

Evaluation of endometrial thickness with transvaginal ultrasonography and histopathology in premenopausal women with abnormal vaginal bleeding

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Abstract

Objective This study was undertaken to investigate cut-off value of the endometrial thickness by transvaginal ultrasonography (TvUSG), and to detect the accuracy of preoperative Pipelle biopsy in premenopausal women with abnormal vaginal bleeding.

Study design This study was included 144 premenopausal women with abnormal bleeding. Their endometrial thickness was measured by TvUSG and then Pipelle endometrial biopsy was performed. Preoperative histopathologic findings of 57 women who were operated were compared with final histopathologic examination.

Results Of the 144 women, 113 (78.4%) had normal and 31 (21.6%) had an abnormal endometrium. The abnormal endometrium was composed of 11.8% hyperplasia (simple + atypical complex), 4.2% endometrial polyp, and 5.5% adenocarcinoma. An optimal sensitivity and specificity (83.6 and 56.4%, respectively) and negative predictive value with 95.6% for detection of abnormal endometrium were obtained with an endometrial thickness of 8 mm.

The accuracy rate of preoperative Pipelle biopsy was 94.7% in a total of 57 women.

Conclusion An endometrial thickness >8 mm is more likely than that of 8 mm or less to be indicated with endometrial biopsy in premenopausal uterine bleeding. Pipelle endometrial biopsy is an accurate diagnostic procedure for the detection of high-grade endometrial lesions in premenopausal women.

Keywords Abnormal uterine bleeding · Premenopause · Endometrial thickness · Transvaginal ultrasonography · Pipelle biopsy

Introduction

Abnormal vaginal bleeding is one of the most common presenting complaints in women regardless of age. This complaint is taken more seriously when it occurs in women of late reproductive age due to some possible malignant causes. The differential diagnosis includes a broad range of conditions, but the vast majority of women with irregular or excessive vaginal bleeding have benign disorders. The most frequently used diagnostic tests to investigate the causes of abnormal bleeding were transvaginal ultrasonography (TvUSG) and endometrial biopsy. Dilatation and curettage (D&C) and office endometrial biopsy are the methods for endometrial sampling. Uterine curettage is an invasive procedure and it must be performed in the operating room with anesthesia and also its diagnostic accuracy is questionable [1]. Effective and less invasive screening methods are needed for this problem.

TvUSG is one method that has been used to evaluate the endometrium and uterine cavity. In addition, endometrial thickness, uterine volume, presence or absence of fibroids,

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endometrial homogeneity and presence of abnormal vascularity within the endometrium can be assessed by TvUSG [2]. In the absence of visible anomalies (e.g. fibroids), endometrial thickness and homogeneity has been used as markers of endometrial pathology. Endometrial thickness measured by TvUSG has been shown as an effective procedure for evaluating abnormal bleeding in postmenopausal women [3, 4]. An endometrial thickness of 4–5 mm is accepted to be a safe cut-off level to differentiate malignant lesions in cases with no hormonal therapy [5–7]. The efficacy of endometrial thickness in abnormal bleeding in premenopausal women is still a controversial issue and a cut-off level of endometrial thickness is unclear.

This study was undertaken to evaluate the endometrial thickness with transvaginal sonography and histopathology in premenopausal women with abnormal vaginal bleeding and to detect the accuracy of preoperative Pipelle biopsy.

Methods

This study was performed in patients attending the outpatient gynecologic clinic of Meram Medical Faculty, between November 2006 and June 2008. The study included 144 premenopausal women with non-cyclic abnormal uterine bleeding, who were more than 36 years old. The patients with an underlying medical problem such as diabetes and hypertension or with users of intrauterine devices and hormonal therapy were excluded from the study. The study was approved by the ethics committee of Meram Medical Faculty. Each patient gave written informed consent to participate.

After a complete history was taken and a physical examination was done, the patients were prepared for endometrial biopsy. Before the endometrial biopsy, TvUSG was performed to measure endometrial thickness and to assess other abnormalities of the endometrial cavity. TvUSG was carried out by one single sonographer (D.K.) using an ultrasound system (Siemens Medical Sonoline G40, Ultrasound Division, Mountain View, CA, USA) equipped with a 4–9-MHz transvaginal transducer. Endometrial thickness was measured in the sagittal plane of the uterus at the thickest part near the fundus. The measurement of TvUSG was included both endometrial layers, from basal layer of the anterior wall to the basal layer of the posterior uterine wall, and any fluid in the uterine cavity was excluded. The mean results of three measurements were recorded for each patient.

