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DIAGNOSTIC VALUE AND CONCORDANCE OF ENDOMETRIAL THICKNESS, SMEAR, AND BIOPSY RESULTS IN WOMEN WITH ABNORMAL UTERINE BLEEDING

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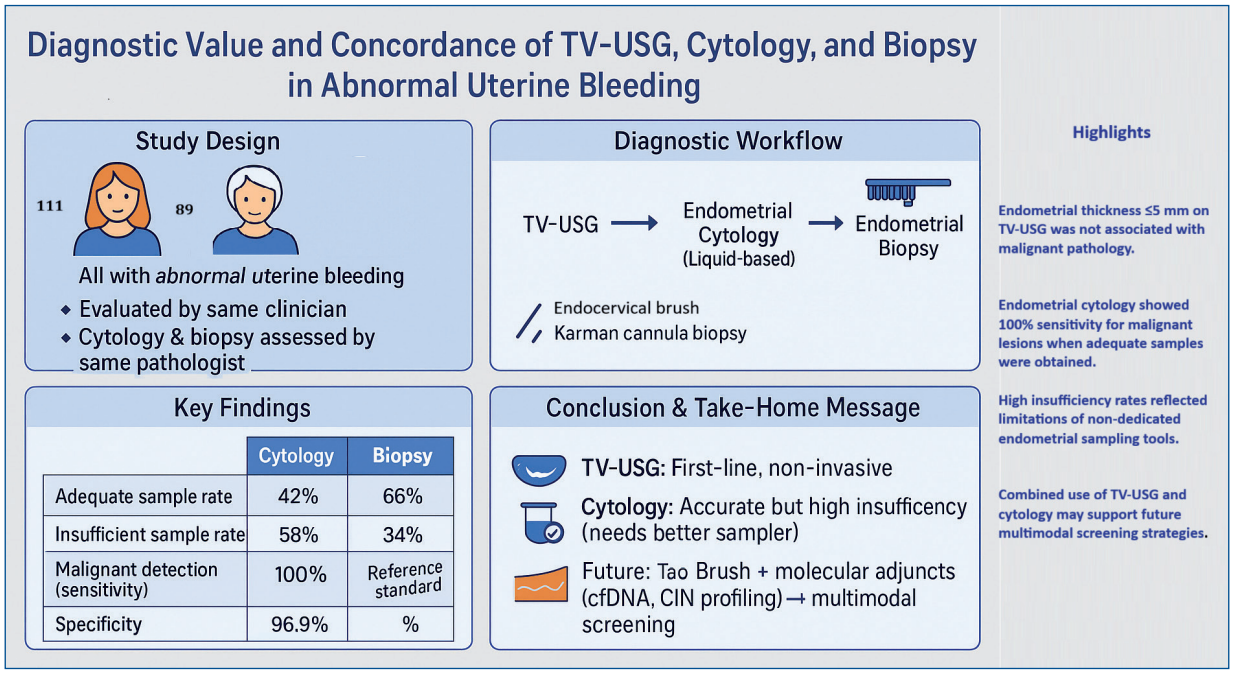
ABSTRACT – ***Objective:*** This study was conducted to investigate whether an effective screening method for endometrial hyperplasia and endometrial cancer can be identified by comparing the results of transvaginal ultrasonography (TV-USG), liquid-based endometrial cytology, and endometrial biopsy.

Materials and Methods: The study included a total of 200 patients with a mean age of 50.04 ± 10.39 years (range: 33-85), who presented with abnormal uterine bleeding during the premenopausal and postmenopausal periods. Following a detailed clinical examination, endometrial thickness was measured using TV-USG in all cases. Subsequently, liquid-based endometrial cytology was obtained using an endometrial brush, followed by an endometrial biopsy using a Karman cannula. All patients were evaluated by the same clinician, and both the cytological and biopsy specimens were assessed by the same pathologist.

Results: No endometrial pathology was detected in cases with an endometrial thickness of ≤ 5 mm as measured by TV-USG. The mean endometrial thickness was found to be 12.66 mm for simple hyperplasia without atypia, 18 mm for complex atypical hyperplasia, and 17.00 mm for endometrial adenocarcinoma. A statistically significant difference was observed among these three groups with endometrial thicknesses ($p < 0.05$). The endometrial thickness in cases with complex atypical hyperplasia and endometrial cancer was significantly higher compared to the others ($p < 0.05$). While 58% of endometrial cytology samples and 34% of biopsy samples were found to be insufficient for evaluation, cytology still appeared to be a useful method for detecting malignant lesions. The high insufficiency rate observed in our series likely reflects the sampling technique employed, as an endocervical-type brush was used rather than a dedicated endometrial sampler, which may have reduced cellular yield and affected adequacy rates. For the diagnosis of malignant lesions, cytology demonstrated a sensitivity of 100%, a specificity of 96.9%, a positive predictive value of 71.43%, and a negative predictive value of 100%.

