



Adenomyosis: Transvaginal Ultrasound and Imaging Innovations for Diagnosis

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Abstract

Purpose of Review There have been considerable advances in recent years using transvaginal sonography (TVUS) to diagnose adenomyosis. The diagnosis, however, is highly dependent upon the recognition of specific sonographic features as defined by the Morphological Uterus Sonographic Assessment (MUSA) statement. The main goal of this article is to review the literature in the last 5 years on specific TVUS features and imaging innovations for its diagnosis. We also sought to identify studies that evaluated the association between imaging-diagnosed adenomyosis and other clinical conditions.

Recent Findings Direct and indirect imaging signs of adenomyosis have been characterized for diagnosis. Although sonographic features and signs such as junctional zone ≥ 8 mm, question mark sign, fan-shaped striations, uterine biometric parameters, and uterine tenderness during the exam have been evaluated for diagnostic accuracy, no conclusions as yet can be made regarding the best TVUS imaging feature or a combination thereof for its diagnosis. Adenomyosis as suggested by TVUS findings is highly associated in patients with endometriosis and infertility. In particular, findings of external adenomyosis compared to internal adenomyosis are strongly correlated to patients with deep endometriosis. Studies suggest that scoring systems utilizing multiple sonographic observations or sonographic observations combined with patient clinical factors may improve accuracy. Imaging innovations using sonoelastography and contrast-enhanced ultrasound hold promise, notably in differentiating adenomyoma from leiomyoma.

Summary The accuracy of various TVUS imaging features and technologies has recently been evaluated for the diagnosis of adenomyosis. Improved recognition and reporting of these patterns will be key to confirming and clarifying the associations of adenomyosis to other conditions such as endometriosis and infertility that may direct clinical management and treatment.

Keywords Adenomyosis · Transvaginal ultrasound · Diagnostic accuracy · Clinical associations · Imaging innovations · Scoring systems

Introduction

Adenomyosis, a benign gynecologic condition, is characterized by the presence of ectopic endometrial gland and/or stromal tissue within the myometrium [1]. Patients affected by the condition may present with abnormal uterine bleeding, painful periods, dyspareunia, and infertility [2]. Historically, confirmation with histopathology from a review of the

hysterectomy specimen is the gold standard to diagnose the disease. More recently, however, there have been significant advances in the use of noninvasive imaging modalities which can help plan medical or surgical therapy. This is particularly helpful for those wishing to retain their fertility [3].

Transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) are the primary modalities used for the diagnosis of adenomyosis. Both have similar diagnostic accuracy [4]. Because MRI is associated with higher costs that limit accessibility, the focus has been placed on the use of TVUS for non-invasive diagnosis. A consensus by an international expert panel to standardize the terminology on the TVUS features for the diagnosis of adenomyosis known as the Morphological Uterus Sonographic Assessment (MUSA) statement was published in 2015 [5]. TVUS features identified by this group include globular uterus, asymmetrical thickening,

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myometrial cysts, hyperechoic islands, subendometrial lines and buds, and irregular junctional zone. A subsequent systematic review and meta-analysis in 2017 evaluating the efficacy of 2D TVUS and 3D TVUS revealed that both are associated with high accuracy with a pooled sensitivity of 84% and 89% and specificity of 64% and 56% [6]. TVUS features of heterogeneous myometrium and globular uterus on 2D TVUS were noted to have the highest sensitivity for the diagnosis. At that time, it was difficult to make conclusive statements concerning other specific TVUS features because of the large variability observed between the studies. Larger well-designed studies were needed to standardize and validate specific TVUS features for the diagnosis of the disease.

The main goal of this article is to review the literature since the systematic review above (i.e., in the last 5 years) to determine what new findings are available regarding the use of TVUS for the diagnosis of adenomyosis. We also include recent studies that evaluate innovations in imaging, the prevalence of the disease, and the implications of adenomyosis on other clinical conditions.

