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UTERINE FIBROIDS AND ENDOMETRIAL LESIONS (T. TULANDI, SECTION EDITOR)

Classification of Uterine Adenomyosis

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Abstract

Purpose of Review The purpose of the present study is to review the existing literature regarding the classifications of uterine adenomyosis and to assess the clinical significance of each classification.

Recent Findings Adenomyosis is a benign gynecological disease characterized by the presence of ectopic endometrial tissue (glands and stroma) within the myometrium surrounded by hyperplastic and hypertrophic smooth musculature within the uterus. There are several classifications of uterine adenomyosis. The disease is mainly classified in focal adenomyosis, diffuse adenomyosis, and adenomyomas.

The histopathologic classification recognizes 4 criteria: the distance of the foci from the endometrium, the depth of the penetration, the pattern of the disease, and the configuration of the lesion.

The sonographic classification includes as criteria the abnormalities in (a) the uterine serosa, (b) the definition of the lesion, (c) the symmetry of the uterine walls, (d) the shape, (e) the contour, (f) the shadowing of the lesion, (g) the echogenicity, (h) the vascularity of adenomyosis, and the (i) regularity of the endometrial rim.

The MRI classification uses as criteria (a) the presence of disease in the inner uterine layer, (b) the presence of disease in the outer uterine layer, and (c) the solidarity of the lesions.

Finally, the clinical, treatment-based classification uses as criteria the extent of the presence of the disease throughout the myometrium, the configuration of the lesion (focal or diffuse), and the consistency of the lesion (cystic/solid, and gland- or muscle-predominant).

Summary There are numerous proposed classifications of uterine adenomyosis, mainly based on histopathological and imaging findings. The current emerging challenge is the integration of the pathogenesis, the clinical phenotype, the imaging features, and the histology of the disease, in a common classification that will allow an accurate treatment decision and further satisfactory prognosis of the adenomyotic lesion in all the affected patients.

Keywords Adenomyosis · Adenomyosis classification · Uterine adenomyosis · Adenomyosis symptoms · MRI · TVUS

Introduction

Background Adenomyosis is a relatively common gynecological disease and is defined as the presence of ectopic endometrium (tissue similar to endometrium, composed of glands and stroma) within the myometrium. These myometrial invasion sites are surrounded by hyperplastic and hypertrophic smooth musculature within the corpus of the uterus [1]. The disease is classified as "Endometriosis of uterus" based on the 10th Revision of International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) World Health Organization (WHO), version for 2019 (https://icd.who.int/browse10/2019/en) [2] and it was first reported and described by von Rokitansky [3].

As far as the pathogenesis of the uterine adenomyosis is concerned, there are many theories that have been developed. In 1921, Samson described the first histopathological classification of adenomyosis and suggested that the disease localized in the inner myometrial layer may be the effect of

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endometrial tissue invasion secondary to a previous trauma of endometrium. He also set the hypothesis of the correlation of adenomyosis with endometriosis and the external invasion of ectopic endometrium in the outer myometrium [4].

Parrot et al. supported that one possible mechanism for the appearance of adenomyosis was the invasion of the endometrium basalis throughout a disturbed junctional zone (JZ) [5]; uterine auto-traumatization and the mechanism of tissue injury and repair were considered as the primary events of uterine adenomyosis, explaining the presence of subendometrial adenomyotic foci [6]. Garget et al. developed their theory regarding the origin of uterine adenomyosis based on the possible metaplasia of embryonic or adult stem cells into myometrial cells, explaining the presence of intramural adenomyotic foci [7]. Moreover, other researchers supported the possible contribution of endometriosis (especially the deep infiltrating endometriosis—DIE) in the pathogenesis of adenomyosis, pointing out the possible invasion of myometrium from outside by endometriotic tissue [8]. Finally, Marcellin et al. suggested that adenomyosis may occur through the outer invasion of the uterine serosa by endometrial tissue after menstruation, explaining the presence of the adenomyotic foci lying at the outer uterine wall [9]. Any genetic susceptibility to adenomyosis cannot be ruled out, and epigenetic alterations have also been demonstrated in the adenomyotic tissues. Thus, despite the fact that there are quite a few theories regarding the pathogenesis of adenomyosis, none of them can completely explain the initial pathways of the disease and, therefore, there is still no consensus for the origin of the disease.