Conclusions: Although TV-USG is not a method that provides a definitive diagnosis, it is highly effective in identifying cases that require further investigation. Moreover, due to its non-invasive nature, it should be considered the first-line diagnostic tool in patients suspected of having endometrial pathology. Despite the high diagnostic accuracy of endometrial cytology in detecting malignant lesions, the relatively high rate of insufficient sample both in premenopausal and postmenopausal patients compared to biopsy represents a notable disadvantage. Therefore, we do not consider endometrial cytology to be a standalone method suitable for screening endometrial cancer and its precursors. However, since malignant lesions were reliably detected when adequate cytology material was obtained, dedicated endometrial samplers and emerging molecular adjuncts should be evaluated in future prospective studies to determine whether cytology can contribute to a multimodal screening strategy.

KEYWORDS: Premenopausal, Postmenopausal, Abnormal uterine bleeding, Transvaginal ultrasonography, Endometrial cytology, Endometrial biopsy.



Graphical Abstract. TV-USG is a reliable first-line tool, and cytology offers high sensitivity for malignancy when adequate samples are obtained, supporting a future multimodal screening strategy.

INTRODUCTION

Abnormal uterine bleeding is a common gynecological problem in premenopausal and postmenopausal women. Approximately 70% of gynecological consultations are due to abnormal uterine bleeding. The early diagnosis is important for abnormal uterine bleeding, especially in women over the age of 40[1,2].

Endometrial biopsy is the most reliable and accurate diagnostic method used to identify endometrial pathologies in premenopausal and postmenopausal cases with bleeding. However, due to the risk of infection, bleeding, adhesions, uterine perforation, and the need for general anesthesia, which is difficult for patients to tolerate, it cannot be used for screening purposes. Early detection of premalignant and malignant lesions and other pathologies of the endometrium is very important. There is a need for research into more sensitive diagnostic methods for screening purposes. These methods should be more economical, non-invasive, and easier to apply[2]. With the use of ultrasound in gynecology, considerable progress has been made in both accurate diagnosis and treatment modalities. The addition of high-resolution 5-7.5 MHz frequency probes that can be applied vaginally to ultrasound has opened up a new avenue for evaluation[3]. Direct cytological sampling from the endometrial cavity is a less invasive and cheaper method than endometrial biopsy, which is used in the diagnosis of endometrial pathologies. It provides a diagnosis in a shorter time. It is noted that it can be used as a screening method in patients at high risk for endometrial cancer and its precursors.

This study aims to answer the question of whether an effective screening method for endometrial cancer and its precursors can be found by comparing the results of TV-USG, endometrial cytology, and endometrial biopsy in cases of abnormal uterine bleeding in premenopausal and postmenopausal women.

MATERIALS AND METHODS

For this study, approval was obtained from the Academic Board of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ondokuz Mayıs University (Protocol No.: 2007/455-2). At that time, the Departmental Academic Board served as the institutional Ethics Committee. In addition, informed consent was obtained from all patients, and written consent forms were signed prior to participation. A total of 200 patients, including 111 premenopausal and 89 postmenopausal women, who presented to the outpatient clinic with vaginal bleeding between January 2008 and January 2009, were included in the study.

Detailed gynecological histories were recorded for all cases, and systemic physical and pelvic examinations were performed. Patients with findings of lower or upper genital tract infection,

positive pregnancy test, oral contraceptive or hormone replacement therapy, breast cancer surgery, systemic disease, or intrauterine device use were excluded from the study.

All patients in the study were evaluated by TV-USG by the same person after routine pelvic examination, regardless of the endometrial phase. TV-USG examination was performed using a Siemens Sonoline Sienna® (Siemens Medical Systems, Erlangen, Germany) series ultrasound device with high resolution and a 6.5 MHz microconvex transvaginal probe. Following this, the vagina and cervix were cleaned with an antiseptic solution of povidone-iodine (Batticon®, Adeka, Samsun, Türkiye), and endometrial cytological sampling was performed. For this procedure, an endocervical brush similar to Gynobrush® (Heinz Herenz Medizinalbedarf GmbH, Hamburg, Germany) but without a sheath was used. Endometrial cytological sampling in this study was performed using an endocervical brush similar to a Gynobrush, but without a dedicated endometrial sampler such as the Tao Brush (Cook Medical, Bloomington, IN, USA). We acknowledge that this sampling tool was not specifically designed for endometrial cavity sampling and that device choice may influence cellular yield and adequacy rates. Once the brush passed through the cervix and reached the endometrial cavity, the sheath was pulled back, and an endometrial tissue sample was taken by rotating it within the endometrial cavity. It was then placed back into the sheath and pulled back through the cervix. This was done to prevent contamination with endocervical cells. The endometrial smear brushes were cut with scissors at a higher level without touching the tip and placed in a labeled SurePath™ (Becton Dickinson, Franklin Lakes, NJ, USA) sample collection container for use with the liquid-based cytology method.

After endometrial cytological sampling, the anterior lip of the cervix was held with a tenaculum, and a paracervical block was performed at the 5 and 7 o'clock positions of the cervix. The cervical os was dilated to a size 5 Hegar dilator, and the entire endometrial cavity was curetted with a Karman cannula. The collected material was placed in 10% formalin, labeled, and sent to the Department of Pathology along with the SurePath™ specimen collection container. The endometrial cytology and endometrial biopsy materials of all patients included in the study were evaluated by the same pathologist.

