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An algorithm including results of gray-scale and power Doppler ultrasound examination to predict endometrial malignancy in women with postmenopausal bleeding

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ABSTRACT

Objective *To determine if power Doppler ultrasound examination of the endometrium can contribute to a correct diagnosis of endometrial malignancy in women with postmenopausal bleeding and endometrium ≥ 5 mm.*

Methods *Eighty-three women with postmenopausal bleeding and endometrium ≥ 5 mm underwent gray-scale and power Doppler ultrasound examination using predetermined, standardized settings. Suspicion of endometrial malignancy at gray-scale ultrasound examination (endometrial morphology) was noted, and the color content of the endometrium at power Doppler examination was estimated subjectively (endometrial color score). Computer analysis of the most vascularized area of the endometrium was done off-line in a standardized manner. Stepwise multivariate logistic regression analysis was carried out to determine which subjective and objective ultrasound and power Doppler variables satisfied the criteria to be included in a model to calculate the probability of endometrial malignancy.*

Results *Endometrial thickness, vascularity index (vascularized area/endometrial area), and use of hormone replacement therapy (HRT) satisfied the criteria to be included in the model used to calculate the 'objective probability of endometrial malignancy'. Endometrial morphology, endometrial color score and HRT use satisfied the criteria to be included in the model to calculate the 'subjective probability of malignancy'. Endometrial thickness ≥ 10.5 mm had a sensitivity with regard to endometrial cancer of 0.88 and a specificity of 0.61. At a fixed sensitivity of 0.88, the specificity of the 'objective probability of malignancy' (0.81) was superior to all other ultrasound and power Doppler variables (*P = *0.001–0.02). The 'objective probability of malignancy' detected more malignancies at endometrium 5–15 mm than endometrial morphology (5/7 vs. 1/7, i.e. 0.71 vs. 0.14;* P = *0.125) with a similar specificity (49/57 vs. 51/57, i.e. 0.86 vs. 0.89).*

Conclusion *Power Doppler ultrasound can contribute to a correct diagnosis of endometrial malignancy, especially if the endometrium measures 5–15 mm. The use of regression models including power Doppler results to estimate the risk of endometrial cancer deserves further development.*

INTRODUCTION

Endometrial carcinoma is the third most common cancer in Swedish women (Swedish Statistics, SCB). Most (90%) patients with endometrial carcinoma present with abnormal bleeding when the cancer is at an early stage[1]. Among women with postmenopausal bleeding 5–15% have endometrial carcinoma[2–4]. Transvaginal ultrasound is a simple, noninvasive technique that can be used to discriminate between benign and malignant endometrium. Endometrial thickness[4] and endometrial morphology, with or without saline infusion (saline contrast sonohysterography (SCSH))[5–9], can be used to obtain a probable diagnosis. Some have suggested that color and spectral Doppler ultrasound examination of the uterine and subendometrial arteries can aid in the differentiation between benign and malignant endometrium[10,11]. Others report substantial overlap between benign and malignant lesions, limiting the clinical usefulness of spectral Doppler examination[12–14]. The power Doppler ultrasound image displays the intensity (amplitude) of the Doppler shift spectrum instead of the frequency. It reflects the number of red blood cells flowing in the vessel but, in contrast to the color Doppler image, it is not directly related the blood flow velocity and not at all to the direction of the blood flow. Power Doppler ultrasound has a higher sensitivity to slow flow than

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color Doppler ultrasound, it is less affected by 'noise' and has a better ability to demonstrate tortuous, irregular vessels[15]. This makes power Doppler a promising technique for detecting and characterizing intratumoral vessels. The pattern of vascular distribution within a lesion, as shown by the power Doppler technique, has been reported to be useful in the diagnosis of malignancy in the liver, lymph nodes, breast, endometrium, cervix uteri and ovaries[16–21]. Objective quantification[17,18,21] might be preferable to subjective assessment[16,19,20] of power Doppler signals.

The aim of this study was to determine if power Doppler ultrasound examination of the endometrium can contribute to a correct diagnosis of endometrial malignancy in women with postmenopausal bleeding and endometrium ≥ 5 mm.

