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Endometrial blood flow mapping using transvaginal power Doppler sonography in women with postmenopausal bleeding and thickened endometrium

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KEYWORDS: postmenopausal bleeding; power Doppler; sonography; thickened endometrium

ABSTRACT

Objective *To evaluate the role of transvaginal power Doppler sonography to discriminate between benign and malignant endometrial conditions in women presenting with postmenopausal bleeding and thickened endometrium at baseline sonography.*

Methods *Ninety-one postmenopausal women (median age, 58 years; range, 47–83 years) presenting with uterine bleeding and a thickened endometrium (≥ 5-mm double-layer endometrial thickness) on transvaginal sonography were included in this prospective study. Endometrial blood flow distribution was assessed in all patients by power Doppler immediately after B-mode transvaginal sonography. Three different vascular patterns were defined: Pattern A: multiple-vessel pattern, Pattern B: single-vessel pattern and Pattern C: scattered-vessel pattern. Histological diagnoses were obtained in all cases. No patient taking tamoxifen citrate or receiving hormone replacement therapy was included.*

Results *Histological diagnoses were as follows: endometrial cancer: 33 (36%), endometrial polyp: 37 (41%), endometrial hyperplasia: 14 (15%), endometrial cystic atrophy: 7 (8%). Blood flow was found in 97%, 92%, 79% and 85% of cases of carcinoma, polyp, hyperplasia and endometrial cystic atrophy, respectively. A total of 81.3% of vascularized endometrial cancers showed Pattern A, 97.1% of vascularized polyps exhibited Pattern B and 72.7% of vascularized hyperplasias showed Pattern C. Sensitivity and specificity for endometrial cancer were 78.8% and 100%. For endometrial polyp these respective values were 89.2% and 87% and for hyperplasia they were 57.1% and 88.3%.*

Conclusions *Transvaginal power Doppler blood flow mapping is useful to differentiate benign from malignant endometrial pathology in women presenting with postmenopausal bleeding and thickened endometrium at baseline sonography.* *Copyright © 2003 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Transvaginal sonography has been shown to be an accurate means to rule out endometrial cancer in women presenting with postmenopausal bleeding. A recent meta-analysis demonstrated that the risk of endometrial cancer when double-layer endometrial thickness as measured by transvaginal sonography is < 5 mm is actually low[1]. However, endometrial thickening is a non-specific finding that may be caused by several processes, such as cancer, polyps, hyperplasia or even endometrial cystic atrophy[2].

Transvaginal color Doppler enables an *in-vivo* assessment of uterine and endometrial vascularization[2]. The role of this technique in differentiating benign from malignant endometrial pathologies has been assessed in several studies with controversial results[2–7]. More recently, power Doppler or color Doppler energy has been introduced in clinical practice. This technique offers some advantages over conventional color Doppler sonography that makes it a better technique for depicting vascular networks[8].

In the present study we aimed to assess the role of transvaginal power Doppler flow mapping to discriminate between benign and malignant endometrial conditions in women presenting with uterine bleeding and a thickened endometrium at baseline B-mode sonography. Furthermore, we assessed whether endometrial carcinoma, polyp and hyperplasia exhibited different 'typical' vascular patterns.

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MATERIALS AND METHODS

Ninety-one patients presenting between January 2000 and June 2002 with postmenopausal bleeding were included in this prospective study.

Inclusion criteria were as follows: (1) natural menopause was established, defining menopause as 1 year of absence of menstruation in women older than 45 years; (2) baseline transvaginal sonography showing a double-layer endometrial thickness ≥ 5 mm; (3) not taking tamoxifen citrate or any kind of hormone replacement therapy; (4) definitive endometrial histological diagnosis obtained at our center. The patients' median age was 58 years, ranging from 47 to 83 years.

Transvaginal sonography was performed in all patients using a Toshiba SSA-370 A machine (Toshiba Medical Systems, Tokyo, Japan) with a 5–7.5-MHz endovaginal probe and equipped with 5-MHz color, power and pulsed Doppler capabilities. First, conventional gray-scale sonography was performed to obtain longitudinal and transverse sections of the uterus. Maximum endometrial thickness (double-layer) was measured in the longitudinal plane. As stated above, only patients with endometrial thickness $\geq$ 5 mm were included.