Prior to the use of imaging techniques, the histopathological examination of the specimens derived from hysterectomy was the "gold standard" for the diagnosis of the disease; at that time, the reported prevalence of adenomyosis ranged widely from 8.8 to 61.5%. This variance is explained by the existed differences in the histopathological diagnosis among the different publications: (i) the definition of adenomyosis is based on the distance of adenomyotic foci below the last endometrial gland, a measurement that may vary from 2 to 8 mm, and (ii) the extent to which the uterus is sectioned for histopathologic analysis when extirpated differs between the various investigators, and the more systematic the process is the higher the prevalence of adenomyosis is found [10, 11].

The clinical manifestations of adenomyosis vary widely from asymptomatic to severe symptoms. Although it is possible that up to 30% of the patients with adenomyosis might be completely asymptomatic and the diagnosis of the disease would be accidental, heavy menstrual bleeding (HMB), pelvic pain, and infertility are a triad of symptoms closely related to adenomyosis [12, 13]. It is very common for patients with adenomyosis to complain about abnormal uterine bleeding (AUB) and, in particular, menometrorrhagia [14]. Pain appears to be another primary clinical symptom of adenomyosis. Chronic pelvic pain, dyspareunia, and more often dysmenorrhea are related with the disease [15]. Moreover, patients with adenomyosis may anticipate fertility problems and adverse pregnancy outcomes, as adenomyosis is a controversial issue in the area of human reproduction. It is suggested that adenomyosis might compromise fertility both by altering the structure and the functionality of the myometrium, and by affecting the molecular background of endometrium receptivity [2]. Finally, in the severe forms of the disease, patients with adenomyosis might present with symptoms from adjacent to the uterus organs, such as dysuria and dyschezia. However, all the aforementioned symptoms are not adenomyosis-specific and might be present in other gynecological diseases.

Clinical examination is useful for the diagnosis of gynecological pathology, providing information on the uterine size, consistency, and mobility as well as on pelvic pain and pelvic masses. Condous et al. pointed out that the bimanual pelvic examination assists the preoperative imaging approach with US in patients who are scheduled to undergo hysterectomy due to adenomyosis [16]. However, it was the progress of imaging technology that actually changed the field in the diagnosis of uterine adenomyosis. The most useful techniques are the transvaginal ultrasound (TVUS, 2-dimension/2D or 3-dimension/3D) and the magnetic resonance imaging (MRI). According to Tellum et al. MRI, 2D TVUS, and 3D TVUS have a sensitivity of 78%, 74%, and 84% and a specificity of 88%, 76%, and 84% for diagnosing adenomyosis, respectively [17].

Aim/Objective The aim of the present study is to review the available literature regarding the various attempts of classification of uterine adenomyosis and to investigate any possible correlation between them and the severity of the symptoms and the prognosis of the disease.

Current Proposals for Classification of Adenomyosis

Histology-Based Classification

Histopathological diagnosis of adenomyosis is unanimously recognized as the presence of ectopic endometrial tissue in the myometrium. The basal endometrial glands and stroma invade the myometrium causing a destruction of the normal myometrial architecture [18]. However, the microscopic cut-off point of myometrial infiltration from endomyometrial borders necessary for disease diagnosis may range from 0.5 low power field (LPF) to, even, a quartile of the total uterine wall thickness, according to the various researchers [19–21].

Before the introduction of imaging techniques, histopathology was the only available tool for the disease

categorization. Thus, the first attempt for histopathological classification of uterine adenomyosis was proposed by Sampson in 1921, categorizing the disease into three different groups according to the extent and the configuration of the lesions into the myometrium [4] (Table 1). This initial proposal tried also to establish a pathogenetic background among the subtypes of adenomyosis: it was presumed that the adenomyotic lesions close to the endometrium were the result of the invasion of the endometrial glands from within (group 1), and the adenomyotic lesions close to the uterine serosa were the result of the invasion of endometrial tissue from without (group 2) in a mechanism similar to endometriosis. Adenomyomas stood out as an independent group of lesions (group 3) [4].