Methods

Search Strategy

A librarian performed a thorough search of PubMed/MEDLINE for all available current literature in English published in the last 5 years, using the search terms “adenomyosis” and “ultrasound” and “adenomyosis” as well as “adenomyosis” and “imaging” as keywords to recover all possible publications using the PubMed database. MeSH terms used included (("Adenomyosis"[MeSH Terms] OR ("Adenomyosis"[MeSH Terms] OR "Adenomyosis"[All Fields] OR "adenomyoses"[All Fields])) AND ("Diagnostic Imaging"[MeSH Terms] OR "Diagnostic Imaging"[MeSH Subheading] OR "Ultrasonography"[MeSH Terms] OR "Ultrasonics"[MeSH Terms] OR ("Diagnostic Imaging"[All Fields] OR ("Diagnostic Imaging"[MeSH Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "Diagnostic Imaging"[All Fields] OR "Diagnostic Imaging"[MeSH Terms] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]))) OR ("Ultrasonics"[MeSH Terms] OR "Ultrasonography"[MeSH Terms]) OR (("ultra"[All Fields] AND ("sound"[MeSH Terms] OR "sound"[All Fields] OR "sounded"[All Fields] OR "soundings"[All Fields] OR "sounds"[All Fields] OR "sound s"[All Fields] OR "sounding"[All Fields])) OR ("Diagnostic Imaging"[MeSH Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "Diagnostic Imaging"[All Fields] OR "ultrasound"[All Fields] OR "Ultrasonography"[MeSH Terms] OR "Ultrasonography"[All Fields] OR "Ultrasonics"[MeSH

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Selection Criteria, Eligibility, and Data Extraction

Both retrospective and prospective studies were included. We included studies that identify the prevalence of adenomyosis, that assess the accuracy of TVUS for the diagnosis of adenomyosis with and without sonoelastography, contrast-enhanced ultrasound, 3D-transvaginal ultrasound, and color Doppler. We also included studies that correlated ultrasound TVUS features of adenomyosis with clinical features (endometriosis, subfertility, and scoring systems for diagnosis of adenomyosis). We excluded single case reports and review articles.

All three authors abstracted and reviewed the data to confirm accuracy.

Results

Prevalence of Adenomyosis

Multiple studies have evaluated the prevalence of adenomyosis using ultrasound to diagnose the disease outside of surgery. In 2012, Naftalin et al. identified adenomyosis in 20.9% (95% CI: 18.5–23.6%) of women attending a gynecologic clinic [7]. A more recent retrospective cross-sectional study performed at a tertiary center reported that in symptomatic women undergoing TVUS, the prevalence for adenomyosis using one of the MUSA criteria was 12% (95% CI: 9–15%) [8]. In patients with subfertility, a systematic review noted a similar overall pooled prevalence of 10% (95% CI: 6–15%) [9]. The pooled prevalence was noted to be greater in this cohort when coexisting endometriosis was found (18%; 95% CI: 9–28%) [9].

Adenomyosis and Endometriosis

Recent studies evaluated the association between adenomyosis and endometriosis. Historically, TVUS features of adenomyosis have been found in 21–42% of patients undergoing surgery for endometriosis [10, 11]. More recently, higher

associations have been noted: 53% of patients with ovarian endometrioma [12] and 89% of patients undergoing laparoscopic surgery for endometriosis had imaging observations for adenomyosis [13].

Adenomyosis has been categorized into two types: external adenomyosis or adenomyosis of the outer myometrium that corresponds to lesions separated from the junctional zone; and internal adenomyosis or adenomyosis of the inner myometrium that is characterized by endometrial implants noted extending into the myometrium and thickening of the junctional zone. Importantly, women with external adenomyosis were more likely to have associated endometriosis compared to women with internal adenomyosis as diagnosed on MR [14••]. Clinical profiles of women with imaging observations of external adenomyosis were evaluated and found to be younger and more likely to be nulliparous compared to women with internal adenomyosis who were more likely to have had a history of uterine surgery. This study suggests a difference in pathogenesis and phenotypes of the two types of adenomyosis and their association with concomitant endometriosis that may provide future treatment directions.

