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Review

Current Non-Invasive Imaging Techniques Used in the Diagnosis of Adenomyosis

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Abstract

Objective: This review aims to provide insights into the current non-invasive imaging methods used in the diagnosis of adenomyosis, as well as to highlight their diagnostic accuracy, advantages, disadvantages and limitations in the detection of this benign uterine condition. At the same time, this paper emphasizes the importance of using consensus-based terminology in the imaging description of these lesions. **Mechanism**: A search of PUBMED database was conducted for articles published between January 1998 and August 2022 and studies which compared non-invasive imaging methods with postoperative histology examination of uterine specimens were primarily selected. Transvaginal two-dimensional ultrasound was for a long time the main non-invasive imagistic method used for assessment of adenomyosis lesions. The introduction of Morphological Uterus Sonographic Assessment (MUSA) group criteria yielded a significantly better diagnostic outcome of adenomyosis in case of conventional ultrasonography, but the distinction of concomitant benign uterine conditions still remained challenging. **Findings in Brief**: The addition of three-dimensional ultrasound or elastosonography to conventional two-dimensional transvaginal ultrasound yielded higher diagnostic sensitivity. Qualitative elastography particularly proved useful in the diagnosis of adenomyosis due to its capacity to achieve differential diagnosis of benign uterine pathologies based on lesion stiffness. Magnetic resonance imaging (MRI) examination presents higher diagnostic specificity and sensitivity, can assess the endometrial and myometrial layers in detail, but its use has been shadowed by costs and significantly longer examination time. **Conclusions**: The imaging terminology established by consensus by the MUSA group in recent years has facilitated the description of adenomyosis-specific lesions. Two-dimensional transvaginal ultrasound in combination with three-dimensional ultrasound or combined with qualitative elastography offers similar diagnostic sensitivity and specificity to MRI. Despite some limitations, MRI remains a reliable diagnostic method for adenomyosis.

Keywords: adenomyosis; transvaginal ultrasound; elastography; magnetic resonance imaging; diagnostic accuracy

1. Introduction

Adenomyosis is a benign uterine pathology that has a major impact on the quality of life in the affected patients [1]. This condition is characterized by abnormal migration of endocavitary endometrial tissue into the surrounding myometrium, thus leading to an increase in uterine volume [2]. The most common clinical symptoms of adenomyosis consist of chronic pelvic pain and abnormal uterine bleeding, which burden the life of these patients, possibly impacting daily life activities [3]. In addition to impaired fertility, this condition was commonly associated with several obstetric complications, including premature delivery, increased risk of miscarriage, postpartum uterine bleeding and pre-eclampsia [4–7]. The prevalence of adenomyosis is uncertain, with studies conducted over time showing that this pathology affects between 20 and 40% of patients [8,9]. Originally, adenomyosis was thought to be a condition of patients aged over 40, but more recent studies performed on patients treated for infertility have demonstrated the presence of these lesions from younger ages [10–14]. Therefore, the precocious identification of adenomyosis requires an accurate, non-invasive diagnosis to guide the subsequent management of these patients [10,13,15].

While minimally invasive diagnostic tools have developed significantly, adenomyosis tends to be discovered incidentally in many cases, following histopathological examinations conducted upon gynaecological surgery specimens [16–23]. Non-invasive methods for the diagnosis of adenomyosis have been mainly based so far on imaging techniques, but various biomarkers, quantifiable in serum blood, with proven role in the pathogenesis of adenomyosis (including microRNAs) have emerged as potential diagnostic tools [24–26]. Still, while biomarker-based tests require validation in future research, ultrasonography and magnetic resonance imaging (MRI) are the imaging methods widely used in the diagnosis of this condition [27]. There are several ultrasound technical applications which are useful in the diagnosis of adenomyosis, with some of these being influenced by the expertise of the examiner [13,28–30]. Depending on the technical features of the ultrasound machine, its probes as well as its software equipment, three-dimensional ultrasonography and elastography can also be performed [31–35]. These techniques combined with two-dimensional abdominal and transvaginal ultrasonography are intended to provide additional diagnostic benefits in the recognition of adenomyosis [36,37]. MRI on the other hand is a minimally invasive technique, useful in the diagnosis of this pathology, but with certain limitations [38], such as prolonged examination time, higher costs and in some rare circumstances, dependence upon the examiner's level of expertise [27,36,37,39].

