Question Mark Sign and Transvaginal Ultrasound Uterine Tenderness for the Diagnosis of Adenomyosis

A Prospective Validation

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Cover image article

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Abbreviations

2D, 2-dimensional; 3D, 3-dimensional; JZ, junctional zone; MUSA, Morphological Uterus Sonographic Assessment; NPV, negative predictive value; PPV, positive predictive value; TVUS, transvaginal ultrasound; US, ultrasound

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Objectives—To evaluate the diagnostic accuracy of the classic ultrasound (US) signs of adenomyosis, the question mark sign and transvaginal ultrasound (TVUS) uterine tenderness, in the diagnosis of adenomyosis.

Methods—This was a prospective study including 78 patients waiting for hysterectomy for uterine benign diseases and undergoing preoperative US examinations to evaluate all criteria for US diagnosis of adenomyosis as reported by the consensus statement of the Morphological Uterus Sonographic Assessment group. A US diagnosis of adenomyosis was made in the presence of 2 or more Morphological Uterus Sonographic Assessment features. Moreover, the question mark sign and TVUS uterine tenderness were evaluated. Ultrasound features were compared with the histologic examination, which was considered the reference standard for the diagnosis of adenomyosis. The Cohen κ coefficient was used to measure the accordance between US and histologic results. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each US feature were calculated.

Results—The prevalence of adenomyosis in the sample was 33.3%. The sensitivity, specificity, PPV, NPV, and accuracy of TVUS in the diagnosis of adenomyosis were 77%, 96%, 91%, 89%, and 90%, respectively. Myometrial heterogeneity was the most frequently encountered feature (100%) but showed low specificity (7%). The question mark sign and TVUS uterine tenderness showed sensitivity, specificity, PPV, NPV, and accuracy of 41%, 96%, 83%, 77%, and 69% and 69%, 65%, 66%, 81%, and 67%.

Conclusions—The question mark sign and TVUS uterine tenderness are useful tools for the diagnosis of adenomyosis.

Key Words—accuracy; adenomyosis; pelvic pain; question mark sign; transvaginal ultrasound; ultrasound

Adenomyosis is a benign condition of the uterus defined by the presence of endometrial glands and stroma within the myometrium.[1] Adenomyosis affects around 20% of women during their fertile age and may be associated with dysmenorrhea, menorrhagia, and infertility.[1,2] Adenomyosis lesions can be difficult to identify during surgery, and hysterectomy remains the most common treatment.[3,4] For this reason, an accurate noninvasive diagnosis becomes essential to treat patients who wish to retain their fertility and to plan conservative surgery or medical therapy.

A diagnosis of certainty can be posed only by a histologic examination.[5,6] Several studies have shown that transvaginal ultrasound (TVUS) can be considered the first-line imaging modality for studying adenomyosis because it is sensitive (75%–88%) and specific (67%–93%).[6–12] Magnetic resonance imaging is also an accurate, noninvasive modality for diagnosing adenomyosis, with specificity of 67% to 99% and high accuracy (85%–95%), but it is more expensive and less available.[6] Recently the Morphological Uterus Sonographic Assessment (MUSA) consensus statement proposed terms, definitions, and measurements that may be used to describe and report the ultrasound (US) features of the myometrium using grayscale, color Doppler, power Doppler, and 3-dimensional (3D) US imaging, with particular attention to 2 conditions: adenomyosis and fibroids.[13] Even though many US features are supposed to be associated with adenomyosis, there is no consensus regarding the most accurate imaging feature or combination of features for the US diagnosis of adenomyosis.[3,13] A particular shape of the uterine rime, called the question mark sign, has recently been described as a typical sign of adenomyosis associated with posterior deep infiltrating endometriosis,[14,15] and it has been included in the International Deep Endometriosis Analysis group statement.[16] Transvaginal US imaging is a dynamic examination,[17] allowing the operator to evaluate the tenderness of an examined anatomic structure by gentle pressure from the transducer. An enlarged and tender uterus, which is painful on mobilization, may suggest adenomyosis.[12] The TVUS uterine tenderness, which is the tenderness of the uterus during the gentle pressure from the transvaginal transducer, could be useful to rule out the presence of adenomyosis, which is often associated with painful uterine mobilization. This study aimed to establish the diagnostic accuracy of US features related to adenomyosis according to the MUSA statement and of 2 additional markers: the question mark sign and TVUS uterine tenderness.

