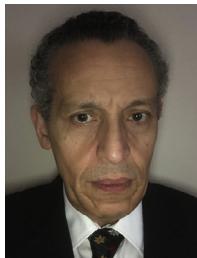


REVIEW



Exploring the challenges for a new classification of adenomyosis



BIOGRAPHY

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KEY MESSAGE

As yet, no widely agreed classification for adenomyosis has been established. Imaging-based diagnosis can supplement but perhaps not replace traditional histological categorisations. The controversy around theories of pathogenesis suggest a limited scope for them to be incorporated into any emerging classification system.

ABSTRACT

The availability of non-invasive diagnostic tests is an important factor in the renewed interest in adenomyosis, as the disease can now be more accurately mapped in the uterus without a need for hysterectomy. An agreed system for classifying and reporting the condition will enhance our understanding of the disease and is envisaged to enable comparison of research studies and treatment outcomes. In this review, we assess previous and more recent attempts at producing a taxonomy, especially in view of the latest proposal for subdivision of adenomyosis into an internal and an external variant. In this context, we also explore the uncertainties linked to classifying involvement of the uterovesical pouch, the pouch of Douglas and lesions in the outer myometrium. Two opposing hypotheses are forwarded to explain the pathogenesis of these variants, namely that disease localized in these areas originates from an invasion by uterine adenomyosis of peritoneal organs; alternatively, that lesions present in the outer myometrium originate from peritoneal endometriosis. At the root of debates around these opposing theories of pathogenesis is fragmentary evidence. Because of the limitations of currently available evidence, and until this issue is resolved, broad agreement on a hypothesis to underpin any proposed classification is unlikely.

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KEYWORDS

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INTRODUCTION

Following early descriptions of the 'invasion of epithelial cells' into the peritoneal cavity and the uterine musculature, and until a nosological distinction was drawn by [Frankl \(1925\)](#) and [Sampson \(1927\)](#), both adenomyosis and endometriosis were subsumed under the common term 'adenomyoma'. Given this, in reconstructing the path towards a modern classification of adenomyosis, irrespective of whether the two conditions are connected, it is important to take into account the early common terminology. Here, we will use the definition proposed by [Bird et al. \(1972\)](#) that considers adenomyosis as: 'the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium'.

The relationship between the ectopic and the eutopic endometrium has been debated for more than a century: [Cullen \(1908\)](#) and others supported the view that 'adenomyoma' involves invasion of the endometrium within the myometrium and, as early as 1908, Cullen was able to establish continuity between the ectopic and eutopic endometrium in 58 out of the 73 cases examined. An apparent lack of continuity between the basal and ectopic endometrium in some cases, however, was used by Cullen to allow for vascular or lymphatic invasion as possible routes for transporting endometrium deep within the muscle layer. Proponents of Cullen's views included [Sampson \(1925\)](#) and [Halban \(1933\)](#) who suggested the designation *hysteroadenosis metastatica* to stress the essence of the theory. [Meyer \(1925\)](#), [von Burg \(1926\)](#) and [Otto \(1957\)](#) demonstrated, through extensive histologic investigations, the existence of a connection between endometrial islands found in the myometrium and the basal endometrium in practically all cases of adenomyosis. [Emge \(1962\)](#) stressed that such a connection was difficult to demonstrate in cases of stromal atrophy and myometrial hypertrophy.

Agreeing on a classification for a disease is an important step in our understanding of its pathology, pathogenesis and clinical manifestations. It allows improved

comparisons of research data and clinical outcomes ([Canis et al., 2018](#)); in this respect, [Sampson \(1921\)](#) attempted a first classification of the lesion, then known as 'adenomyoma', based on a morphological description linked to a theory of aetiology. He proposed that adenomyomas may originate through one of three routes: from invasion of the eutopic endometrium within the myometrium; from invasion from outside the uterus, i.e. from an 'endometrial cyst'; or from misplaced endometrial tissue in the uterine wall. To date, a comprehensive classification has not yet been agreed. At any rate, developing a classification is perhaps best viewed as an evolving process that reflects the current state of knowledge and, given the number of aspects that still need clarification, it is not surprising that a consensus is yet to emerge.

Our understanding of adenomyosis remains limited for several reasons. For some time, an important limitation has been the lack of reliable diagnostic tools, with diagnosis only achievable on a hysterectomy specimen, where selection bias becomes an important factor. In addition, mapping the extent of the disease after hysterectomy is resource intensive and is rarely undertaken because it has no applications outside research. More recently, attempts have been made at a more conservative surgical approach. Non-invasive diagnostic procedures, such as ultrasound and magnetic resonance imaging (MRI) have been available for more than 30 years. Advances in imaging has made it possible to identify the disease in women who do not require or want a hysterectomy, such as cases of infertility and preclinical cases. Imaging diagnosis can also enable the development of clinical datasets and the assessment of progress over time. Detailed imaging diagnosis, however, requires expertise and can suffer from lack of sensitivity and specificity. Cost and availability are likely to favour the use of transvaginal scan (TVS), which can be highly accurate if carried out by expert sonographers ([Vannuccini and Petraglia, 2019](#)). For all subtypes, MRI has a pooled sensitivity of 0.77, specificity of 0.89, positive likelihood ratio of 6.5, and negative likelihood ratio of 0.2 ([Bazot and Darai, 2018](#)), and should be considered a second-line imaging technique when ultrasound is inconclusive.

In view of the availability of modern imaging, efforts aimed at developing a classification for adenomyosis should include the establishment and full clarification of diagnostic criteria based on these techniques and aim to achieve a detailed description of its variants. A classification could also link disease extent with symptoms, with known pathophysiological events or the coexistence of related pathology. With the use of modern high-resolution imaging, small foci of endometrial glands are increasingly being visualized. Often, their clinical significance is unclear, but the identification of such foci can affect the reported prevalence. In this specific setting, some of the smaller lesions may be incidental findings. This calls for more research into the relationship between localized lesions, infertility, menstrual abnormalities and dysmenorrhoea.

Some 15 years ago, the International Federation of Gynaecology and Obstetrics (FIGO) initiated a process to produce an agreed classification ([Gordts et al., 2008](#)), but this did not progress further until recently when the effort gathered renewed momentum. Here, we present an outline of available evidence and consider whether this supports the existence and description of distinct types of adenomyosis.

CLASSIFICATIONS BASED ON HISTOLOGIC CRITERIA

Several attempts have been made to produce a system for the classification of adenomyosis based on histologic findings in uteri removed by hysterectomy. All these attempts relied on observed features, such as the depth of glands within the myometrium, the location of adenomyotic lesions and whether the involvement is diffuse or localized. The latter encompasses focal or nodular lesions in which one or more gland sites are identified within the myometrium.

