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Ultrasound assessment of endometrial morphology and vascularity to predict endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥4.5 mm

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ABSTRACT

Objectives To determine which gray-scale and power Doppler ultrasound variables are useful for discrimination between benign and malignant endometrium in women with postmenopausal bleeding (PMB) and sonographic endometrial thickness ≥4.5 mm and to develop logistic regression models to calculate the individual risk of endometrial malignancy.

Methods One hundred and twenty consecutive patients with PMB and sonographic endometrial thickness ≥4.5 mm underwent transvaginal gray-scale and power Doppler ultrasound examination. The examinations were videotaped for later analysis by two examiners with more than 15 years of experience in gynecological ultrasound. They independently assessed endometrial morphology and vascularity using predetermined criteria. Their agreed upon description was compared with the histological diagnosis. Univariate and multivariate logistic regression were used. The best diagnostic test was defined as the one with the largest area under the receiver operating characteristics curve (AUC).

Results Thirty (25%) endometria were malignant. Interobserver agreement for description of endometrial morphology and vascularity was moderate to good (Kappa 0.49 – 0.78). The best ultrasound variables to predict malignancy were heterogeneous endometrial echogenicity (AUC 0.83), endometrial thickness (AUC 0.80), and irregular branching of endometrial blood vessels (AUC 0.77). A logistic regression model including endometrial thickness and heterogeneous endometrial echogenicity had an AUC of 0.91. Its optimal risk cutoff yielded a positive likelihood ratio of 4.4, and a negative likelihood ratio of 0.1. Adding Doppler information to the model improved diagnostic performance marginally (AUC 0.92).

Conclusions: In selected high-risk women with PMB and an endometrial thickness of $\geq$ 4.5 mm, calculation of the individual risk of endometrial malignancy using regression models including gray-scale and Doppler characteristics can be used to tailor management. These models would need to be tested prospectively before introduction into clinical practice.

Introduction

There is strong scientific evidence that endometrial thickness as measured by ultrasound can discriminate between women with postmenopausal bleeding at low and high risk of endometrial cancer, women with endometrial thickness ≤4 mm having a low risk and those with endometrial thickness ≥5 mm having a high risk[1]. While it seems to be safe[2] to refrain from endometrial sampling in women with endometrial thickness ≤4mm, women with endometrial thickness ≥5 mm need to have their endometrium sampled. Even within the group of women at high risk with respect to endometrial thickness, it would be of clinical value to be able to identify those at the lowest risk and those at the highest risk of endometrial cancer, because this would make it possible to individualize management. We wanted to explore whether other variables than endometrial thickness, e.g., the gray scale ultrasound morphology of the endometrium, the vascularization of the endometrium as assessed by Doppler ultrasound, or clinical variables could help in the discrimination between benign and malignant endometrium in women with postmenopausal bleeding and thick endometrium.

The aims of this study were (1) to determine which endometrial morphology characteristics as assessed by gray-scale ultrasonography and which endometrial vessel characteristics as assessed by power Doppler ultrasound are useful for discriminating between benign and malignant endometrium in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm and (2) to develop logistic regression models to calculate the individual risk of endometrial malignancy in women with postmenopausal bleeding, endometrial thickness ≥ 4.5 mm, good visibility of the endometrium and detectable Doppler signals in the endometrium.

Patients and Methods

Consecutive patients with postmenopausal bleeding, endometrial thickness ≥4.5 mm at transvaginal ultrasound examination (measurement taken using the double layer technique[3]) and without fluid in the intrauterine cavity underwent extended ultrasound examination as described below. A woman was considered to be postmenopausal, if she reported absence of menstruation for at least 1 year after the age of 40 years provided that the amenorrhea was not explained by medication or disease. Postmenopausal bleeding was defined as any vaginal bleeding in a postmenopausal woman not on hormone replacement therapy, or unscheduled vaginal bleeding in a postmenopausal woman on hormonal replacement therapy. Transvaginal sonography was carried out by one of two examiners using a Sequoia 512 ultrasound system (Siemens Medical Solutions Inc., Ultrasound Division, Mountain View, CA) equipped with a 5 – 8 MHz transvaginal transducer. All women were examined in the lithotomy position with an empty bladder. First, conventional gray scale ultrasound examination of the uterus was performed, and then power Doppler ultrasound examination was carried out using predetermined, standardized settings (frequency, 6 MHz; power Doppler gain 50; dynamic range 10 dB; edge 1; persistence 2; color map 1; gate 2; filter 3). The examinations were videotaped for later analysis.

Approximately 12 month after the collection of data had been completed, two examiners, both of whom had more than 15 years of experience in gynecological scanning, reviewed the videotapes. They assessed endometrial morphology and vascularity using a fixed study protocol. This protocol included predetermined definitions of endometrial morphology characteristics and endometrial blood vessel characteristics. To minimize bias when analyzing the power Doppler images, the gray scale images were analyzed several months before the power Doppler images. The

analysis of gray scale endometrial morphology included visual evaluation of the following: presence of bright line(s) separating the endometrial echo from the myometrium (single line, double lines, no lines), presence of middle echo, regularity of the endometrial-myometrial border (regular, irregular, impossible to evaluate), internal endometrial structure (hyperechogenic, hypoechogenic, isoechogenic, cystic, impossible to evaluate), and homogeneity of endometrial echogenicity (homogenous, heterogeneous, impossible to evaluate). Examples of these morphological characteristics are presented in Figure 1.