TVUS Features for the Diagnosis

The use of transvaginal ultrasound for the diagnosis of adenomyosis continues to be associated with high specificity for adenomyosis detection. A retrospective study performed by Zannoni et al. demonstrated that the accuracy of TVUS for the detection of adenomyosis on initial radiology reports was 67.2% (positive predictive value (PPV): 77.8%, negative predictive value (NPV): 66.7%, sensitivity: 10.9%, and specificity: of 98.3%). In this study, retrospective blinded reinterpretation of cases in which images were available for review demonstrated significant improvement from a sensitivity of 12.2 to 53.0%. This suggests that a

specific search for adenomyosis observations is required for diagnostic accuracy [15].

In 2015, a consensus opinion by Van den Bosch et al. created the MUSA (Morphological Uterus Sonographic Assessment) statement. The primary aim was to create terminology to describe the myometrium and myometrial lesions on ultrasound. One of the secondary aims was to use the terminology to describe myometrial lesions of adenomyosis [5]. In 2021, a new consensus was published to revise the MUSA features of adenomyosis [16]. In this consensus, the MUSA features were divided into two categories: direct and indirect. Direct features are thought to be findings that suggest the actual presence of ectopic endometrial tissue within the myometrium. These include myometrial cysts, hyperechoic islands, and echogenic subendometrial lines and buds. Indirect features are thought to be findings that result from the presence of endometrial tissue within the myometrium. These include a globular uterus, asymmetrical myometrial thickening, fan-shaped shadowing, translesional vascularity, irregular junctional zone, and interrupted junctional zone. The evaluation of the junctional zone, requiring expertise in 3D ultrasound, was highlighted as an important feature, particularly in cases of uncertainty in the TVUS diagnosis. Further research focus on this feature has been emphasized.

In addition to the MUSA consensus paper, there have been studies looking at other ultrasound features for the diagnosis of adenomyosis (Table 1). The question mark sign is one of the features that has been found to be a good and independent marker of adenomyosis with accuracy: 69%, sensitivity: 41%, specificity: 96%, PPV: 83%, and NPV: 77%. Compared to the question mark sign, uterine tenderness during the TVUS exam had a slightly lower accuracy (accuracy: 67.3%; sensitivity: 69%, specificity: 65%, PPV: 66), but a high negative predictive value (81%). In the same study, overall TVUS showed excellent accuracy: 90%, sensitivity: 77%, specificity: 96%, PPV: 91%, and NPV: 89%.

Table 1 Studies evaluating TVUS features and associated accuracy for the diagnosis of adenomyosis

TVUS feature or combinations of features	Study author, year	Confirmation of diagnosis of adenomyosis	Sensitivity	Specificity	Accuracy	Positive predictive value (PPV)	Negative predictive value (NPV)
Junctional zone_{max} ≥ 8 mm	Zannoni et al. (2020)	Histology	40%	99%	70%	100%	73%
Fan-shaped striations	Zannoni et al. (2020)	Histology	54%	96%	75.0%	88%	81%
Question mark sign	Zannoni et al. (2020)	Histology	41%	96%	68.8%	83%	77%
Heterogeneous myometrium	Zannoni et al. (2020)	Histology	100%	7%	53.9%	35%	100%
Uterine tenderness	Zannoni et al. (2020)	Histology	69%	65%	67.3%	66%	81%
Biometry:	Raimondo et al. (2022)	Ultrasound	70%	71%	75%	NR	NR
APD ≥ 39.55 mm (95% CI: 36.2–42.8) + LD/APD ratio ≤ 2.05 (95% CI: 1.96–2.13)			70%	70%	72%		

When other specific TVUS features of adenomyosis were evaluated, the most specific were a $JZ_{\max} \geq 8$ mm (accuracy: 70%, sensitivity: 40%, specificity: 99%, PPV: 100%, NPV: 73%), fan-shaped striations (accuracy: 75%, sensitivity: 54%, specificity: 96%, PPV: 88%, NPV: 81%), and the question mark sign (accuracy: 68%, sensitivity: 41%, specificity: 96%, PPV: 83%, NPV: 77%). Heterogeneous myometrium was the most sensitive but had an exceptionally low specificity (accuracy: 53.9%, sensitivity: 100%, specificity: 7%, PPV: 35%, NPV: 100%) [17•].