This review aims to highlight the main methods of non-invasive imaging diagnosis of adenomyosis in light of their diagnostic accuracy, the recent updates in terminology used in the imaging description of these lesions, as well as their limitations.

2. Matherial and Methods

We conducted a search of PUBMED database for literature data published between January 1998 and August 2022 on the subject of non-invasive imaging methods used in the diagnosis of adenomyosis and for published papers on the standardization of imaging criteria used for describing these lesions. We primarily selected articles which compared performance of non-invasive imaging methods with the histopathological diagnosis of post-surgery uterine specimens, still considered the reference standard. Secondarily, in order to analyse the potential superior accuracy of MRI, those papers that used MRI as the referral diagnostic method were also selected. Terms used to sort relevant data were "Adenomyosis AND ultrasonography", "Adenomyosis AND elastography", "Adenomyosis and Doppler", "Adenomyosis AND three-dimensional ultrasonography", "Adenomyosis AND MRI", "Adenomyosis AND ultrasonographic classification", "Benign uterine pathology AND ultrasonography", "Benign uterine pathology AND elastography", "Benign uterine pathology AND MRI" and "Adenomyosis AND imaging terminology". The abstracts of all the papers found were analysed, and in the case of those that were relevant to the topic and complied to the aforementioned criteria, the full text was reviewed. Additionally, the bibliography of each paper was reviewed to identify other potentially relevant sources. The final search was conducted on 30 August 2022.

3. Current Terminology Used for Depiction of Adenomyosis: The MUSA Criteria

The lack of consensus in reporting the imaging semiology of uterine lesions also plays an important role in the lower non-invasive diagnostic accuracy of adenomyosis [19,40]. As a consequence, considerable efforts have been made in recent years to develop a common imaging reporting system, especially in the ultrasound field, for the description of presumed uterine benign conditions such as adenomyosis [20,37,41,42]. One rationale for this approach was to reduce inter-observer variability in the diagnosis of benign uterine pathologies and to counterbalance the expertise bias, where necessary [42]. Firstly, the International Federation of Gynecology and Obstetrics (FIGO) provided the PALM-COEIN classification which depicted etiological conditions of abnormal uterine bleeding (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) and also listed adenomyosis among these conditions [43]. These represented the first consensual terms used for describing benign uterine pathology. The standardisation of ultrasonographic features of benign uterine pathology by the Morphological Uterus Sonographic Assessment (MUSA) group followed shortly [42,44]. In this classification performed by MUSA, the authors focused on building a common language in describing myometrial pathology [42]. Thus, the ultrasonographic features identified and reported in relation to adenomyosis have been described as ill-defined lesions with echogenic striations or echogenic nodules, intramyometrial cysts and/or striations, interrupted junctional zone, an enlarged globular uterus, fan-shaped shadowing of the myometrium and trans-lesional blood flow in suspected lesions [37,42]. Subsequent studies of the MUSA group's published terminology have highlighted its usefulness in describing uterine myometrial lesions, but with some limitations [1,17,40,41]. These limitations have been reported in patients with fine ultrasound signs of adenomyosis and without noisy symptoms, in whom a highly accurate diagnosis requires an experienced examiner [1,37,41]. In order to improve the accuracy of ultrasonographic diagnosis of adenomyosis, a training program in ultrasound gynaecology is essential, as well as a more comprehensive terminology to describe subtle lesions that can be ultrasonographically detected [1,18,41].

