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ABSTRACT

Background:
Uterine imaging techniques, including transvaginal ultrasound (TVUS) and MRI have been demonstrated to be sensitive for the diagnosis of adenomyosis, but systematic reporting of findings is essential to facilitate study of this disorder in a way that reliably informs patients and clinicians regarding prognosis and appropriate management.

Objectives:
To conduct a systematic review of the available histological and image-based classification systems to determine which, if any, provide clinical utility for prognosis or the selection of appropriate therapeutic interventions.

Data Sources:
PubMED as well as the bibliographies of identified publications.

Methods of Study Selection:
A single investigator searched PubMED using MESH terms that included “Adenomyosis”, “Classification”, “Ultrasound Classification”, “MRI Classification” and “Diagnosis”.

Tabulation:
Search results were tabulated in a Microsoft Excel workbook that facilitated identification of duplicated entries. Publications were allocated to separate categories that included histopathologic, ultrasound, and MRI classifications. Identified systems associated with clinical outcomes were separately tabulated.

Integration and Results:
Abstracts of 1,669 papers were reviewed and 278 were identified for review of full text. Twenty-five were considered potentially relevant from the PubMED review and an additional 17 were found in bibliographies. Of the 42 full text papers that were reviewed in detail, 9 histological classifications were identified, 4 of which were accompanied by an attempt at clinical correlation, one of which described correlation with the outcome of medical, procedural or surgical interventions. There were 9 image-based reporting or classification systems, 2 based on TVUS and 7 using MRI, 3 of which included correlations with intervention outcomes, although these were surrogate (imaging), not clinical outcomes.

Conclusion:
There is inconsistency in histopathological definitions, and there is no uniformly accepted or validated system of image-based reporting or classification that can inform clinical decision making. There exists a need for harmonized classification systems for both ultrasound and MRI that comport with the histopathological features of the disorder.

OBJECTIVES

The objective of this work was to conduct a systematic review of the available histological and image-based classification systems to determine which, if any, have been determined to provide clinical utility for prognosis or the outcomes of medical and procedural interventions, the latter including excisional surgery and image guided procedures.

BACKGROUND AND RATIONALE

General Considerations

Adenomyosis is generally defined as the presence of ectopic, non-neoplastic, endometrial, or endometrial-like glands and stroma existing in the myometrium. Typically, the ectopic endometrium is surrounded by hypertrophic and hyperplastic myometrium and the collective process generally but variably enlarges the uterine corpus. The existence of ectopic endometrium or endometrial-like tissue outside the endometrial cavity seems to be somewhat analogous to endometriosis in a number of ways. Indeed, adenomyosis was first described (as *cystosarcoma adenoids uterinum*) in 1860 by Carl von Rokitansky(1), prior to the initial descriptions of endometriosis. Until relatively recently, adenomyosis was usually diagnosed by hysterectomy but with the advent of high resolution ultrasound, and the development of magnetic resonance imaging (MRI), the disorder can be identified without uterine extirpation(2-5), a circumstance that has created the opportunity to investigate its pathogenesis, molecular expressions, clinical impact and outcomes of various medical and procedural interventions.

Prevalence

It is now apparent that adenomyosis is highly prevalent and manifests in a variety of ways, ranging from a complete lack of symptoms, to some combination of pain, infertility, and abnormal uterine bleeding (AUB). Prior to the advent of imaging-based diagnostic techniques, estimates of prevalence ranged widely, from 8.8% ((6)to 61.5%(7) based on retrospective analyses of histopathology reports describing hysterectomy specimens. This approach impacted the determination of prevalence in at least four ways. First, there is potential selection bias since such studies wouldn't include patients who were not undergoing hysterectomy. Second, there existed, and still exists, a spectrum of histopathological definitions of the disorder which have typically been based upon the distance that endometrial-like tissue is seen below the deepest levels of the normal endometrium. A spectrum of such "depths" has been used to define the presence of adenomyosis, ranging from a measured depth 2 to 8 mm below the last endometrial gland, to definitions based upon proportional involvement of the myometrium such as ≥ ¼ or greater than 1/3 the thickness of the myometrium. Third, it is apparent that hysterectomy-based prevalence depends on the extent to which the uterus was sectioned – diagnosis was probably limited by the use of "routine" assessments that didn't systematically analyze the myometrium. More extensive histopathologic processing of the uterus, using systematically obtained additional sections, led one group of investigators to increase the prevalence from 31% to 61.5%.(7) Finally, and possibly related, pathologists themselves may vary in their diligence or interpretation regarding the diagnosis of adenomyosis. For example, in a large study of 1,252 hysterectomy pathology reports in Maryland, thought to represent a relatively homogenous population, the prevalence of

adenomyosis by hospital ranged from 12 to 58 per cent and amongst pathologists it varied from 10 to 88 per cent(8).

The advent of imaging techniques that are relatively sensitive for the diagnosis of adenomyosis has provided the opportunity to estimate the overall prevalence of the disorder in women not undergoing hysterectomy. Using transvaginal ultrasound (TVUS), a UK study demonstrated a prevalence of 20.9%(9) and an Italian group reported findings consistent with adenomyosis in 34.5 per cent of girls and women between the age of 18 and 30 years who were seeking contraception, not care for any particular symptom (10).

Clearly we need more information about the prevalence of adenomyosis by ensuring that our imaging-based systems are both sensitive and specific, and by applying these tools to a spectrum of women in a fashion that considers age, race, parity and other epidemiologically relevant features.

Pathogenesis

Evaluation of the design and utility of imaging-based reporting systems is enhanced by an understanding of what we know about the pathogenesis, prevalence, clinical manifestations, and the diagnosis of the disorder. There are a variety of hypotheses designed to explain the pathogenesis of adenomyosis, but it is likely that more than one is responsible for the spectrum of disease phenotypes now recognized(11). The disorder can manifest as one or a combination of thickening of the internal myometrium, areas of focal or diffuse disease in the inner or outer myometrium, and involvement limited to the outer myometrium, typically contiguous with the uterine serosa(12). These different manifestations may reflect different pathogenic mechanisms – inner myometrial disease may more often derive from “invasion” of the endometrium secondary to trauma while outer myometrial disease may be secondary to invasion by endometriosis, a mechanism first proposed by Samson in 1921 (13). Isolated outer myometrial disease may occur secondary to the presence of of Müllerian rests or pluripotent cells evolving to become localized areas of adenomyosis. Of course, such a mechanism may involve any disease location and more than one mechanism may be present in any given patient with the disorder.

Clinical Manifestations

The proportion of women without symptoms is unknown, but it is likely that the number is relatively high, a circumstance that leaves women vulnerable to unnecessary interventions and challenges physicians to determine when, or if, the symptoms presented are secondary to the visualized disease. Indeed, and based on evaluation of hysterectomy specimens, even the relationship between adenomyosis and any symptoms has been challenged(14, 15). For example, a large, federally funded cohort study conducted in the United States concluded:

> *“Adenomyosis is equally common in women who also have fibroids, endometriosis, pelvic pain, or abnormal uterine bleeding, and women who do not. Therefore, adenomyosis is an incidental finding, not the source of the symptomatology. It appears not to be a "disease" per se but rather a normal variant” (16).*

In the past it was unclear what, if any relationship there was between abnormal uterine bleeding (AUB) and adenomyosis(7, 14, 17, 18). However, with the advent of imaging-based diagnostic techniques, it is apparent that adenomyosis is likely associated with AUB symptoms, and, in particular, with the symptom of heavy menstrual bleeding (HMB) (19-21).