Thereafter, the power Doppler gate was activated for blood flow mapping of the myometrium and endometrium. Power Doppler settings were set to achieve maximum sensitivity for detecting low-velocity flow without noise (frequency, 5 MHz; power Doppler gain, 20 (range, 1–30); dynamic range, 20–40 dB; edge, 1; persistence, 2; color map, 1; gate, 2; filter, 3).

Once the vessels had been identified the pulsed Doppler sample volume was activated to obtain a flow velocity waveform (FVW). Resistance index (RI), pulsatility index (PI) and peak systolic velocity (PSV, cm/s) were automatically calculated from three consecutive FVWs. Conventional color Doppler was not used. In those cases with more than one vessel identified, the lowest RI and PI and the highest PSV found were used for analysis. Pulsed Doppler evaluated only vessels detected within the endometrium.

According to power Doppler flow mapping three different vascular patterns were defined:

1. Multiple-vessel pattern (Pattern A): In this pattern multiple vessels were found within the endometrium and in the myometrial–endometrial interface (Figure 1). This pattern was considered as characteristic of endometrial cancer as it has been demonstrated that important neoangiogenic phenomena occur in endometrial cancer within tumor tissue and the surrounding area[9].
2. Single-vessel pattern (Pattern B): In this pattern a single prevalent vessel was identified penetrating the endometrium from the myometrium (Figure 2). This pattern was considered as characteristic of endometrial polyp as this vessel is thought to correspond to the vascularized polyp's pedicle.
3. Scattered-vessel pattern (Pattern C): In this pattern scanty vessels were identified scattered within the endometrium (Figure 3). This pattern was considered as characteristic of endometrial hyperplasia since some studies have shown that angiogenesis is limited in this pathology[9].

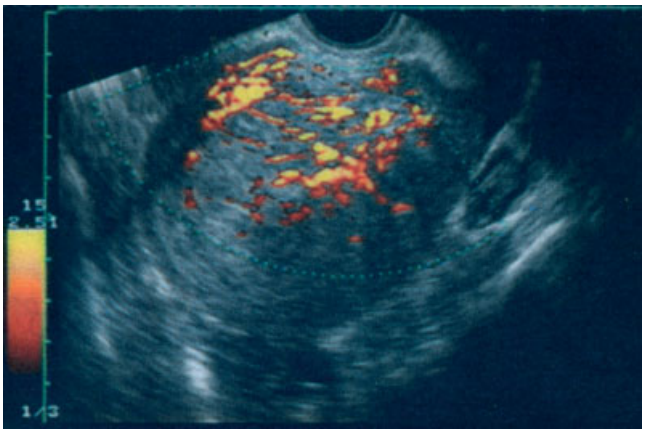

Figure 1 Power Doppler ultrasound image showing a multiple-vessel pattern characteristic of endometrial cancer.

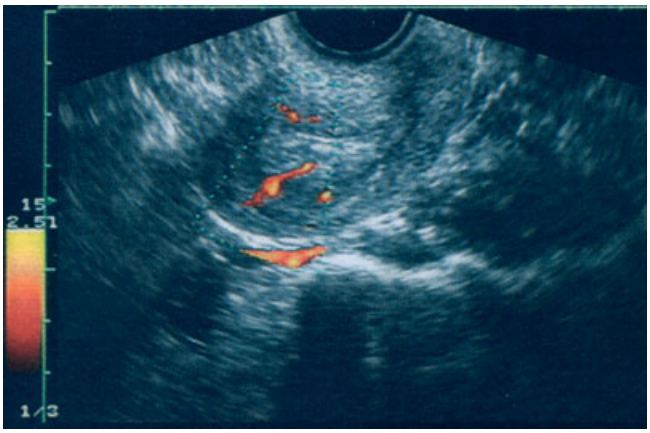

Figure 2 Power Doppler ultrasound image showing a single-vessel pattern characteristic of endometrial polyp.