A further consideration is the number of glands or their density within the myometrium ([Bird et al., 1972](#); [Siegl and Camilien, 1994](#)). The problem is that routine histologic descriptions are limited to assessing the presence or absence of adenomyosis, as thorough mapping of removed uteri is resource intensive. In addition, the incidence of adenomyosis was shown to vary in relation to the number of histologic sections examined, and agreement on a

TABLE 1 PROPOSED HISTOLOGICAL CUT-OFF POINTS FOR THE DIAGNOSIS OF ADENOMYOSIS

| Reference | Diagnostic cut-off point |
|--------------------------------|---|
| Owolabi and Strickler, 1977 | >1 LPF |
| Novak and Woodruff, 1979 | >1 HPF |
| Hendrickson and Kempson, 1980 | >1/4 of total uterine wall thickness |
| Gompel and Silverberg, 1985 | >1 medium-power field (x100) |
| Parazzini et al., 1997 | >0.5 LPF (2.5 mm) |
| Vercellini et al., 1995 | >0.5 LPF (2.5 mm) |
| Zaloudek and Hendrickson, 2002 | >0.5 LPF (2.5 mm) |
| Bergholt et al., 2001 | Prevalence varied when ≥ 1 , ≥ 2 , or ≥ 3 mm from the endometrial-myometrial junction was used as a cut-off point. |

HPF, high-power field; LPF, low-power field.

cut-off point for defining the condition was lacking (TABLE 1), making the situation more complex. In the study by *Bird et al.* (1972), the diagnosis of adenomyosis increased from 31% to 61.5% when obtaining additional histologic sections to those examined routinely. The early classification by *Bird et al.* (1972) used one low-power field (LPF) as the cut-off point for the diagnosis of adenomyosis and suggested three 'grades': grade I (termed adenomyosis sub-basalis), in which glands are confined to one LPF below the basal endometrium (51% of their cases); grade II, when glands are present up to mid-myometrium (36% of their cases) and grade III, in the presence of ectopic glands beyond mid myometrium (13% of their cases). In addition, based on the most marked degree of involvement, samples were graded as 'slight' (one to three glands per LPF), 'moderate' (four to nine glands per LPF), or 'marked' (10 or more glands per LPF). The percentage of their cases fitting this classification was 32.6%, 48.9% and 18.5%, respectively. Incidence in the anterior and the posterior wall was equal. Adenomyosis sub-basalis was found to correlate with the presence of menorrhagia. It is notable, that despite undertaking detailed histologic examination, these investigators made no comment on the possibility that the disease may have different histologic levels of involvement. Twenty years later, *Siegler and Camilien* (1994) also advocated the use of this classification (TABLE 2).

Levgur et al. (2000) attempted to correlate clinical and histologic features in uteri less than 280 g, and reported that the number of adenomyotic foci correlated with symptoms. Their

proposed classification was based only on the depth of glands within the myometrium, after excluding cases with glands within 2.5 mm from the endo-myometrial junction. The term 'superficial adenomyosis' was used where glands were within 40% of myometrial thickness. Glands that were between 40–80% of myometrial thickness were classed as 'intermediate adenomyosis' and lesions beyond 80% of the myometrial thickness were classed as 'deep adenomyosis'. A similar approach was adopted by *Sammour et al.* (2002) who divided adenomyosis into four categories, based on the depth of glands within the myometrium (<25%, 26–50%, 51–75%, and >75% of myometrial thickness). They also commented on the 'spread' of adenomyosis, i.e. the number of glands within the histologic slide. They provided no details, however, of how this was standardized. The number of slides per specimen was determined on the basis of macroscopic appearance, which varied in line with routine histopathology practice.

Vercellini et al. (2006) supported a system based on the criteria proposed by *Bird et al.* (1972) and by *Siegler and Camilien* (1994). In line with the proposal by *Levgur et al.* (2000), they added the criterion of 2.5 mm depth from the endomyometrial border as a cut-off point. Their classification included three 'grades' of depth of penetration and three 'degrees' of spread, based on the number of gland foci per LPF. They also considered lesion configuration, depending on whether the involvement was diffuse, focal or nodular.

More recently, *Pistofidis et al.* (2014) based their classification on histologic

criteria but proposed the gross appearance and tissue consistency at the time of surgery as an additional factor. Their classification distinguishes three variants: the 'diffuse' type was noted to have spongiform texture, which they believed to be explained by the presence of multiple variable-size foci of adenomyosis in the entire uterine wall and by the absence of smooth muscle hyperplasia. On histologic assessment using Masson Trichrome stain, they reported paucity of supporting collagen fibres. This contrasted with the less frequent 'sclerotic' type, which featured irregular thickening of the myometrium and appeared off-white, pale and fibrotic. Sclerotic lesions were hard and friable and were particularly difficult to grasp and suture during surgery. Histologically, the lesions appeared as multiple, variable-sized foci surrounded by densely packed collagen fibres. The 'nodular' type was characterized by spherical, well-defined lesions surrounded by smooth muscle hyperplasia.

A different approach was taken by *Grimbizis et al.* (2014), who proposed a classification aimed at assessing the outcome of uterine-sparing surgery with reference to tissue diagnosis. They distinguished 'diffuse adenomyosis': the extensive form in which foci of endometrial mucosa are scattered throughout the uterine musculature from 'focal adenomyosis'; this condition is restricted to a localized area within the myometrium. They included adenomyomas and the cystic variety within the category of focal adenomyosis. Additional variants included in this classification are 'typical polypoid adenomyomas' and 'atypical polypoid adenomyomas', as well as other rare forms, such as the 'endocervical' and 'retroperitoneal' variants.

Among histologic classifications, a distinction can be underlined between those aimed at providing a description of the lesions and those that attempted to include an assessment of 'severity'. For the latter, *Hulka et al.* (2002) divided adenomyosis in broad terms into one of three categories described as 'mild' and 'severe' (category 1 and 3 respectively) and 'focal' (category 2) disease. Category 1 is taken to refer to disease of the inner third of the myometrium (excluding the innermost 2–3 mm), but also includes cases with microscopic disease of the uterus. Category 3 refers to disease of