Analysis of the videotaped power Doppler ultrasound examinations included visual evaluation of the following: number of blood vessels crossing the myometrial-endometrial border (one, two or many), size of blood vessels (small or large, any large vessel having precedence over small ones), regularity of vessel branching (regular, irregular), presence of large areas of color, i.e., ´color splashes´ (yes, no), presence of area(s) of densely packed blood vessels (yes, no). In addition, endometrial vascularity was classified as multiple vascular pattern (A), single vascular pattern (B), or scattered vascular pattern (C) as proposed by Alcazar et al[4]. The vascular characteristics are illustrated in Figure 2.

To determine interobserver reproducibility of the evaluation of endometrial morphology and vascularity the two observers performed their evaluations of the videotapes independently of each other. Any disagreement in their results was resolved by discussion between the two observers while re-reviewing the tapes together. Their agreed upon classification was used for statistical analysis and the results of the ultrasound examinations were compared with those of histological examination of the respective surgical specimens obtained by dilatation and curettage, hysteroscopic resection or hysterectomy. Staging of malignant tumors was done by the attending

physician in accordance with the classification system recommended by the International Federation of Gynecology and Obstetrics[5].

Exclusion criteria were absence of power Doppler signals in the endometrium, power Doppler artifacts making the power Doppler image uninterpretable, technical problems, e.g. large myomas, making it impossible to study in detail the gray-scale ultrasound morphology and/or the vascularity of the endometrium, incomplete videotaping, absence of histopathological diagnosis, or histopathological diagnosis obtained only by an outpatient endometrial sampling device (e.g., Pipelle® or Endorette®). The reason for excluding samples obtained only by an outpatient endometrial sampling device was that we wanted to be sure that only representative samples were used to establish the final diagnosis[6, 7].

Statistical calculations were undertaken using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA, version 12.02) and the statistical software StatXact (Cytel Inc., Cambrige, MA, USA, version 4). The Mann-Whitney test was used to determine the statistical significance of differences in age and endometrial thickness, and Fisher's exact test was used to determine the statistical significance of differences in use of hormonal replacement therapy. Cohen's Kappa coefficient was calculated to assess interobserver agreement, values of 0.81 - 1 being taken to indicate almost perfect agreement, values of 0.61 - 0.8 good agreement and values of 0.41 - 0.6 moderate agreement[8]. The statistical significance of a possible relationship between endometrial malignancy and clinical variables (age and use of hormonal replacement therapy) and ultrasound variables was determined using univariate logistic regression with the likelihood ratio test. Two-tailed P-values < 0.05 were considered statistically significant.

Multivariate logistic regression was used to build models to predict malignancy. To avoid overfitting a maximum of three predicting variables were allowed in a model, the likelihood ratio test yielding a $P < 0.05$ being the criterion for including a variable in a model. Building logistic regression models we first determined whether any clinical variable (age, use of hormone replacement therapy), gray scale morphology variable or power Doppler variable added information to endometrial thickness. We then studied the effect of adding power Doppler variables to the best gray scale models that included endometrial thickness as one of the gray scale variables. We also built models by adding power Doppler variables to the best gray scale models that did not include endometrial thickness as a variable.

The application of the regression equations to data from each woman gave the probability for that woman to have an endometrial malignancy, the probability ranging from 0 to 1. Receiver operating characteristic (ROC) curves was drawn for single predicting variables as well as for regression equations to evaluate their diagnostic ability. 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 discriminatory potential. For continuous variables the ROC curves were also used to determine the mathematically best cut-off value to predict malignancy for each diagnostic test (single variables as well as logistic regression models), the mathematically best cut-off value being defined as that corresponding to the point on the ROC curve situated most far away from the reference line. The sensitivity, specificity, positive and negative likelihood ratios (LR) of the mathematically best cut-off value with their 95% confidence intervals were then calculated. We defined the best diagnostic test as the one with the largest area under the ROC curve.

The Ethics Committee of Lund University approved the study protocol and informed consent was obtained from all the participants after the nature of the procedures had been fully explained.

Results

A total of 223 consecutive women with postmenopausal bleeding and endometrial thickness ≥4.5 mm were examined in our ultrasound unit. Of these, 103 women were excluded from this study for the following reasons: free fluid in the endometrial cavity (n = 12), absence of power Doppler signals in the endometrium (n = 14), large myomas obscuring the view of the endometrium (n = 9), absence of histological diagnosis (n = 13), histological diagnosis evaluated only from a specimen taken by a simple outpatient sampling device (n = 13), examinations not properly videotaped (n = 42). Among the women excluded, 49 (48%) had benign endometrium, six had malignant endometrium (6%), 22 (21%) underwent endometrial sampling only using a simple outpatient endometrial sampling device (11 of these had benign endometrium, while in the remaining 11 the endometrial samples were insufficient for diagnosis), three (3%) underwent dilatation and curettage but with insufficient material for diagnosis, and 23 (22%) did not undergo any endometrial sampling. Median endometrial thickness in the women excluded was 8.7 mm (range 4.5 – 38.6).