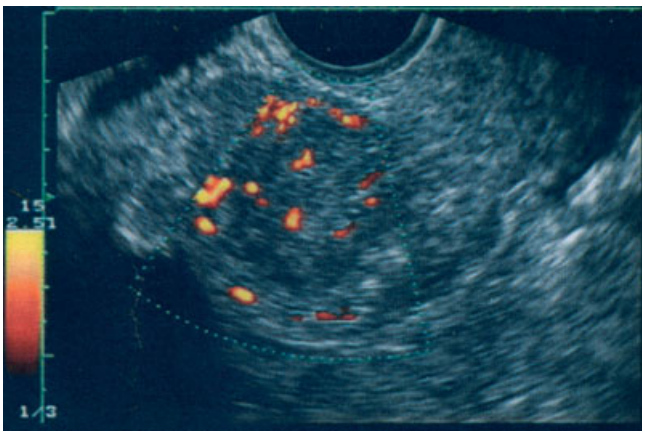

Figure 3 Power Doppler ultrasound image showing a scattered-vessel pattern characteristic of endometrial hyperplasia.

These patterns were defined prior to the start of the study. The same experienced operator (J.L.A.) performed all sonographic examinations. The examiner stated the vascular pattern at the time of sonographic examination.

Table 1 Power Doppler vascular patterns according to histology

	Carcinoma (n (%))	*Polyp* (n (%))	*Hyperplasia* (n (%))	*Cystic atrophy* (n (%))
Multiple-vessel pattern	26 (81.3)	0	0	0
Single-vessel pattern	2 (6.3)	33 (97.1)	3 (27.3)	2 (33.3)
Scattered-vessel pattern	4 (12.5)	1 (2.9)	8 (72.7)	4 (66.7)
Total	32	34	11	6

Table 2 Velocimetric parameters according to histology

	Carcinoma	*Polyp*	*Hyperplasia*	*Cystic atrophy*
RI (mean ± SD)	0.49 ± 0.18	0.55 ± 0.14	0.53 ± 0.09	0.53 ± 0.11
PI (mean ± SD)	0.91 ± 0.67	0.96 ± 0.34	0.90 ± 0.25	0.99 ± 0.37
PSV (cm/s, mean ± SD)	10.9 ± 4.7	9.4 ± 4.2	10.7 ± 2.9	8.2 ± 2.5

Not significant for all comparisons. RI, resistance index; PI, pulsatility index; PSV, peak systolic velocity.

Sonohysterography was performed in cases in which focal lesions, i.e. polyps, were suspected. Definitive histological diagnoses were obtained in all cases after dilatation and curettage ($n = 40$) or hysteroscopic guided biopsy ($n = 51$). The method of endometrial sampling was decided by the patient's clinician. The pathologist was unaware of the sonographic results.

All endometrial cancers were staged according to FIGO criteria[10].

The Kolmogorov–Smirnov test was used to assess normal distribution of continuous data. Continuous data were compared using one-way analysis of variance with the Bonferroni post-hoc test or the Kruskal–Wallis test according to whether or not the distribution was normal. Categorical data were compared using the chi-square test.

Sensitivity, specificity and positive and negative predictive values (PPV and NPV) were calculated for each vascular pattern. These calculations were performed by cross-matching one group which included all the cases with a given specific vascular pattern and a second group which included the cases with all other vascular patterns and also those cases in which no flow was detected, with pathological findings.

A P-value ≤ 0.05 was considered as statistically significant for all tests used. All statistical analyses were performed using the SPSS 9.0 statistical package (SPSS Inc, Chicago, IL, USA).

RESULTS

Histological diagnoses were as follows: Endometrial cancer: 33 cases (36%), endometrial polyp: 37 cases (41%), endometrial hyperplasia: 14 cases (15%) and endometrial cystic atrophy: 7 cases (8%).