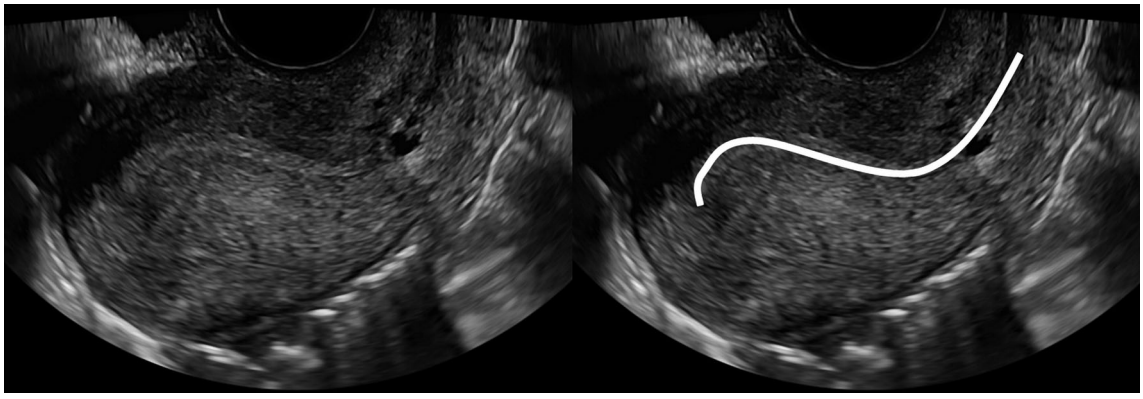
Materials and Methods

Study Design and Population

This was a cross-sectional observational study undertaken at our department between November 2014 and June 2016, enlisting 79 consecutive premenopausal women. Inclusion criteria were a diagnosis of a benign uterine condition (ie, adenomyosis, diffuse leiomyomatosis, fibroids, hysterocele, endometrial polyps, endometrial hyperplasia, or uterine prolapse) scheduled for hysterectomy. Exclusion criteria were a postmenopausal status, presurgical and postsurgical diagnoses of malignancies of the reproductive tract, and intraoperative morcellation of the uterus.

All patients signed informed written consent, and the study was approved by our local Ethics Committee (clinical trial ARC-ENDO, number 149/2014/0/Oss). A data sheet with most relevant information on the medical history of each patient was filled in: age, body mass index, last menstrual period, gravidity and parity, previous diagnosis of endometriosis, previous pelvic surgery, and the presence of various symptoms such as dysmenorrhea, menorrhagia, and dyspareunia.

Figure 1 Transvaginal US image showing the question mark shape of the endometrial stripe and the uterus.



A TVUS examination was performed by using a 2-, 3-, and 4-dimensional microconvex endocavity transducer with a frequency range of 4 to 9 MHz (Voluson E8; GE Healthcare, Zipf, Austria). All TVUS scans were performed by a single gynecologist (L.Z.) with 10 years of experience in gynecologic US. Images, clips, and 3D scans were saved and stored for further examination. The US examination of the myometrium was performed as indicated by the MUSA statement.[13] A US diagnosis of adenomyosis was made in the presence of 2 or more of the following parameters: asymmetry of the uterine walls, hyperechoic striae, anechoic myometrial cysts, hyperechoic islands, echogenic subendometrial lines and buds, and interruption or irregularities of the junctional zone (JZ). Power Doppler signals were considered suggestive of adenomyosis when the vessels were located inside the lesion.[13] The sonographer subjectively evaluated the globular shape of the uterus, the tenderness of the uterus with gentle pressure from the transvaginal transducer, and the presence of the question mark sign (Figure 1).[14,15] A 3D volume of the uterus was stored according to the method of Exacoustos et al[18] to evaluate the JZ (Figure 2). The diagnosis of adenomyosis was made when at least 2 of the examined US features were present.

