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

Classifications of Adenomyosis and Correlation of Phenotypes in Imaging and Histopathology to Clinical Outcomes: a Review

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Abstract

Purpose of Review To provide an update on published classification and reporting systems for adenomyosis. There is an urgent need to standardize reporting of various phenotypes of adenomyosis into a validated and globally recognized system. This can be used to examine the nature and severity of adenomyosis symptoms and inform the design, evaluation, and implementation of appropriate treatment options.

Recent Findings In recent years, several new proposals for adenomyosis classification have emerged. Most are MRI-based and include features such as uterine size, junctional zone thickness, size and location of the lesions, and distribution patterns. To date, none of those proposals has been validated. Only one recent classification based on transvaginal ultrasound was validated for interobserver congruence and correlated to clinical findings. However, the differentiation of diffuse and focal adenomyosis still lacks consensus. In addition, only a few authors advocated imaging-based definitions.

Summary There is a need for one or a combination of a classification and reporting system for adenomyosis. To date, there is no widely accepted and validated system.

Keywords Adenomyosis · Classifications · Imaging · Histopathology · Pathophysiology

Introduction

In medicine, several disorders and conditions are poorly or incompletely understood. They might have a variety of imaging, molecular or other clinical features. Such circumstances beg for creating systems of categorization, or "classification," that support clinical care, patient and trainee education, and the performance of basic, translational, clinical, and epidemiological research. At a scientific level, a classification system can serve to identify categories of a disorder that allows for the comparison of outcomes between different investigators by facilitating systematic review and meta-analysis. From a clinical perspective, classification or categorization can aid diagnosis, prognosis, or inform the selection of management options ranging from expectant to a spectrum of medical and procedural options. Classifications can be based on phenotypical traits including imaging, histopathology, genetic markers, or molecular characteristics.

Despite the first published description of adenomyosis in 1860 [1], understanding of pathogenesis, prevalence, clinical relevance, ideal diagnostic techniques, and appropriate and effective management of adenomyosis remain unclear. Historically, adenomyosis is diagnosed by histopathology of hysterectomy specimen. Diagnosing adenomyosis by myometrial biopsy is impractical and suboptimal. Today, imaging techniques are relatively accurate for the detection of adenomyosis. Yet, there is a lack of standardization [2–4]. While there are several proposed systems, none has been universally adopted—a circumstance that is problematic for both clinicians and investigators and the patients [2, 5].

Sonographic features of adenomyosis have been reported in about 21–34% of women attending gynecology clinics [6••, 7]. The clinical relevance of the disorder has been limited to the two best-known symptoms, which are heavy menstrual bleeding (HMB) and dysmenorrhea [8]. Recent

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studies suggest that adenomyosis may be associated with adverse effects on fertility and might contribute to obstetrical complications, such as preterm labor, fetal growth restriction, and preeclampsia [9–11].

The purpose of our review was to identify and compare studies evaluating adenomyosis features and their clinical relevance, as well as describe classification systems for adenomyosis, based on one or a combination of clinical, phenotypical, histological, molecular, or genetic features. Furthermore, we evaluated studies that assess adenomyosis features and those that correlate a classification or individual characteristics to clinical outcomes.

Diagnostic Classifications

We identified 10 manuscripts describing a histological diagnostic classification system. Six are based on the diagnosis on the depth of myometrial involvement [12–17], two on the proportion of myometrium involvement [18, 19], and two others use other features [20, 21]. For ultrasound a system of terminology for categorizing and describing sonographic features associated with adenomyosis was presented by experts in the so-called Morphological Uterus Sonographic Assessment (MUSA) statement [22••]. This system is currently the most recognized and widely used ultrasound classification of adenomyosis. For magnetic resonance imaging (MRI), several diagnostic accuracy studies were published; however, the consensus is still lacking [23].

Disease Classifications

Histopathology

Identified histology-based classifications are shown in Table 1 [13–17, 19, 21, 24–26]. They focus primarily on disease location or extent. While phenotypical features such as muscular hypertrophy or hyperplasia were described, these were not used as markers in these classifications.