Mean endometrial thickness was significantly greater in patients with endometrial cancer (13.8 mm; SD, 6.5 mm) than in those with cystic atrophy (8.3 mm; SD, 2.2) ($P = 0.04$), but not when compared with endometrial polyps (11.4 mm; SD, 3.8) or endometrial hyperplasia (11.9 mm; SD, 3.7).

Power Doppler signals were found in 97% (32/33) of carcinomas, 92% (34/37) of endometrial polyps, 79% (11/14) of endometrial hyperplasias and 85% (6/7) of cases of endometrial cystic atrophy. A total of 81.3% of vascularized endometrial cancers showed Pattern A, 97.1% of vascularized polyps exhibited Pattern B, and 72.7% of vascularized hyperplasias showed Pattern C. However, 67% (4/6) atrophic endometria showed Pattern C (Table 1). There were no false-positive cases for Pattern A. Pattern B, characteristic of polyps, was associated with seven false-positive cases: two carcinomas arising from a polyp, three endometrial hyperplasias and two cases with cystic atrophy. Pattern C, characteristic of hyperplasia, had nine false-positive cases: four carcinomas, one polyp and four cystic atrophic endometria.

Velocimetric parameters were not statistically different among different pathologies (Table 2 and Figure 4). Sensitivity, specificity, PPV and NPV for different vascular patterns are shown in Tables 3 to 5.

Cancer stages were as follows: Stage Ia, four (12.1%) cases; Stage Ib, 18 (54.6%) cases; Stage Ic, four (12.1%) cases; Stage IIIa, one (3%) case; Stage IIIc, three (9.1%) cases; Stage IV, three (9.1%) cases.

Seventeen of 22 (77.3%) early-stage cancers (Ia and Ib) showed Pattern A as compared with 9/11 (81.8%) advanced-stage ($\geq$ Ic) cancers ($P = 0.83$). Twenty-three

Table 3 Diagnostic performance of power Doppler pattern for carcinomas

	Histology	
	Carcinoma (n)	*Other* (n)
Multiple-vessel pattern	26	0
Other vascular pattern or no flow detected	7	58

Sensitivity, 78.8%; specificity, 100%; positive predictive value, 100%; negative predictive value, 89%.

