Value of three dimensional power Doppler ultrasound in prediction of endometrial carcinoma in patients with postmenopausal bleeding

Sherif Hanafi, Ahmed Abou-gabal, Sherif Akl, Heba Abd El Baset
Department of Obstetrics and Gynecology, Ain Shams University Maternity Hospital, Cairo, Egypt

Abstract

Objective: To determine whether endometrial volume or power Doppler indices measured by 3-dimensional (3D) ultrasound imaging can discriminate between benign and malignant endometrium in women with postmenopausal bleeding and endometrial thickness ≥5 mm.

Material and Methods: The current diagnostic accuracy study was conducted at Ain Shams University Maternity Hospital. Eighty-four patients with postmenopausal bleeding and endometrial thickness ≥5 mm underwent 3D power Doppler ultrasound examination of the corpus uteri. The endometrial volume was calculated, along with the vascularization index (VI), flow index (FI), and vascularization flow index (VFI) in the endometrium. The gold standard was the histopathological diagnosis of the endometrium.

Results: Of the 84 women included in the study, 56 (66.7%) had benign endometrial lesions, and 28 (33.3%) had malignant endometrial lesions. Endometrial thickness, endometrial volume, and flow indices (VI, FI, and VFI) were higher in patients with malignant endometrium than those with benign endometrium. The area under the receiver operator characteristic curve (AUC) of endometrial thickness was 0.83, that of endometrial volume was 0.73, and that of the best power Doppler variable, FI, was 0.93. The best logistic regression model for predicting malignancy contained the variables endometrial thickness and FI; its AUC was 0.93.

Conclusion: The diagnostic performance of endometrial volume measured by 3D imaging with regard to discriminating between benign and malignant endometrium was not superior to that of endometrial thickness measured by 2D ultrasound examination, but 3D power Doppler flow indices are good diagnostic tools in predicting endometrial carcinoma. (J Turk Ger Gynecol Assoc 2014; 15: 78-81)

Key words: Endometrial carcinoma, postmenopausal bleeding, power Doppler, 3-dimensional ultrasound

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Introduction

Bleeding after menopause is a widespread problem, with 10%-15% of cases later suffering from cancer of the endometrium. It differs from other malignancies, in that early symptomatization is common, allowing early cure. Survival drops with late stages and so studies should strive to increase the precision of various diagnostic practices (1). The ideal diagnostic strategy is still debatable. A thin endometrium measuring less than 5 mm by vaginal scanning in PMB excludes about 99% of endometrial cancers. Sampling of the endometrium is considered necessary in those patients with an endometrium ≥5 mm. However, many "normal" women with PMB and thickened endometria will undergo unnecessary diagnostic procedures. (2). Three-dimensional (3D) ultrasonography and power Doppler angiography (PDA) is a novel sonographic diagnostic modality. This technology permits acquisition of the volume of the endometrium and assessment of its vasculature using 3D power Doppler mapping. Using Virtual Organ Computer-aided AnaLysis (VOCAL™) software, three vascularity indices can be obtained automatically: the vascularization index (VI), the flow index (FI), and the vascularization flow index (VFI). This method has been proven to be highly reproducible for analyzing the volume of the endometrium and 3-dimensional power Doppler indices of patients with malignancy of the endometrium (3). This research aimed to establish if volume and power Doppler indices of the endometrium could differentiate cancerous and non-cancerous endometrium in patients who bleed after menopause and have endometrial thickening exceeding 5 mm.

Material and Methods

The current diagnostic accuracy study was performed at Ain Shams University Maternity Hospital between September 2010 and December 2012. The ethics committee of Ain Shams University confirmed the study methodology. Informed consent was taken from all cases after full counseling. Women with PMB and had endometrial thickening over 5 mm by vaginal B-mode scanning conformed with our inclusion criteria. Post-menopause was defined as at least 1 entire year of menstrual cessation after the age of 40. All cases had their histories taken; complete general and local examinations were done. For all included women, 3D transvaginal ultrasound

Address for Correspondence: *Sherif Hanafi, Department of Obstetrics and Gynecology, Ain Shams University Maternity Hospital, Cairo, Egypt. Phone: 201 005 21 92 39 e.mail: docsherif77@yahoo.com*