TABLE 2 HISTOLOGICAL BASED CLASSIFICATION OF ADENOMYOSIS IN DIFFERENT STUDIES

| Reference | Classification |
|---------------------------------|---|
| Bird <i>et al.</i> , 1972 | Depth of invasion: grade I: sub-basal lesions within one LPF grade II: up to mid-myometrium grade III: beyond mid-myometrium. Degree of involvement: slight: one to three glands per LPF moderate: four to nine glands per LPF marked: 10 or more glands per LPF. |
| Sieglar and Camilien, 1994 | A) According to depth of penetration from the basal layer of endometrium: grades 1-3. B) Degree of involvement: mild (one to three islands/LPF), moderate (four to 10 islands/LPF), severe (>10 islands/LPF). C) Configuration: diffuse, discrete (nodular/focal). |
| Levgur <i>et al.</i> 2000 | 2.5 mm depth from the endomyometrial border as a cut-off point: superficial: <40% uterine wall thickness intermediate: between 40-80% wall thickness deep: >80% wall thickness |
| Sammour <i>et al.</i> , 2002 | Group A: up to 25% Group B: 26-50% Group C: 51-75% Group D: >75% of myometrial thickness The 'spread' of adenomyosis, i.e. the number of glands within the histologic slide |
| Hulka <i>et al.</i> , 2002 | Category 1 (mild): only microscopic foci or only affecting the inner 1/3 of myometrium excluding innermost 2-3 mm. Category 2 (focal lesions). Category 3 (severe): affecting the outer 2/3 of the myometrium |
| Vercellini <i>et al.</i> , 2006 | >2.5 mm from endometrial junction. Depth: three 'grades' (mild, moderate, severe 1/3, 1/3-2/3, >2/3 of uterine wall). Grades: based on degree of spread: grade 1, 2, 3 (one to three islet/LPF; four to 10 islets/LPF, >10 islets/LPF). Configuration: diffuse, focal or nodular. |
| Gordts <i>et al.</i> , 2008 | Junctional zone hyperplasia: eight or more but <12 mm on MRI in women aged ≤35 years. Adenomyosis: junctional zone ≥12 mm; high-intensity myometrial foci; involvement of the outer myometrium <1/3, <2/3, >2/3. Adenomyoma: myometrial mass with indistinct margins. Retrocervical, retrovaginal, fallopian tube and bladder types |
| Kishi <i>et al.</i> , 2012 | Subtype I: intrinsic: Inner uterine layer. Subtype II: extrinsic: outer uterine layer (normal junctional zone). Subtype III: solitary adenomyosis no connection to the junctional zone or to the serosa. Subtype IV: indeterminate |
| Pistofidis <i>et al.</i> , 2014 | Included assessment of gross appearance at time of surgery: sclerotic nodular cystic |
| Grimbizis <i>et al.</i> , 2014 | Diffuse: disease scattered throughout the musculature. Focal: affecting a restricted area (includes adenomyoma and cystic variety) Polypoid (typical and atypical) Special (rare forms) |

LPF, low-power field.

the outer two-thirds of the myometrium or the entire uterus.

CLASSIFICATIONS BASED ON IMAGING CRITERIA

The use of ultrasound and MRI provided impetus for devising a non-invasive classification of adenomyosis. This effort started with the establishment of an international group to describe the sonographic features of the

endometrium and intrauterine lesions named the International Endometrial Tumour Analysis (IETA) (Leone *et al.*, 2010). Then, in 2015, *van den Bosch et al.* (2015) published a set of criteria developed through consensus with the acronym MUSA (Morphological Uterus Sonographic Assessment). The hope was that these would enable standardized reporting of myometrial lesions, including adenomyosis. A consensus was built on terms, definitions and measurements to

be used when reporting the sonographic features of the myometrium as seen in grey-scale sonography, colour power Doppler and three-dimensional ultrasound imaging. In 2018, they proposed that reporting of adenomyosis based on MUSA criteria should take the following into account (*Van den Bosch and Van Schoobroeck*, 2018): location of the disease (anterior, posterior, left lateral, right lateral, fundal); classification of the lesions (focal or diffuse); presence or absence of intra-lesion cysts; involvement of the myometrium (limited to the inner portion, invading the body of the uterus, reaching the serosa); extent of the disease (affecting <25%, 25-50%, >50% of the uterine volume); and size of the lesions.

Previous attempts have been made to evaluate disease severity based on the presence of several ultrasound features, including by three-dimensional ultrasound (*Naftalin et al.*, 2014; 2016); however, these were hindered because of the difficulty in quantifying the lesions and related symptoms. It is recognized that symptoms do not necessarily correlate with features observed on ultrasound, or with the extent of adenomyosis in histological sections, as some women with extensive adenomyosis may be asymptomatic (*Habiba and Benagiano*, 2016). A further confounder is the frequent presence of co-existing pathology, such as fibroids, which can render the diagnosis challenging. The presence of fibroids or endometriosis can make attributing symptoms difficult. Image-based diagnosis, however, can enable better understanding of the importance of identified lesions and their natural history.

Although satisfactory sensitivity and specificity have been reported, interpretation of images need to take into account the age, phase of the menstrual cycle, gravidity, parity, hormonal status, previous uterine surgery and uterine contractions. Thus, reliable imaging-based diagnosis may not be uniformly available (*Canis et al.*, 2018), and inter-observer reproducibility remains a challenge. *Lazzeri et al.* (2014) documented good agreement between the scores of two dedicated observers when deciding on the presence or absence of adenomyosis, its type (divided into diffuse, focal or adenomyoma) and the score for each type. In this study, a score of 1-4 was attributed to each feature. To assess the extent of the

disease, the total score was calculated, and the condition was subdivided into mild (range 1–3), moderate (4–6), or severe (>7). Multiple rate agreements to classify the different features and the score of adenomyosis (diffuse, focal adenomyoma, and focal or diffuse alteration of junctional zone) ranged from substantial to almost perfect (Cohen $k = 0.658\text{--}1$), except for adenomyoma score 4, in which inter-observer agreement was moderate ($k = 0.479$). Whether such classification can be used routinely is unclear as its use has not been independently validated.

Recently, *Rasmussen et al. (2019)* attempted to classify the disease when confined to the inner myometrial and junctional zone regions into three separate US-based categories: 'adenomyosis of the inner myometrium'; 'junctional zone disease', characterized by a 'serrated' appearance of the junctional zone and 'linear junctional zone'.

Studies carried out a decade ago, using transabdominal ultrasound indicated high specificity, but low sensitivity. The pooled sensitivities, specificities and positive likelihood ratios for transvaginal ultrasound are 0.72–0.82, 0.85–0.81, and 4.67–3.7, respectively (*Meredith et al., 2009; Champaneria et al., 2010*). The heterogeneity between the studies, however, was found to be too great to allow statistical data pooling (*Dartmouth, 2014*).

Features of the uterine zonal anatomy, initially described on MRI, played a pivotal role in modern diagnosis of adenomyosis. In women of reproductive age, *Hricak et al. (1983)* demonstrated that the uterus displayed three different zones on T2-weighted MRI: the endometrium (high signal), the sub-endometrial myometrium or junctional zone (low), and the outer myometrium (intermediate). Subsequently, it was suggested that the diagnosis of adenomyosis should rely on the presence of a diffuse, low-intensity area accompanied by tiny high-intensity spots seen subjacent to the endometrium. As this area is isointense with the junctional zone, it appears as a localized or diffuse thickening of the junctional zone (*Togashi et al., 1988*).

