Grey scale ultrasound morphology and endometrial vascularity as assessed by color Doppler ultrasound before and during saline infusion for discrimination between benign and malignant endometrium in women with postmenopausal bleeding

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Abstract

Objective: To determine if grey scale ultrasound morphology and endometrial vascular morphology as assessed by color Doppler ultrasound can discriminate between benign and malignant endometrium in women with postmenopausal bleeding.

Methods: In a prospective study 95 consecutive women with postmenopausal bleeding and endometrial thickness $\geq$ 4.5 mm as measured by transvaginal ultrasound were included. Grey scale and color Doppler ultrasound examination of the endometrium was performed before and during saline infusion. The ultrasound examiner characterized the morphology of the endometrium and the endometrial vascular tree using a predetermined classification protocol without suggesting a diagnosis. A histopathological diagnosis was obtained by operative hysteroscopy, D&C or hysterectomy.

Results: There were no statistically significant differences between benign and malignant endometria in results of ultrasound scan performed without fluid in the uterine cavity. Heterogeneous echogenicity, irregular surface, and both heterogenous echogenicity and irregular surface of a focal lesion (or of the endometrium in the absence of focal lesions) in a uterine cavity filled with fluid (spontaneous or infused) were significantly more common in malignant than in benign endometrium. The sensitivity, false positive rate, positive and negative likelihood ratios of these findings were as follows: 80%, 29%, 2.74, 0.28, $p = 0.003$; 89%, 33%, 2.70, 0.17, $p = 0.002$; and 78%, 12%, 6.59, 0.25, $p < 0.001$. Two or more vessels were found in 67% (8/12) of the malignant endometria vs. in 51% (40/79) of the benign endometria (non-significant difference). Vascular branching tended to be more common in malignant endometria (10/11; 91%) than in benign endometria (39/61; 64%), $p = 0.09$.

Conclusion: Heterogeneous echogenicity and an irregular surface of a focal lesion or of the endometrium in a fluid filled uterine cavity were the most useful ultrasound criteria for predicting endometrial malignancy. Assessment of vascular morphology using color Doppler

ultrasound was of limited value – if any – for discrimination between benign and malignant endometrium.

Introduction

Postmenopausal bleeding (PMB) is the most common symptom of endometrial cancer. Therefore all women presenting with PMB should undergo examination to exclude endometrial cancer. Measurement of endometrial thickness using transvaginal ultrasound can discriminate between women at high and low risk of endometrial cancer[1-3]. The odds of endometrial cancer after a negative scan (endometrial thickness $\leq$ 4 mm) are only one tenth of the odds before the scan[3]. Endometrial polyps, fibroids and endometrial cancer may manifest characteristic grey scale ultrasound morphology both at conventional ultrasound examination[4-7] and at saline infusion sonography[8,9], but some research teams found overlapping ultrasound morphology between benign and malignant endometrial lesions[10,11]. Others concluded that the accuracy of transvaginal sonography in detecting endometrial cancer increases if assessment of endometrial morphology and endometrial border appearance is used in combination with endometrial thickness measurements[12,13]. In the studies cited[10-13] predetermined criteria were used when trying to estimate the risk of endometrial cancer in women with PMB. This means, that the best malignancy criteria might not have been used. In one of our own studies saline infusion sonography was not superior to unenhanced grey scale imaging with regard to predicting endometrial cancer in women with PMB[10]. The value of vascular morphology assessment using color Doppler ultrasound in the discrimination between benign and malignant endometrium in women with PMB needs to be determined.

The aim of this study was to determine which features of endometrial morphology at grey scale ultrasound examination with or without fluid (spontaneous or infused) in the uterine cavity and which endometrial vascular features as assessed by color Doppler ultrasound are useful for predicting endometrial cancer in women with PMB and endometrium $\geq$ 4.5 mm or with unmeasurable endometrium.

Patients and methods

The Ethics Committee of the Medical Faculty at Lund University, Sweden, approved the study. Consecutive women presenting at our outpatient department with PMB underwent transvaginal ultrasound examination by the second author (LV). 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 medication or disease did not explain the amenorrhea. Postmenopausal bleeding was defined as any vaginal bleeding in a postmenopausal woman as defined above not on hormone replacement therapy (HRT), or as an unscheduled bleeding in a postmenopausal woman as defined above on HRT. The age at menopause was determined retrospectively on the basis of the woman's information on her last menstrual period. Ninety-five consecutive women, with PMB whose endometrium was unmeasurable or measured $\geq$ 4.5 mm at transvaginal ultrasound examination (the 'double layer measurement technique' was used[14]) and who consented to take part in the study were examined as described below. In women with spontaneous fluid in the cavity, any focal lesion and the fluid in the uterine cavity were included in the measurements of endometrial thickness. 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 to 8 MHz transvaginal transducer. Before saline infusion the ultrasound examiner characterized the endometrial morphology using a predetermined classification protocol without suggesting a diagnosis. The endometrial-myometrial border was classified as regular or irregular (Figure 1). The endometrial echogenicity was described as hyperechoic, hypoechoic, isoechoic, cystic, or as having a mixed echogenicity, or an echogenicity similar to that of a fibroid. In addition, the internal endometrial echogenicity was classified as homogenous or heterogenous (Figure 2). If the endometrium could not be clearly seen, the woman was classified as having an unmeasurable endometrium, and assessment of