PATIENTS AND METHODS

The study was approved by the Ethics Committee of the Medical Faculty at Lund University, Sweden. Consecutive women presenting at the clinic with postmenopausal bleeding underwent transvaginal ultrasound examination by one of two examiners (E.E., L.V.). A woman was considered to be postmenopausal if she reported a period of at least 12 months of amenorrhea after the age of 40 years, provided that the amenorrhea was not explained by medication or disease. A postmenopausal bleeding was defined as any vaginal bleeding in a postmenopausal woman not on hormone replacement therapy (HRT), or as an unscheduled bleeding in a postmenopausal woman on HRT. The age at menopause was determined retrospectively on the basis of the woman's information on her last menstrual period. One hundred and five women whose endometrium measured ≥ 5 mm at transvaginal ultrasound examination (the 'double layer' measurement technique was used[12]), and who consented to take part in the study, were recruited. Twenty-two of them were excluded because of power Doppler artifacts due to electronic disturbances (caused by a bleeper station that was later removed; $n = 15$) or because of incorrect postprocessing of the frozen ultrasound image (by mistake the ultrasound examiner did not change the gray-scale background to a completely black one; $n = 7$). The age, years past menopause, and use of HRT in women included and excluded are shown in Table 1. Hysteroscopy, dilatation and curettage (D & C) and hysteroscopic resection of intracavitary lesions and of the endometrium (if the D & C specimen was scant) were performed within 6 weeks of the ultrasound examination. The curettage of the cervix and corpus, and any resected tissue, were sent to the pathologist of the team (L.S.) for histological analysis. A predetermined classification system for histological diagnosis was used. If the diagnosis differed between specimens, the most relevant diagnosis was considered the final one. The final pathological diagnoses are shown in Table 1.

All women were examined transvaginally in the lithotomy position, with an empty bladder. The ultrasound equipment used was a Sequoia Ultrasound system (Acuson Inc., Mountain View, CA, USA) with a 5–8-MHz transvaginal transducer. Based on subjective evaluation of the endometrial morphology at gray-scale imaging, the ultrasound examiner classified the endometrium as benign or malignant and noted the diagnosis in the research protocol. Malignancy was suspected if there was an irregular endometrial/myometrial junction, or an inhomogeneous endometrial texture. After completion of gray-scale imaging, power Doppler ultrasound examination was carried out using predetermined, standardized settings (frequency 4 MHz, power Doppler gain 50, dynamic range 40 dB, space/time S_2, edge 0, persistence 2, color map E:1, gate 2, filter 3, i.e. S_2/0/2/E:1/2/3). To detect the most vasularized area of the endometrium, the entire endometrium was scanned with power Doppler ultrasound in the sagittal plane from one side to the other. The image of the most vascularized area of the endometrium, as estimated subjectively, was frozen, and the endometrium was outlined with calipers using the trace function of the ultrasound system. Then the image was postprocessed, i.e. the gray-scale echoes were removed, so that the colored power Doppler pixels were shown on a black background (Figure 1). In addition, the most vascularized area of the endometrium was characterized by its color content, as rated subjectively by the examiner on a visual analog scale of 0–100 arbitrary units, the number of units assigned to the endometrium as a whole being designated the endometrial color score. An endometrial color score of zero represents no color within the

Table 1 Characteristics of patients included and excluded

	Included (n = *83*)	*Excluded* (n = *22*)	P-*value*	*Statistical test*
Age, years; mean ± SD	66 ± 11.0	64 ± 11.2	0.50	*t*-test
Years past menopause; mean ± SD	17 ± 10.5	17 ± 15.6	0.87	*t*-test
Hormone replacement therapy, *n* (%)	23 (28%)	5 (23%)	0.43	Chi-squared test
Low potency estrogens, *n* (%)	19 (23%)	3 (14%)	0.56	Fisher's exact test
Final diagnosis, *n* (%)				
Normal endometrium*	13 (16%)	8 (36%)	0.04	Fisher's exact test
Polyp	36 (43%)	7 (32%)		
Myoma	5 (6%)	1 (5%)		
Hyperplasia/focal hyperplasia	9 (11%)	1 (5%)		
Complex atypical hyperplasia	4 (5%)	1 (5%)		
Endometrial cancer	15† (18%)	4 (18%)		
Adenosarcoma	1 (1%)	0 (0%)		

*(Normal endometrium): insufficient sample, proliferative endometrium, secretory endometrium, mixed hormonally induced changes, atrophy.
†Stage 1a ($n = 0$), stage 1b ($n = 11$), stage 1c ($n = 2$), and stage 3a ($n = 2$).