Three-dimensional TVS has been suggested as an additional tool in the diagnosis of adenomyosis, but a recent study (*Rasmussen et al., 2019*) and

a meta-analysis (*Andres et al., 2018*) reported no improvement in overall accuracy using three-dimensional TVS compared with two-dimensional TVS. Recently, also the MUSA expert group concluded that, in the evaluation of adenomyosis, the additional value of three-dimensional imaging, i.e. to examine the coronal plane, requires future studies (*Van den Bosch et al., 2019*).

Increased junctional zone thickness is commonly considered as an indirect indicator of adenomyosis. Its use became widely adopted as a potentially reproducible measurement. Caution, however, should be exercised if junctional zone were to be used alone, because of potential pitfalls: First, the junctional zone is not measurable in 20–30% of women of reproductive age and may not be distinguishable from the outer myometrium. Second, measurement of junctional zone needs to take into account the clinical features that could have a major effect on the interpretation of junctional zone thickness (*Canis et al., 2018*). Third, despite being revised over the years, no uniform agreement has been reached on the cut-off point for diagnosis (*Dartmouth, 2014*). Furthermore, no histologic transition point has been established from the outer to the inner myometrium, as the change in component density is gradual (*Mehasseeb et al., 2011*).

Interest in promoting a classification for adenomyosis may help distinguish between junctional zone hyperplasia and adenomyosis. Although the existence and importance of junctional zone hyperplasia is not uniformly agreed, it was defined as partial or diffuse thickening of the junctional zone from 8 mm and over to less than 12 mm in the absence of additional imaging signs of adenomyosis. In recognition of the known age-related increased junctional zone thickness, it was also suggested that this category is limited to women aged 35 years and younger (*Gordts et al., 2018*). For 2 decades, a maximum thickness of the junctional zone (JZmax), of 12 mm or over, was considered as highly suggestive of adenomyosis, but this has recently been questioned (*Dartmouth, 2014; Tellum et al., 2018; Bazot and Daraï, 2018*). A confident diagnosis requires the presence of the additional feature of numerous high-signal intensity myometrial foci using T2-weighted or less frequently on T1-weighted imaging (*Togashi et al., 1988*).

Some investigators have suggested that adenomyosis could be divided into different categories, based on morphology and location of the lesion. Diffuse adenomyosis would then be represented by the involvement of at least one myometrial wall and could be symmetric or asymmetric (*FIGURE 1*). A further subdivision into three categories according to the depth of involvement reaching less than one-third, less than two-thirds, greater than two-thirds of the myometrium was suggested (*Gordts et al., 2018*). Focal adenomyosis would correspond to uni- or multi-focal myometrial lesions, or to focal thickening of the junctional zone; this needs to be distinguished from focal uterine contractions (*FIGURE 2*). An adenomyoma is represented by a myometrial mass with indistinct margins of primarily low-signal intensity on T2-weighted MRI sequences (*Bazot and Daraï, 2018; Gordts et al., 2018; Tellum et al., 2018*) and it could be solid or cystic; it is commonly located in the mid-myometrium and rarely protrudes into the endometrial cavity or under the serosa (*FIGURE 3*) (*Bazot and Daraï, 2018*). A new variant, external adenomyosis (anterior or posterior), has recently been introduced for lesions found adjacent to the uterine serosa, being significantly associated with pelvic endometriosis (*FIGURE 4*).

Calculated MRI pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were 0.77, 0.89, 6.5 and 0.2, respectively for all subtypes of adenomyosis. Therefore, although MRI is more precise compared with TVS, it has limitations (*Bazot and Daraï, 2018*).

In a recent metanalysis, MRI and two-dimensional or three dimensional TVS were compared; TVS was recommended as first-line method and MRI as a second-line method if TVUS was inconclusive (*Tellum et al., 2019*). Another recent retrospective study compared MRI with TVS carried out within 12 months, and reported that ultrasound had a high specificity of 91.8% (95% CI 88.4 to 94.6%) but was less sensitive (36.8% (95% CI 31.5 to 42.4%) for detecting adenomyosis (*Sam et al., 2019*).

RECENT EFFORTS

After some years with little progress, the International Federation of Gynecology and Obstetrics (FIGO) renewed its efforts to develop a classification for

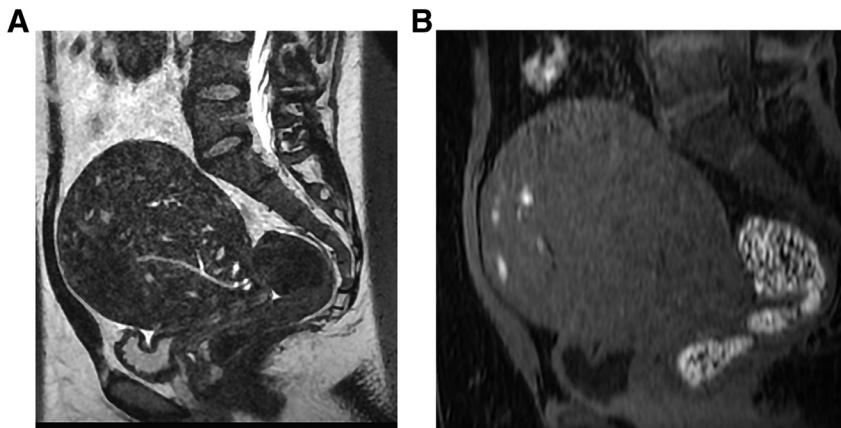


FIGURE 1 Magnetic resonance imaging (MRI) examinations in a 30-year-old woman with sagittal (A) two-dimensional T2-weighted and (B) three-dimensional T1-weighted MRI showing a huge globular uterus containing multiple endometrial foci related to deep diffuse internal adenomyosis.

adenomyosis in 2015 under the auspices of the FIGO 'Menstrual Disorders Group'. Related information has been published (Abbott, 2017). Challenges, however, remain because of the need for classification to have the widest appeal, to be based on imaging rather than histology, to be practical, reproducible, easy to record and accessible to low-resource countries. The work remains

only available in draft form. Anatomical description of lesions in the uterus may take account of the area affected and the extent and depth of lesions. Full reliance on imaging, however, could be challenging as imaging has a sizable error rate and because some lesions such as adenomyomatous polyps require histological diagnosis. It remains unclear whether classifications should describe