The finding of greater than 210° angle of uterine flexion on TVUS has also been noted to be more prevalent in patients with adenomyosis diagnosed using at least two or more of the MUSA criteria compared to those without adenomyosis (25.0% vs. 6.8%; $p < 0.015$) [18]. In addition, the use of multiple biometric parameters has been evaluated [19]. The optimal cutoff points for the biometric parameters, however, could not be established in their cohort. Among the biometric parameters, anteroposterior diameter (APD) ≥ 39.55 mm (95% CI: 36.2–42.8; sensitivity: 70%, specificity: 71%, and accuracy of 75%) and LD/APD ratio ≤ 2.05 (95% CI: 1.96–2.13; sensitivity: 70%, specificity: 70%, and accuracy: 72%) showed the best combination of sensitivity and specificity. It should be noted that even though the angle of uterine flexion and the use of uterine biometry could potentially be used for the diagnosis of adenomyosis, confirmation of findings with histopathology is still needed for validation.

Innovations in TVUS Imaging for Adenomyosis

Sonoelastography

Recent original research articles—ten in the last 5 years—addressed the application of sonoelastography in adenomyosis [20–29]. Of these, one examined both strain elastography (SE) and shear wave elastography (SWE) [20], two examined SWE only [24, 29], and the remainder SE only.

Sonoelastography consists of two main types, strain elastography (SE) and shear wave elastography (SWE). Most SE systems utilize a manual transducer compression technique and measure tissue elasticity along the axis of compression, although strain can be created by an acoustic impulse emitted from the transducer (acoustic radiation force impulse or ARFI). In SWE, ARFI is commonly utilized to induce tissue displacement and the speed of shear waves perpendicular to the applied displacement is measured [30].

Sonoelastography has been used to differentiate adenomyosis from leiomyoma. A study that evaluated both SE and SWE demonstrated a significant difference in elastography scores that allowed discrimination between adenomyosis (stiffest), leiomyoma, and control myometrium (least stiff) [20]. Two additional studies showed similar findings with

SE only [21, 23]. Similarly, a small study presenting both grayscale and SE images to junior and senior observers showed good interobserver agreement in the discrimination of adenomyosis from leiomyoma, with an improved agreement with elastography compared to gray-scale alone [25]. Additionally, one article showed an ability to discriminate adenomyosis from leiomyoma when concomitantly present in the same specimen [24].

Other studies had conflicting findings, however. Two articles utilizing only SWE found a significant stiffness difference between adenomyosis and control myometrium but failed to find a difference between adenomyosis and leiomyoma [22, 29]. Larger well-controlled trials would be helpful to determine the role of elastography in the diagnosis of adenomyosis.

Studies on elastography of the internal os in patients with dysmenorrhea demonstrated interesting observations. One group using SE found a relationship between stiffness of the internal cervical os and intensity of menstrual pain with a subsequent study showing that stiffness of the internal cervical os and menstrual pain were associated with the presence of adenomyosis [26]. Elasticity using SE was noted to be improved in patients with adenomyosis who were treated with GnRH analog therapy and was noted to be associated with spontaneous pregnancy [28].

Contrast-Enhanced Ultrasound (CEUS)

Several articles have been published on the utilization of microbubble contrast ultrasound to evaluate the efficacy of ablative therapies for adenomyosis including high-intensity focused ultrasound (HIFU), microwave ablation, and radiofrequency ablation or the use of microbubble contrast to augment the ablative effect of HIFU. Commonly available microbubble ultrasound contrast agents differ from iodinated and gadolinium-based agents utilized in CT and MR respectively in that they are strictly intravascular with no interstitial diffusion. Enhancement patterns, particularly in the delayed phase, are different in CEUS compared to CT and MR.