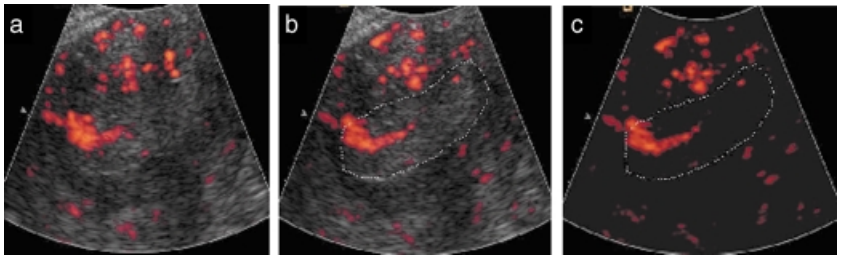

Figure 1 Images of the most vascularized area of the endometrium: (a) gray-scale and power Doppler image; (b) endometrial area traced manually; and (c) gray-scale echoes removed by postprocessing, leaving the power Doppler pixels on a black background.

endometrium, and a score of 100 means that the whole endometrium is colored. The subjective evaluation also took into account the color hue of the power Doppler signals. All ultrasound examinations, including the frozen images, were stored on videotapes, magnetic-optic disks and hard copies, the videotapes being used for computer analysis of the power Doppler images.

Computer analysis of the frozen images of the most vascularized area of the endometrium was done off-line by one examiner (E.E.) after completion of the entire study. The images were transferred from the videotapes to a computer using a QuickCapture frame grabber (Data Translation, Marlboro, MA, USA). Analysis of the pixels in the ultrasound image was carried out using the NIH-Image Software, version 1.55 (National Institutes of Health, Bethesda, MD, USA). This software transforms color pixels into gray-scale pixels and allows analysis of 8-bit images in 256 gray-scale levels. During computer analysis, the outline of the endometrium was retraced manually. The software was used to calculate the endometrial area (in cm^2), and the mean intensity of the pixels in this area (MIEIUM; measured in arbitrary units; range of values from 0 to 256). The vascularized area (in cm^2) was defined by filtering out pixels with an arbitrary intensity of < 25 units. The mean intensity of the pixels in the vascularized area was calculated (MIVA; measured in arbitrary units; range of values from 26 to 256). The percentage area of the endometrium that was vascularized was expressed as the vascularity index (i.e. the vascularized area divided by the area of the endometrium × 100). MIEIUM reflects both the proportion of the endometrium that consists of vessels and the number of blood corpuscles flowing in the endometrial vessels per time unit.

The statistical significance of differences in continuous data was determined using the Mann–Whitney test for data manifesting a skewed distribution, and Student's *t*-test for normally distributed data. The exact *P*-values for the Mann–Whitney test were calculated when the sample size was small. Kolmogorov–Smirnov's test was used to decide if variables manifested a normal or skewed distribution. The Chi-squared test or Fisher's exact test were used as appropriate to test the statistical significance of differences in categorical data. Spearman's rank correlation coefficient (ρ) was calculated to determine correlation between variables. Because of covariation between ultrasound variables, stepwise multivariate logistic regression analysis was carried out, to determine which variables predicted a histological diagnosis of endometrial malignancy. In the first multivariate analysis we tested the following variables: endometrial morphology, endometrial color score, endometrial thickness, ultrasound examiner, age, years past menopause and use of HRT. All ultrasound variables in the first model, except endometrial thickness, were based on subjective assessment. This model was used to calculate a 'subjective probability of endometrial malignancy'. In the second multivariate analysis we tested: endometrial thickness, endometrial area, vascularized area, MIEIUM, MIVA, vascularity index, ultrasound examiner, age, years post menopause and use of HRT. All ultrasound variables tested in the second model were based on objective measurements. This model was used to calculate an 'objective probability of endometrial malignancy'. In all models, endometrial morphology was coded as 1 (endometrial malignancy suspected) or 0 (endometrial malignancy not suspected), and use of HRT was coded as 1 (use of HRT) or 0 (no use of HRT). The objective of the model-building process was to obtain a 'good fit' for the data with the least number of independent variables. The regression equations were derived by stepwise backward elimination of variables, using the likelihood ratio test to determine which variables to include in the model. Receiver operating characteristic (ROC) curves[22] were drawn for endometrial thickness, endometrial area, endometrial color score, vascularized area, MIEIUM, MIVA, vascularity index, subjective probability of malignancy and objective probability of malignancy, to evaluate their individual ability to discriminate between benign and malignant endometrium. The area under the ROC curve and the 95% confidence interval (CI) of this area were calculated. If the lower limit of the CI for the area under the ROC curve was > 0.5, the diagnostic test was considered to have a discriminatory potential. The areas under the ROC curves of the different diagnostic tests were compared as described by Hanley and McNeil[23,24] using a customized computer program, written in MATLAB (Version 6.0.0.88 Release 12) and designed by one of the coauthors (F.D.S.). The ROC curves were also used to determine the best cut-off value for each test, the best cut-off value being defined as the one corresponding to the point on the ROC curve situated furthest away from the reference line[22]. The diagnostic performance of the ultrasound variables and equations was also assessed by comparing their specificity at a fixed sensitivity of 0.88 (i.e. the sensitivity corresponding to the best cut-off value of endometrial thickness). The statistical significance of differences in specificity was determined using the McNemar test. A significance level of 5% was used in all tests. All tests were two-tailed. The statistical analyses (except the testing of

