postmenopausal bleeding and found that endometrial thickness measured by transvaginal ultrasound was significantly higher in women with endometrial cancer compared to those with benign pathology This is consistent with the findings of the current study, which also found a significant higher endometrial thickness in endometrial carcinoma (25.06 mm in our study) compared to the of histopathological diagnosis ($p<0.001$) (17).

The mean endometrial thickness in the studied subjects was 14.42 ± 7.93 mm. Associated ultrasound findings included ovarian cysts in 10.2% of the subjects, a globular uterus in 18.6% of the subjects, adenomyosis in 3.4% of the subjects, and uterine fibroids in 10.2% of the subjects which is within the range reported in previous studies (9).

Moreover, our findings showed that increasing endometrial thickness (25.06 mm in our study) had a significant positive correlation with malignancy, which is consistent with previous studies that have identified endometrial thickness as a predictor of endometrial cancer (18-20)

Our study shows that the accuracy of hysteroscope was 100% in cases of endometrial carcinoma, endometrial hyperplasia, endometrial polyp and 95.65% in atrophic endometrium. This was in the same way as another study which found that hysteroscopy diagnosed endometrial polyps in 80.8%. Hysteroscopy showed 96.4% sensitivity, 74.6% specificity, 93.4% positive predictive value, 84.6% negative predictive value and 91.8% accuracy (21)

As regard validity of ultrasonography vs hysteroscopy in accurate diagnosis of endometrial atrophy, the sensitivity of hysteroscopy was 97.5% compared to 87.5% in ultrasonography.

Meta-analysis results showed that the combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic Odds ratio with hysteroscopic examination for the diagnosis of endometrial hyperplasia was 0.73 (95% CI: 0.68−0.77), 0.92 (95% CI: 0.90−0.93), 9.87 (95% CI: 4.08−23.84), 0.34 (95% CI: 0.22−0.52), and 31.64 (95% CI: 10.34−96.78) respectively (22).

According to Kappa agreement between hysteroscope and ultrasound findings compared to histopathological diagnosis, hysteroscopy showed higher agreement in atrophic endometrium, endometrial carcinoma and endometrial polyp. Hysteroscopy showed similar agreement with ultrasound in endometrial hyperplasia.

One study showed that hysteroscopy was more accurate in diagnosing sensitivity of endometrial polyp (100%), fibroids (83%), hyperplasia (84.2%), and cancer (50%) whereas ultrasounds were more accurate in diagnosing sensitivity to endometrial myoma (90%). ultrasound showed low sensitivity in detecting endometrial cancer 34% like in our study. hysteroscopy in this study show low sensitivity in detecting endometrial cancer 50% unlike in our study show high sensitivity 100% (23).

Similarly, a study found that hysteroscopy was more accurate than ultrasonography in detecting focal endometrial abnormalities, with a sensitivity of 100% compared to 71% for ultrasonography (24).

Regarding the diagnostic accuracy of ultrasonography and hysteroscopy in identifying endometrial carcinoma, the findings of the current study are consistent with those of previous studies as well. A study reported a sensitivity of 87.5% for hysteroscopy compared to 50% for ultrasonography in detecting endometrial carcinoma (23).

Conclusion

In conclusion, this study underscores the efficacy of transvaginal ultrasound, particularly in assessing endometrial thickness, for distinguishing cases of endometrial carcinoma in postmenopausal bleeding. Hysteroscopy emerges as a highly accurate diagnostic tool, particularly proficient in identifying atrophic endometrium, endometrial carcinoma, and endometrial polyps. Hysteroscopic guided endometrial histopathology proves superior in sensitivity and accuracy compared to transvaginal ultrasound for diagnosing endometrial abnormalities in postmenopausal women with bleeding. While ultrasound-based measurement of endometrial thickness holds promise as a screening method for detecting endometrial carcinoma, hysteroscopic guided biopsy remains indispensable for definitive diagnosis.

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