Evaluation of the relationship between both endometriosis and adenomyosis and chronic pelvic pain (CPP) has been confounded by the frequency with which both are present in the same woman, as well as by the plethora of other potential coexisting causes of pain in a given individual. Well-designed investigation has demonstrated that adenomyosis may be present in 21.8% of women undergoing surgery for endometriosis, and, in particular, deep infiltrating endometriosis(22). While initial studies relating adenomyosis to the presence and severity of dysmenorrhea were inconclusive(17), more recent evidence from histopathological evaluation has demonstrated that women with adenomyosis who undergo hysterectomy may be much more likely to have dysmenorrhea and other sources of pelvic pain than those with leiomyomas(7, 20, 23) although some investigators have failed to confirm these findings(18).

The evidence regarding the relationship between infertility and adenomyosis is mixed, and many studies have shown no relationship between adenomyosis and reproductive failure(24, 25). However, systematic reviews suggest that there is an adverse impact of adenomyosis on the success of in-vitro fertilization (IVF) and embryo transfer (ET)(26, 27) and that both surgical and medical interventions may provide benefit(28). It is postulated that adenomyosis may contribute to infertility by changing the normal myometrial architecture and function by altering inner myometrial peristalsis. Increased peristalsis at mid cycle may adversely effect sperm transport and if hyperperistalsis occurs in the normally quiescent luteal phase, there may be a negative impact on the mechanics of embryo implantation. However, and perhaps more importantly, adenomyosis may result in disordered decidualization in ways that reduce endometrial receptivity, a circumstance associated with the presence of defects or other abnormalities in measurable implantation markers. For example, HoxA-10 gene expression, a marker for endometrial receptivity, can be decreased both in the mouse model with experimental adenomyosis (29) and in the secretory phase endometrium of women with adenomyosis(30).

There is relatively recent evidence that adenomyosis may adversely impact pregnancy outcomes ranging from recurrent pregnancy loss, to a spectrum of disorders of later pregnancy including dysfunctional labor and peripartum bleeding(31, 32).

Collectively, while there appears to be a relationship between adenomyosis and various symptoms in some women, it is equally apparent that many are asymptomatic. It is unclear why there is such variation, and how (or if) disease phenotype might contribute to these observations. As a result, it seems important to design research that explores this situation - research that will require a standardized approach to categorizing the features of adenomyosis, not just its presence or absence.

Imaging Based Diagnosis

The use of ultrasound for the diagnosis and characterization of adenomyosis was first described as early as 1979(33), and further developed and reported in the mid 1980s(34, 35). From a diagnostic perspective, and correlated with histopathological evaluation, MRI and TVUS seem to have similar sensitivity and specificity for the diagnosis of adenomyosis, although sonographic accuracy appears to be more operator dependent (2-4). The most recent systematic review of high-quality studies suggests that MRI has a sensitivity of 77% and a specificity of 89% while TVUS, depending on the observer, has a sensitivity ranging from 72 to 82% and a specificity that ranges from 81 to 85%(4).

Rationale for Image-Based Classification or Standardized Reporting Systems

The juxtaposition of a broad spectrum of clinical manifestations, including the frequent lack of systems, and the existence of variable phenotypes detectable by imaging is a circumstance that begs appropriate bench, translational, and clinical research designed to foster and enhance our understanding of this disorder. Unfortunately, at the present time, both research and clinical care are compromised by the absence of a universally accepted and validated system for categorizing the disorder using the various imaging techniques(36). This paper is designed to review the current status of such systems and explore the next steps in this consensus-building process, crucial to our contemporary and future understanding of adenomyosis.

METHODS

Identification of Existing Systems

For the purposes of this work it was necessary to search the literature for systems designed to standardize the diagnosis of adenomyosis, either histopathologically or using one or more imaging techniques. A systematic review was performed following PRISM methodology that is demonstrated in Figure 1. Papers describing correlations of histopathologic or imaging based diagnosis and categorization were sought, including those that analyzed clinical parameters such as symptoms and/or the outcome of medical, procedural, or surgical interventions. The MESH search terms used included “Adenomyosis AND Classification”, “Adenomyosis AND Ultrasound Classification”, “Adenomyosis AND MRI Classifiction”; “Adenomyosis AND MRI, and Ultrasound AND Diagnosis”. Abstracts were screened and potentially relevant papers identifed for full text evaluation. In addition, the bibliographies of each paper was reviewed to identify other potential relevant sources. Since no patient identifiable data were included, no institutional review was required. The final search was performed on qctober 27, 2019.

RESULTS

There were 2,255 listings identified in the search. After removing duplicates, 1,652 were left. Review of the abstracts identified 278 for review of full text. Following review, there were 25 that were considered potentially relevant. From the bibliographies, an additional 17 papers were found also considered to be potentially relevant. Of the 42 full text papers that were reviewed in detail, nine histological classifications were identified (7, 13, 18, 20, 37-41) (Table 1), four of which were accompanied by an attempt at clinical correlation with symptoms(7, 18, 20, 38). Only one of these papers described correlation with the outcome of medical, procedural or surgical interventions, the McCausland study that reported that the rate of

bleeding and pain success of hysteroscopic electrodessication of the endometrium was inversely proportional to the depth of adenomyosis based on hysteroscopic biopsy. There were eight image-based reporting or classification systems identified, one based on TVUS (Table 3) and seven using MRI(12, 42-46) (Table 4), three of which included correlations with intervention outcomes(43-45), although these were surrogate (imaging), not clinical outcomes.

Categorization

General Considerations

Two general categories of classification were identified – one group was histopathologically based, while the others used imaging to make both a presumptive diagnosis of adenomyosis. and to categorize findings by any of a spectrum of ultrasound or magnetic resonance features.

Histopathological Systems

It should be recognized that there is a distinction between defining adenomyosis histopathologically, i.e., presence or absence of the disorder, and using histopathology to categorize findings to define phenotypes that may be useful in research and clinical care based on features such as disease volume, location and appearance. From a histopathological perspective, the studies identified used either retrospective correlation with symptoms, or, in a single instance, a well-defined, prospective methodology to evaluate the uterus by systematic sectioning and microscopic evaluation (7). Many reports seemed to focus on the endometrium and contiguous involvement of the myometrium, perhaps not evaluating the rest of the myometrium separately, an approach that may have missed examples of isolated outer myometrial disease.

Ultrasound-Based Systems

While there are a number of studies evaluating the utility of TVUS for diagnosis, two systems were identified that have been evaluated(46, 47). The ultrasound features associated with adenomyosis seem to have been summarized and evaluated by an ad hoc expert group called the Morphological Uterus Sonographic Assessment (MUSA) Group. The eight sonographic criteria described by the MUSA group (48) have been consolidated into a classification system for adenomyosis that has been recently modified to allow description of findings that are stratified by anterior and posterior location and by involvement with one or more of three defined myometrial layers(46). However, recently published evaluation of this system, evaluating inter rater agreement of a relatively large group (N=13) of imaging professionals demonstrated that the correlations were at best “moderate”, and frequently “poor” when performed by the seven raters with” medium” experience (49). In addition, this system has not been directly subjected to comparison with histopathological analysis following hysterectomy.