Of the 120 women included, 90 had benign and 30 had malignant endometrium. Histological diagnoses are shown in Table 1. Twenty patients (67%) had stage I, four had stage II (13%), four had stage III (13%), one (3%) had stage IV endometrial cancer, and one woman did not undergo a proper staging procedure because of high operative risk. Women with malignant endometrium were older than those with benign endometrium (median 73 years, range 56 – 85, vs. median 63, range 43 – 90; P = 0.023) and they had thicker endometrium (median 17.6 mm, range 6.7 – 50.0, vs. 10.2, range 4.6 – 30.1; P = 0.0005). Seventeen women (14%) were on continuous combined or sequential hormone replacement therapy, 17 (14%) used low dose oral estrogens or local estrogens, 84 (70%) used no hormonal therapy at all, and for two women (2%)

information on use of hormone replacement therapy was lacking. The proportion of women using hormone replacement therapy did not differ significantly between women with benign and malignant endometrium (16%, 14/88 vs. 10%, 3/30; P = 0.56).

The sensitivity, specificity, positive and negative LR, and area under the ROC curve for age, hormone replacement therapy and ultrasound variables are shown in Table 2. The gray-scale ultrasound morphology variable that best predicted malignancy was heterogeneous endometrial echogenicity (area under the ROC curve 0.83, sensitivity 73%, specificity 92%, positive LR 9.4, negative LR 0.3), and the power Doppler ultrasound variable that best predicted malignancy was irregular branching of endometrial blood vessels (area under the ROC curve 0.77, sensitivity 60%, specificity 94%, positive LR 10.8, negative LR 0.4).

The performance of logistic regression models and the mathematical formulas of the best models are shown in Table 3. None of the clinical variables entered a logistic regression model to predict malignancy. The best logistic regression model with only two ultrasound variables was a model including endometrial thickness and heterogeneous echogenicity of the endometrium (area under the ROC curve 0.91). The diagnostic performance improved marginally when we added Doppler information (areas of densely packed blood vessels or irregular branching of endometrial blood vessels) to this model (area under the ROC curve 0.92).

Interobserver agreement for evaluation of endometrial vascularity (Cohen’s kappa 0.49 - 0.78) was superior to that of evaluation of gray-scale ultrasound morphology (Cohen’s kappa 0.50 - 0.66), see Table 4. Agreement was best for color ´splashes´ in the endometrium (Kappa index 0.78), areas of densely packed blood vessels in the endometrium (Kappa index 0.75), branching of endometrial blood vessels (Kappa index 0.67), and homogeneity of endometrial echogenicity (Kappa index 0.66).

Discussion

The results of our study show that endometrial morphology as assessed by gray scale ultrasound and endometrial vascularity as assessed by power Doppler ultrasound are independently related to endometrial malignancy and that both add information to sonographic endometrial thickness in women with postmenopausal bleeding and endometrial thickness $\geq$4.5 mm.

The single best ultrasound variables for predicting endometrial malignancy were (in descending order): heterogeneous endometrial echogenicity, endometrial thickness, irregular branching of endometrial blood vessels, and the presence of areas of densely packed blood vessels in the endometrium or on the border between the endometrium and myometrium. Only heterogeneous endometrial echogenicity was superior[9, 10] to endometrial thickness, but it changed the odds of malignancy only moderately (positive LR 9.4, negative LR 0.3). The internal endometrial structure most suggestive of malignancy was subjectively perceived as being ´moth eaten´ (Figure 1d and 1f). Others have also reported heterogeneous endometrial structure to be associated with endometrial malignancy[11]. Irregular endometrial-myometrial border was also a sign of endometrial cancer, but in agreement with others we found it to be a poorer predictor of malignancy than heterogeneous endometrial structure[12]. The presence of irregular branching of endometrial blood vessels increased the odds of malignancy almost 11-fold. Epstein and Valentin also noted that irregular vessel branching was more common in malignant than in benign endometria[11]. The presence of areas with densely packed blood vessels and ´color splashes´ within the endometrium or in the endometrial-miometrial border increased the odds of malignancy 4-fold. Densely packed vessels or color splashes may not necessarily reflect microvessel density in the endometrium, but it is nonetheless interesting that endometrial carcinoma is associated with increased

microvessel counts[13]. The vascular patterns A, B, and C which worked well in the study of Alcazar et al.[4], did not perform well as predictors of endometrial malignancy in our hands. The discrepancy may be explained by fundamental differences in study design.