The number of foci per power field that were found at the microscopic examination of specimens was later added as an independent criterion for the histopathological categorization of adenomyosis, expressing the density and, potentially, the severity of the disease. Bird et al.were the first who classified histopathologically the uterine adenomyosis using both the depth of the invasion and the number of foci [22]. This team used as diagnostic cut-off the presence of adenomyotic foci > 1 LPF below the endomyometrial border. Then, they classified the disease into grades I–III depending on the penetration of adenomyosis to the sub-basalis, the mid myometrium, or beyond the mid-myometrium, and into slight, moderate, or marked depending on the number of endometrial glands per LPF (Table 1).

In 1994, in their proposal for the histological classification of adenomyosis, Siegler et al. integrated the depth of penetration into the myometrium, the degree of the involvement of the disease expressed as adenomyotic foci per power field, and the configuration of adenomyosis through the uteri corpus [23]. This group used the depth of 2.5 mm into the myometrium as diagnostic criterion, and then classified adenomyosis into grades 1–3 according to the depth of penetration, mild, moderate, or severe according to the number of foci per LPF, and diffuse or focal according to the configuration of the disease (Table 1).

Thus, it appears that there currently exists a minimum agreement in the histopathologic classification of adenomyosis regarding the importance of the afore-mentioned four

Table 1 Main proposals for histopathologic classification of adenomyosis

Feature	Sampson [4]		Bird et al. [22]		Siegler et al. [23]	
	Histologic Description	*Classification*	*Histologic Description*	*Classification*	*Histologic Description*	*Classification*
Cut-off for diagnosis	Not included		Identification of endometrial glands and stroma > 1 LPF below the basal endometrium (endo-myometrial border)		Infiltration of the myometrium ≥ 2.5 mm below the endo-myometrial border	
Depth of penetration	Not included		Sub-basalis (up to one LPF below the "basal" endometrium)	***Grade I***	Inner one-third	***Grade I***
			Penetration up to mid myometrium	***Grade II***	Two-thirds	***Grade 2***
			Penetration beyond mid myometrium	***Grade III***	Entire myometrium	***Grade 3***
Degree of involvement	Not included		1–3 (few) endometrial glands/LPF	***Slight***	1–3 adenomyotic foci/LPF	***Mild***
			4–9 (several) endometrial glands/LPF	***Moderate***	4–9 foci/LPF	***Moderate***
			≥ 10 (many) endometrial glands/LPF	***Marked***	≥ 10 foci/LPF	***Severe***
Configuration of lesion	Invasion of myometrium from within (from the endometrium)	***Group 1***	Not included		Adenomyotic foci scattered through the myometrium	***Diffuse***
	Invasion of myometrium from without (from the uterine serosa)	***Group 2***			Circumscribed lesions	***Nodular/focal***
	Adenomyoma (Intra-myometrial)	***Group 3***				

LPF low power field

criteria: (a) the distance of the foci from the endometrium, (b) the depth of the penetration (up to one-third, one to two-thirds, and greater than two-thirds), (c) the pattern of the disease (1–3 islets, 4–10 islets, and > 10 islets), and (d) the configuration of the lesion (focal/diffuse) [24].

Imaging-Based Classifications

Sonography is a friendly and widely accessible diagnostic resource for the investigation of adenomyosis. Even with the transabdominal approach, the presence of a large uterus with regular external contour, the myometrial wall asymmetry, the presence of intramyometrial cysts, and the heterogeneity of the myometrium are strong indicators of adenomyosis [25]. Naftalin et al. suggested a strict set of criteria for the diagnosis of the disease that involve the findings of asymmetrical myometrial thickening not caused by the presence of other uterine pathology, parallel shadowing, linear striations, myometrial cysts, hyperechoic islands, the presence of adenomyoma(s), and irregular endometrial–myometrial junction that are ultrasound features [26].

In 2011, FIGO has introduced the PALM-COEIN system (polyp, adenomyosis, leiomyoma, malignancy/hyperplasia, coagulopathy, ovulatory, endometrial, iatrogenic, non-classified) for the classification of abnormal uterine bleeding [27]. In order to systematically approach the sonographic findings of the uterus towards this FIGO system, van den Bosch et al. proposed the criteria for the diagnosis of adenomyosis from the MUSA (Morphologic Uterus Sonographic Assessment) group. According to the MUSA group, the sonographic diagnosis of adenomyosis is set when there are abnormalities in any of the following features: (a) the serosal contour of the uterus; (b) the symmetry of the uterine walls; (c) the presence of a myometrial lesion with specific outline, shape, contour, rim, shadowing, echogenicity, and vascularity; and (d) the junctional zone (Table 2) [28•]. The MUSA group suggests that these sonographic diagnostic criteria can be used as a platform for the sonographic classification and reporting system for the diagnosis of adenomyosis. According to them, adenomyosis can be classified considering the location, the presence of diffuse or focal disease, the cystic characteristics of the lesion, the proportion of myometrium layers that is affected, and the extent and the size of the disease [28•]. This classification, however, has still to be proven that approximates respective clinical phenotypes of patients with adenomyosis.