Each patient underwent laparoscopic, laparotomic, or vaginal hysterectomy according to her clinical condition within 1 month from the US examination. A histologic examination was considered the reference standard for diagnosis and was performed in every patient except 1, for whom intraoperative morcellation was required.[5]

All histopathologic examinations were performed by a pathologist with greater than 10 years of experience, who was blinded to the US findings. For each uterus, a series of samples were taken, including the entire wall from the serosa to the endometrium. At least 3 samples were taken from both the posterior and anterior walls. The diagnosis of adenomyosis was made if endometrial stroma and glands were present within the myometrial layer. Adenomyosis was reported as diffuse if endometrial mucosa (glands and stroma) were scattered throughout the uterine walls (Figure 3A) or focal if a hypertrophic and distorted endometrium and myometrium were seen within the regular myometrium (Figure 3B). The degree of invasion was reported as M1 if limited to the internal half of the myometrium (Figure 3C) or M2 if the full thickness of the myometrium was involved (Figure 3D). Additionally, an immunochemical test with the CD10 antibody was performed to highlight the ectopic endometrium.[19] For this study, only the presence or absence of adenomyosis was considered, not the depth of infiltration.

Statistical Analysis

A sample size estimation was performed to assess the diagnostic accuracy (proportion of true-positive and true-negative results) for the question mark sign and tenderness. Assuming that the accuracy of both tests was equal to 0.75, and clinically acceptable precision was no greater than ± 0.1, we calculated that the minimum number of patients to enroll in the study was 73.

All data were recorded in a dedicated Excel file (Microsoft Corporation, Redmond, WA). Patients were divided into 2 groups, according to the presence or absence of adenomyosis on the histologic examination. The mean and standard deviation were calculated for the continuous variables by the Student t test. Relative frequencies were calculated for categorical variables by the χ^2 test or Fisher exact test. $P < .05$ was considered

Figure 2 Three-dimensional US image showing the rendering of the coronal view of the uterus. This technique is necessary to evaluate the JZ (arrow).



statistically significant. A comparison of gravidity and parity was divided into 3 classes. Accordance between TVUS and the histologic diagnosis was measured by the Cohen κ coefficient. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (area under the receiver operator characteristic curve) of each TVUS variable were calculated. Analyses were performed by using SPSS version 16 software (IBM Corporation, Armonk, NY).

Results

Seventy-nine patients were enrolled in this study. One patient was excluded because the uterus weighed more than 1 kg, and it was morcellated during laparoscopic hysterectomy. For this reason, the total number of patients considered in the statistical analysis was 78.

Forty of 78 patients (51.2%) underwent surgery for symptoms related to leiomyomatosis (ie, bleeding

Figure 3 On a histologic examination, adenomyosis is classified as diffuse (**A**) when the endometrial glands or stroma are distributed diffusely within the myometrium and focal (**B**) when circumscribed nodular aggregates are seen. The degree of invasion was defined as M1 when limited to the internal half of the myometrium (**C**) or M2 when the full thickness of the uterus was involved (**D**).