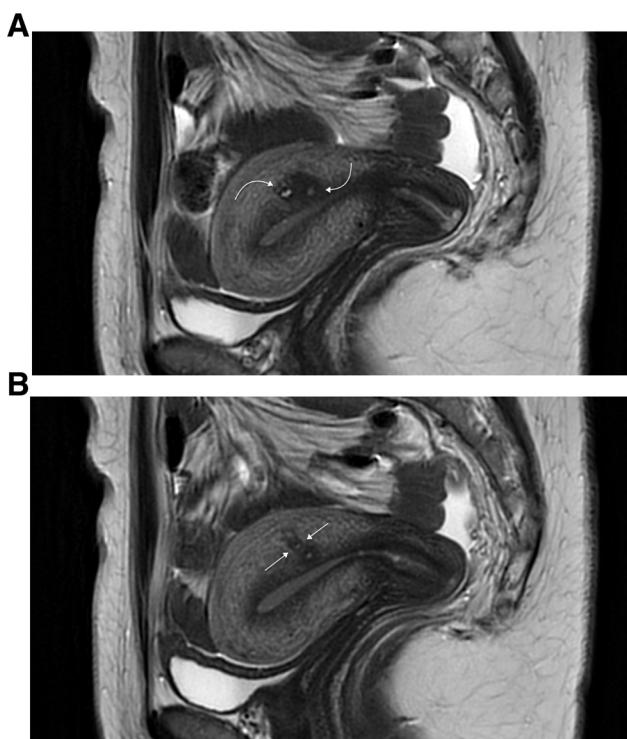


FIGURE 2 Magnetic resonance imaging examination in a 29-year-old woman, G1P0 (abortion retrieved by curettage) with two consecutive sagittal two-dimensional T2-weighted magnetic resonance images showing a (A) hypointense lesion containing small tiny spots (curved arrows) and located in the posterior wall, adjacent to the endometrial cavity related to focal adenomyosis. Note the (B) linear aspect of the lesion (arrows) suggestive of uterine perforation during curettage.

the deepest or the most widespread involvement. A major objective will be to accommodate complex patterns without this becoming unduly cumbersome.

Several proposals have recently been forwarded. *Bazot and Daraï (2018)* stressed that published imaging data were insufficient to distinguish between subtypes of adenomyosis. In accordance with their MRI experience, they also underlined the interest of Sampson's description differentiating intrinsic adenomyosis, extrinsic adenomyosis, and adenomyomas. *Gordts et al. (2018)* advocated a joint hysteroscopic and ultrasonographic approach, combining ultrasound-guided hysteroscopic biopsies with histologic confirmation. Biopsies obtained using the Spirotome™ can be carried out under ultrasound guidance and are probably safer compared with true cut needle biopsies and the risk to adjacent organs is small. Although hysteroscopic biopsies cause only minimal uterine trauma, however, their use remains limited outside research. Endomyometrial biopsies have a specificity of 78.46% with a low sensitivity of 54.32% owing to high false negative rates in the cases of deep adenomyosis (*Dakhly et al., 2016*). *Lazzeri et al. (2018)* have now proposed a classification system for adenomyosis based on ultrasound criteria (TABLE 3). Adenomyosis is classified into diffuse or focal disease affecting the myometrium or the junctional zone. A third category is represented by the adenomyoma. Focal adenomyosis is distinguished from adenomyoma as it is surrounded by normal myometrium, whereas adenomyomas are surrounded by hypertrophic myometrium with intralesional vascularization. Adenomyosis was divided into four different scores based on the number and size of identified lesions and into grades according to the extent into the myometrium. *Lazzeri et al. (2018)* demonstrated a high degree of interobserver agreement using stored two- and three-dimensional images. The problem with this proposal is that a classification should be simple, reproducible and related to surgical or histologic data and it does not seem that these conditions have been met.

IS THERE A RELATIONSHIP BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS?

The question of whether a relationship exists between adenomyosis and

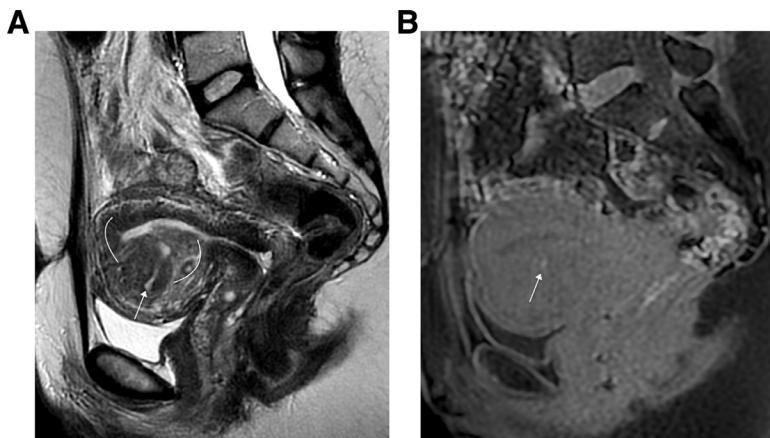


FIGURE 3 Magnetic resonance imaging (MRI) examination in a 43-year-old woman with sagittal two-dimensional (A) T2-weighted and (B) three-dimensional T1-weighted MRI. Anteverted uterus displaying an ill-defined mass located in the anterior wall and endometrial cavity (curved lines). This mass containing small high intense tiny cysts on T2-weighted and T1-weighted images is related to submucous adenomyoma (arrow).

endometriosis has been debated for decades; however, disagreements remain. Several similarities exist between adenomyosis and endometriosis (Larsen *et al.*, 2011). Therefore, a modern classification of adenomyosis should aim to better understand any link or shared pathophysiology, particularly for disease of the pouch of Douglas or the uterovesical pouch. It is well recognized that endometriosis and adenomyosis often co-exist, but the reported degree of association varies widely. Kunz *et al.* (2005) reported MRI findings in women with infertility, either with ($n = 160$) or without ($n = 67$) endometriosis. Endometriosis was minimal or mild in

81/160 cases and moderate or severe in 79/160 cases. No indication was provided on deep endometriotic lesions. Adenomyosis was diagnosed based on MRI features of the junctional zone in 79% in women with, compared to 28% in women without endometriosis. It is noteworthy that this study was criticized for important methodologic issues and may have been based on a highly selected subpopulation (Bazot *et al.*, 2006). Taran *et al.* (2010) carried out a multivariate analysis of women with uteri weighing greater than 150 g and reported coexisting endometriosis in 26.3% versus 2.8% in women with leiomyomas. Leyendecker *et al.* (2015)

reported their finding in 143 women with suspected adenomyosis who also had infertility. Adenomyosis was diagnosed by MRI based on the thickness of the junctional zone in 127 of the 143 cases. Endometriosis was diagnosed in 56 cases and ruled out in 16 cases. The stage of endometriosis was not documented. Adenomyosis was detected at the level of the upper- and middle-third of the uterine cavity in 81% of cases, extended over the whole length of the uterine cavity in 17% and was present in the lower two-thirds of the uterine cavity in only 2% of cases. Prevalence in cases with endometriosis varied from 92.5% to 59% and the incidence of endometriosis in cases with adenomyosis varied from 75.5% to 78%, depending on the cut-off point for diagnosing adenomyosis. Leyendecker *et al.* (2015) suggested a correlation between adenomyosis affecting the junctional zone and inner myometrium and peritoneal endometriosis. No comment was made on rectovaginal disease or of 'extrinsic' adenomyosis. Here again, caution should be exercised in interpreting the findings. First, there could be bias, as suspicion of adenomyosis was an inclusion criterion in the study population; second, because the clinical significance of some of the focal adenomyotic lesions identified is not known; and third, because of the possibility of artefacts related to sporadic myometrial contractions.