endometrial morphology was postponed until during saline infusion. After completion of the grey scale ultrasound examination, color Doppler ultrasound examination was carried out using fixed settings (Space-time, S2; edge, 0; persistence, 2; color scale, V:2; gate, 1; filter, 3. color Doppler gain 50). Vascular morphology was assessed: the vessels seen in the endometrium were counted, and the presence of vascular branching was noted, the branching pattern being characterized as regular or irregular.

Saline infusion was not performed in women with enough spontaneous fluid in the uterine cavity to allow satisfactory assessment of the endometrial cavity (n = 8). In the other women saline was infused into the uterine cavity using a Kremer-Delafontaine intrauterine catheter (without an inflatable balloon) attached to a 20 ml syringe[10]. A uterine cavity filled with fluid (spontaneous or infused) was evaluated by transvaginal ultrasound in a longitudinal and a transverse plane, and morphological assessment of the endometrial cavity was undertaken. The regularity of the endometrial-myometrial border was assessed only in women without focal lesions. A focal lesion was defined as any focal thickening or polypoid lesion irrespective of its size protruding from the endometrial surface into the uterine cavity. The surface of any focal lesion in the uterine cavity was characterized as smooth or irregular (Figure 3) as was the endometrial surface facing the cavity in the absence of focal lesions. Any surface irregularity classified the woman as having 'irregular surface'. During saline infusion, the endometrial echogenicity within a focal lesion or within the endometrium in the absence of focal lesions was classified as either homogeneous or heterogeneous. In addition, the echogenicity was described as mixed, cystic, hyper- iso- or hypoechoic. If there were several focal lesions with different echogenicity, then heterogeneous echogenicity within any lesion classified the woman as having focal lesions with heterogeneous echogenicity. Doppler ultrasound examination was also performed during saline infusion with the aim of examining vascular morphology as described above. However, in 16 (25%) women blood vessels that

had been seen at Doppler examination before saline infusion were no longer visible during saline infusion. Therefore, we considered Doppler results obtained during saline infusion unreliable and decided to present only the results of Doppler examinations before saline infusion.

The statistical significance of differences in proportions was determined using the Chi-squared test or Fisher's exact test. Two-tailed p-values <0.05 are considered statistically significant. The sensitivity, false-positive rate (1 minus specificity), positive and negative likelihood ratios with regard to predicting endometrial cancer were calculated for each ultrasound variable. Likelihood ratios indicate by how much a given test result would raise or lower the odds of having the condition sought for. A likelihood ratio of 1 indicates that the test has no predictive value at all. To achieve high diagnostic accuracy (i.e., an almost conclusive diagnosis) a positive likelihood ratio of >10 and a negative likelihood ratio of < 0.1 is required[15]. Moderate accuracy can be achieved with positive and negative likelihood ratios of 5 – 10 and 0.1 – 0.2, respectively. Likelihood ratios of 1 – 5 and 0.2 – 1 indicate poor test performance. All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA, version 11.5.1, 2002).

Results

The mean age of the women included was 65 years (range 43 – 93). Twenty-seven women (28 %) used HRT, and eight women (8.5%) used low potency estrogens. The remaining 60 women (63%) used no hormones. HRT was used by 24 of 83 (29%) women with benign lesions and by 3 of 12 (25%) women with endometrial malignancy (p = 1.0)**.** A final histopathological diagnosis was obtained by operative hysteroscopy in 60 (63%) women, by D&C in 16 (17%) women, and by hysterectomy in 19 (20%) women. The histological diagnoses were: normal endometrium (i.e., insufficient material, hormonally induced changes or atrophic endometrium), n = 19 (20%); hyperplasia/focal hyperplasia, n = 14 (15%); fibroid, n = 11 (12%); endometrial polyp, n = 39 (41%); endometrial cancer including one case of complex atypical hyperplasia, n = 12 (13%). All but one of the 11 invasive endometrial cancers were stage 1 (stage 1a, n = 3; stage 1b, n = 3; stage 1c, n = 4), the eleventh case was stage 2a.