MRI-Based Systems

Table 2 shows the MRI-based systems using a spectrum of criteria [2, 5, 27•, 28–30]. An early proposal from Kishi et al. distinguished four subtypes of adenomyosis based on the myometrial region involved: subtype I—intrinsic (inner myometrium), subtype II—extrinsic (outer myometrium), subtype III—intramural (surrounded by normal outer myometrium), and subtype IV—indeterminate (not fit into any of the other types) [27•]. The authors concluded that the pathogenesis of these different phenotypes might vary from the concept of myometrial invasion of heterotopic endometrium. Yet, it does not explain the mechanism of subtypes II and III. This classification has since been adapted and modified by many authors. A similar layered concept has been included in the Bazot system [30], which further distinguishes anterior from posterior involvement as well as disease volume and patterns (Table 2).

While all other systems are purely based upon MRI characteristics, Grimbizis et al. added endometrial finding of a polypoid adenomyoma confirmed by histopathology [5].

Several authors postulated that adenomyosis in the outermost aspect of the myometrium ("extrinsic" type) may originate from endometriosis involving the myometrium by "invasion" through the serosa [29, 31–34]. However the extrinsic type is frequently found in women without endometriosis [29]. Since it is difficult to reliably determine the origin of the findings at least by imaging we conclude that "extrinsic" adenomyosis should not be classified as a subtype of endometriosis.

Ultrasound-Based Systems

We identified two studies describing classifications based on transvaginal ultrasound (Table 2) [34–36]. In a consensus work, the MUSA statement [22••] was later modified to allow the description of findings stratified by anterior and posterior location and by involvement with one or more of three arbitrarily defined myometrial layers [35].

Lazeri et al. proposed a system combining the pattern (diffuse adenomyosis, focal adenomyosis, or adenomyoma) with location based on a more "anatomic" two-layer myometrium (inner or outer myometrium) and a grade of disease (severity score 1–4) (Table 2) [36]. The inter-rater reproducibility of this system has been internally validated and found to be suitable for clinical use. In a second publication, this system was correlated with clinical symptoms [34].

Others

Gordts et al. proposed an imaging-based classification that could be used with either MRI or ultrasound [37]. The authors proposed identifying the affected myometrial layer (inner or outer myometrium), the location (anterior, posterior, or fundus), the pattern (diffuse or focal, if focal specified as muscular or cystic), and disease volume.

Adenomyosis Imaging Features and Correlation to Clinical Outcomes

Study characteristics and detailed results of the included studies are shown in Table 3.

Table 1 Histopathological adenomyosis classification systems

Author, year	Category		Pattern	
	Name	Depth	Name	Foci
Sampson [21]	Group 1	Invasion from within	N/A	N/A
	Group 2	Invasion from without	N/A	N/A
	Group 3	Adenomyoma (intramyometrial)	N/A	N/A
Bird et al. [13]	Grade I	Sub-endometrial basalis	Mild	1–3 foci/LPF
	Grade II	Mid-myometrium	Moderate	4–9
	Grade III	Outer myometrium	Severe	≥ 10
Nishida et al. [24]	Type 1	Continuous from endometrium	N/A	Islands/section
	Type 2	Continuous from serosa	N/A	Glands/section
McCausland [25]	Superficial	≤ 1 mm depth	N/A	N/A
	Deep	> 1 mm depth	N/A	N/A
Siegler et al. [19]	Grade 1	Inner 1/3	Mild	1–3 foci/LPF
	Grade 2	2/3	Moderate	4–9
	Grade 3	Entire myometrium	Severe	≥ 10
Levgur et al. [14]	Superficial	< 40%	N/A	Foci/LPF
	Intermediate	40–80%	N/A	N/A
	Deep	> 80%	N/A	N/A
Sammour et al. [15]	N/A	< 25%	N/A	Foci/slide
	N/A	26–50%	N/A	N/A
	N/A	51–75%	N/A	N/A
	N/A	> 75%	N/A	N/A
Hulka et al. [16]	Mild	Inner 1/3 (or microscopic foci)	N/A	N/A
	Focal	Adenomyoma	N/A	N/A
	Severe/diffuse	Outer 2/3 (include entire myometrium)	N/A	N/A
Vercellini et al. [3]	Mild	Up to 1/3	Grade 1	1–3 islets
	Moderate	1/3 to 2/3	Grade 2	4–10 islets
	Severe	> 2/3	Grade 3	> 10 islets
Rasmussen et al. [26]	Intrinsic	≥ 2 mm myometrial invasion without contact to the basal endometrium		
	Serrated junctional zone	> 3 mm myometrial invasion with contact to the basal endometrium (precursor of adenomyosis)		
	Linear junctional zone:	No or marginal myometrial invasion ≤ 3 mm with contact to the basal endometrium		