The crucial question is whether or not gray scale ultrasound morphology and endometrial vascularity as assessed by Doppler ultrasound are superior to, or add to, simple sonographic endometrial thickness measurements in the prediction of endometrial cancer. Even in our high risk group of patients with postmenopausal bleeding and endometrial thickness $\geq$4.5 mm, the risk of malignancy increased with increasing endometrial thickness, and endometrial thickness was a fairly good predictor of malignancy. Heterogeneous endometrial echogenicity was only slightly superior to endometrial thickness, but it did add information to endometrial thickness in a logistic regression model. A model including endometrial thickness and heterogeneous endometrial echogenicity was the best one for predicting malignancy. Using the mathematically optimal risk cutoff of this model misclassified only two of the malignant endometria and only nine of the benign endometria. Adding Doppler variables to this model improved the overall diagnostic performance only marginally, and the use of the respective optimal risk cutoffs of the models including Doppler variables did not result in more endometria being correctly classified. Models not containing endometrial thickness but only heterogeneous endometrial echogenicity and Doppler variables also performed well.

A problem with the evaluation of ultrasound images is its subjectivity. Indeed interobserver agreement for categorizing gray scale ultrasound and Doppler findings was only moderate or good. Some Doppler variables were more reproducible than even the most reproducible gray scale ultrasound variable. In a reproducibility study by Alcazar et al. interobserver agreement for evaluating the vessel pattern in the

endometrium was good between two experts but not between less experienced examiners[14].

Quite clearly, ultrasound evaluation of the endometrium in women with postmenopausal bleeding starts with a proper measurement of the endometrial thickness. In women with postmenopausal bleeding endometrial thickness $\leq$ 4 mm decreases the odds of malignancy 10-fold, the risk of endometrial cancer in such women varying between 1:1000 and 1:100[1]. It is important to bear in mind that our study group included only women with postmenopausal bleeding at high risk of endometrial cancer, i.e. those with endometrial thickness $\geq$4.5 mm, and among these only those without fluid in the uterine cavity, well visible endometrium and detectable power Doppler signals in the endometrium without power Doppler artifacts. Our results are only applicable to similar populations. The rationale for studying only a high-risk group with endometrial thickness $\geq$ 4.5 mm is that first, it would be very difficult to asses endometrial gray-scale and vessel morphology in an endometrium $\leq$ 4.4 mm, and second further risk assessment in women with postmenopausal bleeding and endometrial thickness $\leq$ 4.4 mm seems unnecessary, because in these women the risk of endometrial cancer is so low that it is safe to refrain from endometrial sampling[2]. In the high-risk group with endometrial thickness $\geq$ 4.5 mm, however, a differentiation of risk would allow individualized management. For example, in a woman with an estimated risk of endometrial cancer <1:100 (calculated using our best logistic regression model) at high operative risk it might be appropriate to refrain from endometrial sampling, at least if cervical stenosis – or other factors – makes it impossible to obtain an endometrial sample using an outpatient sampling device. On the other hand, a high risk of malignancy would support not delaying a reliable diagnostic procedure. Needless to

say, our logistic regression models need to be tested prospectively before they can be used in clinical practice.

Acknowledgements

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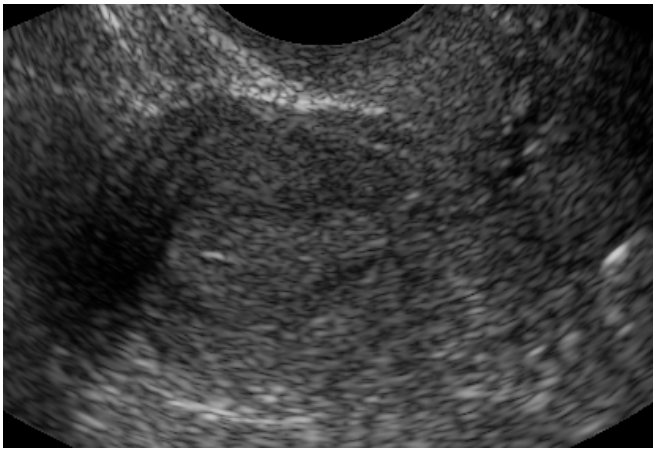
Legends

Figure 1. Illustration of gray scale ultrasound characteristics of the endometrium. (a) Homogeneous endometrial echogenicity with middle echo (histopathological diagnosis: benign estrogen influenced endometrium). (b) Lines separating the endometrial echo from the myometrium (histopathological diagnosis: benign polyp). (c) Cystic endometrial structure and regular endometrial-myometrial borders with lines separating the endometrial echo from the myometrium (histopathological diagnosis: benign polyp). (d) Heterogeneous endometrial echogenicity with irregular endometrial-myometrial border anteriorly (histopathological diagnosis: adenocarcinoma). (e) Irregular endometrial-myometrial border mainly posteriorly (histopathological diagnosis: adenocarcinoma). (f) Heterogeneous endometrial echogenicity and irregular endometrial-myometrial borders (histopathological diagnosis: adenocarcinoma).