A somewhat similar ultrasound-based design that includes a scoring system has been proposed(50) (Figure 2). The scoring system asks the examiner first to identify adenomyosis with at least one of eight sonographic findings, report the findings as diffuse, focal or adenomyoma, and then assign a severity score for each on a 1-4 scale. Diffuse or focal findings that were of the outer myometrium or localized to the junctional zone (JZ) were categorized separately. While some of the scoring details were absent in the original paper, clarifications

were provided in a subsequent publication(47). For example, for outer myometrial findings, myometrial thickness was included (≤20, >20 and ≤30 or >30mm), as was the extent of involvement based on a distinction amongst anterior, posterior and right and left lateral quadrants of the myometrium. For inner myometrial involvement, similar four-quadrant assessments were made considering findings and the thickness of the JZ. Focal adenomyosis was assessed according to the diameter of the largest lesion, while adenomas were categorized by measured diameter ≤20, >20≤30 or >30≤40, >40mm and/or number (1,2, ≥3). The severity scores were categorized by the investigators as mild (1-3), moderate (4-6) and severe (≥7) with a maximum score of 24. The degree of interobserver reproducibility between two expert sonologists, was excellent, including distinction amongst three basic phenotypes – diffuse, focal and adenomyoma. It is important to recognize that this system uses both 2-D and 3-D ultrasound, so that 2-D videos and stored 3-D volumes were used to conduct the study(50).

MRI-Based Systems

A number of MRI-based systems have been published that use a spectrum of criteria for distinguishing amongst women with evidence consistent with adenomyosis (Table 4). Three of these are purely based upon well-described MRI characteristics (4, 12, 42) while one includes these features but adds the endometrial finding of a polypoid adenomyoma that is histopathologically based(41). Each of these four systems recognizes JZ abnormalities manifesting with a thickness that is above predetermined threshold levels, typically 12 mm and all recognize localized disease that involves the outer myometrium. Two also recognize the existence of disease that may originate in the outermost aspect of the outer myometrium, and which, in many cases, may be the consequence of endometriosis involving the myometrium by "invasion" through the serosa(12). The Bazot system adds a degree of fidelity to the other three by distinguishing anterior from posterior involvement as well as some acknowledgement of disease phenotype or volume (4).

A number of other, somewhat unique MRI-based systems were identified. The system reported by Dashottar et al, was presented in the context of an evaluation of the impact of the 52 mg levonorgestrel releasing intrauterine system on MR findings(44). These investigators focused on the JZ and classified cases as either focal or diffuse, with the latter either evenly or unevenly thickened. Also identified were adenomyosis classification systems designed to evaluate the impact of image guided therapy for adenomyosis including uterine artery embolization (UAE)(43) or high frequency focused ultrasound (HIFU)(45, 51). These are a departure from all of the others, instead relying upon characteristics of the adenomyotic features that likely reflect the relative volume of glandular and muscular elements in the given uterus.

System Utility

AUB

Histopathologic Systems

Several histopathological systems have been evaluated for correlation of pathological findings with bleeding symptoms, generally referring to HMB (here called "menorrhagia") by any of a spectrum of techniques. Bird reported no relationship of depth of involvement to bleeding symptoms, instead finding that the number of "islets" of adenomyotic glandular tissue per low

powered field was proportional to the amount of uterine bleeding(7). Relatively similar findings were reported by Sammour *et al* – there was no identified relationship of depth of involvement to the symptom of HMB, but using the number of adenomyotic foci per slide, there was a strong correlation to the reported bleeding volume. Both of these studies are hampered by the retrospective nature of the symptom documentation and the lack of an objective measure of bleeding volume. The outlier in this group of studies is the report by Levgur *et al* where the symptom of HMB ("menorrhagia") was found in 36.8% in women with deep foci and 13.3% of those with "intermediate" depth foci(20).

Only the McCausland study used the reported classification methodology to predict clinical outcome, in this instance, the impact of resectoscopic radiofrequency electricity based electrodesiccation of the endometrium for the symptom of HMB(38). While all but three of the treated patients had a "reduction in bleeding", those with adenomyosis "penetration" ≥2.1 mm experienced a lesser response than those with < 2.1 mm, where 78% had amenorrhea or light bleeding.

Ultrasound-Based Systems

Some investigators have evaluated the relationship of ultrasound features suggesting adenomyosis and estimated menstrual volume. A prevalence study described the use of TVUS, including 3-D imaging, to evaluate a cohort of young women (age 18-30) seeking contraceptive advice in Italy for features of adenomyosis, and then correlated sonographic findings to bleeding patterns and semiobjective measures of menstrual volume(10). The subjects had between one and three criteria for diagnosing diffuse adenomyosis (localized disease was not identified), and the volume of menstrual blood loss increased proportionate to the number of features found. These findings are similar to those reported by Naftalin *et al*, who described a 23% increase in bleeding volume for each additional sonographic finding(21).

No evidence was found evaluating the MUSA system as a predictor of the degree or volume of AUB. However the 2-D and 3-D ultrasound based Italian scoring system, previously discussed(50)(Figure 2), has been evaluated for its relationship to a number of symptoms, including AUB, using pictorial blood loss assessment charts (PBAC)(47). The investigators report that women with diffuse disease of the outer myometrium and a score of 4 (427.2±338.2), had higher PBAC scores than those with a score of 1 (200.7±128.2). There were also differences between focal disease with a score of at least 3 and those with a score of 1, however, sample sizes were small. The authors acknowledge that there may be a number of confounders and limitations, particularly since the study was performed with only two sonographers. Consequently, generalizability will require further evaluation with a larger number of sonographers with a spectrum of experience.

No studies were identified that demonstrated a relationship of either system to defining or predicting the results of medical or procedural interventions.

MRI Systems

There were no MRI systems identified that were evaluated for their utility in correlating

findings to AUB symptoms or for predicting the results of medical or procedural interventions directed at abnormal uterine bleeding.

Pain

Histopathological Systems

The relationship between pain and histopathologically-defined adenomyosis has been evaluated, but there is an absence of rigor in the categorization of the symptoms. There exists a spectrum of potential pain symptoms associated with adenomyosis including dysmenorrhea, dyspareunia, and acyclical pain. Each of Bird, Nishida, and Levgur *et al* demonstrated a correlation between depth of adenomyosis involvement and dysmenorrhea (7, 20, 52), and there was consistent demonstration of a relationship between the number or volume of foci of glandular tissue and this symptom (7, 18, 20, 52). Only Sammour *et al* evaluated dyspareunia and "other pain" and found a poor correlation with depth, but again, a relationship to the number of foci identified histopathologically.

Again, only the McCausland study used the classification to evaluate pain outcomes following resectoscopic electrodesiccation for HMB(38). In this instance, 73% of the patients with less than 2.1 mm invasion had a reduction in pain while only 23% had this experience if their adenomyosis "penetration" was at least 2.1 mm(38).

Ultrasound Systems

As was the case for AUB, no evidence could be found specifically evaluating the MUSA system findings and the presence or severity of dysmenorrhea. The aforementioned report by Pinazuti and another study be Naftalin *et al* have both demonstrated a relationship between the number of ultrasonographically-defined features of adenomyosis and the degree of dysmenorrhea (10, 53). The Naftalin group, from the United Kingdom, found that additional ultrasound features up to N=7 were associated with a numeric pain score increasing from just above five to almost nine out of a maximum of ten(53).