Disease Distribution: Diffuse vs. Focal

Three studies found that women with diffuse adenomyosis were older [7, 8, 34] and suffered more frequently from HMB [34] than those with focal disease. There was no association of the diffuse type with dysmenorrhea in one study [34], while such a relationship was found in another [8]. Pinzauti et al. showed that diffuse adenomyosis was associated with a higher average symptom burden than women without adenomyosis. However, in this population, no focal type adenomyosis was described [7].

Women with focal findings had a higher risk of infertility and miscarriage in one study [34]. This relationship was also found in a study published by Bourdon et al. [38]. Tamura et al. reported no elevated risk of miscarriage [39].

Disease Location: Inner, Middle Outer Myometrium

The terms "inner adenomyosis," "intrinsic adenomyosis," or "JZ disease" are often interchangeably used. Kishi et al. found no difference in pain scores (dysmenorrhea, dyspareunia, or CPP) or HMB based on the location within the myometrium [27•]. Naftalin et al. showed that an irregular JZ was significantly associated with higher pain scores for dysmenorrhea [40].

Iwasawa et al. showed that the location of the adenomyotic lesion did not affect the clinical pregnancy rate in a cohort undergoing embryo transfer [41]. Still, the extrinsic group had fewer pregnancy losses [41]. In a retrospective study, Bourdon showed that infertility was related to focal findings in the outer myometrium but not to diffuse internal

Table 2 Imaging-based adenomyosis classification and grading systems. *MRI* magnetic resonance imaging. *JZ* junctional zone

Author, year	Criteria	Classification
MRI-based systems		
Gordts et al. [2]	T2 -JZ ≥ 8 mm; < 12	JZ Hyperplasia
	Age ≤ 35 years	
	Partial or diffuse	
	JZ ≥ 12 mm	Adenomyosis
	T2 high-intensity foci	
	Involvement of outer myometrium < 1/3; < 2/3; > 2/3	
	Myometrial mass, indistinct margins, low signal intensity	Adenomyoma
	Retrocervical, retrovaginal, fallopian tube, bladder	
Kishi et al. [27•]	Only contiguous with inner myometrium	Subtype I (intrinsic)
	Normal JZ and myometrium between	Subtype II (extrinsic)
	Normal JZ and surrounding myometrium	Subtype III (intramural)
	Doesn't fit the other definitions	Subtype IV (All others)
Grimbizis et al. [5]	1. Diffuse adenomyosis	Diffuse
	2. Focal adenomyosis	Focal
	a. Adenomyoma	
	b. Cystic adenomyosis (single adenomyotic cyst)	
	3. Polypoid adenomyomas (endometrial masses)	Polypoid
	a. Typical	
	b. Atypical	
	4. Other forms	Other
	a. Endocervical	
	b. Retroperitoneal	
Dashottar et al. [28]	Diffuse consistent ("even") JZ thickening ≥ 14 mm throughout uterus	Diffuse even
	Diffuse JZ variable ("uneven") thickening ≥ 14 mm throughout uterus	Diffuse uneven
	Focal widening of the JZ ≥ 14 mm	Focal
Chapron et al. [29]	Three subtypes according to location: outer, middle, and inner myometrium	Focal
	JZmax of at least 12 mm and wallthicknes/JZ ratiomax > 40%	Diffuse
Bazot et al. [30]	A. Focal or multifocal	Internal
	B. Superficial asymmetric	
	C. Superficial symmetric	
	D. Diffuse asymmetric	
	E. Diffuse symmetric	
	F. Solid adenomyoma	Adenomyoma
	G. Cystic adenomyoma	
	H. Submucous adenomyoma	
	I. Subserosal adenomyoma	
	J. External posterior	External
	K. External anterior	
Transvaginal ultrasound–based systems		
Van den Bosch et al. [35]	Presence of diagnostic signs	
	Location: anterior posterior lateral left lateral right fundal	Location
	diffuse, focal (> 25% surrounded by normal myometrium), mixed, adenomyoma	Differentiation
	Measurable, size of the largest lesion	Cystic-non-cystic
	Inner: Type 1	Layer
	Middle (inner to vascular arcade): Type 2	
	Outer: (vascular arcade to serosa): Type 3	
	Multi-layer: (type 1–2, 2–3, or 1 to 3)	