Figure 2. Illustration of vascular characteristics. (a) One blood vessel crossing the myometrial-endometrial border (histopathological diagnosis: benign polyp). (b) Two regular blood vessels crossing the myometrial-endometrial border of the cystic endometrium (histopathological diagnosis: benign polyp). (c) Regular branching of endometrial blood vessels (histopathological diagnosis: benign polyp). (d) Multiple, densely packed endometrial blood vessels (histopathological diagnosis: adenocarcinoma). (e) Irregular branching of endometrial bloodvessels (histopathological diagnosis: adenocarcinoma). (f) Presence of color ´splashes´ (histopathological diagnosis: adenocarcinoma). The dotted line in the images (b, c, d, e, f) outlines the endometrium. The black background in the images (e, f) resulted from elimination of the gray scale image for better visualization of the vessels.

Figure 1

a



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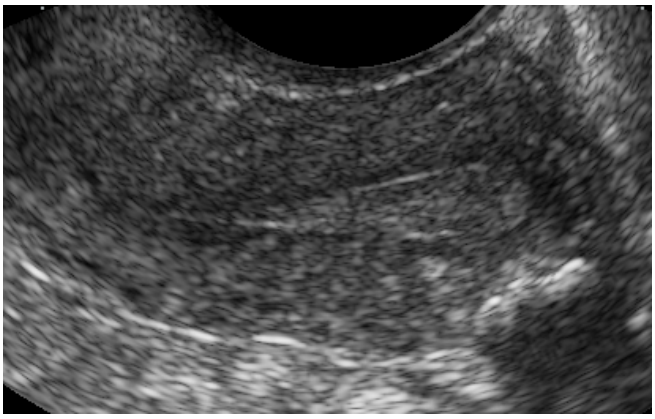

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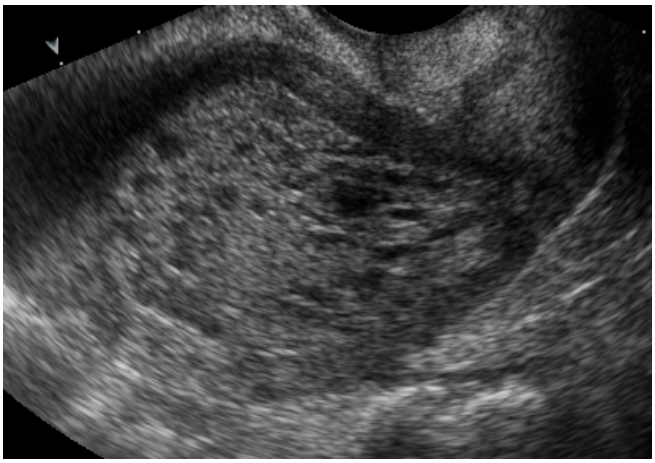

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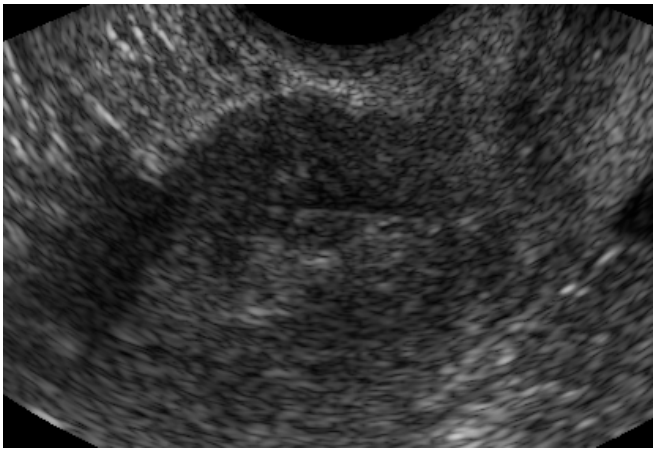

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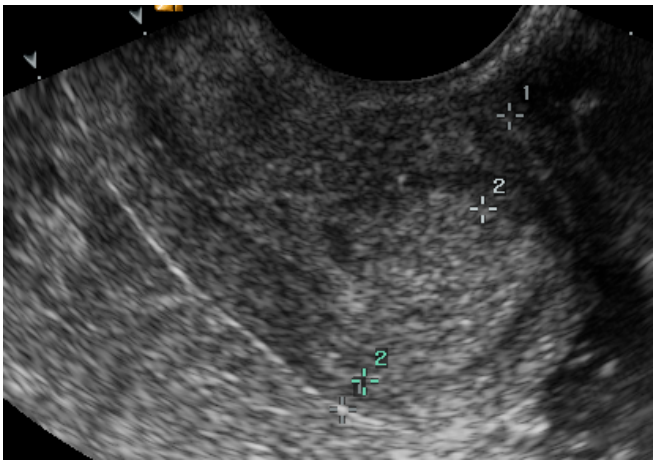