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imaging using (Philips™, Amsterdam, The Netherlands, HD9, ultrasound system equipped with a 6-9 megaHertz transvaginal probe). Transvaginal color Doppler flow mapping was performed using the ascending branch of the uterine artery, which was located in the parametrial area at the level of the internal os. The body of the uterus only was centralized in the 3D sector on the monitor, so as to fill it, and the corporeal volume was taken; then, power Doppler mode was obtained, and the flow indices (VI, FI, VFI) in the endometrium were measured. Power Doppler settings were set to obtain maximum sensitivity to perceive low-velocity flow without noise (frequency=5 MHz; gain=7.4; dynamic range=20-40 dB; edge=1; persistence=2; color map=5; gate=2; wall motion filter=L1; pulse repetition frequency=0.6 kHz). Patients were requested to remain stationary, and volume was obtained in 15-20 seconds. VI reflects the number of color voxels, which represents the vessels in the tissue, and is written as a percentage. FI is the mean color value in the color voxels, which manifests the average intensity of blood flow, and is represented as a number from 0-100. VFI is the mean color value in all voxels in the volume, which represents both vascularization and flow, and is also written as a number from 0 to 100 (4). Endometrial volume and the power Doppler indices were measured using VOCAL.

A total of 84 cases with PMB were included in our study. Endometrial sampling was done for all of them. They were divided into two groups, according to the histological diagnosis obtained at the Early Cancer Detection Unit in Ain Shams University Maternity Hospital. Group 1 was 28 patients with histological diagnosis of endometrial carcinoma, and Group 1I was 56 patients with histological diagnosis of benign disorders.

Statistical Analysis

Statistical assessment was done on a computer using MedCalc© version 12.2.1.0 (MedCalc© Software, Mariakerke, Belgium). The D'Agostino Pearson test was done to assess the normality of the numerical data distribution. A statistically significant test denotes non-normally distributed data. Normally distributed numerical data are shown as mean and standard deviation (SD). Skewed numerical data are shown as median and interquartile range. Qualitative data are presented as number and percentage. Intergroup differences were compared using the independent samples t-test (for normally distributed quantitative data) or the Mann-Whitney U-test (for skewed quantitative data). Qualitative data were compared using the Pearson chi-square test or the chi-square test for trends (for ordinal qualitative data). Exact significance was calculated whenever the expected frequency was <5 in >20% of cells in any contingency table. To examine the value of various ultrasound indices for the prediction of the type of endometrial lesion (endometrial carcinoma versus benign lesions), a series of receiver-operating characteristic (ROC) curves were constructed, and the area under the curve was estimated. The best cut-off criterion of the ROC curve was identified as that associated with the highest Youden's index (J statistic), where J=(sensitivity + specificity) - 1. The DeLong method was used for calculation of the standard error (SE) for the area under the curve (AUC) and of the SE for the difference between any pair of AUCs (5). The 95% confidence interval (CI) for the AUC was calculated based on binomial exact probability, which was used to estimate the statistical significance for the difference between the AUCs of any pair of ROC curves. The validity of study parameters was evaluated in terms of sensitivity, specificity, likelihood ratio (LR+), and negative likelihood ratio (LR-). All P values are two-tailed. $p<0.05$ was considered as denoting statistical significance.

Results

Eighty-four patients with postmenopausal bleeding were assessed with both B-mode transvaginal scanning and 3D power Doppler. Division according to endometrial pathology into 2 groups was done. Group 1 included 28 patients with malignant endometrium. Group 2 was 56 patients with benign endometrium. The histopathological diagnosis of the included women is shown in Table 1. Those with malignant endometrium tended to be older (mean age was 61 years versus 55 years; p=0.001) and had a greater body mass index (BMI) (median, 34 kg/m^2 versus 28 kg/m^2; p=0.008) than those with benign endometrium, but there was overlap between the two groups regarding parity. On the contrary, medical disorders (e.g., diabetes mellitus and hypertension) were more prevalent among patients with benign endometrium. In Group 2, 24 women (43%) had diabetes mellitus, and 25 women (44.7%) were hypertensive, while in Group 1, 10 women (35.7%) were diabetic and 7 women (25%) had hypertension. Endometrioid adenocarcinoma was diagnosed in 12 cases (42.8%), adenocarcinoma was diagnosed in 10 cases (35.6%), clear cell adenocarcinoma and squamous cell carcinoma were diagnosed in 2 cases (7.2%), and serous papillary and sarcoma was diagnosed in 1 case (3.6%) (Table 1). Endometrial thickness, endometrial volume, and flow indices were greater in cases with endometrial malignancy than benign cases, as shown in Table 2. The ultimate discriminator between non-cancerous and cancerous endometrium was FI, with an AUC of 0.937. Endometrial thickness, VI, and VFI had a comparable diagnostic accuracy, all having an AUC of 0.83 (Table 3). As the model with endometrial thickness + FI showed greater specificity (96%), we considered it the best logistic regression model for differentiating between non-cancerous and cancerous endometrium. The mathematically optimal risk cut-off value of this model (0.19) had a sensitivity of 85%, specificity of 96%, an LR+ of 14, and an LR- of 0.15 (Table 4) (Figure 1).