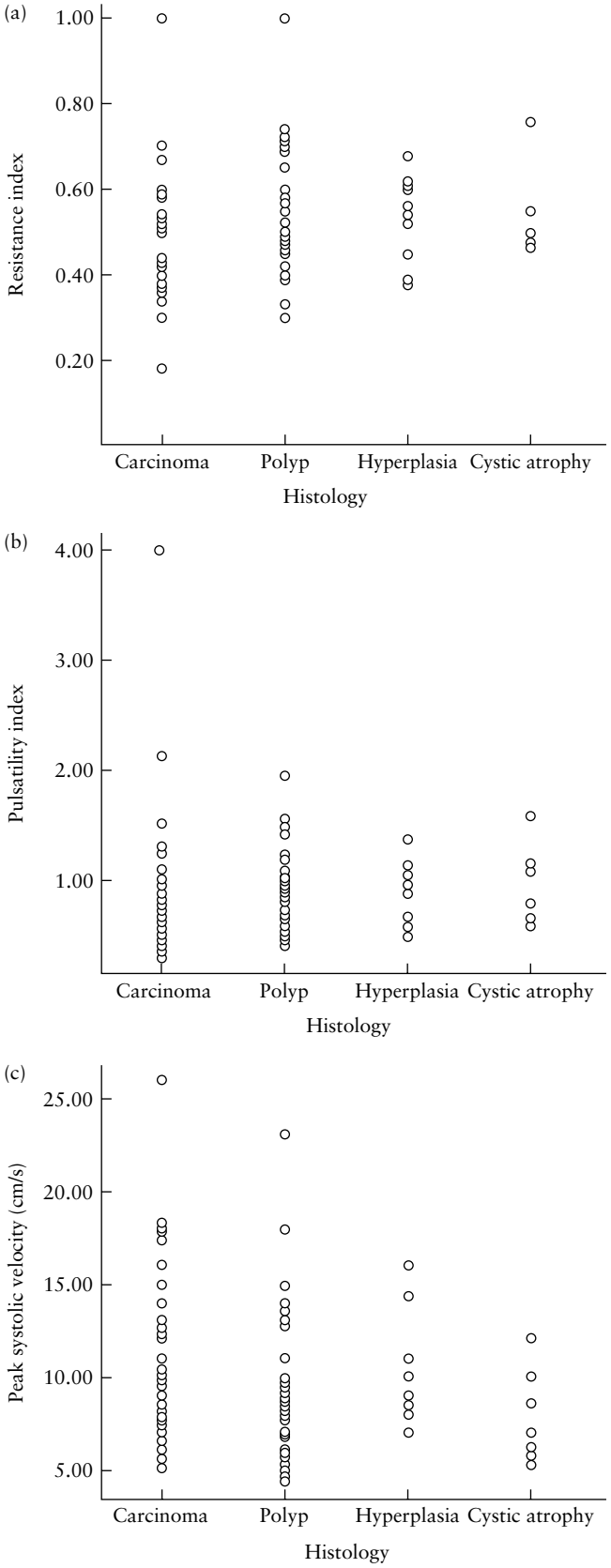

Figure 4 Individual values for resistance index (a), pulsatility index (b) and peak systolic velocity (c) according to histology. A considerable overlap is clearly seen.

(69.7%) tumors invaded < 50% of myometrium and 10 (30.3%) invaded ≥ 50% of myometrium. Seventy-seven percent (17/23) of tumors infiltrating < 50% showed Pattern A as compared with 90% (9/10) of tumors that were deeply infiltrating ($P = 0.57$).

Table 4 Diagnostic performance of power Doppler pattern for polyps

	Histology	
	Polyp (n)	*Other* (n)
Single-vessel pattern	33	7
Other vascular pattern or no flow detected	4	47

Sensitivity, 89.2%; specificity, 87%; positive predictive value, 82.5%; negative predictive value, 92.2%.

Table 5 Diagnostic performance of power Doppler pattern for hyperplasia

	Histology	
	Hyperplasia (n)	*Other* (n)
Scattered-vessel pattern	8	9
Other vascular pattern or no flow detected	6	68

Sensitivity, 57.1%; specificity, 88.3%; positive predictive value, 47.1%; negative predictive value, 91.9%.

DISCUSSION

Endometrial carcinoma is currently the most frequent gynecological cancer in western countries. Postmenopausal bleeding is usually the first symptom. Although only about 10–15% of women presenting with postmenopausal bleeding will actually have an endometrial cancer, definitive diagnosis in this clinical setting is warranted.

Transvaginal sonographic measurement of the endometrial thickness is a non-invasive method that has been demonstrated to be accurate enough to exclude endometrial malignancy in women with postmenopausal bleeding. Smith-Bindman *et al.*[1] showed in their meta-analysis that, using an endometrial thickness cut-off of ≥ 5 mm, the false-negative rate in women with postmenopausal bleeding not taking hormone replacement therapy was as low as 4%.

However, endometrial thickening is a non-specific finding that may be caused by a variety of conditions, such as carcinoma, polyps, hyperplasia, endometritis or cystic atrophy[11], although some authors have argued that endometrial echotexture may help to differentiate carcinoma from polyps and hyperplasia[12].

In patients with thickened endometrium a secondary test, such as power Doppler, could play a role in refining the diagnosis. For this reason we focused this study on women presenting with postmenopausal bleeding

and a thickened endometrium at baseline transvaginal sonography.

Transvaginal color Doppler imaging allows the assessment of endometrial vascularization. Power Doppler or color Doppler energy is a new technology that has some advantages over conventional color Doppler. Power Doppler is based on the amplitude of the Doppler signal but not on the Doppler frequency shift. It is insonation-angle independent, does not have aliasing and is more sensitive to low-velocity blood flow[8]. All these features make this technique advantageous for blood flow mapping by facilitating the detection of flow where present and depicting more clearly and reliably the vascular architecture. The advantages of the power Doppler technique have been demonstrated in adnexal masses by our group[13].