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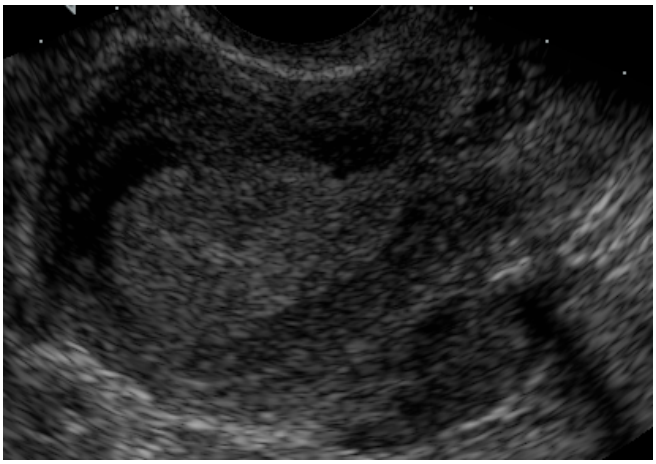
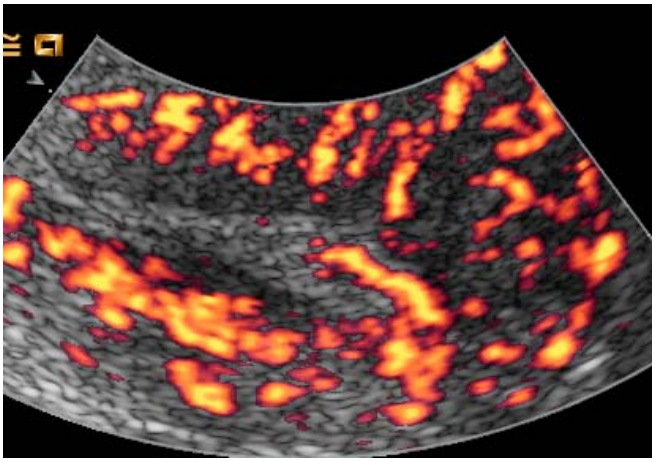


Figure 2

a



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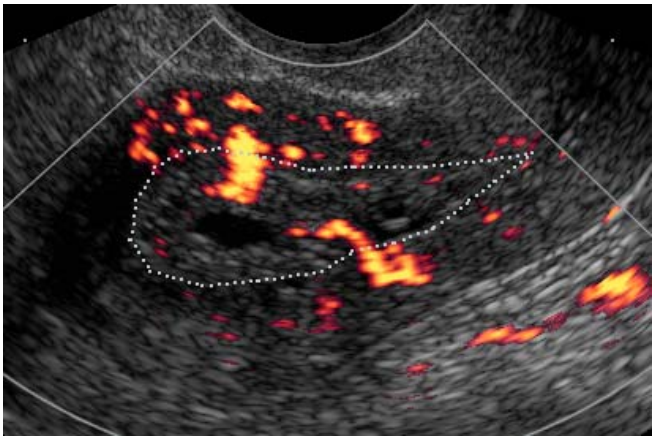

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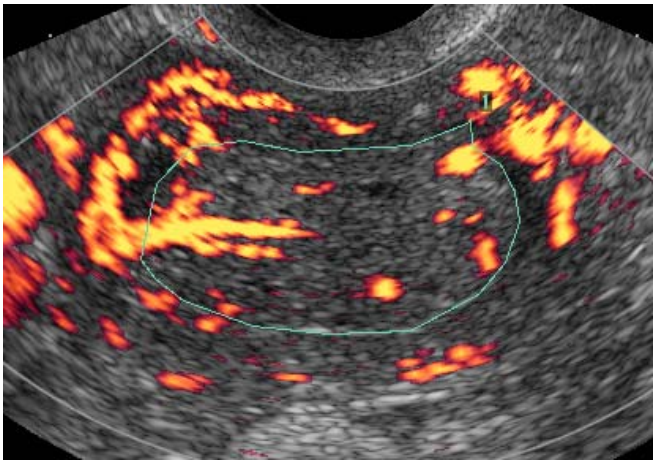

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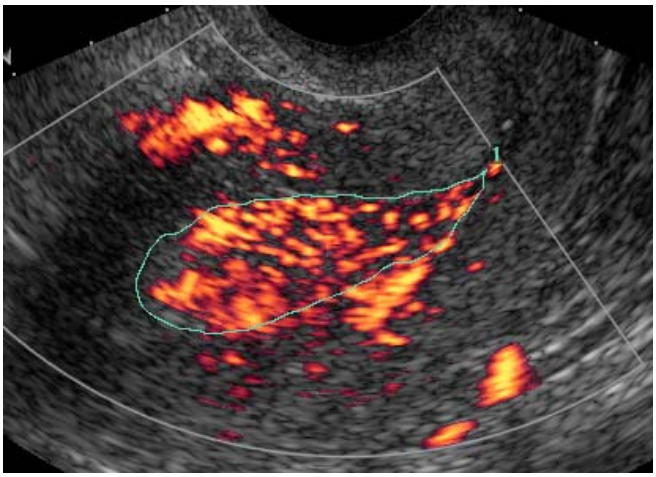