Endometrial biopsy was performed within the luteal phase of menstruation, and 3 days after the evaluation of endometrial thickness with TvUSG. Endometrial sampling was carried out by Pipelle biopsy, standard of care for evaluating all premenopausal women with uterine bleeding. For

endometrial aspiration, the patients were placed in dorsal position, and a bivalve speculum was inserted into the vagina. The cervix was stabilised by a tenaculum if difficulty was encountered during insertion of the sampler. The endometrial cavity was curetted using gentle rotatory and longitudinal movements of the cannula with inner piston. Following a successful attempt, the specimen was placed in formalin and sent for histopathological examination. The endometrial sections were examined by a pathologist who was blinded to the endometrial thickness result. The histopathology findings with proliferative, secretory, atrophy were considered as normal endometrium; hyperplasia, polyp, and adenocarcinoma as abnormal endometrium.

The data were expressed as percentage, mean and standard deviation and analysed using SPSS version 13.0 program. We performed receiver operating characteristics (ROC) analysis to assess the discriminative capacity of endometrial thickness for detection of abnormal endometrium. The area under the ROC curve reflects the diagnostic accuracy of a test, incorporating sensitivity and specificity for all possible thresholds, thus allowing detection of an optimal cut-off point for further clinical management.

Results

The patient's characteristics are shown in Table 1. The mean age of 144 women was 45.31 ± 4.20 (36–53)/year; body mass index was 28.54 ± 2.67 (24–36) kg/m². The mean endometrial thickness measured by TvUSG was found to be 9.36 ± 4.58 mm with a range of 2–30 mm. There was no patient with an underlying medical problem. The median values of gravidity and parity were 4 (0–10) and 4 (0–9), respectively.

The distribution of the endometrial histologies with mean endometrial thickness is displayed in Table 2. The normal and abnormal endometrial histologies were detected in 78.4 and 21.6% of women, respectively. Proliferative endometrium and secretory endometrium were the most common encountered normal findings (37.5 and 36.1%, respectively). The mean endometrial thickness was 7.63 ± 3.82 mm in proliferative endometrium, and 8.65 ± 4.21 mm in secretory endometrium. Endometrial atrophy

Table 1 Demographic characteristics of the study population

Characteristics	Mean \pm SD
Age (year)	45.31 ± 4.20 (36–53)
Gravida (median)	4 (0–10)
Parity (median)	4 (0–9)
Body mass index (kg/m ²)	28.54 ± 2.67 (24–36)
Endometrial thickness (mm)	9.36 ± 4.58

Table 2 Histopathologic findings and mean endometrial thickness

Histopathology	Number (n)	Endomet. thickness (mm)
Normal endometrium	113 (78.4%)	
Proliferative	54 (37.5%)	7.63 ± 3.82
Secretory	52 (36.1%)	8.65 ± 4.21
Atrophy	6 (4.2%)	4.57 ± 2.53
Abnormal endometrium	31 (21.6%)	
Polyp	4 (4.2%)	12.83 ± 2.82
Hyperplasia	17 (11.8%)	12.71 ± 4.25
Simple	13 (9.1%)	12.61 ± 7.42
Complex atypical	4 (2.7%)	13.52 ± 4.52
Endometrial cancer	8 (5.5%)	15.25 ± 8.23

Table 3 Sensitivity, specificity, positive predictive value, and negative predictive value of endometrial thickness at each cut-off level for abnormal endometrial histology

Endometrial thickness(mm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥4	100	8.6	21.6	100
≥5	100	17.3	23.8	100
≥6	98.2	24.3	27.7	100
≥7	93.4	36.2	31.3	93.3
≥8	83.6	56.4	36.3	95.6
≥9	74.7	58.7	39.3	93.2
≥10	62.2	69.2	40.9	92.8
≥11	61.0	78.2	41.7	89.0
≥12	37.2	83.6	47.3	89.3
≥13	27.6	87.0	42.9	84.6
≥14	20.7	93.0	50.0	83.5
≥15	17	96.0	50.0	82.0

was detected in 4.8% of the patients and endometrial thickness was 4.57 ± 3.53 mm. Regarding the abnormal endometrium, endometrial hyperplasia and cancer were founded in 11.8 and 5.5% of the patients, respectively. Only 6 (4.2%) of the patients had endometrial polyp. Endometrial thickness was higher in patients with endometrial cancer (15.25 ± 8.23) than those with endometrial hyperplasia (12.71 ± 4.25) and polyp (12.83 ± 2.82). Any pathologic finding was not detected in endometrial thickness less than 4 mm.