We identified only a single study by Zhang et al. that evaluated the diagnostic efficacy of CEUS in differentiating atypical focal adenomyosis from leiomyoma [31]. In this study, adenomyomas demonstrated short linear vascular enhancement in 57%, gradual peripheral to central enhancement in 43%, and peripheral ring hyperenhancement in none. Among leiomyomas, 27% had short linear vascular enhancement, 43% had gradual peripheral to central enhancement, and 30% had circumferential hyperenhancement. These enhancement patterns grouped together showed a statistically significant difference in enhancement mode between adenomyoma and leiomyoma. Other statistically significant qualitative differences included uneven contrast distribution and unclear boundaries more commonly seen in adenomyoma. After analyzing time-intensity curves, only

temporal variability of enhancement was statistically greater in adenomyoma than in leiomyoma. Furthermore, logistic regression analysis identified four independent risk factors for identifying focal adenomyosis: short linear vessels first enhanced perfusion pattern, uneven contrast agent distribution, unclear post-contrast boundary, and lesion temporal variability > 9.5 s. The odds ratio (OR) for lesion temporal variability > 9.5 s was the largest. The model's sensitivity for detecting adenomyoma was 98%, and the specificity was 70%. Similar to elastography, further research is needed to determine if CEUS would be helpful in its use for the diagnosis of adenomyosis.

3D Transvaginal Ultrasound

Five original research articles were identified on the use of 3D TVUS in adenomyosis [32–36]. A retrospective study of adenomyosis diagnosed by 2D/3D TVUS based on the presence of at least three MUSA signs demonstrated that adenomyosis was more prevalent in women undergoing surgery for endometriosis compared to those who continued conservative management [36]. Additionally, a higher risk of infertility was associated with five or more sonographic signs of adenomyosis, regardless of the severity of endometriosis. The specific impact of the addition of 3D to 2D imaging was, however, not evaluated.

High agreement between 2 and 3D has been demonstrated in cases of uterine myoma and adenomyosis, with a κ value of 0.8 and 0.74, respectively [32]. A significant statistical relationship existed between the quality of the image obtained and the thickness of the endometrium. A thin endometrium was associated with a poor 3D image. The coronal plane was difficult to obtain if the size was < 7.38 mm, suggesting that TVUS evaluation should be performed in the late follicular or secretory phase.

Specific imaging features using 3D TVUS have been evaluated [33]. An interrupted junctional zone was the most common observation of adenomyosis on 3D TVUS at 88%, followed by heterogeneous myometrium at 84%, and echogenic buds at 63% on 2D, > 4 mm JZ difference at 56% on 3D. Patients with severe dyspareunia had more poorly defined JZ than those without severe dyspareunia. On 3D TVUS, patients with abnormal uterine bleeding (AUB) showed more irregular and poorly defined JZ than those without AUB. Sonographic signs of adenomyosis remained significantly associated only in patients > 30 years of age with AUB. When comparing the type of adenomyosis, patients with diffuse adenomyosis were older than patients with focal adenomyosis of the inner myometrium, focal adenomyosis of the outer myometrium, and those without adenomyosis. In addition, all patients with diffuse adenomyosis presented with infertility and AUB, and these frequencies were significantly higher than those in patients with focal or no adenomyosis.

Expert and non-expert recorded 2D/3D volumes have been evaluated [34]. This study found good inter-rater agreement which improved over time for the 2D diagnosis of adenomyosis. The 3D agreement was poor, and 3D junctional zone measurements did not improve the agreement. Furthermore, non-expert acquired images had inferior image quality. In a separate article, the sensitivity/specificity of 2D TVUS was 72/76% compared to 69/86% for 3D utilizing hysterectomy specimens as the gold standard [35]. This difference was not significant, although the specificity of 3D nearly reached statistical significance (p 0.06). The most accurate 3D feature noted in this study was junctional zone irregularity ($JZ(\max) - JZ(\min) \geq 5$ mm). A combination of two or more 2D and two or more 3D features was highly accurate (AUC: 0.77).

Color Doppler

In a study of 150 patients with histopathologically confirmed adenomyosis, TVUS 3D color Doppler showed improved sensitivity and specificity in diagnosing adenomyosis compared to transabdominal color Doppler ultrasound, 81/90% versus 68/51%. This study did not evaluate all MUSA criteria, instead only globular uterus, increased echogenicity or heterogeneous echogenicity of the myometrium, anechoic foci, hyperechoic foci, anterior/posterior myometrial asymmetry, and short branch-like or short stripe blood flow. The study described no 3D observations other than color flow [37].