The endometrial-myometrial border was ill defined in 13 women (14%) making measurement of endometrial thickness impossible. In the remaining 82 women the median endometrial thickness was 10 mm (range 4.5 – 56.0) and the mean (SD) thickness was13 mm (+/- 9.7). The endometrium measured 4.5 – 7.9 mm in 26 women (32%), 8.0 – 14.9 mm in 30 women (37%), and $\geq$ 15.0 mm in 26 women (32%).

Detailed information on results of endometrial grey scale ultrasound morphology and endometrial vascularity as assessed by Doppler ultrasound in benign and malignant endometrium are shown in Table 1. In uteri without fluid in the uterine cavity neither grey scale nor Doppler ultrasound findings differed significantly between benign and malignant endometria, even though vascular branching was found more often in malignant than benign endometria. Eight women had spontaneous fluid in the uterine cavity obviating the need for saline infusion. Saline infusion failed in nine (9%) of the 87 women where it was attempted.

Focal lesions were detected in a fluid filled uterine cavity at ultrasound examination in 90% of women with benign endometrium and in 90% of those with malignant endometrium. Heterogeneous echogenicity of a focal lesion and irregular surface of a focal lesion seen in a fluid filled uterine cavity were the only ultrasound findings that were statistically significantly associated with endometrial cancer. The positive and negative likelihood ratios of heterogeneous echogenicity of a focal lesion with regard to predicting endometrial cancer were 2.52 and 0.32 (sensitivity 78%, false-positive rate 31%, $p = 0.01$). The corresponding values for irregular surface of any focal lesion were 2.58 and 0.18 (sensitivity 88%, false-positive rate 34%, $p = 0.006$), Table 1. The presence of focal lesions with both irregular surface and heterogeneous internal echogenicity was associated with a positive likelihood ratio of 5.77 and negative likelihood ratio of 0.29, (sensitivity 75%; 6/8, false positive rate 13%; 8/63, $p < 0.001$). Including also women without focal lesions the sensitivity, false positive rate, positive and negative likelihood ratios with regard to endometrial cancer of 1) heterogeneous echogenicity of the endometrium/ focal lesion, 2) irregular surface of the endometrium/ focal lesion or 3) the presence of both heterogeneous echogenicity and irregular surface of the endometrium/ focal lesion were as follows: 80%, 29%, 2.74, 0.28, $p = 0.003$; 89%, 33%, 2.70, 0.17, $p = 0.002$; and 78%, 12%, 6.59, 0.25, $p < 0.001$. A combination of heterogeneous echogenicity and irregular surface of the endometrium/ any focal lesion facing the uterine cavity during saline infusion was more common in malignant lesions than in benign lesions also in women with endometrial thickness < 15 mm (75% [3/4] vs. 11% [5/45], $p = 0.01$). There was no statistically significant difference between benign and malignant endometria in the echogenicity of the endometrium/focal lesion when the echogenicity was described as hyper- hypo-, iso-echoic, cystic, mixed, or with echogenicity similar to a fibroid.

The sonographic findings in women with endometrial cancer are summarized in Table 2.

Discussion

We found that assessment of endometrial grey scale ultrasound morphology was useful in the diagnosis of endometrial cancer but only when there was fluid (spontaneous or infused) in the uterine cavity. Focal lesions were equally common in benign and malignant endometria, but heterogeneous echogenicity and /or irregular surface of a focal lesion or of the endometrium in the presence of spontaneous or infused fluid in the uterine cavity increased the odds of endometrial cancer. Assessment of the morphology of endometrial vessels was not useful in the prediction of endometrial malignancy. Because the number of women with endometrial cancer in our study is small, our estimates of sensitivity with regard to detecting endometrial cancer is imprecise, and so are, of course, our likelihood ratios. It may well be that heterogenous endometrial echogenicity in the absence of uterine fluid is indeed a good discriminator between benign and malignant endometrium, but that our study lacked power to detect a true difference as statistically significant (our p-value was 0.08).

According to the positive and negative likelihood ratios the best ultrasound criteria to predict endometrial cancer – i.e., heterogenous echogenicity and/or irregular surface of a focal lesion or of the endometrium in a fluid filled uterine cavity – were associated with at most moderate diagnostic accuracy. The pre-test odds of endometrial cancer in our study were 0.14 (12:83 i.e., 1:7). The post-test odds rose to 0.92 (i.e., almost 1: 1) in the presence of an endometrium or focal lesion with heterogenous echogenicity and irregular surface. The absence of such findings decreased the odds from 0.14 (1:7) to 0.035 (1: 28). The conclusion to be drawn from our results is that ultrasound assessment of endometrial grey scale morphology either before or during saline infusion is not good enough to obviate the need for obtaining a histopathological diagnosis in women with postmenopausal bleeding and unmeasurable endometrium or endometrial thickness ≥ 4.5.mm. On the other hand, the presence of both irregular surface and heterogenous echogenicity of a focal lesion – or of the

endometrium in the absence of focal lesions – in a fluid filled uterine cavity should alert us to a high probability of cancer and to the need of obtaining a representative sample of the endometrium for histopathological diagnosis without delay. In women at high operative risk, a low risk of cancer could be an argument for refraining from risky invasive procedures should such procedures be necessary to obtain an endometrial sample.