Exacoustos et al. suggested another sonographic classification system which recognizes three different main categories of adenomyosis: the diffuse adenomyosis, the focal adenomyosis, and the adenomyomas [29]. This group defines the sonographic diagnosis of the adenomyotic variants according to the abnormalities in (a) the uterine serosa, (b) the definition of the lesion, (c) the symmetry of the uterine walls, (d) the shape, (e) the contour, (f) the shadowing of the lesion, (g) the echogenicity, (h) the vascularity of adenomyosis, and the (i) regularity of the endometrial rim (Table 3). Then, each category is graded from 1 to 4 regarding the severity of the findings. In cases of diffuse or focal disease, there might be a separate categorization considering the presence of the adenomyotic foci on the outer myometrium or the JZ [29]. In this classification, the patient receives a total score (1 to 20 points) and is further classified in three groups indicating the sonographic severity of the disease: mild (scores 1–3), moderate (scores 4–6), and severe (scores > 7). In the same study, this group attempted to perform a correlation of the above classification to clinical phenotype and severity of disease; the patients were investigated using a pictorial blood loss analysis chart (PBAC) for the menorrhagia, and a 1–10 visual analogue scale (VAS) for the dysmenorrhea and dyspareunia. Patients with heavier HMB had increased adenomyosis scores; however, patients with dysmenorrhea and dyspareunia did not show significantly increased adenomyosis scores [30•].

In order to exist a logical continuity between histopathologic and imaging findings, the sonographic features should have a basic correspondence to histology. Vandermeulen et al. in a very interesting study where 10 uterine specimens investigated with 3D ultrasound were postoperatively compared to the histology results, found that half of the adenomyotic lesions were missed pre-operatively, whereas there were five cases of false-positive results (including one case of endometrioid adenocarcinoma) [31]. Luciano et al. however, in a prospective study where preoperative 3DUS examination was compared to histology, showed that even though the sensitivity and specificity of each adenomyotic sonographic feature separately range from 35 to 92%, the diagnostic accuracy of the combination of two or more features was 90% [32]. Thus, although ultrasound findings may not correspond to specific histologic lesions, the combination of > 2 markers is strongly indicative of the disease, and therefore its clinical value remains significant.

MRI-Based Classification

MRI offers a meticulous, reproducible, operator-independent result, although burdensome for the patient diagnostic approach. The MRI classification of adenomyosis is based on the diagnosis of JZ abnormalities (usually 12 mm thick) and the presence of localized adenomyotic foci in the inner or the outer myometrium, features that reflect the invasiveness of the glandular and muscular elements of the disease in the given uterus.

The first systematic approach for classification of uterine adenomyosis according to MRI findings was proposed from Gordts et al. in 2008 [33]. This classification included three categories: JZ hyperplasia, adenomyosis, and adenomyoma

Table 2 MUSA group proposal for ultrasound classification of adenomyosis [1]