The Italian group also evaluated the relationship of their system (Figure 2) to the presence of pain, both dyspareunia and dysmenorrhea(47). They were able to demonstrate that dysmenorrhea scores were higher in women with diffuse findings and a score of 4 versus 1 or versus focal findings and a score of 4. There were no differences in the dyspareunia scores regardless of disease location or severity.

MRI Systems

As was the case for AUB, there were no MRI systems identified that were evaluated for their utility in correlating findings to pain symptoms or for predicting the results of medical or procedural interventions.

Infertility

Only the recently published Italian study presented data relating the findings of an imaging system with infertility(47)(Figure 2). The authors report that women with sonographic findings

consistent with focal disease of the outer myometrium (18/22) were more likely to have infertility (greater than 12 months) than those with other findings (Diffuse Outer 22/42; Diffuse Inner 33/62). Furthermore, there is no comparison with women without sonographic findings of adenomyosis.

No evidence was found linking imaging-based adenomyosis classification systems with the outcome of medical or surgical interventions for infertility.

Obstetrical Outcomes

The only study identified in this systematic review that evaluated obstetrical outcomes was the recently published Italian study(47)(Figure 2). Again, there were no normal controls, but, compared to women with diffuse adenomyosis, those who conceived with focal disease of the junctional zone were more likely to have had at least one "miscarriage" (11/15 versus 15/42).

A previously published systematic review suggested that the adverse impact of adenomyosis on outcomes such as pre-eclampsia and intrauterine growth restriction may occur proportionate to the number of sonographic criteria known to be related to adenomyosis(54). Nevertheless, the sample sizes were too small to support conclusions. There were no available data examining interventions to reduce the incidence of adverse obstetrical events related to adenomyosis.

Other Outcomes

Molecular Outcomes

Bourdon and colleagues from Paris have correlated MRI findings with serum cytokine profiles and found that levels of IL-17F, IL-23, IL-25, IL-31 and IL-33 were lower in women with adenomyosis compared to controls, where levels of inflammatory cytokines such as IL-6 and IL-1β were similar(55). For women with both focal and diffuse adenomyosis, the levels of IL-23, IL-25, IL-31 and IL-33 were lower than controls and for women with focal adenomyosis the IL-17F levels were lower than controls. TNFα levels were lower in women with focal disease compared to those with diffuse adenomyosis. They also found that IL-25 and IL-31 levels correlated with the ratio of junctional zone thickness to overall myometrial thickness and there was no correlation of these levels with the presence or volume of focal adenomyotic disease.

Surrogate Imaging Outcomes

A number of investigators have correlated their own classification system with outcomes of image guided therapies. Indeed, these are surrogate imaging outcomes because none of the studies identified correlated the baseline imaging appearance to clinical outcomes.

One group (Gong *et al*) was identified that reported correlation of the results of ultrasound-guided focused ultrasound (MRgFUS) therapy with a MRI-based classification system(45, 51). Their system included location of adenomyosis, and adenomyosis volume that included the number of T2 hyperintense foci visualized in an MRI "slice". They used the "surrogate outcome" of contrast MRI-determined nonperfused volume following treatment and found that anterior wall adenomyosis in the anteverted uterus, relatively free of T2 hyperintense foci, was

associated with an increased chance of nonperfusion. Sonication time was also less when there were less than 5 T2 hyperintense spots per slice. Kserci *et al,* also evaluating MRgFUS, demonstrated that the T1 weighted, perfusion based "time signal intensity curve" was predictive of an imaging outcome – non perfused volume (NPV) of disease(56). The immediate NPV ratios were over twice as high in the cohort with a signal intensity curve lower than the myometrium as opposed to those with a curve similar to, or higher than that of the normal appearing myometrium (89.2 ± 6.7% and 42.4 ± 19.0%).

Both these studies suggest that the relative amount of glands and stroma in the adenomyotic mass can impact the results of hyperthermic therapy – at least based on the imaging outcomes.

DISCUSSION

Adenomyosis is a disorder of increasing interest, in part because of its newfound and apparently high prevalence, based on imaging, and in part because of its perceived variable impact on clinical outcomes such as infertility, pelvic pain, AUB and pregnancy-related disorders. It is apparent that adenomyosis is often asymptomatic. Furthermore, it can be assumed that even if the patient has symptoms – AUB, infertility, dysmenorrhea – in association with image-based evidence of adenomyosis, there is frequently not a cause and effect relationship.

These observations, along with the spectrum of disorder phenotypes, begs the performance of research designed to assist both patients and clinicians in making informed decisions when imaging-based techniques indicate the possible or likely presence of adenomyosis. Such research requires both an accurate diagnosis, and methods by which disease phenotypes are identified and categorized in a standardized fashion. A standardized reporting system would facilitate meaningful comparison of a spectrum of outcomes including the performance of metaanalysis of studies of patients with similar disease characteristics. It is quite likely that features other than static images will be of value, including molecular examination of endometrial and/or myometrial specimens, as well as dynamic imaging of myometrial function.

The results of this review suggest that, based on comparison of imaging with histopathological findings, both MRI and ultrasound as currently used may have similar sensitivity and specificity for the diagnosis of adenomyosis. The skill of the sonographer appears to be more important for ultrasound than for MRI, perhaps, in part because of the ability to store MR images in a standardized fashion that is amenable to detailed post acquisition review. It is not clear that 3-D TVUS provides the increased utility that was hoped for, but additional refinement in technique and image storage may still demonstrate its value. The role for TVUS-based elastography is yet to be defined, but it may provide an additional dimension of diagnostic utility and could provide clues to the impact of the disease on myometrial structure and function.

The accuracy of imaging-based diagnosis is still a work in progress. Many of the studies correlating TVUS and MRI with histopathological examination have been performed using older

equipment, a circumstance that implies a need for updated studies such as that by Tellum *et al* that suggested alterations in our perception of the most discriminatory MRI findings; JZ thickness may not be as sensitive as initially proposed(57). In unaffected women, the JZ itself is a normal finding that is thought to depict the inner myometrium, a circumstance that must be considered when determining the volume of adenomyosis, particularly when it is apparently limited to the inner myometrium.

While histopathology remains the "gold standard" for diagnosis, it is not practicable for women who wish to retain their uterus. Furthermore, the study by Bird et al(7), demonstrated that "standard" sectioning techniques may result in a substantial reduction in sensitivity, a circumstance that must be considered when designing studies comparing imaging to histopathology, particularly when hysterectomy is used. The utility of biopsy for the diagnosis of adenomyosis is still in question and may be of greater value for molecular studies where the uterus remains in situ(58).

While the need for a uniform system for categorization of adenomyosis is paramount, such a system does not yet exist. It is apparent that, for TVUS, the number, location and/or volume of ultrasound-detected features may be correlated to at least some outcomes(10, 21, 47, 53), an observation that requires further study. Regardless, the apparent sensitivity, specificity and accessibility of TVUS will make it the first line of assessment in the majority of offices, institutions and health-care systems.

