



Examining the Association between Endometrial Thickness in Transvaginal Ultrasound and Results of Pipelle Endometrial Sampling in Perimenopausal Women with Abnormal Uterine Bleeding

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ABSTRACT

Aims Since there is no consensus on the best diagnostic method for perimenopausal women with abnormal uterine bleeding. The aim of this study was to investigate the association between endometrial thickness in transvaginal ultrasound and the results of Pipelle endometrial sampling in perimenopausal women with abnormal uterine bleeding.

Materials and Methods In this cross-sectional descriptive study, all perimenopausal women with abnormal uterine bleeding who referred to Rasoul Akram and Akbarabadi Hospitals, Tehran, Iran in 2016 and 2017 were considered. The current study was carried out on a corpus of 68 perimenopausal women with abnormal uterine bleeding. All these patients underwent a transvaginal ultrasound conducted by an operator. Afterward, all of them had a Pipelle endometrial sampling performed by a gynecologist. The current study was carried out on a corpus of 68 perimenopausal women with abnormal uterine bleeding. A chi-square, Mann Whitney, and Kruskal Wallis tests were used. The obtained data were analyzed using SPSS 22.

Findings A statistical mean endometrial thickness in patients with benign diagnoses was 7.55 ± 2.72 mm and it was 15.57 ± 2.99 mm in patients with malignant diagnoses which indicated no statistically significant difference ($p < 0.001$). Evaluating a receiver operating characteristic curve (ROC) demonstrated that the cut-off point of endometrial thickness was 10.50 with a sensitivity of 85% and a specificity of 85%.

Conclusion Determining the cut-off point of 10.50 mm for endometrial thickness using transvaginal ultrasound in perimenopausal women is a suitable, non-invasive method, the results of which can predict the results of Pipelle endometrial sampling well.

Keywords Ultrasonography; Endometrial Neoplasms; Pipelle; Metrorrhagia

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Introduction

In the past, dilatation and curettage (D&C) under general anesthesia were regarded as a gold standard for examining abnormal bleedings [1]. In subsequent studies, it has been indicated that D&C should not be used as the first step in the evaluation of abnormal bleeding [2]. Some studies have shown that in 60% of patients undergoing D&C, less than 50% of the uterine cavity was curetted [3]. In these studies, it has been demonstrated that nearly 15% of endometrial malignancies cannot be diagnosed by this method. Moreover, it has also been shown that in every 1,000 cases of patients undergoing D&C, 5 cases had to undergo a major surgery due to complications of curettage [4].

Alternative methods include endometrial biopsy by Pipelle with or without an ultrasound or hysteroscopy conducted in an outpatient setting and hysteroscopy or curettage in an inpatient setting. The value of hysteroscopy in the evaluation of abnormal uterine bleeding has been confirmed by many researchers and many have suggested this method as a gold standard for examining bleedings [5-9].

Transvaginal ultrasound is a valuable and non-invasive diagnostic method for examining uterine pathologies, especially when it is performed by expert persons [10-12]. In some studies, it has been indicated that vaginal ultrasound alone had a diagnostic value of 100% in examining malignancies in postmenopausal women [10]; however, in some other studies, it has been shown that, by considering 5mm as a cut-off point, 6% of malignancies may not be detected [13].

There are a plethora of tools for performing an endometrial biopsy in outpatients. Pipelle is one of the most commonly used tools which is made of soft plastic and is able to pass through the cervix with the least pain and discomfort. In many studies, Pipelle's diagnostic value was reported to be desirable and comparable to curettage [14-18]. This is while, in some studies, the diagnostic value of Pipelle alone was low and only about 67% of malignancies could be detected by this method [19].

There is a possibility of not diagnosing submucosal polyps or fibroids, it is the main problem with sampling outpatients [5, 20]. This is particularly important in postmenopausal women who are at a greater risk of developing malignant polyps [21]. These cases are more commonly detected with vaginal ultrasound [22].

Endometrial cancer is found in 1 to 25% (10% on average) of postmenopausal women with abnormal bleeding [18, 23, 24] and it is the most prevalent cancer among gynecologic malignancies [25]. More than 90% of this disease occur in people over 50 years of age and its most common symptom is abnormal bleeding [26-29].

Before 1982, a diagnostic examination of abnormal bleeding was conducted by dilatation and curettage. Now, a catheter biopsy with a sensitivity of more than 85% is performed for a carcinoma examination of outpatients with better patient acceptance and lower costs [27, 28].