The sensitivity and specificity for values of endometrial thickness in detecting abnormal endometrial histologies are shown in Table 3. The endometrial thickness at 8 mm revealed the optimal sensitivity and specificity (83.6 and 56.4%, respectively) to detect an abnormal endometrium with 95.6% negative predictive value (NPV) and 36.3% positive predictive value. The ROC curve for the endometrial thickness and the abnormal endometrial histologies (hyperplasia, polyp, and adenocarcinoma) is shown in

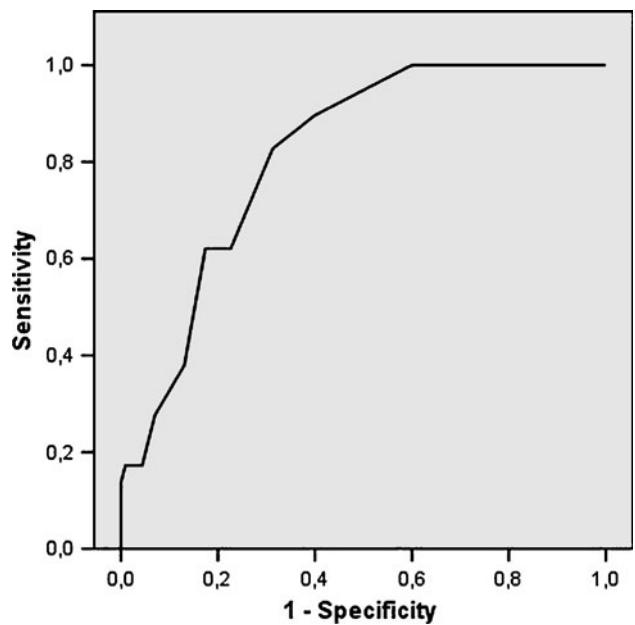
**Fig. 1** ROC curve of the endometrial thickness and abnormal endometrial histology with AUC value of 0.815 (95% CI = 0.742–0.888)

Fig. 1. The area under the curve is 0.815 (95% CI = 0.742–0.888). Two women with simple hyperplasia and one woman with polyp had endometrial thickness less than 8 mm.

The agreement between preoperative Pipelle endometrial sampling and hysterectomy diagnosis was detected accurately in 54/57 of the patients who were operated (Table 4). The accuracy of preoperative Pipelle biopsy was found as 94.7% in the study population. The results of pre-operative endometrial biopsy in two patients were proliferative endometrium but their final pathology showed submucous myoma. Although preoperative sampling in one patient was simple hyperplasia, final examination revealed endometrial polyp associated with hyperplasia. Pipelle endometrial biopsy only seems to be insufficient in detecting the focal lesions such as endometrial polyp or submucous myoma. No endometrial carcinoma or hyperplasia was missed after Pipelle sampling.

Discussion

Abnormal uterine bleeding can signify an underlying malignant lesion affecting the female genital tract. Abnormal bleeding is observed in 80–90% of pre- and postmenopausal women with endometrial cancer [2]. Perimenopausal women with abnormal uterine bleeding make up the majority of patients that present to gynecologists with vaginal bleeding. A careful diagnostic approach is necessary in premenopausal women with abnormal uterine bleeding

Table 4 The agreement between preoperative endometrial histopathology and hysterectomy diagnosis

Preoperative histopathology	Postoperative histopathology						
	Proliferative (n = 15)	Secretory (n = 13)	Polyp (n = 5)	Simple hyperplasia (n = 10)	Atypical complex (n = 4)	Endometrial cancer (n = 8)	Submucous myoma (n = 2)
Proliferative (n = 17)	15						2
Secretory (n = 13)		13					
Polyp (n = 4)			4				
Simple hyperplasia (n = 11)				1	10		
Atypical complex (n = 4)						4	
Endometrial cancer (n = 8)							8
Submucous myoma (n = 0)							

because of potential malignant conditions. Surgical interventions may be required for these endometrial pathologies in many such patients. Uterine curettage or endometrial sampling is usually performed to demonstrate the underlying causes of abnormal bleeding. Because this conventional approach is invasive and not convenient for either the patient or the physician, questions have arisen regarding the appropriateness of performing endometrial biopsies on all patients with bleeding [2]. TvUSG have been reported as efficient in detecting pathologies of the uterine cavity in postmenopausal bleeding [3–7]. However, there are limited studies for endometrial thickness measurement in premenopausal women with abnormal uterine bleeding.