It is important to be aware that sensitivity and specificity of endometrial morphology and vascularity as assessed by ultrasound with regard to malignancy are highly dependent on the type of benign histopathological diagnoses in the study population and on the stage of the endometrial cancers. In a previous study, we found that saline infusion did not improve the diagnostic accuracy of endometrial morphology assessment with regard to predicting endometrial cancer[10]. The difference in results may be explained by differences in study design but also by differences in the mix of histopathological diagnoses and the success rate of saline infusion sonography. The ability to predict endometrial cancer on the basis of grey scale ultrasound morphology assessment also depends on endometrial thickness[11]: quite clearly, the more endometrial tissue there is, i.e., the thicker the endometrium, the easier it is to evaluate its ultrasound morphology and vascularity. However, our results suggest that heterogenous echogenicity and irregular surface of the endometrium/ any focal lesion when there is fluid in the uterine cavity can discriminate between benign and malignant endometrium also when the endometrium is < 15 mm. In a previous study, subjective evaluation of the gray scale ultrasound morphology of the endometrium could not be used discriminate reliably between benign and malignant endometria in women with endometrial thickness < 15 mm[10,11].

Concerns have been raised that saline infusion might lead to intraperitoneal dissemination of malignant cells in women with endometrial cancer. Seeding of malignant cells was found in one of 14 women (7%) with endometrial cancer stage I, undergoing saline infusion at the

time of laparotomy[16]. The long term consequences of saline infusion in women with early endometrial cancer have not been specifically studied. However, the 5-year survival has been reported to be the same in women with early endometrial cancer who have undergone hystesteroscopy before laparotomy as in those who have not undergone preoperative hysteroscopy[17]. This leads us to regard saline infusion sonography as a safe procedure even in women with endometrial cancer.

We found that the vascular morphology was best evaluated before and not during saline infusion, because many of the vessels that had been detectable with color Doppler within the endometrial echo before saline infusion disappeared during saline infusion. Increased intrauterine pressure might explain the disappearance of color Doppler signals during saline infusion. We found no differences in vascular morphology between benign and malignant endometria. This is in contrast to the results of Alcazar and co-workers. They classified endometrial vascularity into three predetermined vascular patterns: multiple vessel pattern, single vessel pattern, and scattered vessel pattern[18]. They found multiple vessel pattern in 81% (26/32) of vascularized endometrial malignancies at a false positive rate of 0% (0/51), a single vessel pattern in 97% (33/34) of vascularized polyps at a false positive rate of 14% (7/49), and a scattered vessel pattern in 72% (8/11) of cases with hyperplasia at a false positive rate of 12% (9/73). The difference between the results of our study and that of Alcazar and colleagues may be explained by differences in study design and study population. The use of the predetermined classification system of vascular morphology used by Alcazar and co-workers is dissimilar to the descriptive system used in our study, Alcazar and co-workers used power Doppler ultrasound[18] (which has a high ability to demonstrate tortuous irregular vessels[19,20]) whereas we used color Doppler ultrasound, and their study population was clearly different from ours with a higher proportion of cancers (36% vs. 13%), fewer

normal endometria (7% vs. 20%), and no fibroids. It is likely that their study population was a selected one, not a consecutive series. The thickness of the endometrium in their study was not reported with enough detail to allow comparison with endometrial thickness in our study. If the endometrium is thin, it is difficult to detect tiny vessels even with an ultrasound system with high Doppler sensitivity. In our study two-thirds of the endometria were < 15 mm.

The clinical usefulness of subjective evaluation of endometrial grey scale ultrasound morphology and vascularity may be limited in postmenopausal women, because they are more difficult to examine than women of fertile age. Their uterus is often in an upright position so that the angle between the insonating ultrasound beams and the endometrium is unfavorable, and a stenotic cervix sometimes prevents saline infusion (reported failure rate 10 - 26%)[8,10]. A weakness of subjective evaluation of endometrial grey scale ultrasound morphology and color or power Doppler findings in the endometrium is that these methods are completely subjective. Consequently, results are likely to be biased by clinical information. Color Doppler findings may also be biased by grey scale ultrasound findings. The reproducibility of subjective evaluation of endometrial grey scale ultrasound morphology and endometrial vascularity using color or power Doppler ultrasound should be determined, and standardized terms and definitions to describe findings are needed.

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Legends.