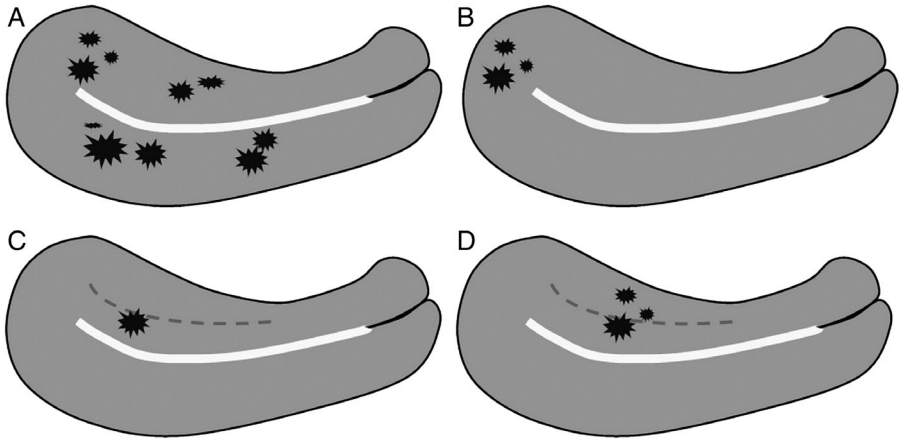


Table 1. Clinical Characteristics of the Patient Population According to the Presence or Absence of Adenomyosis at the Histologic Examination

	Adenomyosis at Histologic Examination (n = 78)		
Characteristic	**Present (n = 26)**	**Absent (n = 52)**	***P***
Age, y	48.2 ± 3.9 (15)	47.1 ± 3.9 (17)	NS
Body mass index, kg/m^2	24.6 ± 1.1 (4.3)	25.5 ± 1.0 (4.5)	NS
Parity			NS
0	10 (38.4)	12 (23.1)	
1	6 (23.2)	16 (30.8)	
>1	10 (38.4)	24 (46.1)	
Gravidity			NS
0	8 (30.8)	10 (19.2)	
1	6 (23.1)	14 (26.9)	
>1	12 (46.1)	28 (53.9)	
Uterine volume, mL	230 ± 189	295 ± 306	NS

Data are presented as mean ± SD (range) and number (percent). NS indicates not significant.

Table 2. Clinical Symptoms and Association With Previous Pelvic Surgery and Endometriosis According to the Presence or Absence of Adenomyosis at the Histologic Examination

	Adenomyosis at Histologic Examination (n = 78)		
Symptom	**Present (n = 26)**	**Absent (n = 52)**	***P***
Dysmenorrhea	20 (77)	26 (50)	NS
Dyspareunia	12 (46)	16 (31)	NS
Menorrhagia	22 (85)	26 (50)	.045
Previous pelvic surgery	12 (46)	24 (46)	NS
Presence of endometriosis	8 (30)	8 (15)	NS

Data are presented as number (percent). NS indicates not significant.

refractory to medical therapy, bloating, and pain), 24 (30.8%) for symptoms related to adenomyosis (ie, bleeding and pain), 10 (12.8%) for uterine prolapse, and 4 (5.1%) for fibroids with an atypical US appearance. Hysterectomy was performed by laparoscopy in 62 of 78 (79.5%) patients, laparotomy in 6 (7.7%), and the vaginal route in 10 (12.8%).

Histologic examinations were performed in 78 patients. Adenomyosis was present in 26 patients (33.3%); among them, 16 of 26 (61.5%) also had fibroids, and 6 (23.1%) also had adenomyomas. Among the 52 of 78 (66.6%) patients without adenomyosis, 41 (52.5%) had fibroids; 1 (1.2%) had spindle-like cell neoplasia with myogenic differentiation and a mitotic index of less than 4 mitoses per 10 high-power fields; and 10 (12.8%) showed hysterocele that was not associated with myometrial disease.

The clinical characteristics of the cohort are shown in Table 1. There were no statistically significant differences between groups with and without adenomyosis for age, body mass index, parity, and gravidity.

Symptoms and correlations with previous pelvic surgery or endometriosis are shown in Table 2. Only menorrhagia was more frequent ($P = .045$) in patients with adenomyosis. All diagnoses of suspected endometriosis nodules by TVUS were confirmed by histologic examinations.