Diagnosis			
	Serosal contour of uterus	Often globally enlarged uterus	
	Definition of lesions	Diffuse adenomyosis: ill-defined Adenomyoma: well-defined	
	Symmetry of uterine walls	Myometrial anteroposterior asymmetry	
	Lesion		
	Outline	Ill-defined	
	Shape	Ill-defined	
	Contour	Irregular or ill-defined	
	Rim	Not defined	
	Shadowing	No edge shadows, fan-shaped shadowing	
	Echogenicity	Non-uniform: mixed echogenicity	
		Cysts, Hyperechogenic islands, subendometrial lines and buds	
	Vascularity	Translesional flow	
	Junctional Zone (JZ)		
	JZ thickness, regularity	Thickened; irregular or ill-defined	
	JZ interruption	Interrupted JZ	
Reporting & classification			
	Location	Anterior wall	
		Posterior wall	
		Left lateral side	
		Right lateral side	
		Fundus	
	Differentiation (form)	Focal (adenomyoma)	> 25% of the circumference of the lesion is surrounded by normal myometrium
		Mixed type (focal and diffuse)	Co-existing both diffuse and focal adenomyosis in different locations of the uterus
		Diffuse	< 25% of the circumference of the lesion is surrounded by normal myometrium
	Cystic appearance (Consistency)	Cystic	Presence of measurable myometrial cysts (largest diameter > 2 mm)
		Non-cystic	
	Uterine layer involvement	Inner myometrium (JZ)	Type 1
		Middle myometrium	Type 2
		Outer myometrium (Subserosa)	Type 3
	Extent of adenomyosis	Mild (< 25% of myometrium)	
		Moderate (25–50% of myometrium)	
		Severe (> 50% of myometrium)	
	Size of adenomyotic lesion	US estimation	

[33]. In JZ hyperplasia, the JZ was found thickened up to 12 mm and it could be either partial of diffuse. In adenomyosis, the JZ was ≥ 12 mm thick and the disease was extended to the outer myometrium. In adenomyomas, the myometrial mass had indistinct margins. The extra-uterine adenomyotic foci were classified in a separate group (Table 4) [33].

Based on the localization of MRI lesions, Kishi et al. suggested the classification of uterine adenomyosis in four subtypes: intrinsic, extrinsic, intramural, and indeterminate [34•]. The intrinsic subtype occurs in the inner layer whereas the outer uterine structures remain healthy. The extrinsic subtype occurs in the outer myometrium layer whereas the junctional zone remains healthy. The intramural subtype has no geographic relationship to the junctional zone or the serosa and is described as "solitary" adenomyosis. The indeterminate subtypes cannot be categorized in any of the previous categories (Table 4) [34•].

Table 3 Exacoustos's proposal for ultrasound classification of adenomyosis [30•]

Feature	Diffuse adenomyosis	Focal adenomyosis	Adenomyoma
Serosa	Globally enlarged uterus	Regular	Lobulated/regular
Definition of lesion	Ill-defined	Ill-defined/well-defined (cystic lesions), surrounded by normal myometrium	Well-defined, surrounded by hypertrophic myometrium
Uterine walls symmetry	Asymmetrical	Symmetric	Asymmetrical
Shape	Ill-defined	Ill-defined/oval (cystic lesions)	Round, oval, lobulated
Contour	Ill-defined	Irregular or ill-defined	Regular or ill-defined
Shadowing	No edge shadows, fan-shaped shadowing Linear hypoechoic striation	No edge shadows	Edge shadows, fan-shaped shadowing
Echogenicity	Nonuniform diffuse Intramyometrial diffuse areas of • Mixed echogenicity • Small cyst • Hyper-echogenic islands • Subendometrial echogenic lines	Focal, surrounded by normal myometrium Intramyometrial diffuse areas of • Mixed echogenicity • Small/large cyst • Hyper-echogenic islands • Subendometrial echogenic lines/ buds	Focal, lobulated Intramyometrial diffuse areas of • Mixed echogenicity • Small/large cyst • Hyper-echogenic islands
Vascularity	Translesional flow Diffuse minimal/few vessels	Diffuse minimal Sporadic vessels	Translesional flow Diffuse vessels or circumferential flow
Endometrial rim	Irregular or ill-defined Distirted or imprinted	Regular or imprinted by subendometrial focal lesion	Regular or distorted by the lobulated lesion

In 2015, Dashottar et al. proposed another classification of uterine adenomyosis, categorizing it as focal, diffuse even, and diffuse uneven, regarding the characteristics of JZ thickening [35]. Moreover, one other classification system evaluated the T2 signal intensity ratio to predict the effect of uterine artery embolization on these patients [36].

Bazot and Darai classified uterine adenomyosis as internal, which may be focal, superficial, or diffuse, external, which is further classified as anterior or posterior, and adenomyoma which is divided in intramural solid adenomyoma, intramural cystic adenomyoma, submucosal adenomyoma, and subserosal adenomyoma [37•]. According to this classification, in internal adenomyosis, the lesions are either localized or disseminated but remain close to the sub-endometrial layer; in external adenomyosis, the lesions are ill-defined myometrial masses associated with deep endometriosis, and the adenomyomas are ill-defined myometrial lesions with either solid or cystic appearance (Table 4) [37•].