The prevailing perspective is that MRI may ultimately be the most accurate arbiter of disease phenotype. However, the cost of MRI makes it less accessible to patients, particularly in low resource environments, and, while there exist a number of promising MRI-based classification proposals (4, 12, 41, 42), none have been subjected to rigorous evaluation for their relationship with symptoms, clinical outcomes, or the results of medical or procedural outcomes, including uterus-sparing surgery. One possible advantage of MRI may exist in the ability to identify imaging patterns, such as T2 hyperintense foci, that might correlate to hysterectomy-based histopathology studies that suggested that symptoms, including pain and HMB, may be related to the amount of glandular tissue observed within the myometrium (7, 52). The observation that some image guided procedures may be more successful depending on the MRI appearance(43, 45) also suggests that the observed disease pattern may be an important inclusion in a system of disease categorization.

It quite possible, if not likely, that imaging-based disease phenotype will not adequately correlate to clinical manifestations or prognosis of therapeutic interventions. Assessment of molecular expressions be they obtained from serum, endometrial aspirates, or endometrial or myometrial biopsy specimens, may be important in determining the impact of adenomyosis in a given patient, a circumstance that may have particular importance in women with reproductive failure or who are undergoing embryo transfer(29, 30, 59-67). Their potential role should be accounted for in the design of any system. Another potential mechanism of adenomyosis-related morbidity, in particular infertility, is the impact of the disorder on myometrial contractility, either via an impact on sperm transport(68), or on endometrial receptivity(69).

Such challenging mechanisms, while difficult to study, require further evaluation using appropriate dynamic imaging techniques.

Finally, the rapidly developing field of machine learning and artificial intelligence (AI), seem appropriate approaches that may support or even augment the interpretation of TVUS or MRI images for a number of diagnoses, including adenomyosis. It seems reasonable to develop reporting systems that are amenable to inclusion in the design of AI initiatives for adenomyosis.

CONCLUSIONS

It is apparent that adenomyosis *may* contribute to clinical symptoms including AUB symptoms such as HMB as well as dysmenorrhea, infertility, and a number of adverse obstetrical outcomes. However, the results of this review suggest that no system or technology has been demonstrated to have clear utility to aid the clinician regarding prognosis or the impact of medical or procedural interventions across a spectrum of disease phenotypes. Clearly, it is necessary to combine our relatively newfound ability to diagnose this disorder without hysterectomy, improve the diagnostic accuracy, and design and interpret research in a fashion that allows for better understanding of the various outcomes associated with the disorder(70). Indeed, as Bird stated in 1971"….adenomyosis can occur silently and…certain uteri significantly involved with this process are possessed by an asymptomatic owner"(7).

There is an urgent need for harmonized classification systems for both ultrasound and MRI that comport with the histopathological features of the disorder. Any system that is created should be carefully and rigorously evaluated for utility and generalizability amongst the spectrum of imaging clinicians who assess women who may have adenomyosis. While it is likely that results will be optimal when imaging is performed by specialists in uterine disorders, it would be preferable if systems are designed allow a larger population of clinicians to identify the presence of the disorder and at least categorize in a rudimentary fashion. Fortunately, initiatives involving the international radiological and gynecological communities are underway that are designed to achieve these goals so that clinicians, investigators, and especially patients will benefit from an increased understanding of adenomyosis.

REFERENCES

1. von Rokitansky C. "Uber Uterusdru¨ sen-Neubildung. Z Gesellschaft Aerzte (Wien). 1860;16:577-81.
2. Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. Am J Obstet Gynecol. 2009;201(1):107 e1-6.
3. Champaneria R, Abedin P, Daniels J, Balogun M, Khan KS. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. Acta Obstet Gynecol Scand. 2010;89(11):1374-84.
4. Bazot M, Darai E. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril. 2018;109(3):389-97.
5. Andres MP, Borrelli GM, Ribeiro J, Baracat EC, Abrao MS, Kho RM. Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2018;25(2):257-64.
6. Molitor JJ. Adenomyosis: a clinical and pathological appraisal. American Journal of Obstetrics & Gynecology. 1971;110(2):275-84.
7. Bird CC, McElin TW, Manalo-Estrella P. The elusive adenomyosis of the uterus--revisited. Am J Obstet Gynecol. 1972;112(5):583-93.
8. Seidman JD, Kjerulff KH. Pathologic findings from the Maryland Women's Health Study: practice patterns in the diagnosis of adenomyosis. International Journal of Gynecological Pathology. 1996;15(3):217-21.
9. Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D. How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. Hum Reprod. 2012;27(12):3432-9.
10. Pinzauti S, Lazzeri L, Tosti C, Centini G, Orlandini C, Luisi S, et al. Transvaginal sonographic features of diffuse adenomyosis in 18-30-year-old nulligravid women without endometriosis: association with symptoms. Ultrasound Obstet Gynecol. 2015;46(6):730-6.
11. Garcia-Solares J, Donnez J, Donnez O, Dolmans MM. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertil Steril. 2018;109(3):371-9.
12. Kishi Y, Suginami H, Kuramori R, Yabuta M, Suginami R, Taniguchi F. Four subtypes of adenomyosis assessed by magnetic resonance imaging and their specification. Am J Obstet Gynecol. 2012;207(2):114 e1-7.
13. Sampson JA. Perforating hemorrhagic (Chocolate) cysts of the ovary: Their importance and especially their relation to pelvic adenomas of endometrial type ("Adenomyoma" of the uterus, rectovaginal septum, sigmoid, etc.). Transactions of the American Gynecological Society. 1921;46:162-241.
14. Kilkku P, Erkkola R, Gronroos M. Non-specificity of symptoms related to adenomyosis. A prospective comparative survey. Acta Obstet Gynecol Scand. 1984;63(3):229-31.
15. Vercellini P, Parazzini F, Oldani S, Panazza S, Bramante T, Crosignani PG. Adenomyosis at hysterectomy: a study on frequency distribution and patient characteristics. Hum Reprod. 1995;10(5):1160-2.

16. Weiss G, Maseelall P, Schott LL, Brockwell SE, Schocken M, Johnston JM. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). Fertil Steril. 2009;91(1):201-6.
17. Vercellini P, Ragni G, Trespidi L, Oldani S, Panazza S, Crosignani PG. Adenomyosis: a deja vu? Obstet Gynecol Surv. 1993;48(12):789-94.
18. Sammour A, Pirwany I, Usubutun A, Arseneau J, Tulandi T. Correlations between extent and spread of adenomyosis and clinical symptoms. Gynecol Obstet Invest. 2002;54(4):213-6.
19. McCausland AM. Hysteroscopic myometrial biopsy: its use in diagnosing adenomyosis and its clinical application. Am J Obstet Gynecol. 1992;166(6 Pt 1):1619-26; discussion 26-8.
20. Levgur M, Abadi MA, Tucker A. Adenomyosis: symptoms, histology, and pregnancy terminations. Obstet Gynecol. 2000;95(5):688-91.
21. Naftalin J, Hoo W, Pateman K, Mavrelos D, Foo X, Jurkovic D. Is adenomyosis associated with menorrhagia? Hum Reprod. 2014;29(3):473-9.
22. Di Donato N, Montanari G, Benfenati A, Leonardi D, Bertoldo V, Monti G, et al. Prevalence of adenomyosis in women undergoing surgery for endometriosis. Eur J Obstet Gynecol Reprod Biol. 2014;181:289-93.
23. Taran FA, Weaver AL, Coddington CC, Stewart EA. Understanding adenomyosis: a case control study. Fertil Steril. 2010;94(4):1223-8.
24. Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Hum Reprod Update. 2012;18(4):374-92.
25. Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The Impact of Adenomyosis on Women's Fertility. Obstet Gynecol Surv. 2016;71(9):557-68.
26. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Steril. 2017;108(3):483-90 e3.
27. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod. 2014;29(5):964-77.
28. Rocha TP, Andres MP, Borrelli GM, Abrao MS. Fertility-Sparing Treatment of Adenomyosis in Patients With Infertility: A Systematic Review of Current Options. Reprod Sci. 2018;25(4):480-6.
29. Guo S, Li Z, Yan L, Sun Y, Feng Y. GnRH agonist improves pregnancy outcome in mice with induced adenomyosis by restoring endometrial receptivity. Drug Des Devel Ther. 2018;12:1621-31.
30. Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil Steril. 2011;95(3):1133-6.
31. Bruun MR, Arendt LH, Forman A, Ramlau-Hansen CH. Endometriosis and adenomyosis are associated with increased risk of preterm delivery and a small-for-gestational-age child: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2018;97(9):1073-90.