In the cytopathological evaluation, cases defined as atrophic, secretory, and proliferative were classified as the physiological group; cases defined as non-atypical hyperplasia were classified as the malignancy-negative group; and cases defined as atypical hyperplasia, malignancy-suspicious, and carcinoma were classified as the malignancy-positive group[4]. In cytological examination, fewer than two endometrial cell groups were considered insufficient for diagnosis, two to four endometrial cell groups were considered limited for diagnosis, and more than four endometrial cell groups were considered sufficient for diagnosis (Figures 1-4).

Statistical analysis

Excel 2000 for Windows and SPSS (Statistical Package for Social Sciences) for Windows 13.0 (SPSS Inc., Chicago, IL, USA) statistical analysis software were used to evaluate the findings obtained in the study. When evaluating the study data, descriptive statistical methods (mean, standard deviation) were used, and the Kruskal-Wallis test was used for general comparisons between groups of parameters that did not show a normal distribution in the comparison of quantitative data, and the Mann-Whitney U test was used to

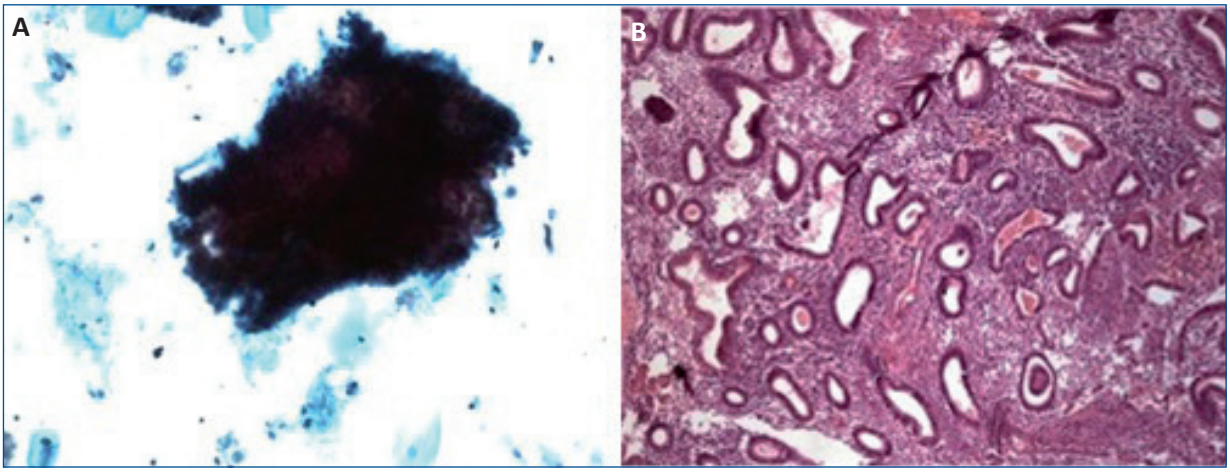


Figure 1. A, ×200 Unclassifiable, cytology sample and (**B**) ×100 simple non-atypical endometrial hyperplasia biopsy sample.

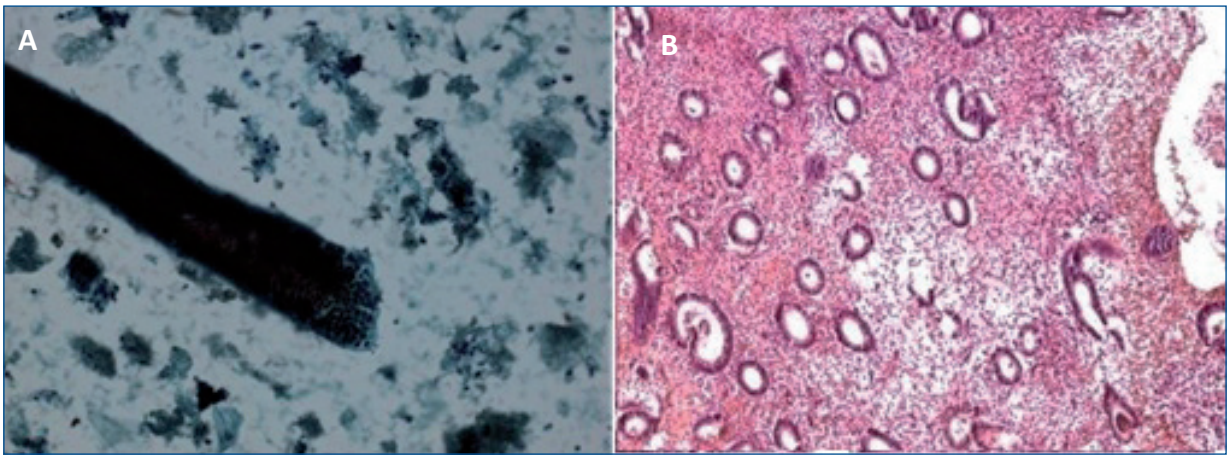


Figure 2. **A**, ×200 malignancy negative cytology sample and (**B**) ×100 proliferative endometrium biopsy sample.