Among the 26 patients with positive histologic results, 20 had US features of adenomyosis (sensitivity, 77%); among the 52 patients with negative histologic results, 50 had no US features of adenomyosis (specificity, 96%). Among the 22 patients with US features of adenomyosis, 20 had true-positive results (PPV, 91%); among the 56 patients with no US features of

Table 3. Ultrasound Features According to the Presence or Absence of Adenomyosis at the Histologic Examination

	Adenomyosis at Histologic Examination (n = 78)			
Feature	**Present (n = 26)**	**Absent (n = 52)**	**NA**	***P***
Globular shape	20 (77)	28 (54)	0	NS
Heterogeneus myometrium	26 (100)	48 (92)	0	NS
Fan-shaped striations	14 (54)	2 (4)	0	.001
Myometrial cysts	8 (31)	4 (8)	0	NS
Poorly defined interface	22 (85)	22 (42)	1	.037
Question mark sign	10 (38)	2 (4)	2	.005
Wall asymmetry	16 (62)	4 (8)	20	.001
Tenderness	18 (69)	18 (35)	0	.044
Doppler	8 (31)	4 (8)	2	.011
$JZ_{max} \geq 8$ mm	8 (31)	0 (0)	13	.015
$\Delta JZ \geq 4$ mm	12 (46)	4 (8)	13	.027
JZ interruption	14 (54)	4 (8)	13	.008

Data are presented as number (percent). NA indicates nonassessable; and NS, not significant.

Table 4. Diagnostic Capacities of Each US Features Associated With the Diagnosis of Adenomyosis

Feature	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Globular shape	77	46	42	80	61.5
Asymmetry	80	70	72	78	78.9
Heterogeneous myometrium	100	7	35	100	53.9
Poorly defined interface	85	56	50	88	70.3
Fan-shaped striations	54	96	88	81	75.0
Myometrial cysts	30	92	67	73	61.5
Question mark sign	41	96	83	77	68.8
Tenderness	69	65	66	81	67.3
$JZ_{max} \geq 8$ mm	40	99	100	73	70.0
JZ interruption	70	88	78	82	78.8
ΔJZ	60	87	75	76	73.8
Doppler	55	88	66	82	71.5

adenomyosis, 50 had true-negative results (NPV, 89%). The global accuracy of TVUS was 90%. The κ analysis showed an accordance of greater than 70% between histologic results and TVUS (κ = 0.760).

Table 3 shows the statistical significance of each US feature included in the study according to the presence or absence of adenomyosis at the histologic examination. Hyperechoic islands and subendometrial lines and buds were not present in the examined samples. Table 4 shows the diagnostic capabilities of each US marker. A heterogeneous myometrium showed the highest sensitivity and NPV (both 100%). The most specific markers were a maximum thickness of the JZ (JZ_{max}) of 8 mm or greater, fan-shaped striations, and the question mark sign (99%, 96%, and 96%, respectively), with PPVs 100%, 88%, and 83%.

Discussion

In this study, we strictly applied the MUSA indications[13] to prospectively validate the importance of each of the main US features in the diagnosis of adenomyosis in a sample of 78 hysterectomies. Moreover, we assessed the question mark sign and TVUS uterine tenderness, showing that diagnostic accuracy was greater than 60%.

In the study, 2-dimensional (2D), 3D, and power Doppler US features were associated with the diagnosis of adenomyosis, achieving superior diagnostic capabilities to those of Kepkep et al[20] and similar results as those obtained in other studies, which reported sensitivity of up to 89% and specificity of up to 100%.[21–23] According to Bazot et al,[23] TVUS is very specific but prone to produce false-negative results, which is the best condition for a test aiming to diagnose a benign condition. Furthermore, our data showed that the diagnostic accuracy of TVUS was reduced in the presence of comorbidities, as already demonstrated, such as in the presence of fibroids of the uterus[8,23]: all US diagnostic mistakes (4 false-negative and 2-false-positive results) were made in patients affected by fibroids. A recent meta-analysis of 8 trials reported sensitivity and specificity of US-diagnosed adenomyosis to be as high as 92% and 88%, respectively.[3] Our data showed similar sensitivity but greater specificity. In our study, we found similar specificity but greater sensitivity than Kepkep et al,[20] who found that the sensitivity and specificity of TVUS for the diagnosis of adenomyosis were 65.0% and 97.5%, respectively. These outcomes suggest that the addition of these new markers may improve the diagnostic accuracy for adenomyosis.