32. Razavi M, Maleki-Hajiagha A, Sepidarkish M, Rouholamin S, Almasi-Hashiani A, Rezaeinejad M. Systematic review and meta-analysis of adverse pregnancy outcomes after uterine adenomyosis. Int J Gynaecol Obstet. 2019;145(2):149-57.
33. Walsh JW, Taylor KJ, Rosenfield AT. Gray scale ultrasonography in the diagnosis of endometriosis and adenomyosis. AJR Am J Roentgenol. 1979;132(1):87-90.
34. Murao F, Hata K, Shin K, Hata T, Yoshino K, Yamamoto K, et al. Ultrasonography for the diagnosis of adenomyosis. Nihon Sanka Fujinka Gakkai Zasshi. 1986;38(11):2073-7.
35. Bohlman ME, Ensor RE, Sanders RC. Sonographic findings in adenomyosis of the uterus. AJR Am J Roentgenol. 1987;148(4):765-6.
36. Benagiano G, Habiba M, Brosens I. The pathophysiology of uterine adenomyosis: an update. Fertil Steril. 2012;98(3):572-9.
37. Siegler AM, Camilien L. Adenomyosis. J Reprod Med. 1994;39(11):841-53.
38. McCausland AM, McCausland VM. Depth of endometrial penetration in adenomyosis helps determine outcome of rollerball ablation. Am J Obstet Gynecol. 1996;174(6):1786-93; 93-4.
39. Hulka CA, Hall DA, McCarthy K, Simeone J. Sonographic findings in patients with adenomyosis: can sonography assist in predicting extent of disease? AJR Am J Roentgenol. 2002;179(2):379-83.
40. Vercellini P, Trespidi L, Panazza S, Bramante T, Mauro F, Crosignani PG. Laparoscopic uterine biopsy for diagnosing diffuse adenomyosis. J Reprod Med. 1996;41(4):220-4.
41. Grimbizis GF, Mikos T, Tarlatzis B. Uterus-sparing operative treatment for adenomyosis. Fertil Steril. 2014;101(2):472-87.
42. Gordts S, Brosens JJ, Fusi L, Benagiano G, Brosens I. Uterine adenomyosis: a need for uniform terminology and consensus classification. Reprod Biomed Online. 2008;17(2):244-8.
43. Jung DC, Kim MD, Oh YT, Won JY, Lee DY. Prediction of early response to uterine arterial embolisation of adenomyosis: value of T2 signal intensity ratio of adenomyosis. Eur Radiol. 2012;22(9):2044-9.
44. Dashottar S, Singh AK, Debnath J, Muralidharan CG, Singh RK, Kumar S. Comparative analysis of changes in MR imaging of pre and post intrauterine progesterone implants in adenomyosis cases. Med J Armed Forces India. 2015;71(2):145-51.
45. Gong C, Setzen R, Liu Z, Liu Y, Xie B, Aili A, et al. High intensity focused ultrasound treatment of adenomyosis: The relationship between the features of magnetic resonance imaging on T2 weighted images and the therapeutic efficacy. Eur J Radiol. 2017;89:117-22.
46. Van den Bosch T, de Bruijn AM, de Leeuw RA, Dueholm M, Exacoustos C, Valentin L, et al. Sonographic classification and reporting system for diagnosing adenomyosis. Ultrasound Obstet Gynecol. 2019;53(5):576-82.
47. Exacoustos C, Morosetti G, Conway F, Camilli S, Martire FG, Lazzeri L, et al. New sonographic classification of adenomyosis: do type and degree of adenomyosis correlate to severity of symptoms? J Minim Invasive Gynecol. 2019.
48. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium

and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46(3):284-98.
49. Rasmussen CK, Van den Bosch T, Exacoustos C, Manegold-Brauer G, Benacerraf BR, Froyman W, et al. Intra- and Inter-Rater Agreement Describing Myometrial Lesions Using Morphologic Uterus Sonographic Assessment: A Pilot Study. J Ultrasound Med. 2019;38(10):2673-83.
50. Lazzeri L, Morosetti G, Centini G, Monti G, Zupi E, Piccione E, et al. A sonographic classification of adenomyosis: interobserver reproducibility in the evaluation of type and degree of the myometrial involvement. Fertil Steril. 2018;110(6):1154-61 e3.
51. Gong C, Yang B, Shi Y, Liu Z, Wan L, Zhang H, et al. Factors influencing the ablative efficiency of high intensity focused ultrasound (HIFU) treatment for adenomyosis: A retrospective study. Int J Hyperthermia. 2016;32(5):496-503.
52. Nishida M. Relationship between the onset of dysmenorrhea and histologic findings in adenomyosis. Am J Obstet Gynecol. 1991;165(1):229-31.
53. Naftalin J, Hoo W, Nunes N, Holland T, Mavrelos D, Jurkovic D. Association between ultrasound features of adenomyosis and severity of menstrual pain. Ultrasound Obstet Gynecol. 2016;47(6):779-83.
54. Sharma S, Bathwal S, Agarwal N, Chattopadhyay R, Saha I, Chakravarty B. Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients. Reprod Biomed Online. 2019;38(1):13-21.
55. Bourdon M, Santulli P, Chouzenoux S, Maignien C, Bailly K, Andrieu M, et al. The Disease Phenotype of Adenomyosis-Affected Women Correlates With Specific Serum Cytokine Profiles. Reprod Sci. 2019;26(2):198-206.
56. Keserci B, Duc NM. The role of T1 perfusion-based classification in predicting the outcome of magnetic resonance-guided high-intensity focused ultrasound treatment of adenomyosis. Int J Hyperthermia. 2018;34(3):306-14.
57. Tellum T, Matic GV, Dormagen JB, Nygaard S, Viktil E, Qvigstad E, et al. Diagnosing adenomyosis with MRI: a prospective study revisiting the junctional zone thickness cutoff of 12 mm as a diagnostic marker. Eur Radiol. 2019.
58. Tellum T, Qvigstad E, Skovholt EK, Lieng M. In Vivo Adenomyosis Tissue Sampling Using a Transvaginal Ultrasound-guided Core Biopsy Technique for Research Purposes: Safety, Feasibility, and Effectiveness. J Minim Invasive Gynecol. 2019.
59. Xiao Y, Sun X, Yang X, Zhang J, Xue Q, Cai B, et al. Leukemia inhibitory factor is dysregulated in the endometrium and uterine flushing fluid of patients with adenomyosis during implantation window. Fertil Steril. 2010;94(1):85-9.
60. Tremellen KP, Russell P. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. II: adenomyosis and macrophages. J Reprod Immunol. 2012;93(1):58-63.
61. Zhihong N, Yun F, Pinggui Z, Sulian Z, Zhang A. Cytokine Profiling in the Eutopic Endometrium of Adenomyosis During the Implantation Window After Ovarian Stimulation. Reprod Sci. 2016;23(1):124-33.
62. Jiang Y, Jiang R, Cheng X, Zhang Q, Hu Y, Zhang H, et al. Decreased expression of NR4A nuclear receptors in adenomyosis impairs endometrial decidualization. Mol Hum Reprod. 2016;22(9):655-68.