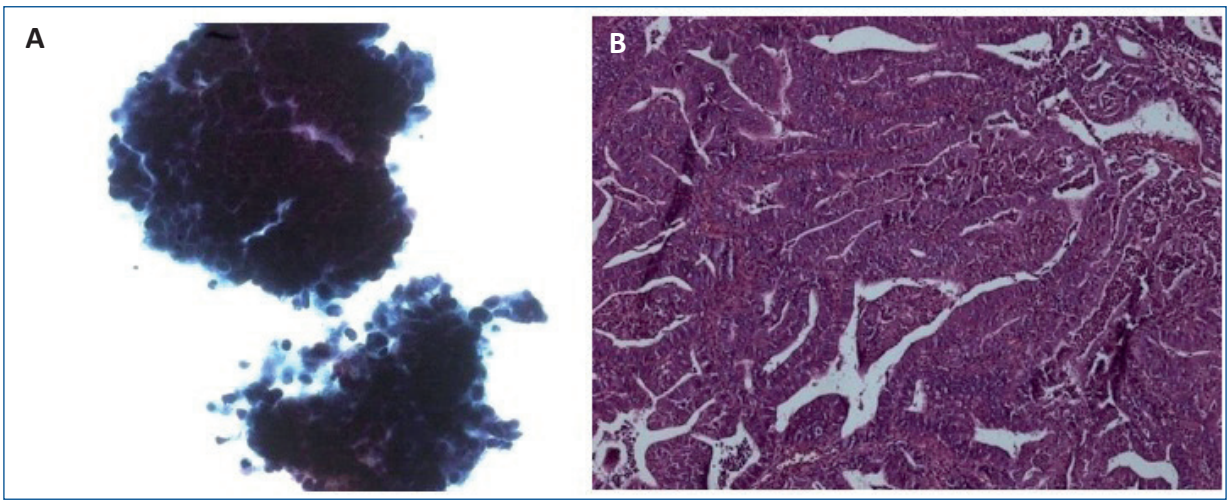


Figure 3. **A**, ×400 suspected malignancy cytology sample and (**B**) ×100 endometrioid Grade I biopsy sample.

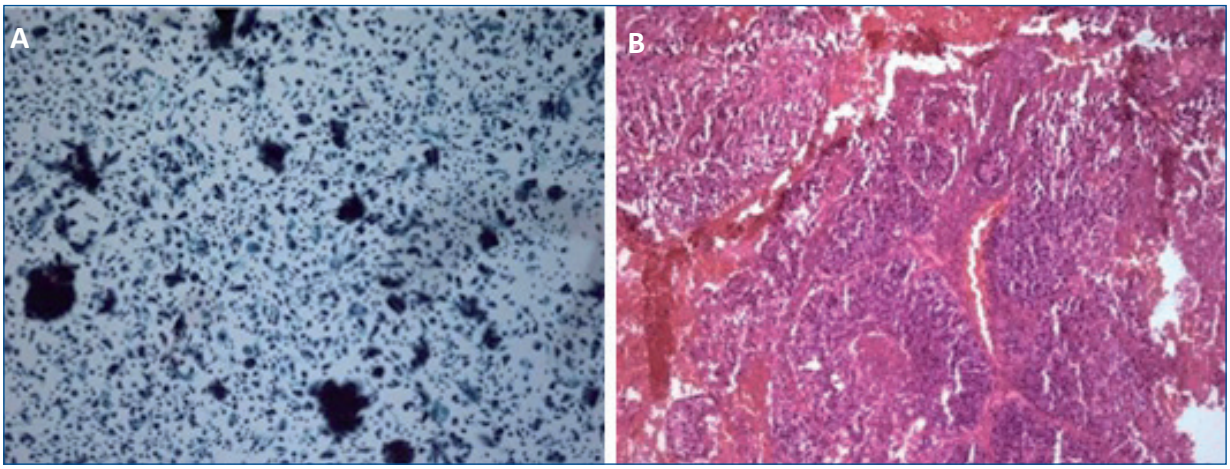


Figure 4. **A**, ×100 high-grade malignant tumor cytology sample and (**B**) ×100 high-grade mixed epithelial tumor biopsy sample.

determine the difference between two groups. The Pearson Chi-Square test was used to compare qualitative data. The results were evaluated at a 95% confidence interval and a significance level of $p < 0.05$.

RESULTS

Of the 200 patients with a mean age of 50.04 ± 10.39 (33-85), 111 (55.5%) were premenopausal 43.22±4.50 (33-53), and 89 (44.5%) were postmenopausal 58.55 ± 9.32 (39-85).

Patients were evaluated in 5 different groups based on endometrial thickness measured by TV-USG. When the distribution of endometrial thickness in premenopausal cases was examined, the largest group consisted of 65 cases (58.6%) with endometrial thickness of 6-10 mm, while in postmenopausal cases, the largest group consisted of 44 cases (49.50%) with a thickness of 6-10 mm (Table I). A significant relationship was found between endometrial thickness and menopausal status ($\chi^2 = 16.282$; $p < 0.01$).

When the distribution of endometrial biopsy materials obtained with a Karman cannula was examined according to histopathological diagnoses, the majority of cases in the premenopausal group consisted of non-diagnostic, proliferative endometrium, secretory endometrium, and endometrial polyps, while in the postmenopausal group, the majority of cases were non-diagnostic, endometrial polyps, and atrophic endometrium (Table I).