In a cross-sectional study from a tertiary referral centre, again with a highly selected study population, Chapron *et al.* (2017) carried out an MRI-based diagnosis followed by surgical assessment in 292 symptomatic women referred to a tertiary centre. Endometriosis was diagnosed in 237 (81.2%) cases and deep infiltrating endometriosis (DIE) was diagnosed in many of these ($n = 166$ [70%]). Adenomyosis was present in 175 (59.9%) of the total group. On the basis of MRI, isolated 'diffuse adenomyosis' or 'focal adenomyosis of the outer myometrium' (FAOM) was present in 53 (18.2%) and 74 (25.3%) women, respectively. A total of 48 (16.4%) women, however, had both diffuse and FAOM. Diffuse adenomyosis was defined by the association of two criteria: JZ_{max} of at least 12 mm and ratio max (e.g. $ZJ_{max}/\text{myometrial thickness}$) $> 40\%$. The term 'focal adenomyosis' was applied only to adenomyotic foci located in the outer shell of the uterus if separated from the junctional zone by interposing

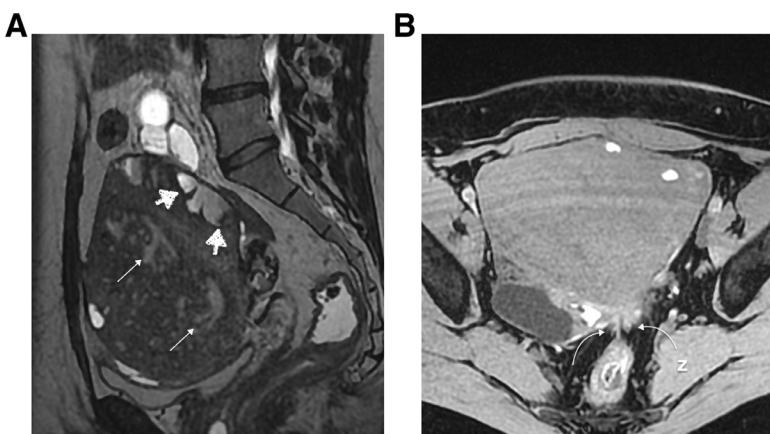


FIGURE 4 Magnetic resonance imaging (MRI) examinations in a 35-year-old woman, with previous myomectomy showing on (A) sagittal two-dimensional T2-weighted and (B) axial three-dimensional T1-weighted MRI. A huge globular uterus with extensive thickening of anterior junctional zone containing multiple high intensity spots (arrows) related to deep diffuse internal adenomyosis can be seen. Note the presence of large cystic posterior lesions adjacent to posterior uterine serosa (large arrows) associated with deep endometriotic lesions of torus, uterosacral ligaments and rectosigmoid colon related to external adenomyosis (curved arrows, Z).

TABLE 3 PROPOSED ULTRASOUND CLASSIFICATION FOR ADENOMYOSIS. DATA EXTRACTED FROM LAZZERI ET AL., 2018

| Diffuse adenomyosis | | Focal adenomyosis | | Adenomyoma |
|--|---|--|--|---|
| Diffuse myometrium and uterine wall thickening | | Diffuse JZ and JZ thickening | Lesions in outer myometrium | Lesion in the JZ |
| Score 1 | One wall affected, ≤20 mm thick | $JZ_{\max} > 6$ to ≤8 mm or $JZ_{\text{dif}} > 4$ to ≤6 mm or diffuse JZ infiltration ≤20 mm in length | One lesion ≤10 mm | One hyperechoic lesion or cystic areas ≤10 mm |
| Score 2 | Two walls affected, ≤20 mm thick or one wall affected, between >20 to ≤30 mm | $JZ_{\max} > 8$ mm or $JZ_{\text{dif}} > 6$ mm or diffuse JZ infiltration <20 mm in length or <50% of the uterus | Two or more lesions ≤10 mm or one lesion >10 to ≤20 mm | Two or more lesions ≤10 mm; or one lesion >10 to ≤20 mm |
| Score 3 | One wall affected, >30 mm thick or two walls affected, >20 to ≤30 mm thick | Diffuse JZ infiltration >50% to ≤80% of uterus | Two or more lesions >10 to ≥20 mm or one lesion >20 mm | Two or more lesions >10 to ≤20 mm or one lesion >20 mm |
| Score 4 | Two walls affected, >30 mm thick or all uterus affected and globally enlarged | 80% total JZ infiltration | Two or more lesions >20 mm | Two or more lesions >20 mm |
| | | | | One or more lesions >40 mm |

The extension of each type of adenomyotic lesion in the external myometrium and in the JZ was divided into four grades according to the ultrasonographic features. JZ, junctional zone. JZ_{\max} , maximum JZ thickness; JZ_{\min} , minimum JZ thickness; JZ_{dif} , $JZ_{\max} - JZ_{\min}$.

healthy muscular tissue. Therefore, they applied the term FAOM only to disease affecting the outer myometrium, which contrasts to previous studies that included disease of the outer, middle and inner myometrium as possible sites for focal adenomyosis (Kishi *et al.*, 2012; Tellum *et al.*, 2018). Interestingly, most (66%) women with DIE had FOAM and for women with FOAM ($n = 122$) most (90%) also had DIE. The study population was highly selected, which is reflected in the high percentage of women with DIE. They also excluded women with endometriosis who did not have histological confirmation. This will necessarily limit the generalizability of the study conclusions.

Larsen *et al.* (2011) compared the incidence of adenomyosis in 153 patients with suspected DIE (also referred to as rectovaginal endometriosis) and a reference group of 129 women (29 women with cervical cancer and 100 women undergoing hysterectomy for benign conditions). Adenomyosis was identified by MRI in 34.6% of the women in the study group compared with 19.4% of the control group. In 75.8% of patients suspected with the disease, DIE was present, and 34.5% of these had adenomyosis but adenomyosis was present in 35.1% of the group without rectovaginal endometriosis ($P > 0.05$). These findings do not support a link between rectovaginal disease and adenomyosis beyond the increased risk linked to endometriosis at any site. Similar

to other studies in the field, however, the study group is highly selected and poorly defined. No information is available on the basis on which the study group was suspected to have DIE. In addition, the diagnosis of adenomyosis was based on MRI features of the junctional zone, and no reference is made to involvement of the subserosal myometrium. Verecellini *et al.* (2014) reviewed published research on the pregnancy rate after surgical resection of rectovaginal and colorectal endometriosis. Outcomes were available on 231 cases, of which 59 (25.5%) had adenomyosis. Co-existing adenomyosis had negative effect on fertility (Ballester *et al.*, 2012). Finally, when considering the relationship between adenomyosis and endometriosis, it is important to remember that endometriosis itself has distinct phenotypes (Nisolle and Donnez, 1997), and that deep endometriotic nodules may be distinct from superficial peritoneal endometriosis (Donnez *et al.*, 1996).