the statistical significance of differences in area under the ROC curve) were carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA, version 10.0.5, 1999).

RESULTS

There were 67 women with benign endometrium and 16 (19%) with endometrial malignancy. The age and the number of years past menopause did not differ between women with benign and malignant endometrium (mean age ± SD, 65 ± 10.9 vs. 67 ± 11.6 years, $P = 0.52$; mean time past menopause, 17 ± 11.0 vs. 16 ± 8.8 years, $P = 0.85$). Use of HRT was six times less common in women with endometrial malignancy (6% vs. 37%, i.e. 1/16 vs. 25/67; $P = 0.02$). There was a strong positive correlation between all power Doppler variables (ρ-values ranging from 0.64 to 0.97, $P < 0.01$) and a weaker but statistically significant positive correlation between endometrial thickness or area and all Doppler variables (ρ-values ranging from 0.31 to 0.73, $P < 0.01$). The strongest positive correlations were found between the vascularity index and the endometrial color score ($\rho = 0.892$, $P < 0.01$) and between vascularity index and MIEIUM ($\rho = 0.966$, $P < 0.01$).

Power Doppler signals in the endometrium were detected by the ultrasound examiner in 77% (10/13) of women with normal endometrium, in 85% (46/54) of those with benign pathological endometrium, and in 100% (16/16) of those with endometrial malignancy. Values for endometrial thickness, endometrial area, endometrial color score, MIEIUM, MIVA and vascularity index were significantly higher in malignant than in benign endometria (Table 2).

Values tended to be lower for women with endometrial cancer of stage 1a or 1b ($n = 11$), than of those with endometrial cancer of stage 1c or more ($n = 4$). However, the differences were only significant for endometrial thickness and vascularized area (median 14 vs. 23 mm, $P = 0.04$; 0.3 vs. 1.5 cm^2, $P = 0.04$).

Stepwise multivariate logistic regression analysis showed that endometrial morphology, endometrial color score and use of HRT satisfied the criteria to be included in the equation $[e^z/(1 + e^z)]$ to calculate the 'subjective probability of malignancy', where $z = -3.568 + (2.129 \times$ endometrial morphology) + (0.068 × endometrial color score in arbitrary units) – (2.17 × HRT use). Endometrial thickness, vascularity index and use of HRT satisfied the criteria to be included in the equation $[e^z/(1 + e^z)]$ to calculate the 'objective probability of malignancy', where $z = -3.543 + (0.078 \times$

Table 2 Results of ultrasound examination in benign and malignant endometria

	Benign	*Malignant*	P-*value*
Endometrial thickness, mm; median (range)	9 (5–53)	18 (7–44)	< 0.001
Endometrial area, cm^2; median (range)	1.26 (0.16–15.0)	2.48 (1.1–22.2)	0.001
Vascularized area, cm^2; median (range)	0.1 (0–8.6)	0.9 (0.01–6.9)	< 0.001
Endometrial color score; mean ± SD	16.4 ± 14.4	44.9 ± 26.7	< 0.001
MIEIUM; mean ± SD	21.3 ± 6.8	30.3 ± 10.7	< 0.001
MIVA; mean ± SD	51.9 ± 16.2	60.7 ± 10.1	0.04
Vascularity index (%); mean ± SD	14.0 ± 13.0	31.5 ± 18.5	< 0.001
Subjective probability of malignancy*; median (range)	0.06 (0.003–0.55)	0.71 (0.01–0.99)	< 0.001
Objective probability of malignancy†; median (range)	0.06 (0.001–0.74)	0.56 (0.007–0.96)	< 0.001