Table 2 (continued)

Author, year	Criteria	Classification
	Mild: < 25%	Extent
	Moderate: 25–50%	
	Severe: > 50%	
	Focal: plane of largest diameter of largest lesion	Size
	Diffuse: myometrial thickness	
Exacoustos et al. [34]	Score 1: single myometrial wall involvement with thickness ≤ 20 mm	Diffuse outer
	Score 2: double myometrial wall involvement with thickness ≥ 20 mm or	
	Single myometrial wall involvement with thickness ≥ 20– ≤ 30 mm	
	Score 3: single myometrial wall involvement with thickness ≥ 30 mm or	
	double myometrial wall involvement with thickness ≥ 20– ≤ 30 mm	
	Score 4: Double myometrial wall involvement with thickness ≥ 30 mm or whole uterus involved with global enlargement	Diffuse inner
	Score 1: JZmax ≥ 6- ≤ 8 mm or diffuse infiltration of the JZ ≤ 20 mm in length	
	Score 2: JZmax ≥ 8 mm or diffuse infiltration of the JZ ≤ 20 mm in length or ≤ 50% of the uterus	
	Score 3: diffuse infiltration of the JZ ≥ 50% ≤ 80% of the uterus	
	Score 4: diffuse infiltration of the JZ ≥ 80% of the uterus	
	Score 1: One focal intramyometrial lesion < 10 mm	Focal outer
	Score 2: ≥ 2 intramyometrial lesions < 10 mm or one focal intramyometrial lesion of 10–20 mm	
	Score 3: ≥ 2 intramyometrial lesions 10–20 mm or one focal intramyometrial lesion of > 20 mm	
	Score 4: ≥ 2 intramyometrial lesions > 20 mm or ≥ 3 focal intramyometrial lesions	
	Score 1: One focal lesion in JZ or cystic areas ≤ 10 mm	Focal inner
	Score 2: ≥ 2 focal lesions of the JZ ≤ 10 mm or one focal intramyometrial lesion of 10–20 mm	
	Score 3: ≥ 2 focal lesions of the JZ 10–20 mm or one focal lesion of the JZ of > 20 mm	
	Score 4: ≥ 2 focal lesions of the JZ > 20 mm or ≥ 3 focal lesions of the JZ	

adenomyosis. They defined adenomyosis as a JZ 12 mm or more in thickness and involving at least 40% of the total myometrial thickness [38]. These findings appear to be in contrast to a prospective study from Maubon et al. that demonstrated that embryo transfer failure was more common when the mean JZ thickness was more significant than 7 mm and the maximum thickness more than 10 mm [42].

Disease Pattern: Cystic vs. Hypertrophic

Role of disease patterns in clinical manifestations is unclear. Naftalin et al. found that the presence of myometrial cysts was not explicitly associated with a higher dysmenorrhea score [43]. Hemorrhagic lesions that can be discriminated from cysts without hemorrhage in T1-weighted MRI were more frequently found in intrinsic or extrinsic adenomyosis when compared to isolated adenomyosis in the middle myometrium [27•]. Yet, the number of cases was relatively small and involved a selected group of women. Bourdon et al. found no association between infertility and the presence of bright spots on T2 [38].

Several investigators have correlated MRI-based signal intensity (T2 hyperintense foci or T1 lesion signal) to the success of high-intensity focused ultrasound (HIFU) therapy [44–47]. These studies suggest that the relative amounts of glands and stroma in the adenomyotic mass can impact the results of hyperthermic treatment—at least based on the imaging outcomes.