INTERNAL AND EXTERNAL (INTRINSIC AND EXTRINSIC) FORMS OF ADENOMYOSIS

Several investigators have argued that 'internal' and 'external' adenomyosis are distinct. 'Internal adenomyosis' is defined as the presence of focal or multifocal intra-myometrial tiny cystic structures on MRI. This may be accompanied by an increased junctional zone thickness (Togashi *et al.*, 1988) and can be superficial or deep, symmetric or

asymmetric, diffuse or local. The term 'external adenomyosis' is applied to lesions in the external (outer) portion of the myometrium, close to the peritoneal lining (Bazot and Darai, 2018). Lesions can affect the posterior, anterior, or lateral uterine wall and be associated with either posterior, anterior or lateral deep endometriotic lesions.

Some investigators view this distinction to entail consequences to our understanding of the relationship between adenomyosis and endometriosis, as it implies the possibility that the external variant may be the product of an invasion of the myometrium by endometriotic lesions. An alternative view is that the external variant infiltrates the uterine wall and surrounding structures leading to what may also be considered as variants of endometriosis, namely DIE and bladder lesions. The relationship between these conditions continues to be debated. If established, it is also possible that any link is determined by genetic or epigenetic factors that predispose to the development of aberrant endometrial tissue. As this issue remains unresolved, it complicates classifying DIE lesions in the pouch of Douglas and lesions in the uterovesical pouch.

IS ADENOMYOSIS AT THE ORIGIN OF SOME FORMS OF ENDOMETRIOSIS?

Donnez *et al.* (2000) reported on 17 cases of bladder endometriosis, which

constituted 0.2% of the women treated for endometriosis in their department. Of those 17, six had no other endometriosis lesions, six also had rectovaginal adenomyotic nodules (including two with other pelvic of endometriosis), and the remaining five had pelvic endometriosis (but no rectovaginal lesions). None of this group with bladder endometriosis was identified with uterine adenomyosis. Excised lesions had active endometrial glands but were not always accompanied by stroma. Most of the nodules were made of smooth muscle hyperplasia. The bladder mucosa was intact in all but one case, and 13 women were considered to have primary bladder endometriosis, with no connections to the overlying peritoneum. The association and similarities with rectovaginal nodules led the authors to conclude that primary bladder endometriosis is a retroperitoneal adenomyotic nodule and the consequence of metaplasia of Müllerian rests. A point worthy of mention is that, although the metaplasia theory has not been refuted, accepting it does not necessarily entail designating bladder nodules as adenomyotic in the sense of them being derived from a variant of uterine adenomyosis. Accepting *Bird et al.*'s (1972) definition of adenomyosis, means that only lesions derived from an endometrial invasion of the myometrium (in this case, going all the way to the outer myometrium and through the peritoneal serosa) should be classified as a variant of adenomyosis. Furthermore, the evidence provided by *Donnez et al.* (2000) does not show an association between bladder 'adenomyosis' and uterine lesions. Their publication gives no indication of the proportion of women with rectovaginal disease who had bladder disease. Alternative theories proposed to explain these lesions are infiltration from peritoneal lesions (Vercellini et al., 1996) or extraperitoneal disease spread (Koninckx and Martin, 1992).

Donnez et al. (1997) had also reported a series of 500 cases with lesions they labelled 'rectovaginal septum adenomyotic nodules'. Histologically, the lesions were circumscribed nodular aggregates of abundant smooth muscle, surrounding endometrial glands and scanty endometrial stroma. Stroma was absent in some instances. There is no indication if any of the patients involved had uterine adenomyosis or required resection involving the uterus

or cervix. More recently, *Donnez et al.* (2019) reported finding external uterine adenomyosis, diagnosed by MRI, in 97 out of 100 patients with clinically confirmed deep posterior endometriotic nodules measuring 3 cm or more in size. The presence of adenomyotic lesions was observed in the posterior portion of the cervix in 40 cases, in the posterior part of the uterus in 39 cases and in the lowest part of the cervix involving the posterior fornix in 20 cases. The junctional zone was thickened in 27 of these cases and the rectosigmoid was involved in 95 cases. The presence of this association is in agreement with the theory that adenomyosis of the outer myometrium (and more specifically the cervical variant) may be the origin of at least some forms of DIE. A discrepancy seems to exist in phenotype between this and their earlier report (*Donnez et al.*, 1997), as MRI suggests a greater degree of involvement of the cervix and posterior myometrium compared with the earlier report that describes pouch of Douglas obliteration, posterior vaginal fornix and deeper involvement of the rectovaginal septum. Interestingly, the reported histology does not refer to cases of endocervicosis as might be expected if the lesions originated in the region of the cervix.

The possibility that DIE may originate from adenomyotic lesions of the outer myometrium brings into focus old images published by *Cullen* (1920). Although these could be interpreted as supporting an origin from cervical adenomyosis, as documented by *Batt et al.* (2014), these illustrations are in fact examples of endometriosis affecting the upper vagina and related to the posterior fornix, not the rectovaginal septum. To clarify this distinction, *Batt et al.* (2014) referred to this structure as the 'rectocervical septum' and argued that previous studies that refer to rectovaginal lesions (Vercellini et al., 2000; *Chapron et al.*, 2002; 2004) are all consistent with DIE nodules located above the upper edge of the rectovaginal septum. This distinction is important to aid our understanding of the pathophysiology of DIE. *Cullen* (1920) reported 19 cases of adenomyoma; the term that was then applied to lesions in and outside the uterus, affecting the rectovaginal septum. He wrote that such a lesion 'usually starts just behind the cervix... As the growth increases in size, it spreads out laterally and at the same time becomes

blended with the adjacent anterior rectal wall. Later it may invade the broad ligaments, encircling the ureters, or may envelop pelvic nerves. With extension of the growth, it may push down into the posterior vaginal vault forming definite and well-formed vaginal polyps, and finally, it may break into the vagina'. The description is that of a nodule that originates outside the uterus but becomes fixed to the posterior aspect of the cervix (*Cullen*, 1920). *Sampson* (1925) accepted that it is possible that uterine mucosa may reach the peritoneal surface of the uterus by direct extension through the myometrium and that peritoneal implantation may arise as a result of the reaction of this mucosa to menstruation. He added, however, that he had not seen any case in which he thought this had occurred. On the other hand, *Sampson* (1922) believed that implanted endometrium from retrograde menstruation or a ruptured ovarian chocolate cyst can give rise to an adenoma of the affected organ.