Histopathological examination revealed that the average endometrial thickness in the physiological condition group (proliferative, secretory, menstrual, and atrophic endometrium) was 8.02 ± 3.67 mm. In the malignancy-negative group, the average endometrial thickness in pathological lesions (endometrial polyps, chronic endometritis, simple non-atypical endometrial hyperplasia) was found to be 10.34 ± 4.79 mm. For the malignancy-positive group, the average endometrial thickness was found to be 17.5 ± 3.55 mm. When these three groups were compared with each other, there was a statistically significant difference in endometrial thickness ($p < 0.05$). After the Kruskal-Wallis test, a difference was found between the endometrial thicknesses of the groups. After the post-hoc analysis, a significant difference was found between all groups at the $p < 0.05$ level (Table II). The mean endometrial thicknesses of cases with simple non-atypical endometrial hyperplasia were found to be significantly higher than those with atrophic, proliferative, and insufficient endometrium ($p < 0.05$).

The diagnoses of endometrial samples obtained by endometrial brush and subjected to liquid-based cytological processing are presented in Table III.

When assessing adequacy based on cell count in cytological examination, 58% (n=116) of cytological samples were found to be insufficient for diagnosis, 37.5% (n=75) were sufficient, and 4.5% (n=9) were borderline. The group that was limited for diagnosis was re-evaluated and received a cytological diagnosis, and was defined as sufficient. Thus, adequacy was accepted as 42% (n=84). For histopathological diagnosis, 66% (n=132) of biopsy samples were sufficient, and 34% (n=68) were insufficient (Table IV).

Cytology adequacy did not change significantly according to menopausal status (χ^2: 1.98, $p = 0.159$), while biopsy adequacy changed significantly according to menopausal status (χ^2: 30.02, $p = 0.001$). Biopsy was found to be adequate more frequently in the premenopausal group.

According to the Chi-square test results, a statistically significant relationship was found between endometrial thickness and both cytology ($\chi^2 = 27.24$, $p < 0.001$) and biopsy ($\chi^2 = 22.81$, $p < 0.001$) adequacy. As endometrial thickness increases, the likelihood of samples being adequate also increases (Table V).

In premenopausal patients, at a 95% confidence interval, the sensitivity of cytological examination compared to biopsy was 51.087%; specificity was 73.684%; positive predictive value was 90.385%; and negative predictive value was 23.729%. In postmenopausal patients, the sensitivity was 57.500%, the specificity was 81.633%, the positive predictive value was 71.875%, and the negative predictive value was 70.175%.

Endometrial cytological sampling in postmenopausal patients showed a statistically significant difference compared to the premenopausal group ($p < 0.05$), but no statistically significant superiority of endometrial cytological examination over endometrial biopsy was found in either group ($p > 0.05$).

The cytology materials of all patients diagnosed with endometrial cancer and complex atypical endometrial hyperplasia were sufficient for diagnosis and consistent with the histopathological diagnosis.

In cytological diagnosis, 6 patients were suspected of malignancy, and 1 patient was positive for malignancy. In 4 patients with suspected malignancy, the biopsy result was endometrial adenocarcinoma, in 1 patient it was complex atypical endometrial hyperplasia, and in 1 patient it was an endometrial polyp. In one patient evaluated

Table I. Distribution of histopathological biopsy diagnoses by endometrial thickness (mm) and menopausal status.

Biopsy diagnosis	Menopausal status	0-5 mm	6-10 mm	11-15 mm	16-20 mm	21-25 mm	Total
Non-diagnostic	Pre/Post	3/23	13/23	2/3	0/0	1/0	19 (17.1%)/49 (55.1%)
Proliferative endometrium	Pre/Post	6/0	11/0	1/2	0/0	0/0	18 (16.2%)/2 (2.2%)
Secretory endometrium	Pre/Post	2/0	15/0	4/0	0/0	0/0	21 (18.9%)/0
Endometrial polyp	Pre/Post	0/1	9/12	7/1	3/0	0/1	19 (17.1%)/15 (16.9%)
Atrophic endometrium	Pre/Post	2/3	1/5	1/0	0/0	0/0	4 (3.6%)/8 (9%)
Menstrual endometrium + Endometrial polyp	Pre/Post	2/0	0/0	0/0	0/0	0/0	2 (1.8%)/0
Proliferative endometrium + Endometrial polyp	Pre/Post	0/1	1/0	0/0	0/0	0/0	1 (0.9%)/1 (1.1%)
Secretory endometrium + Endometrial polyp	Pre/Post	0/0	0/0	0/0	2/0	0/0	2 (1.8%)/0
Chronic endometritis	Pre/Post	0/1	3/1	0/0	0/0	0/0	3 (2.7%)/2 (2.2%)
Chronic endometritis + Endometrial polyp	Pre/Post	0/0	0/1	0/0	0/0	0/0	0/1 (1.1%)
Disordered proliferative endometritis	Pre/Post	0/0	2/0	3/0	0/0	0/0	5 (4.5%)/0
Endometrioid adenocarcinoma	Pre/Post	0/0	0/0	0/2	0/2	0/0	0/4 (4.5%)
Leiomyosarcoma	Pre/Post	0/1	0/0	0/0	0/0	0/0	0/1 (1.1%)
Simple non-atypical endometrial hyperplasia	Pre/Post	0/0	5/1	1/0	0/2	0/0	6 (5.4%)/3 (3.4%)
Chronic endometritis + Endometrial polyp	Pre/Post	0/0	0/1	0/0	0/0	0/0	0/1(1.1%)
Leiomyosarcoma	Pre/Post	0/1	0/0	0/0	0/0	0/0	0/1(1.1%)
Early proliferative endometrium	Pre/Post	0/0	0/0	0/0	2/0	0/0	2 (1.8%)/0
Early secretory endometrium	Pre/Post	0/0	0/0	0/0	0/0	0/0	1 (0.9%)/0
Chronic endometritis + Proliferative endometrium	Pre/Post	1/0	3/1	0/0	0/0	0/0	4 (3.6%)/1 (1.1%)
Late secretory endometrium	Pre/Post	0/0	0/0	0/0	1/0	0/0	0/1 (1.1%)
Complex atypical endometrial hyperplasia	Pre/Post	0/0	0/0	0/0	0/1	0/0	0/1 (1.1%)
High-grade mixed epithelial tumor	Pre/Post	0/0	0/0	0/0	0/1	0/0	0/1 (1.1%)
Mixed Mullerian tumor	Pre/Post	0/0	1/0	0/0	0/0	0/0	1 (0.9%)/0
Focal hyperplasia	Pre/Post	1/0	1/0	0/0	0/0	0/0	2 (1.8%)/0
Total	**Pre/Post**	**17 (15.3%)/ 30 (33.8%)**	**65 (58.6%)/ 44 (49.5%)**	**19 (17%)/ 8 (9%)**	**8 (7.2%)/ 6 (6.7%)**	**2 (1.8%)/ 11 (1.1%)**	**111/89**