A relationship between histopathologic and MRI findings was hypothesized in the initial classification of Gordts et al.; thickening of the JZ could nicely be depicted in the MRI and, then, ideally might be confirmed in the histology specimen as smooth muscle hyperplasia associated with ectopic endometrium [33]. However, it was the study of McCausland that offered a solid platform to support this notion [38]; the punctuate high T2 intensity foci within low intensity lesions in MRI are correlated with ectopic cystically dilated endometrial glands; the ill-defined low T2 intensity solid smooth muscle nodule within the myometrium in MRI is histologically correlated with adenomyomas; the high T2 intensity linear striations of into the myometrium in MRI are related with the benign invasion of endometrial basalis within the adjacent inner myometrium; and, finally, the high T2 intensity cystic lesion within the myometrium in MRI area is related to adenomyotic cysts [17].

Champaneria et al. in their systematic review found that MRI had a pooled sensitivity of 77% and specificity of 89% in the diagnosis of adenomyosis [39]. This evidence, however, is derived from a comparison of MRI diagnosis of adenomyosis with histology using a variety of histopathologic definitions of the disease in the different studies, and the separate MRI features of adenomyosis were not controlled to the corresponding histologic features apart from the JZ variations [39].

Overall, the MRI classification uses mainly topographic and morphological criteria: (a) the presence of disease in the inner uterine layer, or (b) in the outer uterine layer, and (c) the solitarity of the lesions.

Treatment-Based Classification

Grimbizis et al. in an attempt to correlate the extent and the severity of the disease with the feasibility of uterus-sparing surgery and the successful control of symptoms, classified the disease as diffuse adenomyosis, focal adenomyosis (adenomyomas and adenomyotic cysts), polypoid adenomyomas (typical and atypical forms), adding some special extra-uterine variants (such as endocervical and

Table 4 Main proposals for MRI classification of adenomyosis

Gordts et al. [33]		**Kishi et al.** [34•]		**Bazot et al.** [37•]		
Classification	**MRI findings**	**Classification**	**MRI Findings**	**Classification**		**MRI findings**
				Main CLASS	**Subclass**	
JZ hyperplasia	JZ thickened (8–12 mm) Partial or diffuse type	**Subtype I/intrinsic**	Inner uterine layer adenomyosis/healthy outer structures	**Internal Adenomyosis (Ai)**	Focal adenomyosis (Ai0)	Localized intramyometrial tiny cystic component with or without JZ bulging
					Superficial adenomyosis (Ai1)	Disseminated subendometrial tiny cystic component without JZ hypertrophy
					Diffuse adenomyosis (Ai2)	Disseminated intramyometrial tiny cystic component with JZ hypertrophy
Adenomyosis	JZ thickened ≥ 12 mm Involvement of the outer myometrium	**Subtype II/extrinsic**	Outer uterine layer adenomyosis with healthy junctional zone	**External adenomyosis (Ae)**	Posterior external adenomyosis (Ae1)	Ill-defined subserosal posterior myometrial mass associated with deep endometriosis
					Anterior external adenomyosis (Ae2)	Ill-defined subserosal anterior myometrial mass associated with deep endometriosis
Adenomyoma	Myometrial mass with indistinct margins	**Subtype III/intramural**	"Solitary" adenomyosis with no geographic relationship to junctional zone or serosa	**Adenomyomas (Ad)**	Intramural solid adenomyoma (Ad1)	Ill-defined myometrial lesion with tiny cystic component
					Intramural cystic adenomyoma (Ad2)	Ill-defined myometrial lesion with hemorrhagic cystic cavity
					Submucosal adenomyoma (Ad3)	Ill-defined myometrial lesion with tiny cystic component and intracavitary protrusion
					Subserosal adenomyoma (Ad4)	Ill-defined subserous myometrial lesion with tiny cystic component
Other	Rectocervical, retrovaginal, fallopian tube & bladder types	**Subtype IV/indeterminate**	Indeterminate adenomyosis/no categorization criteria mentioned earlier; MRI geography obscure and indeterminate			