Various studies have been carried out to determine the extent to which thinness of the endometrium can reject the probability of cancer. These studies have shown that when the thickness of 4 or 5mm was considered as a threshold for cancer in menopausal women, there was a sensitivity of 95% for finding cancer [4, 30].

Due to its simplicity, some doctors prefer transvaginal ultrasound to begin examining bleeding to endometrial biopsy. Compared with endometrial biopsy, ultrasound is better tolerated and has a greater diagnostic value (>95%) [4, 28]. Additionally, in some patients, an outpatient biopsy cannot be performed properly due to cervical stenosis, the patient's intolerance, or the fact that the sample does not provide sufficient data to reject cancer (In 5 to 15% of cases) [10, 31-33].

Furthermore, in cases of endometrial sampling when no diagnoses can be reached, a transvaginal ultrasound is helpful. A thin and homozygous endometrium has a high negative predictive value for performing other invasive procedures such as dilatation and surgical curettage.

Pipelle sampling is carried out by a thin device with an external diameter of usually 3mm sampled by an aspiration. Although it often passes through the cervix easily, it is sometimes accompanied by pain. Approximately 4% of the uterine cavity is sampled by this method. The sensitivity of this method to evaluate endometrial abnormalities is about 85% [30, 34].

The aim of this study was to investigate the association between endometrial thickness in ultrasound and the results of Pipelle endometrial sampling.

Materials and Methods

In this cross-sectional descriptive study, all women with abnormal uterine bleeding including menorrhagia, irregular menstruation, post-intercourse bleeding, and metrorrhagia who referred to Rasoul Akram and Akbarabadi Hospitals, Tehran, Iran in 2016 and 2017 were considered. 75 people were studied, out of which 70 people were eligible and were included in the study. Among these patients (n=70), the results of Pipelle endometrial sampling of 2 patients were non-diagnostic; therefore, they were excluded from the study. Finally, 68 perimenopausal women with abnormal uterine bleeding were examined. Inclusion criterion was perimenopausal people aged 35 to 55 years with abnormal uterine bleeding and the exclusion criteria were people with a history of cervical

surgery, susceptibility to local anesthesia, hemodynamic instability, hemorrhage due to systemic diseases such as coagulation and/or thyroid diseases, regular drug-induced bleeding, virgin women, bleeding caused by cervical and vaginal diseases, and fibroids.

After inquiring into the patient's history and carrying out physical examinations, the patients were subjected to a transvaginal ultrasound. In a transvaginal ultrasound, various criteria such as uterine size, endometrial echymosis, fibroids and polyps, and adnexal masses were evaluated. All ultrasounds were performed by an operator. The procedures were explained to all of these patients. The data related to their age, main complaints, duration of the problem, history of previous illnesses, history of menstrual-based problems, blood problems, and general physical examinations, as well as examinations of the abdomen and pelvis of these patients, were recorded in the relevant checklists. A chi-square, Mann Whitney, Kruskal Wallis, and Spearman tests were used. The obtained data were analyzed using SPSS 22.

Findings

The mean age of the participants was 47.09 ± 4.33 years (The youngest person was 40 years old and the oldest person was 56 years old). Additionally, the mean duration of menometrorrhagia in these patients was 22.43 ± 5.28 months, which was reported to be at least 1 month and at most 166 months.

There was no significant association between clinical characteristics of the patients in the benign and malignant groups except the history of C-section (Table 1).

There was no significant association between the results of Pipelle endometrial sampling and taking the medications (Diagram 1; $p=0.24$).

It was indicated that the proliferative endometrium with a prevalence of 27 cases (39.7%) was the most common pathologic finding in this study. Moreover, the prevalence of malignancy in perimenopausal women with abnormal uterine bleeding was reported as 10.3% (Table 2).

According to the ultrasound results, the mean thickness of the endometrium was reported to be 8.38 ± 3.67 mm, with a minimum thickness of 3mm and a maximum of 19mm. The mean endometrial thickness in the patients with benign diagnoses was 7.55 ± 2.72 mm and in the patients with malignant diagnoses was 15.57 ± 2.99 mm, which was not statistically significant ($p < 0.001$).

Statistical means of endometrial thickness obtained from vaginal ultrasounds in pathological diagnoses of Pipelle endometrial sampling showed that the mean thickness of the endometrium was

significantly greater in malignant diagnoses (Table 3; $p=0.001$).