Table II. Average values of endometrial thickness according to histological diagnoses.

Group	Histological diagnosis	Endometrial thickness mean ± SD	*p*	Post-hoc
Physiological condition (1)	Non-diagnostic	5.93 ± 2.98		
	Proliferative endometrium	8.00 ± 3.92		
	Secretory endometrium	9.43 ± 3.67		
	Atrophic endometrium	6.25 ± 1.89		
Malignancy negative (2)	Endometrial polyp	11.73 ± 4.66		1-2: 0.024*
	Chronic endometritis	8.00 ± 2.82	0.001**	1-3: 0.010*
	Simple non-atypical endometrial hyperplasia	12.66 ± 5.50		2-3: 0.037*
Malignancy positive (3)	Complex atypical endometrial hyperplasia	18 ± 0		
	Endometrial adenocarcinoma	17.00 ± 3.55		
	High-grade mixed epithelial tumor	19.00 ± 0		

*$p < 0.05$, **$p < 0.001$.

Table III. Distribution of cytology diagnoses according to menopausal status.

Diagnosis	Pre-menopause	Post-menopause	Total
Non-diagnostic	59 (53.15%)	57 (64.06%)	116 (58%)
Malignancy negative	43 (38.75%)	20 (22.47%)	63 (31.5%)
Malignancy suspicious	1 (0.90%)	5 (5.61%)	6 (3%)
Unclassifiable	8 (7.20%)	6 (6.74%)	14 (7%)
Malignancy positive	0	1 (1.12%)	1 (0.5%)
Total	**111**	**89**	**200**

Table IV. Analysis of cytology and biopsy adequacy according to menopausal status.

		Pre-menopause f (%)	Post-menopause f (%)	χ^2	*p*
Cytology	Sufficient	52 (46.8%)	32 (36%)	1.98	0.159
	Insufficient	59 (53.2%)	57 (64%)		
Biopsy	Sufficient	92 (82.9%)	40 (44.9%)	30.02	0.001**
	Insufficient	19 (17.1%)	49 (55.1%)		

**$p < 0.001$.

Table V. Analysis results according to measured endometrial thicknesses for cytology and biopsy adequacy.

		Endometrial thickness						
		0-5 mm f (%)	6-10 mm f (%)	11-15 mm f (%)	16-20 mm f (%)	21-25 mm f (%)	χ^2	*p*
Cytology	Sufficient	8 (17%)	45 (41.3%)	18 (66.7%)	11 (78.6%)	2 (66.7%)	27.24	0.001**
	Insufficient	39 (83%)	64 (58.7%)	9 (33.3%)	3 (21.4%)	1 (33.3%)		
Biopsy	Sufficient	19 (40.4%)	75 (68.8%)	24 (89%)	12 (85.7%)	2 (66.7%)	22.81	0.001**
	Insufficient	28 (59.6 %)	34 (31.2%)	3 (11%)	2 (14.3%)	1 (33.3%)		

**$p < 0.001$.

as positive for malignancy, the biopsy result was a high-grade mixed epithelial tumor. The sensitivity of cytology in identifying malignant lesions was 100%, the specificity was 96.923%, the positive predictive value was 71.429%, and the negative predictive value was 100%.

DISCUSSION

In this study, the results of TV-USG, endometrial cytology, and endometrial biopsy were evaluated in both premenopausal and postmenopausal patients with abnormal uterine bleeding.