Volumetric Relationships: Lesion Size and Disease Extent

Bird et al. studied the association between depth of adenomyosis involvement and symptoms. They found no relationship with recorded bleeding symptoms, but they demonstrated that the number of "islets" of adenomyotic glandular tissue per low powered field was proportional to the subjectively determined volume of menses [13]. Similar findings were described by Sammour et al. and Rasmussen et al., who also reported no relationship between depth of myometrial involvement and the symptom of HMB [15, 26]. However, Rasmusen et al. reported that symptom improvement after

Table 3 Studies correlating adenomyosis features to clinical outcomes. *MRI*, magnetic resonance imaging; *TVUS*, transvaginal ultrasound; *2D*, two dimensional; *3D*, three dimensional; *GnRHa*, gonadotropin releasing hormone agonist; *HMB*, heavy menstrual bleeding; *JZ*, junctional zone; *CPP*, chronic pelvic pain

First author, year	Study design	*N*, population characteristics	Mode of diagnosis	Classification feature	Clinical outcomes	Limitations
Iwasawa et al. [41]	Retrospective cohort	136 embryo transfers in 52 infertile women with adenomyosis, undergoing in vitro fertilization (fresh and frozen)	MRI + TVUS	• Advanced (invades the full thickness of the uterine myometrium) • Extrinsic (localized on the serosal side) • intrinsic (localized on the endometrial side) • Adenomyoma *(not present in this population)*	• Fertility outcomes • Pregnancy complications • Obstetric outcomes	Retrospective, endometriosis as confounder, phenotype groups unevenly distributed, some received GnRHa-treatment
Bourdon et al. [49]	Same as Bourdon 2020	Same as Bourdon 2020	MRI	• Internal vs. external adenomyosis • JZ thickness	• HMB • Dysmenorrhea • Non-cyclic CPP • Dyspareunia	
Bourdon et al. [38]	Retrospective observational, cross-sectional cohort	248 women with adenomyosis out of nonpregnant women between 18 and 42 years of age who underwent surgery for benign gynecological pathologies	MRI	• Focal: localized, ill-defined, low signal intensity mass, inhomogeneous circumscribed area located in the outer shell of the uterus, with indistinct margins separated from the JZ • Lesion size • Location (anterior/ posterior)	• Infertility (none/ primary/secondary)	Retrospective design; Single timepoint; Male factor as confounder not assessed
Exacoustos et al. [34]	Prospective cohort	108, premenopausal women referred for pelvic pain assessment	TVUS (2D/3D)	• Adenomyosis severity score • Diffuse vs focal vs adenomyoma	• HMB • Dysmenorrhea • Dyspareunia • Infertility • Miscarriage • Endometriosis	Relatively low n, selection bias (pelvic pain)
Tamura et al. [39]	Retrospective, multicenter, questionnaire-based cohort	262 pregnant women with adenomyosis, without fibroids/ endometriosis	MRI and/or TVUS	• Focal/diffuse, lesion size, location (anterior/ posterior)	• Pregnancy and obstetric complications	Recall bias, selection bias
Li et al. [50]	Prospective case–control; consecutive cohort	578 (298 with adenomyosis, 280 matched controls)	MRI or TVUS	• Uterine size	• Lower urinary tract symptoms	
Orazov et al. [52]	Prospective translational	90 (60 adenomyosis + pain; 30 adenomyosis without pain but HMB)	TVUS + MRI + Histology	• VEGF expression in adenomyosis and eutopic tissues	• Dysmenorrhea	No adjustment for confounders

Table 3 (continued)