4. Transvaginal Ultrasound: Diagnostic Accuracy Evolution with Implementation of MUSA Criteria

Prior to the implementation of MUSA criteria for the ultrasonographic diagnosis of adenomyosis, transvaginal ultrasound was described as having a high diagnostic sensitivity, of 84%, and a low specificity, of 44%, as reported by a study conducted by Hanafi *et al.* [45]. Sonographic features included in this research were: lack of endometrial junction, asymmetry between the anterior and posterior uterine wall, intra-myometrial cysts and heterogeneous appearance of the myometrium [45]. In another study conducted during the same period, Naftalin *et al.* [9] identified a diagnostic sensitivity and specificity of transvaginal ultrasound of 81% for adenomyosis. In this article, the following diagnostic ultrasonographic criteria were used: asymmetry between myometrial walls, fan shaped shadowing, intra-myometrial cysts, hyperechogenic nodules, ill-defined intra-myometrial lesions and interrupted junctional zone [9]. The above criteria partially overlapped with the MUSA diagnostic criteria for adenomyosis [37,41,42].

Kepkep *et al*. [46] pointed out in 2007 that the presence of subendometrial linear striations, intramyometrial cysts and globular uterus are pathognomonic sonographic signs for adenomyosis. Among these, the authors reported that adenomyosis was most frequently associated with the presence of linear subendometrial striae, which was also demonstrated in subsequent studies [46,47]. During the same period, Margit Dueholm *et al*. [48] implied that transvaginal ultrasound is the first-line diagnostic technique in symptomatic adenomyosis, but in case of asymptomatic adenomyosis this diagnostic tool has strong detection limitations related to the examiner's experience. On the other hand, in a study that sums up the sonographic characteristics listed above, Bazot *et al*. [49] suggested that the transabdominal or transvaginal sonographic diagnosis of adenomyosis is closely dependent on the clinical characteristics of the patient. Another important variable that can significantly influence the precision diagnosis of adenomyosis seemed to be represented by the possible association with other benign gynaecological pathologies, such as uterine leiomyomatosis and endometriosis [50].

Ultrasonographic features outlined herein were selected and composed the first article describing adenomyosis and other benign uterine pathologies, which was published in 2015 by the MUSA group and subsequently republished, as an agreed consensus by highly experienced examiners in this field [42]. Following these published criteria, numerous studies on the ultrasonographic diagnosis of adenomyosis have followed [31,51–54]. Out of these, most studies were observational and did not correlate ultrasonographic suspicion with histopathological findings, while experimental studies were rare [54–58]. Among observational studies, the diagnostic specificity and sensitivity of transvaginal ultrasound in the diagnosis of adenomyosis was reported to be somewhat higher than in experimental studies [27,59]. Therefore, the highest diagnostic sensitivity and specificity of ultrasonography was reported as high as 89% for both variables [27,60]. In case of experimental studies, the reported diagnostic sensitivity and specificity of adenomyosis by transvaginal ultrasonography appeared to be slightly lower [13,51,53,61]. Still, the highest sensitivity and specificity of ultrasonography was reported to be 85% and 78%, respectively [1]. Those findings were provided based on the study conducted by Tellum *et al*. [1,59], who is one of the authors of the MUSA guidelines for examination and an expert in gynecological ultrasonography.

5. Improved Diagnostic Accuracy with Addition of 3D Transvaginal Ultrasound and Doppler Examination to Conventional 2D Ultrasonography

In order to increase the diagnostic accuracy of adenomyosis using techniques combined with two-dimensional ultrasonography, three-dimensional ultrasonography and elastography have also been suggested [27,36,42,59,62,63].