The most significant limitation encountered was the insufficiency of material for cytological and histopathological evaluation. The relatively high rate of insufficient cytology samples in our study (58%) should be interpreted in light of the sampling method we employed. We used a brush not specifically designed for endometrial sampling, which may partly explain the limited adequacy. Recent evidence[5] suggests that dedicated endometrial samplers, such as the Tao Brush, can provide higher adequacy and diagnostic accuracy while avoiding cervical dilatation and minimizing patient discomfort. Likewise, large-scale studies[6] have confirmed that liquid-based endometrial cytology, particularly when combined with transvaginal ultrasonography, achieves high diagnostic performance in detecting endometrial cancer.

The sensitivity and specificity of endometrial cytology were found to be higher in postmenopausal patients compared to premenopausal patients. Moreover, cytology demonstrated high sensitivity and specificity in detecting malignant endometrial lesions. In all patients, endometrial cytologic examination was not statistically significantly superior to endometrial biopsy.

Irregular uterine bleeding is one of the most important complaints of premenopausal and postmenopausal women[7]. Endometrial biopsy is one of the most commonly used methods to examine the endometrium. Since endometrial biopsy is an invasive method and in some cases, sufficient endometrial tissue cannot be obtained for histopathologic evaluation, especially in postmenopausal women, less invasive methods have been investigated[7-9].

In recent years, there has been an increase in studies on the detection of endometrial pathologies with endometrial thickness measurements by TV-USG and histopathological examinations[10-12]. Granberg et al[13] performed TV-USG and then curettage in all patients in their study in postmenopausal bleeding patients. They did not detect endometrial cancer in any of the patients with endometrial thickness less than 8 mm. They reported a mean endometrial thickness of 18.2 mm in endometrial cancer and 3.4 mm in atrophic endometrium. When the cut-off limit of the endometrium evaluated by TV-USG was taken as 5 mm, they recommended that diagnostic curettage should not be performed in 70% of cases. They also reported that the possibility of malignancy was very low in premenopausal patients with an endometrial thickness of 8 mm or less in abnormal uterine bleeding[13]. In postmenopausal women with endometrial thickness ≤ 4 mm, the likelihood of malignancy is lower, but routine endometrial biopsy is recommended in patients at risk for endometrial cancer[14,15]. Similarly, Varner et al[16] failed to detect pathology in postmenopausal patients with endometrial thickness of 4 mm and below. However, there is a very rare study[8] in which hyperplasia was detected at a thickness of 4 mm. With the increasing use of sensitive measurements, it has been reported that both low and high endometrial thickness thresholds can be equally effective in detecting endometrial carcinoma and atypical endometrial hyperplasia, especially in the postmenopausal period, and sensitivity can be increased at cut-off values of 3 mm and 5.9 mm[17]. In this study, endometrioid-type adenocarcinoma was detected in 4 postmenopausal patients, and a high-grade mixed epithelial tumor was detected in one patient. The mean endometrial thickness in the adenocancer group was 17.0 ± 3.55 mm, similar to the literature, and there was no malignancy in patients with endometrial thickness less than 13 mm. In the case with a high-grade mixed epithelial tumor, the endometrial thickness was 19 mm. Similar to the literature, no case of hyperplasia or carcinoma was detected in any patient with an endometrial thickness of less than 5 mm. The mean endometrial thickness was 9.00 mm in premenopausal women and 7.44 mm in postmenopausal women. The significant difference in the mean endometrial thickness measured in patients with physiologic conditions, malignancy-negative and malignancy-positive, which we analyzed in 3 groups according to biopsy diagnoses, showed that the evaluation of TV-USG and biopsy together is important for accurate diagnosis.

Studies have particularly emphasized the diagnostic value of liquid-based endometrial cytology. Garcia et al[18] reported 96% specificity and 78% sensitivity in a prospective study of 103 symptomatic women. The rate of insufficient material was 15% for cytology and 26% for biopsy. Kipp et al[19] determined that endometrial cytology has a high sensitivity in detecting endometrial cancer. They stated that it can be considered as a screening test because of its low discomfort to the patient and easy applicability. Papaefthimiou et al[20] emphasized the low rate of insufficient material, high sensitivity and specificity, high positive and negative predictive values of the liquid-based endometrial cytologic method. In another study[4] with 917 patients, hysteroscopy was performed first, followed by endometrial cytology and biopsy. They stated that endometrial cytology alone is an effective diagnostic method, but when combined with TV-USG, diagnostic accuracy will increase, and more invasive or more expensive diagnostic methods, such as D&C or hysteroscopy, will decrease[12]. It is clear that the

use of endometrial cytology in combination with TV-USG will contribute to diagnostic accuracy. In our study, the increase in cytology adequacy as endometrial thickness increased supports the use of TV-USG and cytology together.

In a study[21] comparing endometrial biopsy and endometrial cytology in symptomatic postmenopausal patients, it was reported that the sensitivity of endometrial cytology in diagnosing atypical endometrial hyperplasia was 100%, specificity was 99%, positive predictive value was 83% and negative predictive value was 100%, while these rates were 100%, 99%, 97% and 100% for malignancy. In our study, the sensitivity of cytology in identifying malignant lesions was 100%, specificity 96.9%, positive predictive value 71.4% and negative predictive value 100%. As a result, the power of endometrial cytology to identify malignant lesions is quite high.