The question mark sign has been proposed by our group as a marker of adenomyosis that is strongly associated with posterior deep infiltrating endometriosis.[14,15] In this study, the question mark sign proved to be an independent marker of adenomyosis from the presence of endometriosis. The question mark sign also showed great specificity (96%) and PPV (83%) for the 2D US features. In this population, only 4 of the 10 patients affected by posterior deep infiltrating endometriosis showed an association with the question mark sign that was not significant. These outcomes suggest that the question mark sign might have a wider application in diagnosing adenomyosis than previously thought.

To our knowledge, this work was also the first prospective study proposing TVUS uterine tenderness as a marker of adenomyosis, showing an 81% NPV and 67.3% accuracy. Original descriptions of adenomyosis reported an association between the disease and "a great deal of pain." Several later studies reported similar findings,[24–26] but others did not confirm the prevalence of pain in women with adenomyosis.[27–29] A possible confounder in the interpretation of pain could be the presence of coexisting endometriosis, which is a common cause of pain in women of reproductive age. The use of TVUS, as a dynamic examination,[17] can show whether the pain is related to gentle pressure and mobilization of the uterus and can also show tenderness that is related to a different location of endometriosis, if present.

Among the US features of adenomyosis, the most specific were a JZ_{max} of 8 mm or greater, fan-shaped striations, and the question mark sign. Our outcomes were comparable with previous studies for the high specificity of fan-shaped striations[20–23] and myometrial cysts,[18] whereas the JZ_{max} in our study showed better values than previously shown.[18] A heterogeneous myometrium is once again the most sensitive marker, but with very low specificity.[3,23] The main problem with the use of histologic results for the diagnosis of adenomyosis is the heavy selection bias incurred; indeed, we had a very high percentage of leiomyomatosis, which is typically associated with a

heterogeneous myometrium at TVUS. The prevalence of adenomyosis in our sample was 33.3%, which was consistent with the literature, in which mean values of 20% to 30% in patients undergoing hysterectomy for various indications were given.[27,30,31]

Differently from the literature,[10,11,13] an association between an increased uterine volume and adenomyosis was not found. In this regard, it must be considered that patients without adenomyosis were often affected by leiomyomatosis, which also increases the uterine volume. Nevertheless, Exacoustos et al[18] showed a significant correlation between a decreased uterine volume and adenomyosis in comparison with the absence of uterine fibroids.

The strengths of this study were the prospective design and the use of high-end US equipment by a single operator, minimizing interobserver variability. Another strength was the comparison between US and the histologic examination, which is considered the reference standard for the diagnosis of adenomyosis.[5] It is noteworthy that all endometriotic nodules that were suspected by TVUS were confirmed histologically. Moreover, the choice of using extensive inclusion criteria reduced the selection bias and allowed us to evaluate adenomyosis also in the presence of numerous potentially confounding variables, such as fibroids, which often reduce diagnostic accuracy.[8,23] The extensive inclusion criteria could also have been a potential weakness of this study, as confounding factors, such as fibroids and hormonal treatments, prevented some features from being detectable in several patients. A potential limitation of the study was the inclusion of only patients undergoing hysterectomy, creating a selection bias, as patients who choose surgery are more symptomatic than those who do not. Another weakness was that although a sample size estimation was performed to assess the diagnostic accuracy of the question mark sign and site-specific tenderness, the study was not powered to provide such accurate estimates of sensitivity and specificity, which would require a much larger trial.

In conclusion, this study confirms the accuracy of TVUS in diagnosing adenomyosis, strengthening the role of TVUS as the first-line examination modality for its effectiveness, safety, and cost. Moreover, we evaluated US features of adenomyosis in a sample with many confounding factors, providing an update of the diagnostic capabilities of TVUS that could be applied in everyday clinical practice. The new proposed features, the question mark sign and TVUS uterine tenderness, have shown promising results and have proven useful for the diagnosis of adenomyosis. Further prospective studies are needed to demonstrate their efficacy in larger populations.

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