Three-dimensional ultrasound has a relatively short acquisition time and can be a valuable investigation used in selected cases in the diagnosis of adenomyosis [18]. Therefore, this method can be used individually with a sensitivity of 65–98% and specificity of 86–97% [59,64]. In the evaluation of three-dimensional sonographic features of adenomyosis, Luciano *et al*. [64] reported a sensitivity and specificity of 90% and 83%, respectively, following correlation with the result of histopathological examination. For the aforementioned study, the endometrial junctional area, uterine wall symmetry, uterine volume, myometrial homogeneity and the presence of intramyometrial cysts and striations were assessed [64]. Three-dimensional ultrasound added to two-dimensional ultrasound can also achieve a diagnostic sensitivity and specificity of 83% and 89% respectively in the assessment of adenomyosis [65]. These diagnostic performance parameters can be achieved when at least two of the above mentioned criteria are identified by two-dimensional and three-dimensional ultrasonographic analysis, as demonstrated by the study of Exacoustos *et al*. [65]. Another study, conducted by Rasmussen *et al*. [66], which evaluated the diagnostic accuracy of two-dimensional ultrasonography combined with three-dimensional ultrasonography for adenomyosis suggested a diagnostic sensitivity and specificity of 62% and 91%, respectively. Results obtained in this study could have been influenced by the fact that several examiners participated in the interpretation and acquisition of images [66]. In this study, two-dimensional transvaginal ultrasound was priorly used to assess uterine heterogeneity, the presence of anechoic lacunae, uterine wall asymmetry, the presence of intramyometrial cysts and myometrial fan shaped shadowing, in accordance with previously described criteria in a previous article published by the authors [32,66]. For the acquisition of three-dimensional volumes while evaluating adenomyosis, the thickness, regularity and disruption of the junctional zone, as well as the presence of subendometrial striations or cysts, were taken into consideration [66,67].

An additional benefit in the diagnosis of adenomyosis can be obtained by addition of Doppler examination and evaluating the index of resistance and pulsatility over the vascularization of the lesional tissue [68]. According to a study conducted by Sharma *et al*. [68], a pulsatility index below 1.2 and resistivity index below 0.7 is pathognomonic in suspicious lesions of uterine leiomyomatosis, while a pulsatility index above 1.2 and resistivity index above 0.7 is assigned to adenomyosis. Diagnostic specificity and sensitivity of the method reported by this survey is 93.4% and 95.6%, respectively [68]. However, this study also shows that two-dimensional ultrasound combined with three-dimensional ultrasound and Doppler examination can be useful in the differential diagnosis between adenomyosis and leiomyomatosis [68].

6. The Addition of Elastography and Contrast-Enhanced Ultrasound Imaging to Transvaginal Ultrasound

Elastography is a diagnostic technique recently introduced into gynaecological practice which appears to show similar results in terms of diagnostic specificity and sensitivity of adenomyosis to MRI [35,36,69,70]. Currently, elastography consists of two major techniques, namely shear wave elastography and strain ratio elastography, which are accessible through optional softwares provided by new ultrasound machines used in clinical practice [35]. They have both been used in an attempt to diagnose benign uterine pathologies, particularly adenomyosis [33,34]. Out of these two methods, shear wave elastography has proved to be useful in differentiating benign uterine pathologies from underlying tissue, but with some limitations [33,71,72]. These limitations occurred in the coexistence of several benign uterine pathologies [33,71,72]. Under these circumstances, shear wave elastography could not be able to differentiate between benign uterine pathologies within the same specimen, as is the situation of coexisting adenomyosis and leiomyomatosis [33,71,72]. A unique exception is represented by the study of Görgülü *et al*. [30], who highlighted the usefulness of shear wave elastography in the differential diagnosis of adenomyosis, which was achieved by abdominal approach and using a laborious examination protocol. However, strain-ratio elastography provided a highly sensitive and specific diagnosis of adenomyosis [34,73]. The maximum diagnostic sensitivity and specificity of strain ratio elastography for adenomyosis was 100% and 96.23%, respectively, in a study of 79 patients [74]. Similar values for the diagnostic sensitivity and specificity of qualitative elastography combined with transvaginal ultrasound have been reported in other studies evaluating this diagnostic tool [30,34,69,73]. In most studies of this diagnostic procedure, histopathological examination was the reference standard [30,33,34,62,71,73–75]. In addition, this method has proven its efficacy in studies conducted so far and in the distinction of adenomyosis in case of coexisting benign uterine pathologies [70,75].