Mann–Whitney's test was used throughout. HRT, hormone replacement therapy; MIEIUM, mean intensity of pixels in the endometrium (theoretical range 0–256); MIVA, mean intensity of pixels in the vascularized area (theoretical range 26–256); vascularity index (%) = 100 × vascularized area divided by endometrial area. *The variables included are: use of HRT, endometrial morphology, endometrial color score. †The variables included are: use of HRT, endometrial thickness, vascularity index.

Table 3 The ability of gray-scale and power Doppler variables and of 'subjective and objective probability of malignancy' to discriminate between benign and malignant endometria

	Area under ROC curve (95% CI)	*Best cut-off value**	*Sensitivity†*	*Specificity†*
Endometrial thickness	0.81 (0.70–0.92)	10.5 mm	0.88	0.61
Endometrial area	0.78 (0.67–0.89)	1.03 cm^2	1.0	0.43
Vascularized area	0.84 (0.74–0.95)	0.34 cm^2	0.75	0.79
Endometrial color score	0.82 (0.71–0.94)	26.5	0.75	0.78
MIEIUM	0.79 (0.68–0.91)	24.4	0.75	0.76
MIVA	0.67 (0.54–0.80)	44.5	1.0	0.33
Vascularity index	0.79 (0.67–0.91)	18.0	0.81	0.66
Endometrial morphology			0.63	0.88
Subjective probability of malignancy	0.88 (0.76–0.99)	0.32	0.75	0.96
Objective probability of malignancy	0.88 (0.77–0.98)	0.21	0.88	0.81

CI, confidence interval; MIEIUM, mean intensity of pixels in the endometrium; MIVA, mean intensity of pixels in the vascularized area; ROC curve = reciever operating characteristic curve; vascularity index = 100 × vascular area divided by endometrial area. *Best cut-off value corresponds to the point on the ROC curve situated furthest away from the reference line, values ≥ cut-off indicating malignancy. †Sensitivity and specificity have been calculated on the basis of the best cut-off value of each test.

endometrial thickness in mm) + (0.066 × vascularity index, %) – (3.357 × HRT use).

The 'subjective and objective probability of malignancy' in benign and malignant endometria are shown in Table 2. The area under the ROC curve, the best cut-off value, and the sensitivity and specificity with regard to malignancy for each gray-scale and power Doppler variable and of the 'subjective and objective probability of malignancy' are shown in Table 3. According to the areas under the ROC curves, all variables had a discriminatory ability, with the two logistic regression models having the largest area under the ROC-curve followed in descending order by the vascularized area, the endometrial color score and the endometrial thickness, the latter three being the best single variables (Table 3). Only the differences between the four best tests (i.e. 'the objective probability of malignancy', 'the subjective probability of malignancy', the vascularized area and the endometrial color score) and the poorest test (i.e. MIVA) were statistically significantly different from each other at the 5% level ($0.008 \leq P \leq 0.04$). In addition, the difference between the area under the ROC-curves of MIEIUM and MIVA was almost statistically significant (0.79 vs. 0.67, $P = 0.054$). The other areas did not differ significantly. Figure 2 shows the ROC curves of the two multivariate logistic regression models and of the continuous individual variables included in the models. Endometrial morphology had the lowest sensitivity (0.63) of all variables (when comparison was based on the best cut-off value of each test), but the diagnostic properties of endometrial morphology varied with endometrial thickness. The sensitivity and specificity of endometrial morphology and of the 'objective and subjective probability of malignancy' at endometrium ≤ 15 mm and > 15 mm are shown in Table 4.