Figure 1. (a) regular endometrial-myometrial border, (b) irregular endometrial-myometrial border

Figure 2. (a) homogenous internal ehogenicity, (b) heterogeneous ehogenicity

Figure 3. Fluid in the uterine cavity (a) regular surface of a focal lesion, (b) irregular surface of a focal lesion

Table 1. Grey scale and color Doppler ultrasound findings in benign and malignant endometria

	Benign endometrium n = 83	Endometrial cancer n = 12	p-value
Grey scale morphology			
Assessment without fluid in the uterine cavity			
Endometrium ≥ 15 mm*, n (%)	20/72 (28%)	6/10 (60%)	0.15
Irregular endometrial-myometrial border**, n (%)	23/70 (33%)	6/11 (55%)	0.19
Hetreogeneous echogenicity***, n (%)	24/68 (35%)	7/10 (70%)	0.08
Assessment with intracavitary fluid (spontaneous or during saline infusion)			
Focal lesion[#], n (%)	68/76 (89%)	9/10 (90%)	1.0
Heterogeneous echogenicity[##], n (%)	21/67 (31%)	7/9 (78%)	0.01
Irregular surface[###], n (%)	22/64 (34%)	7/8 (88%)	0.006
No focal lesion[#], n (%)	8/76 (10%)	1/10 (10%)	1.0
Irregular endometrial myometrial border [‡], n (%)	0/6 (0%)	0/1 (0%)	1.0
Irregular surface of endometrium[‡], n (%)	1/6 (17%)	1/1 (100%)	0.29
Heterogeneous echogenicity of			

endometrium‡‡, n (%)	0/5 (0%)	1/1 (100%)	0.16
Vascular morphology			
Assessment without fluid in the uterine cavity (spontaneous or during saline infusion)			
Number of vessels visible			
No vessel†, n (%)	15/79 (19%)	1/12 (8%)	
One vessel†, n (%)	24/79 (30%)	3/12 (25%)	0.53
Two or more vessels†, n (%)	40/79 (51%)	8/12 (67%)	
Vascular branching			
Branching vessels seen††, n (%)	39/61 (64%)	10/11 (91%)	0.09
Irregular branching, n (%)	0/39 (0%)	1/10 (10%)	0.20

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*Unmeasurable endometrium in 13 cases

**Spontaneous fluid in the cavity in eight cases, the endometrial-myometrial border could not be seen with enough clarity in six cases,

*** Spontaneous fluid in the cavity in eight cases, the endometrium could not be clearly seen in seven cases, no information about echogenicity in two cases

Saline infusion failed in nine cases

In one case it was not possible to evaluate the echogenicity of the focal lesion

The surface of the lesion could not be evaluated properly because of suboptimal saline infusion in five cases

‡In two cases the examiner forgot to classify the endometrium

‡‡In two cases the examiner forgot to classify the endometrium, and in one case the endometrial ecogenicity could not be properly evaluated

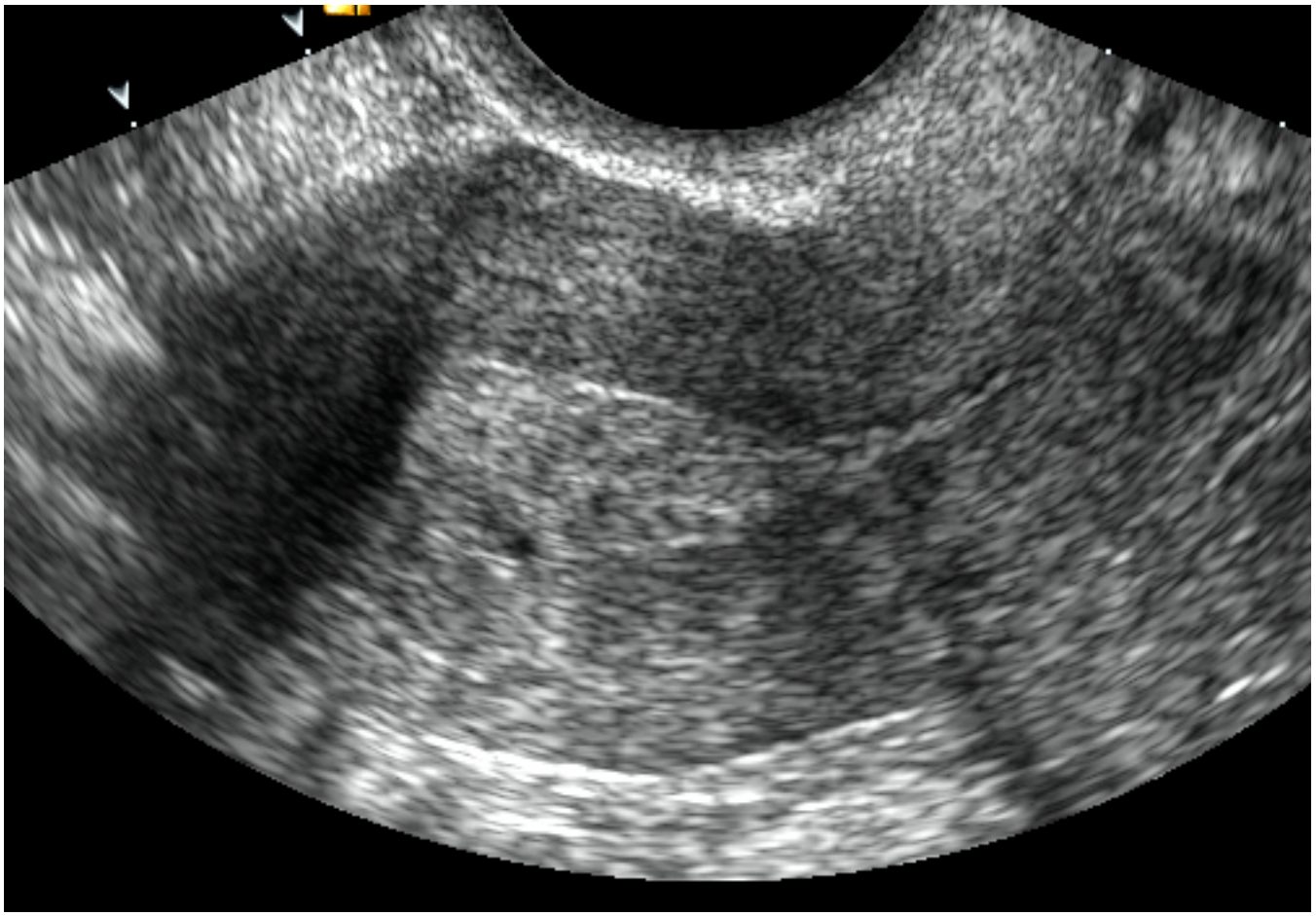
† Unsuccessful Doppler examination because of technical problems in four cases