An imaging technique more recently introduced in medical clinical practice that appears to have potential application in the diagnosis of adenomyosis is contrast-enhanced ultrasound (CEUS) [76]. This imaging technique is able to visualize micro- and macro-vascularization of lesions by contrast medium injected intravenously and partially filled with gas. In the few published studies available in the literature, it has proven its efficacy in detecting focal adenomatous lesions, but the method needs to be certified in larger populations [76,77].

7. Magnetic Resonance Imaging: A Truly Better Diagnostic Method?

One of the most accurate diagnostic imaging techniques available for adenomyosis is MRI [19,40]. There is much controversy regarding the use of the appearance of junctional endo-myometrial zone in the diagnosis of adenomyosis and MRI can provide information regarding this endometrial barrier either in the T1 or T2 sequence [40,78]. However, there is no consensus on the usefulness of changes detected in this area for the identification of adenomyosis. Moreover, a diagnosis of adenomyosis based on imaging changes in this barrier is highly dependent on the experience of the examiner [40,78]. Thus, from the MRI examination studies performed so far, the unanimously accepted imaging criteria for describing adenomyosis have been an ill-defined myometrial mass that is hypointense in T2 and containing high-intensity central cystic areas detectable in T2 and sometimes in T1 as well [40,78–80]. Using this diagnostic criteria, adenomyosis can be apparently diagnosed with high accuracy by an experienced examiner, even in the case of a focal adenomyotic lesion [78]. Despite its high diagnostic sensitivity and specificity (77% and 89% respectively), according to the wide majority of studies, it is not the first diagnostic choice for this pathology [19,36,59]. The reason for this is the longer examination period and the more limited accessibility to this diagnostic approach [36]. Nevertheless, it may be mentioned that in most observational studies, MRI has served as a reference standard to assess the accuracy of ultrasonographic and elastosonographic diagnosis of adenomyosis [57,58,60,69,70].

When comparing the diagnostic suspicion of adenomyosis established by ultrasonography or MRI with the large-scale histopathological result, however, a significant discrepancy between lesions that are imagistically suspected and the confirmed histopathological result arises [17]. This is highlighted by Zanolli *et al*. [17], who noted that in the absence of specific adenomyosis symptoms, diagnosis of this condition can be truly challenging even for an experienced examiner in the field. The authors concluded that the adenomyosis is misdiagnosed in many situations in which patients did not present with typical symptoms, requiring surgical treatment for other related disorders [17].

8. Conclusions

In conclusion, the imaging terminology established through consensus in recent years as a result of the efforts of working groups such as MUSA has significantly improved the non-invasive diagnosis of adenomyosis. Two-dimensional ultrasonography can have a high diagnostic sensitivity and specificity for adenomyosis, as long as it is used by experts in gynaecological ultrasonography, and in cases in which the symptoms are suggestive of adenomyosis and accessible examination conditions are met. Three-dimensional ultrasonography, qualitative elastography and contrast-enhanced ultrasound performed by endovaginal approach have a high diagnostic capability, even with reduced training time, but need to be certified in larger population-based studies. Despite shortcomings, such as long examination time, higher costs and minimal examiner bias, in the non-invasive diagnosis of adenomyosis, nuclear magnetic resonance remains a reliable diagnostic tool for this pathology.

Abbreviations

MUSA, Morphological Uterus Sonographic Assessment; FIGO, International Federation of Gynecology and Obstetrics; PALM-COEIN, polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified.

Author Contributions

VS and CM conducted literature search, were involved in the conceptualization of the paper and drafting the original manuscript. LP was involved in reviewing the original version of the manuscript, addition of supplementary recent literature data and writing the final version of the manuscript, together with VS and CM. All authors have read and agreed to the current version of the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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