63. Feng T, Wei S, Wang Y, Fu X, Shi L, Qu L, et al. Rhein ameliorates adenomyosis by inhibiting NF-kappaB and beta-Catenin signaling pathway. Biomed Pharmacother. 2017;94:231-7.
64. Carrarelli P, Yen CF, Funghi L, Arcuri F, Tosti C, Bifulco G, et al. Expression of Inflammatory and Neurogenic Mediators in Adenomyosis. Reprod Sci. 2017;24(3):369-75.
65. Yen CF, Liao SK, Huang SJ, Tabak S, Arcuri F, Lee CL, et al. Decreased Endometrial Expression of Leukemia Inhibitory Factor Receptor Disrupts the STAT3 Signaling in Adenomyosis During the Implantation Window. Reprod Sci. 2017;24(8):1176-86.
66. Streuli I, Santulli P, Chouzenoux S, Chapron C, Batteux F. Serum Osteopontin Levels Are Decreased in Focal Adenomyosis. Reprod Sci. 2017;24(5):773-82.
67. Lai TH, Chang FW, Lin JJ, Ling QD. Endometrial L-selectin ligand is downregulated in the mid-secretory phase during the menstrual cycle in women with adenomyosis. Taiwan J Obstet Gynecol. 2018;57(4):507-16.
68. Kissler S, Hamscho N, Zangos S, Wiegratz I, Schlichter S, Menzel C, et al. Uterotubal transport disorder in adenomyosis and endometriosis--a cause for infertility. BJOG. 2006;113(8):902-8.
69. Kuijsters NPM, Methorst WG, Kortenhorst MSQ, Rabotti C, Mischi M, Schoot BC. Uterine peristalsis and fertility: current knowledge and future perspectives: a review and meta-analysis. Reprod Biomed Online. 2017;35(1):50-71.
70. Horton J, Sterrenburg M, Lane S, Maheshwari A, Li TC, Cheong Y. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Hum Reprod Update. 2019.

Table 1. Histopathological Diagnostic Criteria

Author and year	Diagnosis
Based on Depth of Myometrium Involved	
Sammour A, et al. 2002 (18)	≥2 mm below endo-myometrial junction; myometrial hyperplasia
Levgur et al. 2000 (20)	≥2 mm below endo-myometrial junction; myometrial hyperplasia
Hulka CA et al 2002.(39)	>2-3mm (one half low power field)
Bird et al 1972(7)	Presence of glands and stroma at least one low-power field below the "basal" layer of endometrium and surrounded by myometrium.
Vercellini P et al. 1993 (17)	>4mm (one low power field)
Sandberg EG & Cohn F. 1962 (60)	>8mm (two low power fields)
Based on Proportion of Myometrium Involved	
Hendrickson MR & Kempson RL. 1987 (61)	Invasion more >1/3 thickness of the uterine musculature
Ferenczy A. 1998 (62)	Distance between endomyometrial junction to nearest adenomyotic focus should be >25% of the myometrial thickness.
Based on Other Histopathological Features	
Uduwela AS et al. 2000 (63)	Normal boundary between the endometrium and the myometrium is disrupted
Bazot M et al. 2001 (64)	The ectopic endometrium is basal type non secretory tissue with a direct connection to the eutopic basalis

Table 2. Histopathological Adenomyosis Classification Systems

Author	Year	Category		Pattern	
		Name	Depth	Name	Foci
Samson(13)	1921	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(7)	1972	Grade I	Sub-endometrial basalis	Mild	1-3 foci/LPF
		Grade II	Mid-myometrium	Moderate	4-9
		Grade III	Outer myometrium	Severe	≥ 10
Nishida(52)	1991	Type 1	Continuous from endometrium	N/A	Islands/Section
		Type 2	Continuous from serosa	N/A	Glands/Section
McCausland(19)	1991	Superficial	≤1 mm depth	N/A	N/A
		Deep	>1 mm depth	N/A	N/A
Siegler(37)	1994	Grade 1	Inner 1/3	Mild	1-3 foci/LPF
		Grade 2	2/3	Moderate	4-9
		Grade 3	Entire myometrium	Severe	≥ 10
Levgur(20)	2000	Superficial	<40%	N/A	Foci/LPF
		Intermediate	40-80%	N/A	N/A
		Deep	>80%	N/A	N/A
Sammour(18)	2002	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 (39)	2002	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(65)	2006	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

Table 3. MUSA Ultrasound-Based Classification System(46)

Item	Feature/Appearance
Presence	Enlarged globular uterus
	Asymmetrical thickening
	Myometrial cysts
	Echogenic subendometrial lines and buds
	Hyperechogenic islands
	Fan-shaped shadowing
	Irregular or interrupted junctional zone
	Translesional vascularity (Doppler)
Location	Anterior
	Posterior
	Lateral left
	Lateral right
	Fundal
Differentiation	Focal (>25% surrounded by normal myometrium)
	Diffuse
	Mixed
	Adenomyoma (surrounded by hypertrophic)
Cystic-Non-Cystic	Measurable
	Report largest diameter of largest cyst
Layer	Inner: Type 1
	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)
Extent	Mild: <25%
	Moderate: 25-50%
	Severe: >50%
Size	Focal: Plane of largest diameter of largest lesion
	Diffuse: Myometrial thickness

Table 4. MRI Based Adenomyosis Classification Systems

Author	Year	Criteria	Classification
Gordts(42)	2008	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	
Jung(43)	2012	T2 weighted signal intensity ratio - above 0.475 predicted imaging response to UAE	NS
Kishi(12)	2012	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(41)	2014	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(44)	2015	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
Gong(45)	2017	<5 foci - lower sonication time, and higher NPV ratio	NS
		Anterior adenomyosis (anteverted uterus) higher NPV ratio	NS
Bazot(4)	2018	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	