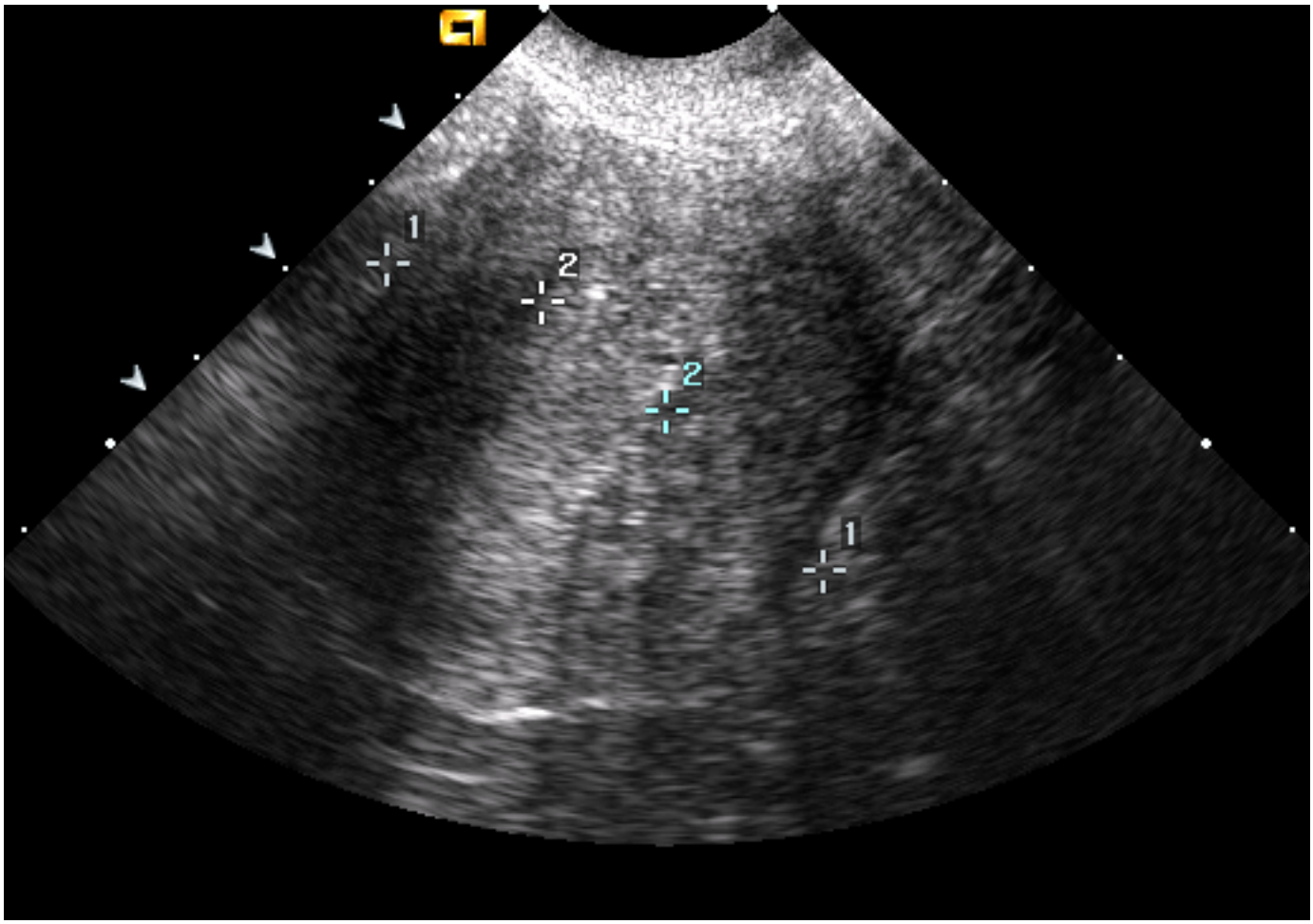
[††]In three cases branching could not be properly evaluated because of suboptimal Doppler examination