Table 1. Histopathological diagnosis of the included women

Histological diagnosis	n (%)
Polyps and myomas	30 (53.6)
Atrophic endometrium	4 (7.2)
Hormone-influenced endometrium	4 (7.2)
Hyperplasia without atypia	17 (30.3)
Hyperplasia with atypia	1 (1.7)
Endometrioid adenocarcinoma	12 (42.8)
Clear cell adenocarcinoma	2 (7.2)
Serous papillary	1 (3.6)
Adenocarcinoma	10 (35.6)
Squamous cell carcinoma	2 (7.2)
Sarcoma	1 (3.6)

Table 2. Ultrasonic parameters among the studied population

Variable	Benign endometrial lesions (number=56)	Endometrial carcinoma (number=28)	p value
Endometrial thickness, mm	8 (7-9)	12 (9.5-16.5)	<0.001
Endometrial volume, mm^3	1.55 (0.88-3.16)	3.86 (2.94-6.57)	<0.001
VI	0.063 (0.039-0.288)	0.687 (0.657-0.687)	<0.001
FI	21.019 (19.231-22.228)	25.59 (24.039-28.403)	<0.001
VFI	0.013 (0.007-0.063)	0.193 (0.073-0.522)	<0.001

Analysis using independent samples t-test
VI: vascularization index; FI: flow index; VFI: vascularization flow index

Table 3. Comparison of AUC of different ROC curves

Ultrasound parameter	AUC	SE of AUC	95% CI of AUC
Endometrial thickness	0.834	0.045	0.737 to 0.906
Endometrial volume	0.737	0.059	0.692 to 0.827
VI	0.823	0.050	0.725 to 0.898
FI	0.937	0.029	0.863 to 0.979
VFI	0.838	0.047	0.741 to 0.909

AUC: area under the curve; CI: confidence interval; FI: flow index; ROC: receiver operator characteristic; SE: standard Error; VFI: vascularization flow index; VI: vascularization index

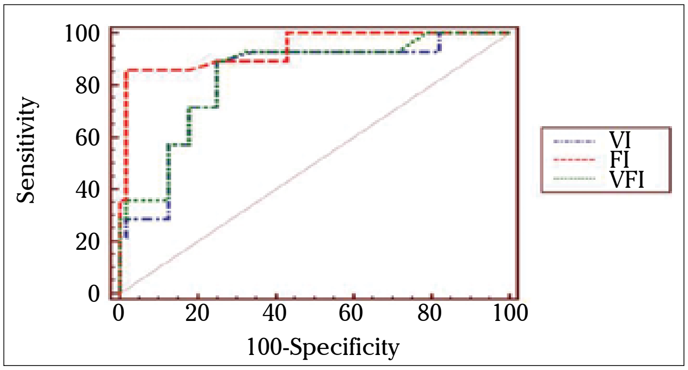

Figure 1. Comparison of areas under the three receiver operator characteristic (ROC) curves. Area under the ROC curve for flow index (FI) is significantly larger than the area under the ROC curve for either the vascularization index (VI) (p=0.031) or the vascularization flow index (VFI) (p=0.041) ROC curves

Discussion

The current study authenticated that even though the endometrial volumes were significantly greater in cancerous than in non-cancerous endometrium (mean volume of the endometrium was 1.55 cc and 3.86 cc in the two groups, respectively (p<0.001)), volume measurements by 3D imaging were not better than simple endometrial thickness measurements by B-mode examination (AUC 0.737 vs. AUC 0.834). They also showed that logistic regression models with thickness and flow indices (VI, FI, VFI) did better than models containing thickness alone (AUC 0.894, 0.931, and 0.904 vs. AUC 0.834).

Four different studies have attempted to identify the diagnostic accuracy of 3D ultrasound scanning in differentiation between non-cancerous and cancerous endometria (6-9). A fifth study assessed the potential of 3D ultrasound to differentiate endometrial carcinoma and hyperplasia (3), and a sixth paper assessed the potential to differentiate malignancy and hyperplastic tissue from other non-cancerous conditions (10).

The six studies discussed the diagnostic accuracy of endometrial volume measurement, and four also reported on that of 3D power Doppler flow indices (3, 7, 9, 10).