First author, year	Study design	*N*, population characteristics	Mode of diagnosis	Classification feature	Clinical outcomes	Limitations
Naftalin et al. [40]	Prospective observational consecutive cohort	718 premenopausal women, 157 with adenomyosis	TVUS (2D, 3D)	• Asymmetrical myometrial thickening • Parallel shadowing • Linear striations • Myometrial cysts Hyperechoic islands Adenomyomas • Irregular endometrial–myometrial junction	• Dysmenorrhea	
Pinzauti et al. [7]	Prospective observational consecutive cohort	156 women, 18 and 30 years, regular menstrual cycle, nulligravid, no endometriosis or fibroids	TVUS (2D, 3D)	• MUSA criteria • Diffuse vs focal adenomyosis (focal not present in population)	• Dysmenorrhea • HMB • Dyspareunia • CPP	Only diffuse adenomyosis found in this cohort
Wang et al. [51]	Prospective translational	80; (40 adenomyosis + dysmenorrhea; 20 no adeno dysmenorrhea, 20 controls)	TVUS + histology/hysterectomy	• CD65 expression in adenomyosis tissue	• Dysmenorrhea	Hysterectomy specimen
Li et al. [8]	Retrospective cohort; consecutive	734 with adenomyosis (97% premenopausal)	Histology/Hysterectomy specimen	• Uterine size (TVUS based) • Diffuse/focal (histology diagnosis)	• HMB • Dysmenorrhea • Metrorrhagia • Time from symptom onset to diagnosis • CPP	Retrospective, hysterectomy
Naftalin et al. [48]	Prospective observational consecutive cohort	714 premenopausal women, 100 with adenomyosis	TVUS (2D, 3D)	• Number of TVUS features for adenomyosis found	• Menstrual blood loss	Different blood loss assessment measures in same cohort
Kishi et al. [27•]	Retrospective cohort	152, surgical treatment for adenomyosis (hysterectomy or adenomyomectomy)	MRI	• Location: • Type I: intrinsic • Type II: extrinsic • Type III: middle only • Type IV: does not fit other category • T2/T1 high intensity spots	• Dysmenorrhea • HMB • CPP	Retrospective, surgical cohort with expected high symptom scores
Levgur et al. [14]	Retrospective cohort	111 (17 with adenomyosis alone, 19 with adenomyosis with leiomyomas, 39 with leiomyomas alone, and 36 with neither)	Histology/Hysterectomy specimen	• Invasion: • Deep (above 80%), intermediate (40–80%), and superficial (under 40%), • Number of adenomyotic foci	• Dysmenorrhea • HMB	Uterus weight under ≤ 280 g, clinical data were collected retrospectively from patient records, possibly underpowered

transcervical endometrium resection was greater with minimal depth of involvement of the myometrium [26].

The outlier in this group of studies is the report by Levgur et al., where the symptom of HMB was 36.8% in women with deep foci and 13.3% in those with "intermediate" depth foci [14]. Sammour et al., who evaluated dyspareunia and "other pain" found a poor correlation with depth, but again, there was a correlation with the number of foci identified histopathologically. A few authors reported a correlation between depth of adenomyosis involvement as well as the number or volume of foci of glandular tissue and dysmenorrhea [13, 14, 24].

Naftalin et al. and Pinzauti et al. reported a linear relationship between ultrasound diagnosis of adenomyosis and dysmenorrhea and HMB symptom severity [7, 40, 48].

Volumetric Relationships

Lesion Volume

Estimated adenomyosis volume and clinical manifestations have been examined by Exacoustos et al. who showed that symptom severity was associated with disease severity mainly based on lesion size and %-involvement of the myometrium [34]. However, it seems that the size of an adenomyoma, defined as a subgroup of focal adenomyosis surrounded by hypertrophic myometrium, is not associated with more pain, as demonstrated in two studies [34, 48]. There have been early evaluations of the volume of adenomyosis findings and pregnancy outcomes. Tamura et al. found the rates of miscarriage and cervical insufficiency were higher in the group with large lesions [39].

Uterine Volume

Another feature associated with adenomyosis, and indirectly, with disease volume, is uterine volume. Li et al. showed that large uterine size was independently associated with bothersome lower urinary tract symptoms (LUTS) and HMB, but not dysmenorrhea or chronic pelvic pain (CPP) [50]. Another group showed that smaller uteri were associated with more CPP (8). Disease duration and age were also positively associated with the uterine size, supporting the progressive nature of adenomyosis.

Molecular Markers

An evolving approach to evaluating the potential impact of adenomyosis is using molecular markers, not only for diagnosis but also as instruments to monitor response to therapeutic interventions. Wang showed that CD65 expression was higher in women with dysmenorrhea than those without dysmenorrhea and controls [51]. The same association was also found for VEGF expression and dysmenorrhea [52]. VEGF was found in hypertrophic muscular bundles [52]. Bourdon et al. correlated MRI findings with serum cytokine profiles. They found that in women with both focal and diffuse adenomyosis, the levels of IL-23, IL-25, IL-31, and IL-33 were lower than in controls. The levels of IL-17F levels were lower in women with focal adenomyosis than in controls. TNFα levels were lower in women with focal disease compared to those with diffuse adenomyosis [53].