Based on the appearance of the typical vascular networks of endometrial cancer, polyps and hyperplasia as derived from immunohistochemical studies[9], we defined three different power Doppler vascular patterns in an attempt to differentiate endometrial carcinoma from endometrial polyps and hyperplasia. Although it could be argued that blood flow within intratumoral microvessels would not be detectable by power Doppler with currently available ultrasound machines, a recent study has demonstrated a high correlation between microvessel density and power Doppler findings in breast carcinoma[14].

We did not include patients taking tamoxifen citrate or receiving hormone replacement therapy because it is known that these treatments increase uterine and endometrial blood flow as compared with controls[15–17]. It could be speculated that power Doppler vascular mapping could show different vascular patterns in these groups of patients.

Our results indicate that the use of these patterns as depicted by power Doppler is useful to discriminate endometrial carcinoma and endometrial polyps from other pathological processes but it is not useful to distinguish endometrial hyperplasia (sensitivity: 57%).

In the case of endometrial cancer, only one case did not show endometrial vascularization (3%). This is in contrast to previous studies using conventional color Doppler, in which as many as 44–57% of the cancers had no color signals[6,7]. This may be explained by the technical factors previously mentioned.

In our series 81.3% of the vascularized endometrial cancers showed the typical multiple-vessel pattern. Two (6.2%) patients had the single-vessel pattern (typical of polyps). These two cases were endometrial carcinoma Stage IA G1 arising from an endometrial polyp. Four patients (12.5%) showed the scattered-vessel pattern.

In the case of endometrial polyps, 34/37 (92%) showed power Doppler signals and 33 (97%) of them presented the single-vessel pattern. Other authors using conventional color Doppler have also reported this typical pattern[18].

In the case of endometrial hyperplasia, most cases showed a scattered-vessel pattern (72.7%). However, this pattern was also shown in most cases of endometrial cystic atrophy (66.7%), which makes it difficult to differentiate between them.

Regarding velocimetric parameters, our results are in agreement with those of previously reported studies[2,5,7]. A considerable overlap of RI, PI and PSV values was found, which limits their clinical use.

Previous studies using power Doppler for the diagnosis of endometrial pathology are rare. Amit *et al.*[19] used power Doppler to identify endometrial vessels but then used PI (cut-off PI ≤ 1.0) as a selection criterion to discriminate between endometrial carcinoma and benign conditions. They found that power Doppler plus PI had higher sensitivity and specificity as compared with measurement of endometrial thickness alone. However, they did not analyze conventional color Doppler imaging.

Kurjak *et al.*[20] reported on the use of three-dimensional power Doppler sonography to diagnose endometrial cancer. They found that this technique had a higher sensitivity as compared with two-dimensional conventional color Doppler (89% vs. 67%) with identical specificity (97% for both). However, three-dimensional equipment is still expensive and not available in most ultrasound units.

We have not compared power Doppler with conventional color Doppler because all examinations were performed by the same operator and the use of color Doppler before or after power Doppler could introduce a bias when evaluating the findings of power Doppler blood flow mapping.

Our results are in agreement with a recent report of Epstein *et al.*[21], who found that power Doppler can contribute to a correct diagnosis of endometrial malignancy in women with postmenopausal bleeding and endometrial thickness > 5 mm. However, in contrast to our study they used a rather more sophisticated approach by applying logistic regression models and they focused on the specific diagnosis of endometrial carcinoma.

A possible limitation of our study is the high prevalence of endometrial cancer in our series (36%) (three times higher than expected) representing a potential selection bias. This can be explained by the fact that our sample was a selected one (only patients with thickened endometria were included) and because our institution is a tertiary care university hospital specializing in gynecological oncology. Furthermore, we did not assess reproducibility in this study, which represents a weakness.

In conclusion, the use of power Doppler blood flow mapping as a secondary test in women not taking hormone replacement therapy or tamoxifen presenting with postmenopausal bleeding and a thickened endometrium at baseline sonography is useful to discriminate carcinoma and polyps from other causes of endometrial thickening.

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