retroperitoneal adenomyosis) (Table 5) [40•]. According to this classification, diffuse adenomyosis could affect both inner and outer myometrium lacking surrounding borders and deranging the thickness of the junctional zone, focal adenomyosis included adenomyomas both solid and cystic, characterized by defined myometrial borders, whereas polypoid adenomyotic lesions, adenomyomas of endocervical type, and retroperitoneal or rectovaginal lesions were classified separately [40•]. Finally, Grimbizis et al. defined the rates of symptom control after application of uterus-sparing techniques in patients with adenomyosis. In this review, the reduction of dysmenorrhea was found to be almost equal after complete excision of adenomyosis, partial excision of adenomyosis, and complete excision of adenomyomas (81–85% less pain). The reduction of HMB was higher after complete excision of adenomyosis (68%) compared to partial excision of adenomyosis (50%) [40•]. It appears that a clinically orientated classification serves better the aim of treatment results, at least in terms of pain, menorrhagia, and the reduction of uterine volume [41]. However, this type of classification remains still unmatched to the majority of sonographic or MRI findings.

Another attempt to meaningfully classify the disease was made be McCausland into superficial (< 1-mm depth into the myometrium) and deep adenomyosis (> 1-mm depth), trying also to correlate the histopathologic findings with the severity of menorrhagia [42].

Based on both histopathological and laparoscopic findings, Pistofidis et al. categorized adenomyosis as diffuse, sclerotic, nodular, and cystic [43].

Thus, the treatment-based classification uses as criteria the extent of the presence of the disease throughout the myometrium, the configuration of the lesion (focal or diffuse), and the consistency of the lesion (cystic/solid, and gland- or muscle-predominant).

Correlation of Classifications with History and Symptoms

Today, it is difficult to support that there is any correlation of the classification of adenomyosis with the patient's history, and the type and the severity of the clinical symptoms. Vercellini et al. noted that there is a proportional correlation between the number of births and miscarriages or induced abortion and the presence of adenomyosis [19]. Moreover, previous uterus trauma [44] and previous cesarean section [45] seem to increase the odds for the presence of the disease in patients.

In general terms, adenomyosis can be either diffuse or focal (adenomyoma or adenomyotic cyst). The adenomyomas are grossly circumscribed nodules of adenomyotic tissue embedded within the myometrium. Adenomyosis could also take the from of endometrial cavity polyp, characteristically described by the presence of endometrial glands between the smooth muscle bundles [40•]. Although many patients with histologically proven adenomyosis are asymptomatic, it appears that the disease is related to a group of symptoms, which they may be indicative but not pathognomonic of the disease. The presence of several symptoms in patients, such as dysmenorrhea and AUB, is related to an apparent malfunction of the adenomyotic uterus [46]. Abnormal uterine bleeding is a symptom that is relatively common between the patients with uterine adenomyosis. Bird et al. [22] and Sammour et al. [47] noticed that the amount of bleeding was irrelevant to the depth of the invasion of ectopic endometrium, whereas there was correlation between the HMB and the number of adenomyotic foci found on the specimens. On the other hand, Levgur et al. noted that there might be connection between the depth of invasion with the HMB [15]. Naftalin et al. found that there might be correlation between the severity of ultrasound evidences of adenomyosis and HMB [14]. Similar findings were noted in young women with diffuse adenomyosis, aged between 18 and 30, in another research [46], whereas there were no evidences to support the classification of MUSA group as a tool for the prognosis of the presence and the amount of HMB [1]. Munro suggests that there is no evidence to support the correlation between the MRI systems of classification and HMB [27].

Pelvic pain is another clinical feature of adenomyosis. Several studies indicate that there may exist a correlation between the depth of adenomyosis and the number of adenomyotic foci with the severity of dysmenorrhea [15, 22]. Levgur et al. noted an impact of depth and number of foci on the grade of dyspareunia [15]. Furthermore, two studies noticed a proportional relationship of ultrasound findings with the degree of dysmenorrhea [14, 46], whereas Weiss et al. did not confirm these findings [48]. Finally, Munro suggests that there is no evidence to prove any correlation between pain and MRI classification of adenomyosis [27].