Discussion

Adenomyosis is a disorder of increasing interest, in part because of its newfound high prevalence on ultrasonic and magnetic resonance imaging and in part because of its variable impact on clinical outcomes such as infertility, pelvic pain, abnormal uterine bleeding, and pregnancy-related disorders. It is still unclear how imaging features of adenomyosis correlate to symptoms or other adverse outcomes such as infertility or pregnancy loss. There exists an urgent need, at least for a standardized reporting system to harmonize the design and interpretation of basic science and clinical investigation as well as education and clinical care.

In this review, we found various reporting or classification systems based on histopathological, MRI, or TVUS features. While most systems are designed to include the location, the extent, and the distribution pattern of adenomyosis features (focal or diffuse), few describe more specific phenotypical patterns such as the presence, size, or types of cysts, or the location and extent of findings suggesting the presence of muscular hyperplasia. We identified studies that correlated clinical findings with phenotypical traits of adenomyosis, suggesting that a variety of features could be relevant in the design of a reporting or classification system.

There have been conflicting results regarding the clinical significance of the disease pattern (diffuse, focal, and adenomyoma). The differences in patient populations, the low number of participants in some studies, and the different definitions of those groups are likely the reason for these incongruencies. Also, as those traits are assessed by subjective pattern recognition, a high inter-rater variation is likely an important reason for these conflicting results.

The clinical significance of myometrial cysts (with and without hemorrhage) and muscular hyperplasia remains unclear. In a study investigating treatment response of high-intensity focused ultrasound (HIFU) in different phenotypes, the absence of T2 hyperintense spots in MRI was associated with an increased chance of nonperfusion and thus treatment response [45].

As a result of these considerations, it would seem prudent to include disease patterns in a reporting system. Such an approach would allow investigators to evaluate further the relationship of such findings to clinical manifestations of adenomyosis and characterize responses to various types of medical, ablative, and surgical therapy.

We found that the disease extent is likely to be linked to symptom severity. This was consistently shown in

histopathological, MRI-based, and ultrasound-based studies. Furthermore, it was demonstrated that treatment efficacy depended on disease extent, which is not surprising [26, 44]. These observations, along with the spectrum of disorder phenotypes, beg for evidence-based information to assist patients and clinicians in informed decision-making.

While the need for a uniform system for reporting should lead to a valuable classification of adenomyosis, it is equally apparent that such a system does not yet exist. We suggest that the research needed to obtain such information requires an accurate diagnosis and methods by which some composite of disease phenotype and molecular expressions are identified and documented. Categorizing the phenotype in a standardized fashion would allow for meaningful comparison of symptoms and clinical outcomes of medical and procedural interventions in patients with similar disease characteristics. It might lead to a better understanding of adenomyosis in a fashion sufficient to inform more tailored therapeutic approaches.

Imaging modalities are now widely accepted to be reliable tools and the first choice in diagnosing adenomyosis. Histopathology, while once the "gold standard" for diagnosing adenomyosis, requires extensive sections throughout the whole uterus to be reliable, which is not given in standard clinical practice [13, 54]. Furthermore, using a hysterectomy specimen introduces a selection bias that does not allow to draw conclusions on, for example, symptoms [55•].

Therefore, a classification and reporting system needs to be based on imaging. Previous reviews suggest that both MRI and ultrasound, as currently used, may have similar sensitivity and specificity for diagnosing adenomyosis [23]. As MRI potentially provides greater accuracy in determining disease volume, distribution, location, and pattern, it seems to be best suited to develop a classification system. However, as TVUS is widely available and either the only or the first-line tool in diagnosing adenomyosis, a universally useful classification needs to be applicable for ultrasound.

Assessment of molecular and genetic expressions, be they from serum, endometrial aspirates, or endometrial or myometrial biopsy specimens, may be necessary for determining the impact of adenomyosis in a given patient: a circumstance that may have particular importance in women with reproductive failure or who are planning to undergo embryo transfer. The place for such variables should be considered in the design of any system.

Conclusions

In summary, there is a need for a harmonized reporting system for both ultrasound and MRI that would allow performing research, which could be used to develop a disease classification system. In both reporting and classification systems, imaging modalities should take into account the histopathological features of the disorder. Fortunately, initiatives involving the international radiological and gynecological communities are underway. They are designed to achieve this goal so that clinicians, investigators, and especially patients will benefit from an increased understanding of this disorder.

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• Of importance
•• Of major importance

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