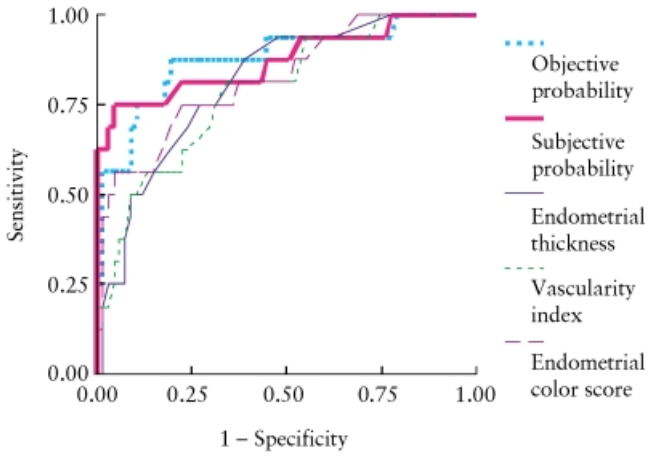

Figure 2 Receiver operating characteristic curves of 'objective and subjective probability of malignancy' and of the variables included in the equations used to calculate the probability of malignancy.

At a fixed sensitivity of 0.88 (corresponding to the best cut-off of endometrial thickness, see Table 3), the 'objective probability of malignancy' had the highest specificity (0.81). It was significantly higher than the corresponding specificity of all other variables (endometrial thickness 0.61, $P = 0.02$; endometrial area 0.55, $P = 0.002$; endometrial color score 0.48, $P < 0.001$; vascularized area 0.64, $P = 0.007$; MIEIUM 0.55, $P < 0.001$; MIVA 0.40, $P < 0.001$; vascularity index 0.46, $P < 0.001$; and 'subjective probability of malignacy' 0.57, $P < 0.001$).

DISCUSSION

The results of this study show that power Doppler ultrasound examination can contribute to a correct diagnosis of endometrial malignancy in women with postmenopausal bleeding and endometrium ≥ 5 mm. The greater the color content of the endometrium (whether subjectively evaluated by an ultrasound examiner or objectively determined by a computer) the greater the risk of endometrial malignancy, irrespective of endometrial thickness, endometrial morphology and HRT use. Our method of individual risk estimation allowed better discrimination between benign and malignant endometrium than subjective evaluation of endometrial morphology in women with endometrium 5–15 mm (even though the differences in sensitivity and specificity did not reach statistical significance). However, in women with endometrium > 15 mm, endometrial morphology tended to be superior to risk calculation. A reliable risk estimation of endometrial malignancy can contribute to optimal timing and choice of endometrial biopsy procedures. It may even allow us to refrain from further invasive diagnostic procedures (D & C or hysteroscopy) in women at low risk of endometrial cancer but at very high risk of operative complications. However, it must be borne in mind that our results are based on an 'optimal fit' for the population studied. Our models must be cross-validated prospectively to determine whether their performance is reproducible in a different study population. It would certainly be worthwhile to try to develop a multivariate logistic regression model specifically designed to discriminate between benignity and malignancy in endometria ≤ 15 mm, because endometrial morphology is

Table 4 Sensitivity and specificity of endometrial morphology, 'subjective and objective probability of malignancy' at endometrial thickness ≤ 15 mm and > 15 mm

	≤ 15 mm		*> 15 mm*	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
Endometrial morphology	0.14 (1/7)	0.89 (51/57)	1.0 (9/9)	0.8 (8/10)
'Subjective probability of malignancy'	0.43 (3/7)	1.0 (57/57)	1.0 (9/9)	0.7 (7/10)
'Objective probability of malignancy'	0.71 (5/7)	0.86 (49/57)	1.0 (9/9)	0.5 (5/10)

None of the differences was statistically significant ($0.13 \leq P \leq 1.0$; McNemar's test). The optimal cut-off for 'subjective and objective probability of malignancy' were used (i.e. 0.32 and 0.21).

not a good discriminator between benignity and malignancy in these women. However, we do not have enough data for such an analysis to be meaningful, because endometrial cancer was diagnosed in only seven women with endometrial thickness ≤ 15 mm.