Examining 124 patients with MR-diagnosed adenomyosis, Li et al. demonstrated that color Doppler distribution of blood flow in adenomyosis was only subtly different from unaffected myometrium [38]. The blood flow signal in the periphery of adenomyosis was reticular or short-linear, while the internal color observations were dot-like, short-line, small reticular dense, and diffuse. After intravenous infusion of oxytocin, the peripheral blood supply of affected myometrium disappeared completely in 4% and decreased in 92%. The internal blood supply completely disappeared in 12% and decreased in 80%. Changes in the blood flow volume of peripheral and internal arteries using various oxytocin infusion rates were compared, and a rate of 0.12 U/min showed a statistically better decrease in blood flow without increased adverse effects. This has implications for the use of oxytocin during ablative therapies.

Innovations of Using TVUS as a Component for Scoring Systems

In our review of the literature, we found two recent studies that have produced scoring systems that incorporate TVUS features. The first one used a multicenter, prospective, observational study in which they developed a new scoring system that correlated the type and degree of adenomyosis to

symptoms, including fertility, based on transvaginal ultrasound features [39•]. When they compared diffuse adenomyosis with focal disease, they identified a statistically significant difference for women with diffuse adenomyosis. They were noted to be older (p value 0.04) and had heavier menstrual bleeding (p value 0.04). Using a pictorial blood loss analysis chart, higher values of menstrual bleeding were seen with severe diffuse adenomyosis (279.2 ± 233); however, the highest value was seen in those with adenomyomas (243.3 ± 163.7). In patients trying to conceive, focal disease in the outer myometrium was associated with a higher percentage of infertility (82%) when compared with diffuse disease. Focal involvement of the junctional zone showed a higher percentage of at least one miscarriage (69%). Even though they were able to find clinical differences, they were not able to correlate between severity and ultrasound features of the disease. The other study developed a scoring system using common methods that are used for clinical evaluations to predict the presence of adenomyosis [40]. The clinical scoring system used parity, menarche, VAS scores of dysmenorrhea and dyspareunia, myometrial heterogeneity in ultrasonography, and the presence of tenderness during a pelvic exam. This scoring system has yet to be validated to see if it can be incorporated into clinical practice. Both studies open the possibility of correlating TVUS and clinical symptoms for the non-surgical diagnosis of adenomyosis.

Conclusion

There have been considerable advances in the use of transvaginal sonography to diagnose adenomyosis over the past 5 years, placing it potentially on par with MR for the diagnosis. However, the diagnosis is dependent upon the recognition of specific sonographic observations as articulated and recently clarified by the MUSA group. Such observations depend on the acquisition and reporting of careful 2D imaging, especially video clips along with 3D renderings of the endometrial-myometrial interface and color Doppler characterization of lesional flow patterns. It appears clear that improved sonographic equipment better characterizes direct observations such as microcysts, echogenic lines and buds, and echogenic islands in the myometrium. Yet, current practice protocols (e.g., the 2020 ACR–ACOG–AIUM–SPR–SRU Practice Parameter for the performance of ultrasound of the female pelvis) [41] do not mandate such acquisitions. It is incumbent upon interpreting sonologists to obtain high-quality images for review and to routinely report on both direct and indirect adenomyosis observations to translate the work of recent research into improved patient diagnosis and care.

Scoring systems utilizing multiple sonographic observations or sonographic observations combined with patient clinical factors may improve accuracy. Sonoelastography and CEUS hold promise, notably differentiating adenomyoma from leiomyoma.

Adenomyosis is increasingly recognized as at least two distinct radiographic and pathophysiologic patterns. First, an inside-to-outside process of ectopic endometrial cell implantation progresses from the endometrial-myometrial interface towards the myometrium, logically associated with prior uterine instrumentation. Second, outside-to-inside implantation of endometrial cells from the uterine serosa into the myometrium is strongly associated with deep endometriosis. Given these new findings, we propose that identification of the second pattern should prompt a thorough sonographic search for other evidence of deep endometriosis, such as involvement of the uterosacral ligaments and mid-rectum, particularly when the posterior uterine serosa is affected. Recognition and reporting of these patterns will be key to confirming and clarifying these associations and directing treatment.

Compliance with Ethical Standards

Conflict of Interest All three authors have no financial disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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