A further challenge to the theory of an adenomyotic origin of DIE is that many women with such lesions do not have adenomyosis. It is possible that this variant represents an advanced stage of endometriosis that develops through genetic or epigenetic changes. *Cullen* (1920) described some cases with fibroids, but no cases of adenomyoma of the uterus in association with his cases in which the rectovaginal septum was affected. In addition, localization of adenomyosis in the cervix is relatively rare. In the study by *Leyendecker et al.* (2015), adenomyosis was present in the lower two-thirds of the uterus in only 2% of the 127 women. In addition, MRI features suggestive of cervical involvement are often inconclusive, with changes in the outer aspect of the cervix limited to 3–4 mm. Finally, in most studies of DIE and adenomyosis, the adenomyotic lesion and location or extent is not specified.

ENDOMETRIOSIS AS A CAUSE OF ADENOMYOSIS

Kishi et al. (2012) examined 163 women who had a hysterectomy ($n = 40$) or adeno-myomectomy ($n = 123$); 11 were excluded as their MRI was not available. On the basis of the MRI, they differentiated cases into four subtypes based on MRI appearance: subtype I (termed 'intrinsic' adenomyosis) involves

lesions directly connected to the eutopic endometrium and is characterized by a thickened junctional zone; subtype II (termed 'extrinsic' adenomyosis) represents cases in which lesions are noted in the outer myometrium, and the junctional zone seems to be intact on MRI; subtype III (labelled 'intramural' adenomyosis) is the variant in which foci are separate from the junctional zone and from the serosa; and subtype IV (coined 'indeterminate' adenomyosis) includes cases that do not conform to any of the above criteria.

In the study by *Kishi et al. (2012)*, 38.2% (58/152) were classed as subtype I and 33.6% (51/152) were classed as subtype II. A total of 14.5% (22/152) were subtype III and 13.2% (20/152) were indeterminate or subtype IV. They proposed that subtype I best fitted the classic definition of adenomyosis. The features in the classical descriptions by *Cullen (1920)*, however, are a better fit to what they termed subtype II or III. It is the case that the extent of uterine involvement with adenomyosis describes different phenotypes, but the absence of junctional zone thickness on MRI does not exclude adenomyosis. Therefore, arguably insufficient evidence exists for the absence of connection between the endometrium and other disease subtypes. It is also the case that adenomyosis with features of subtype II and III do exist, including in the original descriptions of Cullen, for which no evidence is available on breach to the serosa. This argues against invasion from outside the uterus as a cause of this subtype.

Kishi et al. (2017) compared subtype I and subtype II adenomyotic lesions using cytoskeletal proteins, type I and III collagen, TGF- β and its signalling molecules. They found a significant staining of non-muscle myosin IIB, TGF- β , and phosphorylated TGF- β type I receptors only in the smooth muscle cells of subtype II (the 'extrinsic' variant). The finding of differences in staining characteristics, however, is not in itself indicative of a different origin. Using a similar approach, *Khan et al. (2019)* compared staining characteristics of lesions from intrinsic and extrinsic adenomyosis who had co-existing DIE lesions. They argued that, because of similarities in staining characteristics between extrinsic adenomyosis and coexisting DIE, the former should be

considered as adenomyosis externa. They go on to propose that these lesions originate through direct invagination of co-existent DIE into the cervix, followed by ascending migration or extension along the uterine serosa (*Khan et al., 2019*). Although the description provided of these lesions is incomplete, the relationship between adenomyosis affecting different parts of the uterus cannot be established based on differences in the proportion of glands or stroma. Critically, the absence of a connection between these lesions and the eutopic endometrium conflicts with histological descriptions dating from the 1920s and subsequently (*Meyer, 1925; von Burg, 1926; Otto, 1957*). Histological confirmation can itself be particularly difficult in some cases, such as in the presence of myometrial hypertrophy. As such, MRI features will require histologic confirmation.

DISCUSSION

Renewed interest in producing a classification of the multiple phenotypes of adenomyosis reflects the increased recognition of the importance of this disease and the increased availability of non-invasive ultrasound- and MRI-based diagnoses. It was previously believed that imaging diagnosis should be based on the single criterion of a junctional zone thickness over 12 mm. Today, however, a 'sole criterion'-based diagnosis has been called into question and a broader approach has been proposed (*Bazot and Daraï, 2018*). The advantages of an agreed classification cannot be overstated, as it will enable comparison of research findings and of outcomes of the emerging conservative treatment options. The effort, however, remains hampered by the lack of clinical correlates that can enable a better appreciation of the effect of the disease. Within the affected uterus, MRI provides a means of disease mapping without requiring a hysterectomy. MRI is becoming increasingly available and, although still expensive, is less labour intensive compared with systematic histologic examination of the uterus. It is recognized as the most accurate imaging diagnostic modality and available research suggests good sensitivity and specificity. Published research, however, comes from specialist centres with highly selected patient groups and with a high level of specialized expertise. In addition, the cited sensitivities and

specificities relate only to the diagnosis of adenomyosis, not to its location or mapping. Therefore, no indication on how imaging-based mapping correlates with histology exists. Histology has traditionally been considered the gold standard. Disagreement remains on the optimal imaging technique to be followed.

A second important challenge for a comprehensive classification is whether it could or should contain inferences to aetiology. On the one hand, attempts to achieve this can stimulate interesting debate, but it also risks stifling further understanding if it leads to over-estimation of the strength of available evidence.

The traditional definition of adenomyosis is that it represents invasion of endometrium within the myometrium. Earlier writings by Sampson (*Sampson, 1925; 1927*) drew analogies between aberrant benign endometrial tissue and cancer. This theory is supported by evidence that the eutopic endometrium in women with adenomyosis, as well as endometriosis, possesses 'an invasive phenotype' (*Mehasseeb et al., 2010; Benagiano et al., 2014; Kishi et al., 2017; García-Solares et al., 2018; Khan et al., 2019*). Supporting evidence, however, is still fragmentary and incomplete, and the factors that enable glands and stroma to be aberrantly located within the myometrium or the pouch of Douglas are yet to be fully understood. The genesis of surrounding myometrium is another critical consideration.

The relationship between 'external' or 'extrinsic' adenomyosis and variants of endometriosis has attracted debate. Here, two opposing theories have been proposed: one view is that DIE and bladder endometriosis originate as adenomyotic nodules in the posterior uterine or cervical wall and invade the rectovaginal space, the digestive tract or the bladder. Alternatively, it is proposed that adenomyosis in the outer uterine myometrium results from invasion by endometriosis first implanted on the peritoneum. To advance their viewpoints, proponents have used MRI imaging and immunohistochemical features that suggested similarities or differences between tissues obtained from different locations. Unresolved questions related to MRI mapping, however, remain, and differences in staining characteristics

should take into account the effect of the microenvironment as well as the significant potential of confounding when using immune-histological techniques especially given the small tissue samples represented (Kim *et al.*, 2016). Add to this, the possible effect of regional clonality of endometrial glands (Tanaka *et al.*, 2003) and the issue seems far from being resolved. It also remains to be explored how adenomyosis from the cervix or lower segment can expand to form nodules outside the posterior wall of the uterus.

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