Table 1) A comparison of the patients' clinical data based on the results of Pipelle endometrial sampling: benign and malignant (n=68, the numbers in parentheses represent percentage)

Variable	Benign (n=61)	Malignant (n=7)	p-value
Body mass index (kg/m²)-number (%)			
Normal (18.5-24.9)	28 (41.2)	6 (8.8)	0.17
Overweight (25-29.9)	28 (41.2)	1 (1.5)	
Obese (30-34.9)	5 (7.3)	-	
Duration of menometrorrhagia			
1 year \geq	37 (54.4)	4 (5.9)	0.85
1 year<	24 (35.3)	3 (4.4)	
Diabetes			
Yes	7 (10.3)	-	0.34
No	54 (79.4)	7 (10.3)	
Thyroid diseases			
Yes	12 (17.6)	-	0.19
No	49 (72.1)	7 (10.3)	
History of cardiovascular diseases			
Yes	17 (25.0)	2 (2.9)	0.96
No	44 (64.7)	5 (7.4)	
History of breast cancer			
Yes	2 (2.9)	-	0.62
No	59 (86.8)	7 (10.3)	
Gravidity			
≥ 3	34 (50.0)	5 (7.4)	0.42
>4	27 (39.7)	2 (2.9)	
Parity			
≥ 3	44 (64.7)	5 (7.4)	0.96
>4	17 (25.0)	2 (2.9)	
Live birth			
≥ 3	45 (66.2)	5 (7.4)	0.89
>4	16 (23.5)	2 (2.9)	
Abortion			
Yes	24 (35.3)	-	0.3
No	37 (54.4)	7 (10.3)	
Dead birth			
Yes	5 (7.3)	-	0.43
No	56 (82.4)	7 (10.3)	
Type of delivery			
C-section	26 (38.2)	7 (10.3)	0.2
Natural	22 (32.4)	-	
C-section + natural	13 (19.1)	-	
History of TL			
Yes	7 (10.3)	1 (1.5)	0.82
No	54 (79.4)	6 (8.8)	
History of C-section			
Yes	30 (44.1)	-	0.01
No	31 (45.6)	7 (10.3)	
History of D&C			
Yes	14 (20.6)	-	0.15
No	47 (69.1)	7 (10.3)	
History of other gynecological surgeries			
Yes	5 (7.4)	1 (1.5)	0.59
No	56 (82.3)	6 (8.8)	

Table 2) Frequency distributions of Pipelle endometrial sampling results (n=68, the numbers in parentheses represent percentage)

Type of histopathology	Frequency
Proliferative endometrium	27 (39.7)
Secretory endometrium	18 (26.5)
Endometrial polyp	9 (13.2)
Endometritis	7 (10.3)
Endometrial hyperplasia with atypia	1 (1.5)
Endometrial hyperplasia without atypia	6 (8.8)

Table 3) Statistical mean of endometrial thickness in various pathologic findings

Type of histopathology	Mean±SD
Proliferative endometrium	6.86±2.91
Secretory endometrium	7.78±2.73
Endometrial polyp	7.94±2.27
Endometritis	9.14±1.95
Endometrial hyperplasia with atypia	19
Endometrial hyperplasia without atypia	15±2.28

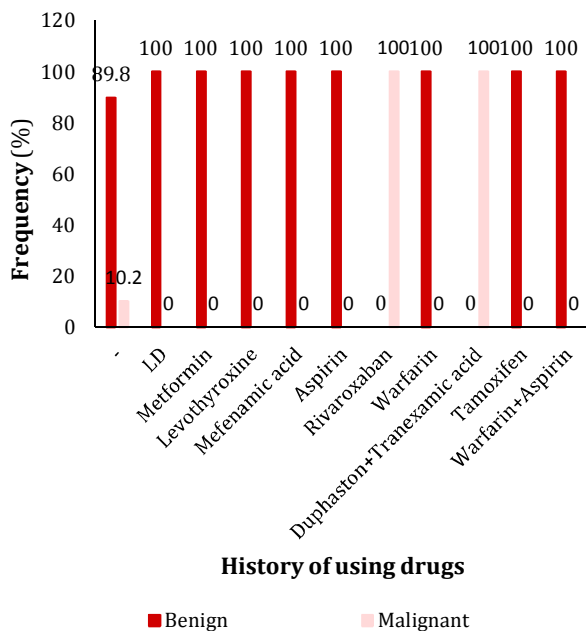


Diagram 1) A distribution of frequency of taking medications in the patients under study based on their benign and malignant diagnoses

When investigating the correlation between the patient's age and their endometrial thickness, the results obtained from ultrasounds revealed that the age of patients was significantly and positively correlated with the endometrial thickness. In other words, by growing older the thickness of the endometrium increases ($r=0.32$, $p=0.007$). In addition, there was no significant correlation between the duration of bleeding and endometrial thickness ($r=0.04$, $p=0.74$).