The use of the 'subjective probability of malignancy' has the advantage over the 'objective probability of malignancy' of not requiring computer analysis of power Doppler signals. The subjective probability can be calculated at the time of the ultrasound examination using a personal computer, thus aiding in the clinical decision making. On the other hand, the objective probability score has the advantage of probably being less dependent on the experience of the ultrasound examiner. In our study there was a strong correlation between the endometrial color score and the vascularity index, suggesting that subjective estimation and objective quantification of the color content of the endometrial scan reflect the same thing, presumably the endometrial vascularization. At the time of the study we had to perform the computer analysis of power Doppler signals off-line, but it would probably be easy to create software for ultrasound systems that would make it possible to automatically calculate both vascularity index and the 'objective and subjective probability of malignancy' on-line. However, it is important to emphasize that power Doppler results are highly dependent on ultrasound equipment and machine settings. Had we used another ultrasound system or other machine settings, our results would almost certainly have been different in terms of absolute values. Moreover, our models are based on the ultrasound examiner choosing the most vascularized area, which could be a source of bias. Therefore, both intra- and interobserver reproducibility of subjective and objective quantification of power Doppler signals need to be examined. However, reproducibility analysis is out of the scope of this article. Imprecision in the analysis of power Doppler signals might be overcome by computerized analysis of the power Doppler signals in a volume (three-dimensional), which is possible with some ultrasound systems. However, the latter method has its own problems.

HRT use was the most powerful individual variable in our logistic regression models. HRT use considerably lowered the risk of malignancy. Smith-Bindman and coworkers, too, found a negative association between HRT use and endometrial cancer[4]. This may reflect that postmenopausal bleeding is a common complication in HRT users, or that HRT use protects against endometrial cancer. Most women on HRT (16/23, 70%) in our study used continuous combined therapy, and indeed there are data supporting that continuous combined HRT therapy reduces the risk of endometrial cancer[25].

Adding more individual risk factors to the logistic regression model might improve its diagnostic performance. Ferrazzi and coworkers found that the risk of endometrial cancer increased with increasing body mass index (BMI)[26]. A retrospective analysis where BMI was added as an independent variable to our multivariate logistic regression analyses (height and weight data were found in the records of 63 of the 83 women) showed that BMI did not satisfy the criteria to be included in our models. Still, it might be worthwhile to include BMI as an independent variable, if new logistic regression models were to be created.

In our study the areas under the ROC curves differed substantially between several tests, but most of the differences were not statistically significant. This was not unexpected, because according to calculations made as described by Hanley and McNeil[23,24], one would need a sample size of 302 women (151 women with benign endometrium and 151 with malignant endometrium) to be able to detect—with 80% power—a true difference between the area under the curve of the 'objective probability of malignancy' (0.88) and that under the curve of endometrial thickness (0.81) as statistically significant at the 5% level (two-sided test).

To the best of our knowledge, there is no study which has tried to objectively quantify power Doppler signals in the endometrium with the aim of distinguishing benign from malignant endometrium. Amit and colleagues subjectively counted the number of endometrial blood vessels detected by power Doppler ultrasound in women with postmenopausal bleeding[27]. They found vessels in 86% (12/14) of the women with endometrial malignancy and in 26% (12/46) of those with benign endometrium[27]. In another study on women with postmenopausal bleeding the presence of 'new, irregular vessels' was subjectively evaluated and found in 81% of women with endometrial cancer, in 12% of women with hyperplasia, but in none with normal endometrium[20]. However, results with regard to the presence of 'normal vessels' within the lesions were not presented, nor was there any definition of neovascularization as opposed to other vascularity[20]. We detected power Doppler signals in all women with endometrial malignancy and in 84% of those with benign endometrium. The differences in results between studies are probably to be explained by differences in ultrasound equipment, machine settings, experience of the examiners, and by lack of standardized criteria for subjective evaluation of endometrial vascularity. Objective quantification of power Doppler signals using computer analysis has been used in the diagnosis of cervical carcinoma[17,28]. Cheng and coworkers found that in women with cervical carcinoma a power Doppler vascularity index (defined as vascular area divided by tumor area, i.e. an index similar to our vascularity index) showed a linear correlation with microvessel density and was significantly positively correlated to tumor size, depth of stromal invasion and the presence of lymph node metastases[17]. These results suggest that tumor vascularity as assessed by power Doppler ultrasound may be useful in the diagnosis and characterization of malignancy.

To sum up, using multivariate logistic regression models, including the results of gray-scale and power Doppler ultrasound examination and of clinical risk factors, the probability of endometrial malignancy can be calculated for each individual. The use of these probabilities may lead to detection of small endometrial malignancies not suspected on the basis of subjective evaluation of gray-scale morphology. It would be particularly attractive to develop software for ultrasound systems for on-line analysis of power Doppler signals and on-line risk calculation of endometrial malignancy.

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