Infertility and adverse pregnancy outcomes are aspects of health that seem to be affected from adenomyosis. Infertility and pregnancy adverse outcomes such as miscarriages, dysfunctional labor, peripartum bleeding, preterm delivery, preterm premature rupture of membranes, and small for gestational age newborns are related to adenomyosis [49–52]. According to Exacoustos et al. the presence of focal adenomyosis in the outer myometrium is more likely to be related with infertility. Moreover, the same study pointed out that the presence of focal disease at the JZ is correlated with enhanced possibility of a miscarriage [29]. Several mechanisms have been incriminated. Abnormal utero-tubal transport was supported by Kissler et al. [53], whereas an altered molecular of endometrial receptivity was proposed by Prašnikar et al. [2]. Moreover, Campo et al. suggested that

Table 5 Grimbizis' proposal for clinical classification of adenomyosis [40•]

Main class	Description	Subclasses	Description
Diffuse adenomyosis	The extensive form of the disease, characterized by foci of endometrial mucosa (glands and stroma) scattered throughout the uterine musculature		
Focal adenomyosis	A restricted area of hypertrophic and distorted endometrium and myometrium, usually embedded within the myometrium. Histologic characteristics may differ from patient to patient, from almost solid to only cystic (adenomyotic cysts)	Adenomyoma	Any disease that infiltrates a restricted area of the myometrium with more or less clear borders and with mainly solid characteristics. Practically: grossly circumscribed adenomyotic masses
		Cystic adenomyosis	An extreme form of adenomyosis characterized mainly by the presence of a single adenomyotic cyst within myometrium
Polypoid adenomyomas	Circumscribed endometrial masses composed of predominantly endometrioid glands and a stromal component predominantly of smooth muscle	Typical polypoid adenomyomas	Polypoid adenomyomas without architectural or cellular atypia
		Atypical polypoid adenomyomas	A rare variant of polypoid adenomyomas characterized by atypical endometrial glands, often squamous metaplasia, and a cellular smooth muscle stroma
Other forms		Adenomyomas of the endocervical type	Rare forms of adenomyomatous polyps in the uterine cervix that contain epithelial component of endocervical type. Differentiation from adenoma malignum
		Retroperitoneal adenomyomas	Adenomyotic nodules that are thought to arise from metaplasia of mullerian remnants beneath the peritoneum and in the area of upper rectovaginal septum

downregulation in fertility may be the result of distress in myometrial structure and endometrium function [54].

In conclusion, there is a continuing debate whether adenomyosis is an incidental finding or the source of burdensome symptoms. The hypothesis of adenomyosis being not a disease but a normal variant is confirmed every time that adenomyosis is a posteriori diagnosed in a woman with other uterine or pelvic pathology [11].

It seems, therefore, that in spite of the abundance of proposed classifications for uterine adenomyosis, there is not, still, an established correlation between the topography and the morphology of the lesions of the disease on one hand, and the severity of the symptoms and its prognosis on the other.

Furthermore, all those proposals share some common aetiologic, clinical, and prognostic questions to be answered: (a) why do the adenomyotic lesions of the external myometrium appear to have different clinical behavior compared to the internal myometrial lesions? (b) Why do these lesions have the different types of adenomyosis (i.e., diffuse adenomyosis versus adenomyoma), common symptoms, and prognosis? (c) Do these lesions have distinct pathophysiological mechanisms, risk factors, and clinical profiles [13]? And, finally, (d) is there a specific subtype of adenomyosis related with the development of subsequent malignant lesions [55]?

Conclusions

Adenomyosis represents a clinical challenge due to its various histological forms and due to the fact that it infiltrates the myometrium. However, both ultrasound and MRI are extremely useful tools with high diagnostic accuracy; MRI has the additional advantage of the excellent correlation of findings with histology. There are numerous publications throughout the existing literature over the several types of proposed classifications of uterine adenomyosis. However, there is no classification of adenomyosis that is unanimously approved regarding the prognosis or the severity of symptoms of adenomyosis. An ideal classification of adenomyosis should have the following characteristics: a close relationship to pathogenesis, a clear basis on definitive and unanimous histopathologic characteristics, a strong correlation with clinical symptoms, certain reproducible diagnostic criteria, a direct correspondence to medical and surgical treatment, and a clinical meaningful prognosis of the disease. There are still several aspects that remain to be further investigated by future well-designed studies regarding the classification of uterine adenomyosis, in order to achieve the desired result of the proper management of patients with uterine adenomyosis. Top research priorities should be the correlation between diagnostic criteria and histology, the exploration of adenomyotic clinical phenotypes, and the decryption of the natural history of the disease.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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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