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
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 consenus 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.
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 1: Histopathological adenomyosis classification systems

| Author, year | Category | Depth | Name | Pattern | 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 I | Inner 1/3 | Mild | 1–3 foci/LPF |
|              | Grade II | 2/3 | Moderate | 4–9 |
|              | Grade III | 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 | N/A | N/A |
|              | Serrated junctional zone | > 3 mm myometrial invasion with contact to the basal endometrium (precursor of adenomyosis) | N/A | N/A |
|              | Linear junctional zone | No or marginal myometrial invasion ≤ 3 mm with contact to the basal endometrium | N/A | N/A |
| 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 |
| | T2 high-intensity foci |
| | Involvement of outer myometrium < 1/3; < 2/3; > 2/3 |
| | Myometrial mass, indistinct margins, low signal intensity |
| | 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 wall thickness/JZ ratio max > 40% Diffuse |
| Bazot et al. [30] | A. Focal or multifocal Internal |
| | B. Supercificial asymmetric |
| | C. Supercificial symmetric |
| | D. Diffuse asymmetric |
| | E. Diffuse symmetric |
| | F. Solid adenomyoma Adenomyoma |
| | G. Cystic adenomyoma |
| | H. Submucous adenomyoma |
| | I. Subserosal adenomyoma |
| | J. External posterior |
| | K. External anterior External |

| 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) |
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, Rasmussen et al. reported that symptom improvement after

| Author, year | Criteria | Classification |
|--------------|----------|----------------|
| 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 | |
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)                     | • Fertility 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                                                   | • HMB                                                    |                                                                           |
| 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 | • 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                                                          | • HMB                                                    | 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)                            | • Infertility, Miscarriage, Endometriosis                 | 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 adenomyosis, 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 |
| Levger 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

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
myometrial biopsy specimens, may be necessary for deter-

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 identi-

Imaging modalities are now widely accepted to be reliable tools and the first choice in diagnosing adenomyosis. Histopathology, while once the “gold standard” for diagnos-

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-

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 con-

Conclusions

In summary, there is a need for a harmonized reporting sys-

features of the disorder. Fortunately, initiatives involving the international radiological and gynecological communities are underway. They are designed to achieve this goal so that clini-

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Compliance with Ethical Standards

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Consent to Participate Not applicable.

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Code Availability Not applicable.

Compliance with Ethical Standards

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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