Table 2. Ultrasound findings in women with endometrial cancer

Stage	Endomertrial thickness, mm	Without fluid in the uterine cavity			With fluid in the uterine cavity	
		Endometrial-myometrial border	Echogenicity	Number of vessels	Surface of focal lesion/ endometrium	Ecogenicity of focal lesion/ endometrium
CAH	7	regular	regular	0	regular	regular
1a	unmeasurable	regular	regular	≥2	failed/suboptimal SIS	failed/suboptimal SIS
1a	unmeasurable	irregular	poor image quality	≥2	failed/suboptimal SIS	failed/suboptimal SIS
1a	20	irregular	irregular	1	failed/suboptimal SIS	failed/suboptimal SIS
1b	9	irregular	irregular	≥2	irregular	irregular
1b	13	regular	irregular	1	irregular	irregular
1b	15	irregular	irregular	1	irregular	irregular
1c	16	irregular	irregular	≥2	irregular	irregular
1c	20	regular	irregular	≥2	irregular	irregular
1c	32	irregular	irregular	≥2	irregular	irregular
1c	33	spontaneous fluid	spontaneous fluid	≥2	irregular	regular
2a	8	regular	regular	≥2	irregular	irregular

CAH = complex atypical hyperplasia, SIS = saline infusion sonography

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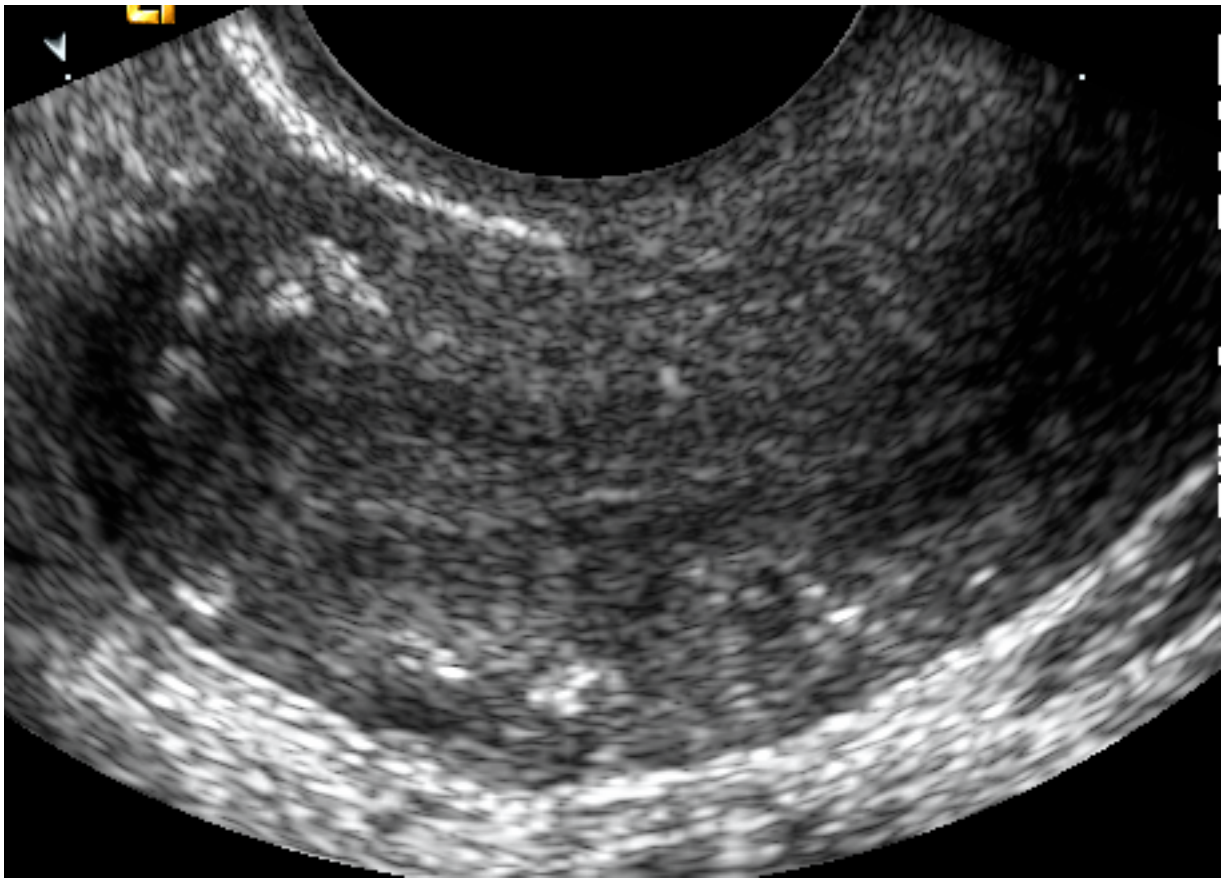