Based on the evaluation of the receiver operating characteristic curve (ROC) curve, the cut-off point for endometrial thickness was calculated to be 10.50, with a sensitivity of 85% and a specificity of 85% (Diagram 2).

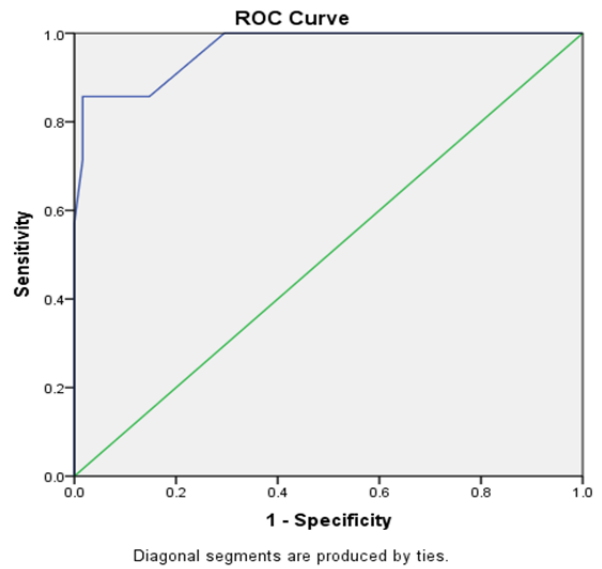


Diagram 2) The ROC curve showing the correlation between endometrial thickness characteristics and sensitivity in benign or malignant diagnoses made based on Pipelle endometrial sampling (Area under the curve: 0.96; $p<0.001$ Confidence interval 95%: 0.90-1)

The sensitivity and specificity of endometrial thickness at the cut-off point, i.e. 10.50, in the diagnosis of malignant histopathologies was 86% (60-100%) and 85% (76-94%), respectively. The positive predictive value was 40% (15-65%), the negative predictive value was 98% (94% -100%), the positive likelihood ratio was 5.81 (2.96-11.71), and the negative likelihood ratio was 0.17 (0.33-0.03).

Discussion

The aim of this study was to investigate the association between endometrial thickness in ultrasound and the results of Pipelle endometrial sampling.

By performing different analyses and evaluating the thickness of endometrium in the perimenopausal women, it was concluded that endometrial thickness was significantly increased in malignant histopathologies obtained from Pipelle endometrial sampling. In complementary studies in histopathologic diagnosis, it was determined that endometrial thickness in the histopathology of the endometrial hyperplasia with atypia had the highest thickness with an average thickness of 19mm. Another significant finding in this study was the effect of age's positive feedback on endometrial thickness. In other words, as women grow older, an increase in endometrial thickness is not unexpected. In the present study, the cut-off point for endometrial thickness in the perimenopausal women with abnormal uterine bleeding was 10.50. Based on this finding, it can be stated that if a transvaginal ultrasound reports a thickness more

than the cut-off point, the patient is suspected and there is a need for carrying out an endometrial sampling. In a few studies, endometrial thickness was used to predict endometrial disorders before and after menopause. According to the associated diagnostic methods, the precision used in the samples, and the different objectives of carrying out these studies, different thicknesses of the endometrium have been reported [35]. What is being addressed in the present study is the diagnostic accuracy of endometrial thickness in detecting malignancies from Pipelle endometrial sampling. Therefore, due to the importance of early detection of malignancies in perimenopausal women and considering timely treatment for these patients, a positive step was taken towards diagnosing these malignancies using endometrial thickness.

Based on widespread searches, few studies have been carried out on endometrial thickness in perimenopausal women. According to available evidence, this is the first study that investigated the diagnostic value of the thickness of endometrium in benign or malignant diagnoses made based on Pipelle endometrial sampling.