FIGURE LEGENDS

Figure 1. Prisma Diagram

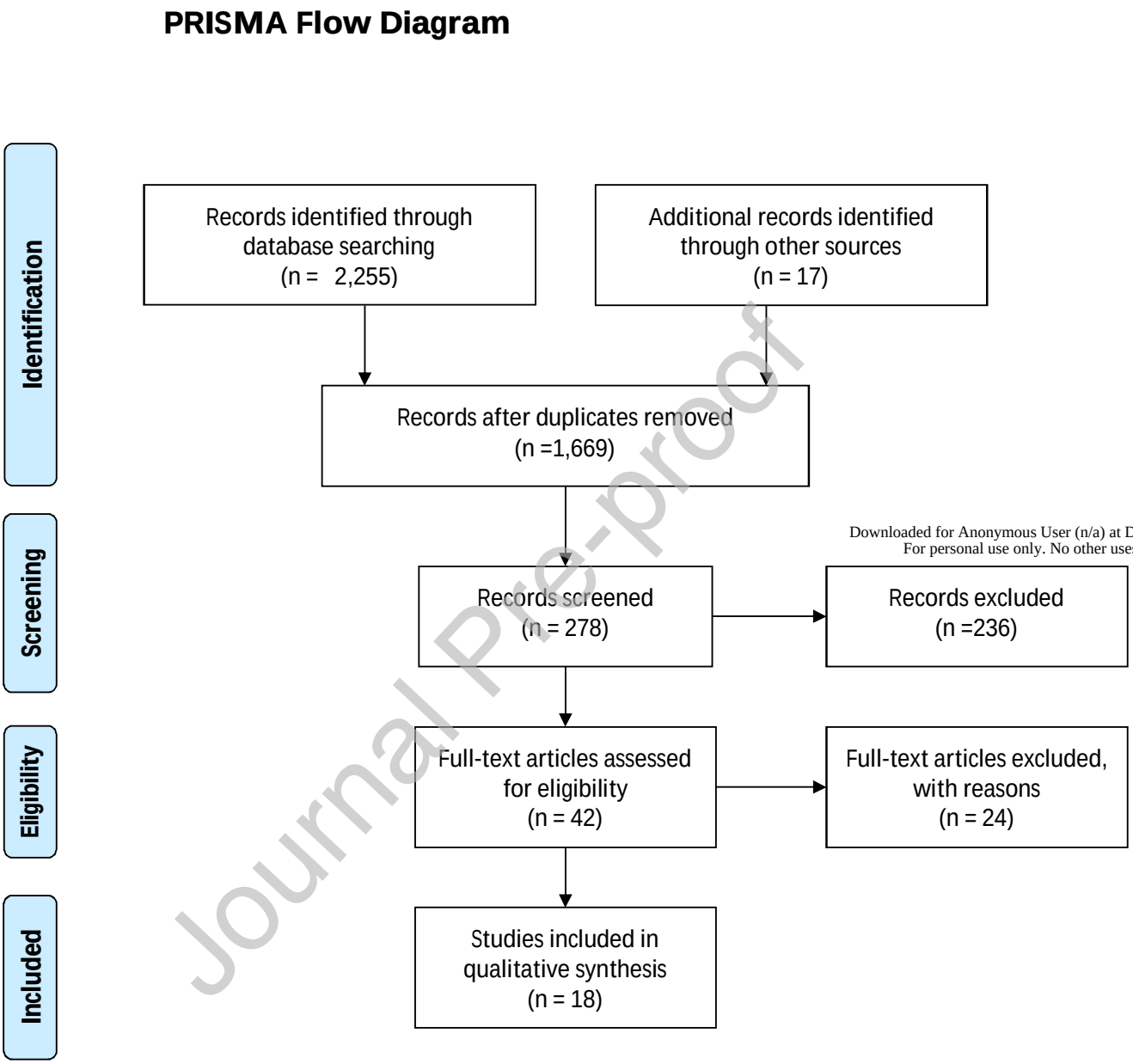

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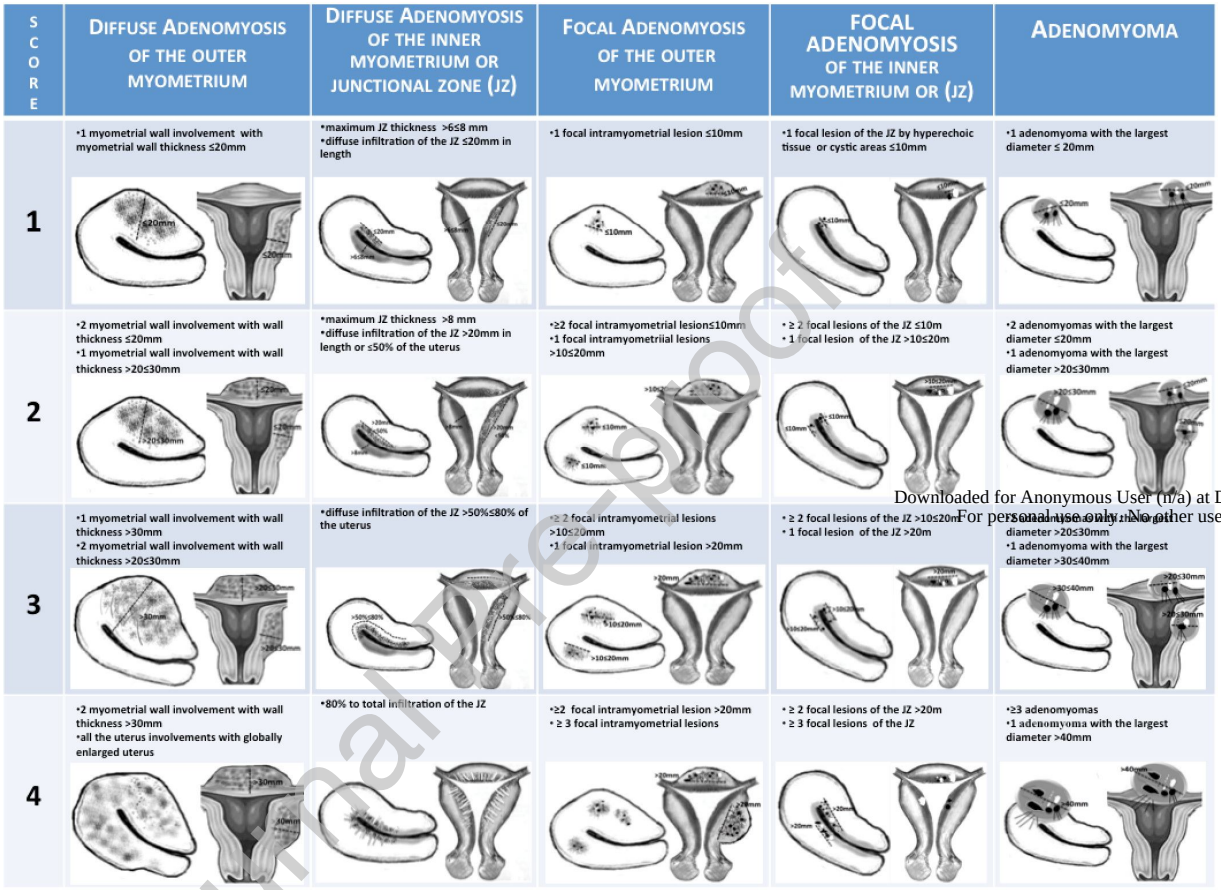
Figure 2. Transvaginal Ultrasound-Based "Sonographic Classification of Adenomyosis"
This scoring system is largely based on diagnostic criteria published by the MUSA group(46), but has been expanded to reflect disease volume/extent of uterine involvement and then correlated with a number of symptoms including AUB, dysmenorrhea and infertility(47). Findings (diffuse outer, diffuse inner, focal inner, focal outer, and adenomyoma) are each assigned severity scores ranging from 1-4 and then totaled. Mild (1-3), moderate (4-6) and severe (≥7) with a maximum score of 24. Used with permission.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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