Regarding the efficacy of endometrial thickness in abnormal bleeding in premenopausal women, a small number of studies have been reported on this controversial issue. A study by Vercellini et al. [8] showed a good specificity and high NPV for TvUSG in identifying intrauterine diseases. They suggested TvUSG as the initial investigation in menorrhagic patients, limiting hysteroscopy to cases with positive or doubtful sonographic findings. Goldstein et al. [9] suggested an ultrasonography-based triage and they used a thickness of 5 mm as the cut-off point for the screening in abnormal perimenopausal bleeding. They also performed a further saline infusion sonography (SIS) with a single layer measurement of the endometrium. They have proposed that nondirected office biopsy alone without imaging would have potentially missed the diagnosis of focal lesions such as polyps, submucous myomas, and focal hyperplasia in 18% of the patients. Similarly, in our study, preoperative diagnosis of some focal lesions including submucous myoma and polyp, were missed after the Pipelle sampling without a prior SIS or hysteroscopy.

A study by Schwarzler et al. [10] showed that SIS had a better diagnostic value than the conventional TvUSG for abnormal bleeding in patients from reproductive age to the late menopausal age. These findings were confirmed by other studies [11, 12]. These previous studies usually have

promoted the role of SIS and they included small data concerning a safe cut-off value for endometrial thickness in women with premenopausal bleeding. SIS may not also be an appropriate approach in women with active bleeding. A recent study investigating endometrial thickness in premenopausal bleeding showed optimal sensitivity and specificity of an endometrial thickness of 8 mm in screening endometrial abnormalities [13]. The cut-off level of the endometrial thickness in this study was not different when submucous myoma was excluded. The present study was in accordance with this study. We also obtained optimal sensitivity and specificity for detection of abnormal endometrial findings at endometrial thickness of 8 mm with similar sensitivity and specificity.

Dueholm et al. investigated a cut-off level for endometrial thickness with TvUSG and they were unable to find an optimal thickness [14]. They expressed that low levels of endometrial thickness reduced the possibility of abnormalities such as polyps and hyperplasia, but did not increase the diagnostic performance in cases with normal sonograms. Similarly, we did not determine abnormal endometrial histopathology at where endometrial thickness was less than 6 mm. As we reduced the cut-off level to endometrial thickness of 6 mm, no abnormal histopathologic findings were missed but specificity for detection of abnormal endometrium also decreased. Due to the absence of preoperative diagnosis of submucous myoma, we did not evaluate the endometrial thickness for submucous myoma. In the suspicion of focal lesions, TvUSG associated with SIS may be useful for increasing the diagnosis of these lesions.

A wide variety of endometrial biopsy devices with different sensitivities and specificities have been developed. Pipelle endometrial biopsy is widely used as an inexpensive outpatient procedure for histological assessment. Despite sampling, only a small proportion of the endometrial surface and having limitations in identifying focal lesions, it has been shown to have a high degree of sensitivity and specificity for the detection of endometrial carcinoma

[15, 16]. In the present study, only focal lesions such as submucous myoma and polyp were not determined by Pipelle biopsy. Overall accuracy rate of preoperative Pipelle sampling for detection of endometrial pathologies was 94.7% in the study population when compared with hysterectomy results. A meta-analysis of 39 studies that included 7,914 women, who had endometrial sampling, using various techniques in pre- and postmenopausal women, revealed that the detection rate for endometrial cancer was higher in postmenopausal women compared with premenopausal women [17]. In both post- and premenopausal women, the Pipelle was found as the best device with detection rates of 99.6 and 91%, respectively. In the present study, no endometrial cancer subject was missed after Pipelle sampling. Other endometrial lesions including simple and atypical hyperplasia were not also missed by Pipelle sampling in the present study.

In conclusion, TvUSG may still serve as the first-line diagnostic technique in assessment of premenopausal women with abnormal bleeding. An endometrial thickness ≤ 8 mm on ultrasonography is less likely to be indicated for endometrial biopsy in low risk premenopausal women. The clinician should pay attention to other findings from the TvUSG, such as, regularity of the midline echo, homogeneity of the endometrial texture as well. Pipelle endometrial biopsy is a well tolerated, minimally invasive procedure with a high accuracy for the diagnosis of high-grade endometrial lesions in premenopausal women after TvUSG. In suspicion of focal lesions, a further sonohysterography or hysteroscopy may be recommended before endometrial sampling.

Conflict of interest statement None.

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