One of the most important findings of this study was the calculation of the endometrial thickness cut-off point. According to the result, the cut-off point obtained was 10.50 and this can be helpful in detecting malignancies in perimenopausal women with abnormal uterine bleeding using Pipelle endometrial sampling. It should be noted that in a few studies examined endometrial thickness to predict the probability of occurrence of significant disorders, different cut-off points have been reported [35]. In a study carried out by Getpook *et al.*, the cut-off point for endometrial thickness in perimenopausal women with abnormal uterine bleeding was reported to be 8mm, with a sensitivity and specificity of 80% and 53.8%, respectively, in cases where submucous myoma was set aside [36]. In the current study, submucous myoma was not detected; therefore, the sensitivity and specificity of this diagnosis were expressed without such a diagnosis. Goldstein *et al.* indicated that the transvaginal ultrasound and cut-off point of 5 for endometrial thickness were the first screening lines in detecting abnormal bleeding in perimenopausal women [37]. The cut-off point obtained in this study was slightly higher than that mentioned in the Getpook's study. However, the inadequacy of the samples in a percentage of biopsy cases can be one of the most important factors explaining this difference. The area under the curve in the present study was 0.96, it indicated that endometrial thickness was practical as a screening tool for perimenopausal women with abnormal bleeding. It should be noted that in all perimenopausal women with abnormal uterine bleeding, endometrial hyperplasia or malignancy should be excluded [38].

Vercellini *et al.* stated that a transvaginal ultrasound is the first diagnostic method for perimenopausal with abnormal uterine bleeding. Their study showed that the transvaginal ultrasound detected submucous myoma with a sensitivity of 80 and a specificity of 69% [39]. Studies have shown that the use of endometrial sampling alone may lead to a lack of diagnosis in 10% to 33% of cases; therefore, supplementary tests, such as transvaginal ultrasound, are recommended [40]. By obtaining a cut-off point for endometrial thickness in perimenopausal women with abnormal uterine bleeding not only we can reduce unnecessary samplings, but also we can offer a less costly, less risky, and noninvasive method.

Based on the results of this study, the perimenopausal women with abnormal uterine bleeding whose endometrial thickness was less than 10.50mm in their transvaginal ultrasounds should be considered as low risk women and they may require sampling based on other conditions. This is while it should also be noted that a study conducted by Dueholm *et al.* surveyed the effectiveness of endometrial thickness in separating polyps and hyperplasia and failed to achieve an optimal cut-off point for endometrial thickness in their study [41]. The difference between the results of the mentioned study and the findings of this study can be due to various characteristics of the population studied.

In this study, the prevalence of malignant lesions was 10.3%, and the most common finding in Pipelle endometrial sampling was proliferative endometrium. The prevalence of cancer and endometrial hyperplasia cases was reported to be 8.6% in a study that carried out by Kim *et al.* [42]. This difference in the incidence of malignancies between the study conducted by Kim *et al.* and the current study could be due to the difference in the sample size of the two studies (In the present study, the sample size was 68 cases and it was 162 cases in Kim's study). In examinations conducted using biopsy, there has been always a high incidence of inadequate samples [43]. In this study, the prevalence of inadequate samples was very low, which adds to the strength of the present study in confirming the diagnosis.

Based on the results of this study, the mean thickness of the endometrium was significantly higher in women with malignant diagnoses than in women with benign diagnoses. Therefore, the results of this study indicated the association between endometrial thicknesses in transvaginal ultrasound with malignant diagnoses made based on Pipelle endometrial sampling. By carrying out an ultrasound and determining the thickness of the endometrium, a great deal of sampling is reduced. Using the endometrial thickness parameter in vaginal ultrasound can be effective in predicting benign or malignant endometrial sampling.

Incomplete data of patients can be ensured by using computer systems to ensure that the file is complete. Also, the inadequacy of sample size is considered as another constraint, which is justified by the lack of cooperation of the patients.

It is suggested a study with a larger sample size be performed in different communities with different demographic characteristics to determine the cut-off point in premenopausal women in that area. It is also suggested to study factors such as obesity, diabetes, hypertension, and others endometrial cancer risk factors.

Conclusion

Determining the cut-off point of 10.50mm for the endometrial thickness using transvaginal ultrasound in perimenopausal women is a suitable, non-invasive method, the results of which can predict the results of Pipelle endometrial sampling well.

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