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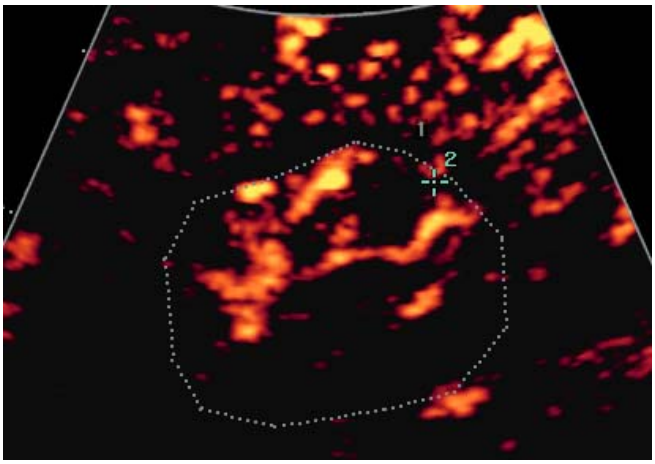

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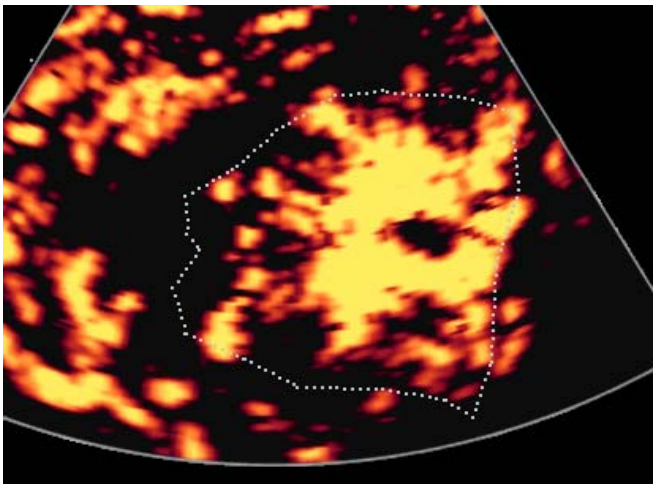

Table 1 Histopathological diagnoses

	Number (%)
Benign	90 (75%)
Polyp	62 (52%)
Atrophic endometrium	11 (9%)
Estrogen influenced endometrium	10 (8%)
Hyperplasia	7 (6%)
without atypia	5 (4%)
with atypia	2 (2%)
Malignant	30 (25%)
Adenocarcinoma	27 (23%)
Carcinosarcoma	3 (2%)
Total	120 (100%)

Table 2 Sensitivity and specificity with regard to malignancy, positive and negative likelihood ratios, and area under the receiver operating characteristics curve of clinical and ultrasound variables

Variable	ROC area Estimate	Optimal cut-off*	Sensitivity %, (n)	Specificity %, (n)	LR+	LR-	P-value**
Endometrial thickness	0.80	15 mm	73 (22/30)	77 (69/90)	3.1	0.3	0.0005
Age	0.64	61 years	87 (26/30)	40 (36/90)	1.4	0.3	0.041
Hormone replacement therapy	0.47	-	10 (3/30)	84 (74/88)	0.6	1.1	0.41
Gray scale analysis							
Heterogeneous echogenicity	0.83	-	73 (22/30)	92 (83/90)	9.4	0.3	0.0005
Irregular border	0.71	-	67 (20/30)	76 (68/90)	2.7	0.4	0.0005
Cystic endometrium	0.67	-	23 (7/30)	42 (38/90)	0.4	1.8	0.001
Hyperechogenic endometrium	0.67	-	53 (16/30)	62 (56/90)	1.4	0.8	0.137
Hypoechogenic endometrium	0.54	-	10 (3/30)	99 (89/90)	9.0	0.9	0.032
Isoechogenic endometrium	0.54	-	13 (4/30)	96 (86/90)	3.0	0.9	0.114
No lines	0.50	-	50 (15/30)	50 (45/90)	1.0	1.0	1.0
Power Doppler analysis							
Irregular branching	0.77	-	60 (18/30)	94 (85/90)	10.8	0.4	0.0005
Areas of densely packed vessels	0.76	-	67 (20/30)	84 (76/90)	4.3	0.4	0.0005
Color ´splashes´	0.72	-	60 (18/30)	84 (76/90)	3.9	0.5	0.0005
Many vessels	0.68	-	83 (25/30)	52 (47/90)	1.7	0.3	0.0005
Vascular pattern A***	0.67	-	80 (24/30)	54 (49/90)	1.8	0.4	0.001
Branching of vessels	0.67	-	87 (26/30)	47 (42/90)	1.6	0.3	0.001
Large vessels	0.57	-	90 (27/30)	23 (21/90)	1.2	0.4	0.094

*Values above the cut-off indicate malignancy; **Univariate logistic regression with likelihood ratio test; ***Vascular pattern A according to Alcazar et al[4]; LR, likelihood ratio; ROC, receiver-operating characteristic.