In the study by Gruboeck et al. (6), ROC curves highlighted that endometrial volume was better than endometrial thickness in diagnosing endometrial malignancy. The best cut-off value of endometrial thickening in diagnosing malignancy was 15 mm, with a sensitivity of 83.3% and positive predictive value of 54.5%. A cut-off level of 13 ml for endometrial volume had a sensitivity of 100% and a positive predictive value of 91.7%. Both thickness and volume were greater in cases with late and less-differentiated malignancies. The measurements of endometrial volume were better than endometrial thickness as a diagnostic test for detecting endometrial malignancy in symptomatizing postmenopausal women (6). Yamen et al. (8) authenticated that both endometrial volume and thickness measurements by 3D and 2D scanning, respectively, were adequately reproducible but that the reproducibility of 3D was superior. Merce et al. (3) stated that endometrial volume and 3D power Doppler indices (VI, FI, and VFI) were significantly greater in carcinoma than hyperplasia and that a VFI of 2.07 was the ideal cutoff for prediction of carcinoma, with a sensitivity of 76.5% and specificity of 80.8%. No important differences were seen for endometrial thickness. As regard to the study by Odeh et al. (10), mean thickness was 11 mm and 15.5 mm in the normal and pathologic groups, respectively (p<0.005). The mean volume was 6.87 cc and 15.5 cc in both groups, respectively (p<0.001). The VI was 2.27% and 2.95% in both groups, respectively (p=0.022). The FI was 18.6 and 23.6 in both groups, respectively (p=0.014). The VFI was 0.68 and 0.89 in both groups, respectively (p=0.018). Endometrial volume and 3D-PDA are valuable diagnostic modalities in the prediction of endometrial malignancy and hyperplasia in women with post- and peri-menopausal bleeding (10).

Opolskiene et al. (9) showed that the diagnostic accuracy for differentiating between benign and malignant endometria by 3D ultrasonography was not better than endometrial thickness assessed by B-mode ultrasonography, and 3D power Doppler scanning yielded little more than thickness or volume. Models

Table 4. Diagnostic performance of single ultrasound variables and logistic regression models

	AUC	Cut -off value	Sensitivity	Specificity	LR+	LR-
ET	0.834	>9 mm	75	80.36	3.82	0.31
EV	0.737	>1.94 cm	78.57	62.5	2.1	0.34
VI	0.823	>4.0 %	89.29	75	3.57	0.14
FI	0.937	>23.3	85.7	98.2	14.6	0.15
VFI	0.838	>1.4	89.29	75	3.57	0.14
ET+EV	0.829	0.16	94	53	2.15	0.2
ET+VI	0.894	0.19	92	80	4.73	0.089
ET+FI	0.931	0.19	85	96	14	0.15
ET+VFI	0.904	0.17	89	80	4.55	0.13

AUC: area under the curve; ET: endometrial thickness; EV: endometrial volume; FI: flow index; LR-: negative likelihood ratio; LR+: positive likelihood ratio; SE: standard error; VFI: vascularization flow index; VI: vascularization index

with volume and flow indices were inferior to thickness alone (AUC 0.79 vs. 0.82). Both thickness and volume were significantly greater in cancerous than in normal endometria, and flow indices in the endometrium and endometrial shell were significantly greater. The AUC of endometrial thickness was 0.82, while that od endometrial volume was 0.78, and those of the two best power Doppler variables (VI and VFI in the endometrium) were 0.82 and 0.82. The best logistic regression model for predicting malignancy contained endometrial thickness (odds ratio 1.2; 95% CI, 1.04-1.30; p=0.004) and VI in the endometrial 'shell' (odds ratio 1.1; 95% CI, 1.02-1.23; p=0.01) (9).

The variable findings in the six published studies, together with the differences in findings between our study and the other six, can confidently be explained by marked variations in study populations and design. Although all publications cited included only women with abnormal uterine bleeding, there were variations in menopausal state, rate of endometrial cancer, mix of benign histological findings, use of hormone replacement treatment, and endometrial thickening. Also, there were differences in group comparisons between the studies [cancer versus hyperplasia in the study by Merc´e et al. (3) and cancer or hyperplasia versus other benign conditions in the study by Odeh et al. (10)]. There was benign versus malignant in the studies by Gruboeck et al. (6), Yamen et al. (8), Alcazar et al. (7), and Opolskiene et al. (9), and there were also variations in the methods used to determine diagnostic performance. There were 2 limitations to the analysis reported in the current study. The first was the relatively small sample size, and the second concerned the fact that ultrasound examination was done by a single observer; so, there was no comment on the reproducibility of the 3D ultrasound imaging. The diagnostic performance of endometrial volume measured by 3D imaging regarding discrimination between benign and malignant endometria was not better than that of endometrial thickness measured by B-mode scanning, but 3D power Doppler flow indices are good diagnostic tools in predicting endometrial carcinoma.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of the Ain Shams University.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

Peer-review: *Externally peer-reviewed.*

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