In this study, the sensitivity, specificity, positive predictive value and negative predictive value of cytologic examination in premenopausal patients were 51.087%, 73.684%, 90.385% and 23.729%, respectively. In postmenopausal patients, sensitivity was 57.5%, specificity 81.633%, positive predictive value 71.875%, and negative predictive value 70.175%. There was no statistically significant superiority of endometrial cytologic examination over endometrial biopsy in all patients.

Our findings, therefore, highlight that cytology alone, with the technique applied in this study, cannot be recommended as a primary screening tool. However, the reliable detection of malignant lesions in adequate samples and recent advances such as molecular adjuncts, including cell-free DNA analysis and chromosomal instability profiling[22,23], indicate that cytology may become a more valuable component of multimodal screening strategies in the future.

Inadequate material in the biopsy is an important obstacle in the elucidation of endometrial pathologies. In previous studies[24,25], inadequate specimens constituted 2% to 60% of endometrial specimens. In our study, 58% of cytology and 34% of biopsy specimens were found to be inadequate in total, without differentiating between premenopausal and postmenopausal patients. In the premenopausal patient group, biopsy failure rate was 17.1% and cytology failure rate was 53.2%; in the postmenopausal patient group, biopsy failure rate was 55.1% and cytology failure rate was 64%. As endometrial thickness increases, the likelihood of obtaining adequate samples from both biopsy and cytology also increases. These rates suggest that menopausal status has no significant effect on the adequacy of cytology sampling. The reason for cytologic inadequacy may be postmenopausal thinning of the endometrium due to atrophy and decrease in cellular debris. Biopsy failure may be due to inadequate tissue collection, endometrial atrophy, and technical difficulty in sampling. In conclusion, the rate of obtaining adequate samples by both cytology and biopsy methods decreases in the postmenopausal period. Nonetheless, the difference is more prominent and statistically significant in the biopsy group. Therefore, it may be recommended that more sensitive and directed sampling methods should be preferred for the diagnosis of endometrial pathologies in postmenopausal women. The high rate of insufficient material is an important problem and limits the use of endometrial cytology alone for the screening of endometrial cancer and its precursors in both premenopausal and postmenopausal patients, because cytologic diagnosis of endometrial lesions requires an adequate number of cells, distinct morphologic features, and proper cellular arrangement[26]. Compared to the literature[27,28], the rate of insufficient cytologic material in this study was quite high. This may be due to the fact that endometrial sampling was not always performed by the same person and the original endometrial brush was not used. Non-diagnostic cytology may be due to inadequate material collection, inadequate preservation or preparation, degradation of cells during sampling, lack or insufficient clinical knowledge, and inadequate cell counts[27]. In this study, the intrauterine device sheath was used outside the brush in order to perform endometrial sampling and to minimize endocervical contamination. However, the cytology materials of all patients with histopathologic diagnosis of endometrial cancer and endometrial hyperplasia with complex atypia were adequate and the cytology results were completely compatible with the histopathologic results.

CONCLUSIONS

Endometrial cytology demonstrated high accuracy in detecting malignant lesions when adequate material was obtained; however, the high proportion of insufficient samples in both cytology and biopsy remains a major limitation. Therefore, cytology alone cannot be recommended as a standalone screening tool and should always be interpreted in conjunction with transvaginal ultrasonography and histopathological evaluation, which together provide reliable guidance in differentiating malignant and non-malignant

conditions. Nonetheless, recent advances, including the use of dedicated endometrial samplers such as the Tao Brush, liquid-based cytology combined with TV-USG, and novel molecular adjuncts (e.g., cell-free DNA and chromosomal instability profiling), suggest that cytology may play a more prominent role in future multimodal screening strategies for endometrial cancer and its precursors.

Conflict of Interest
The authors declare that there are no conflicts of interest.

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Authors' Contributions
Seniye Burcu Torumtay Alic: Contributed to the conceptualization of the study, data collection, manuscript drafting, and served as the corresponding author. Data analysis, interpretation of results, and writing and editing of the manuscript.
Haluk Erdal Malatyalioglu: Provided expert guidance on methodology, contributed to manuscript review, and ensured the overall scientific quality of the study.

Data Availability
The data that support the findings of this study are not publicly available due to ethical considerations and to protect the privacy of research participants. However, the data are available upon reasonable request from the corresponding author.

Ethics Approval
This study was conducted as part of a medical specialty thesis in the Department of Obstetrics and Gynecology, Faculty of Medicine, Ondokuz Mayıs University. At the time of the study, institutional practice required approval from the Academic Board of the Department rather than a separate Institutional Review Board. Accordingly, the study was approved by the Academic Board of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ondokuz Mayıs University, on March 15, 2007 (Protocol No.: 2007/455-2). The research was conducted in accordance with international ethical standards, including the guidelines of the Committee on Publication Ethics (COPE), the International Committee of Medical Journal Editors (ICMJE), and the World Association of Medical Editors (WAME).

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Informed Consent
Informed consent was obtained from all patients, and written consent forms were signed prior to participation.

AI Disclosure
ChatGPT was used for language editing and translation support during the preparation of the manuscript. The authors take full responsibility for the scientific content of the present article.

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