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Table 3 Multivariate logistic regression models to predict malignancy

Model	ROC area Estimate	Optimal probability cut-off*	Sensitivity, %, (n)	Specificity %, (n)	LR+	LR-
Endometrial thickness and						
heterogenous echogenicity[1]	0.91	0.12	93 (28/30)	79 (71/90)	4.4	0.1
irregular border	0.84	0.31	80 (24/30)	87 (78/90)	6.0	0.2
cystic endometrium	0.84	0.27	77 (23/30)	86 (77/90)	5.3	0.3
hyperechogenic endometrium	0.81	0.31	70 (21/30)	87 (78/90)	5.3	0.3
Endometrial thickness and						
irregular branching[2]	0.86	0.29	77 (23/30)	88 (79/90)	6.3	0.3
areas of densely packed vessels[3]	0.85	0.28	83 (25/30)	82 (74/90)	4.7	0.2
color ´splashes´	0.83	0.33	77 (23/30)	82 (74/90)	4.3	0.3
many vessels	0.82	0.24	80 (24/30)	77 (69/90)	3.4	0.3
pattern A**	0.81	0.26	77 (23/30)	77 (69/90)	3.3	0.3
Endometrial thickness and heterogenous echogenicity and						
areas of densely packed vessels[4]	0.92	0.28	83 (25/30)	89 (80/90)	7.5	0.2
irregular branching	0.92	0.15	87 (26/30)	83 (75/90)	5.2	0.2
color ´splashes´	0.91	0.31	80 (24/30)	90 (81/90)	8.0	0.2
Endometrial thickness and irregular border and						
areas of densely packed vessels	0.86	0.44	73 (22/30)	92 (83/90)	9.4	0.3
color ´splashes´	0.85	0.52	67 (20/30)	96 (86/90)	15.0	0.3
Heterogenous echogenicity and						
areas of densely packed vessels[5]	0.89	0.41	73 (22/30)	92 (83/90)	9.4	0.3
color ´splashes´	0.87	0.42	73 (22/30)	92 (83/90)	9.4	0.3
irregular branching	0.87	0.23	80 (24/30)	88 (79/90)	6.5	0.2
branching	0.86	0.32	73 (22/30)	92 (83/90)	9.4	0.3
pattern A**	0.86	0.34	73 (22/30)	92 (83/90)	9.4	0.3

Continued

Table 3 continued

Model	ROC area Estimate	Optimal probability cut-off*	Sensitivity, %, (n)	Specificity %, (n)	LR+	LR-
Irregular endometrial-myometrial border and						
areas of densely packed vessels	0.80	0.56	57 (17/30)	97 (87/90)	17.0	0.4
color ´splashes´	0.78	0.55	50 (15/30)	98 (88/90)	22.5	0.5
branching	0.77	0.40	63 (19/30)	88 (79/90)	5.2	0.4
many vessels	0.75	0.39	67 (20/30)	84 (76/90)	4.3	0.4
pattern A**	0.75	0.40	67 (20/30)	87 (78/90)	5.0	0.4

LR, likelihood ratio; ROC, receiver-operating characteristic; CI, confidence interval; *Values above the probability cut off indicate malignancy; **Vascular pattern A according to Alcazar et al[4].

The probability of malignancy is calculated as [ez/1+ez] where e = 2.718 (base value of natural logarithms) and z is calculated for each logistic regression model as follows:

[1] z = -3.988 + (0.125 x endometrial thickness in mm) + (3.012 x echogenicity coded 0 if homogeneous and 1 if heterogeneous)

[2] z = -4.151 + (0.156 x endometrial thickness in mm) + (2.886 x branching coded 0 if regular and 1 if irregular)

[3] z = -4.411 + (0.167 x endometrial thickness in mm) + (2.151 x areas of densely packed vessels coded 0 if absent and 1 if present)

[4] z = -4.462 + (0.113 x endometrial thickness in mm) + (2.832 x echogenicity coded 0 if homogeneous and 1 if heterogeneous) + (1.907 x areas of densely packed vessels coded 0 absent and 1 if present)

[5] z = -3.037 + (3.243 x echogenicity coded 0 if homogeneous and 1 if heterogeneous) + (2.050 x areas of densely packed vessels coded 0 if absent and 1 if present).

Table 4 Inter-observer agreement

	Cohen's Kappa	Agreement (%)
Gray scale analysis		
Homogeneity of endometrial echogenicity	0.66	87
Endometrial echogenicity (cystic, hyper-, hypo- or iso-echogenic)	0.61	77
Endometrial lines	0.56	73
Regularity of endometrial-myometrial border	0.50	76
Power Doppler analysis		
Color´splashes´	0.78	92
Areas of densely packed vessels	0.75	90
Branching of vessels	0.67	84
Branching regularity	0.59	74
Size of vessels	0.52	85
Vascular pattern A, B, C*	0.49	69
Number of vessels	0.49	68

*Vascular pattern A, B, C according to Alcazar et al[4].