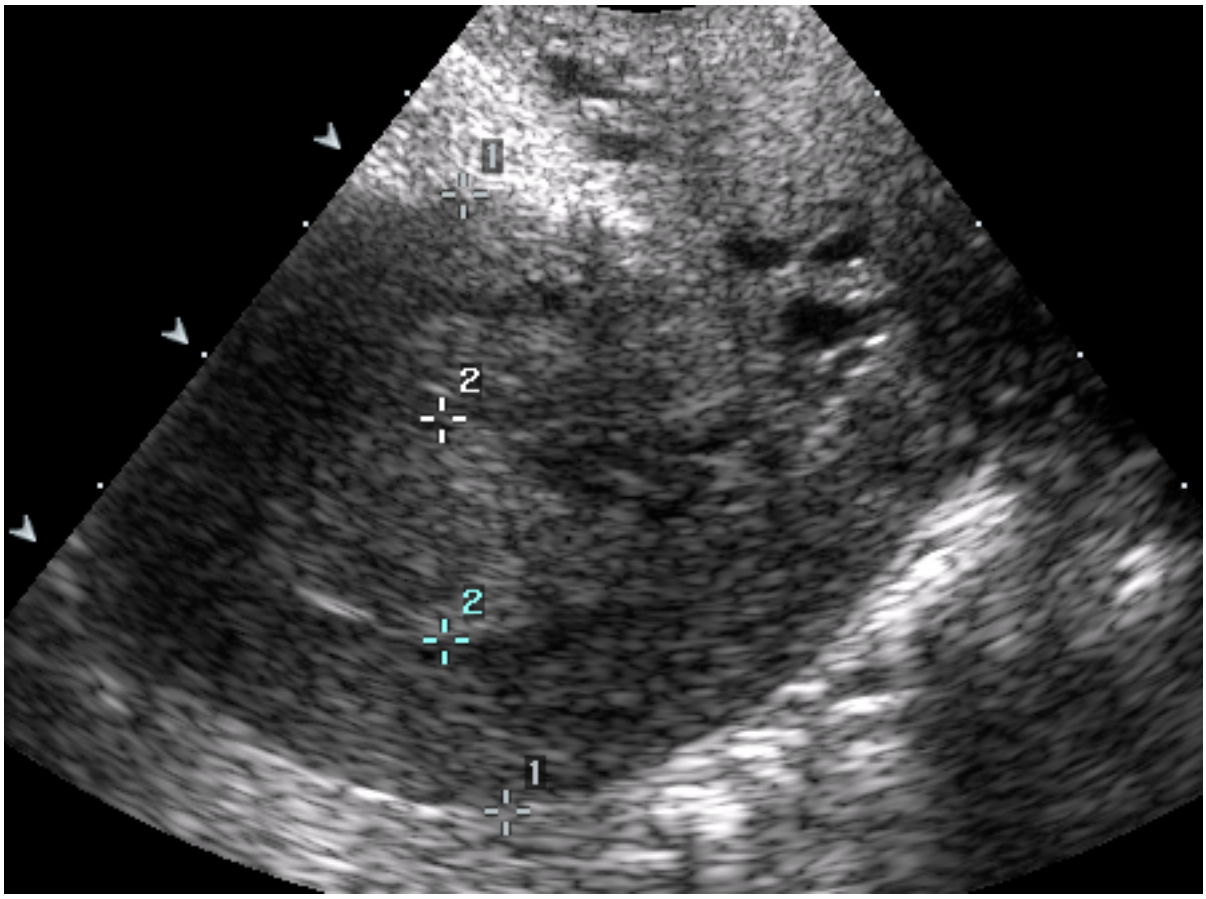
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