EXPLORING THE CHALLENGES FOR A NEW CLASSIFICATION OF ADENOMYOSIS

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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 comparing research studies and treatment outcomes. In this article, we review 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 affections of the uterovesical pouch, the pouch of Douglas and lesions in the outer myometrium. Two opposite hypotheses are put forward to explain the
pathogenesis of these variants, namely that disease localised 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.

200 words

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1. INTRODUCTION

Following the 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 relation between the ectopic and the eutopic endometrium has been debated for more than a century: Cullen 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 (Cullen, 1908). However, an apparent lack of continuity between the basal and ectopic endometrium in some cases 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. It is the case that to this day, 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 remain to be clarified, it is not surprising that a consensus is yet to emerge.

Our understanding of adenomyosis remains limited because of a number of factors. For a long time, an important limitation has been the lack of reliable diagnostic tools and diagnosis could only be made on a hysterectomy specimen, where selection bias becomes an important factor. In addition, mapping the extent of the disease following hysterectomy is resource intensive and is rarely done 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 (US) and magnetic resonance imaging (MRI) have become available for more than 30 years. Advances in imaging made it
possible to identify the disease in women who do not require or want a hysterectomy, such as cases of infertility and preclinical affection. Imaging diagnosis can also enable the development of clinical datasets and the assessment of progress over time. However, detailed imaging diagnosis requires expertise and can suffer from lack of sensitivity and specificity. Cost and availability are likely to favour the use of TVS which can be highly accurate if performed by expert sonographers (Vannuccini and Petraglia 2019). 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 for all subtypes (Bazot and Daraï, 2018) and should be considered a second-line imaging technique when ultrasound is inconclusive.

In view of the availability of modern imaging, efforts aiming 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, or with known pathophysiologic events, or the coexistence of related pathology. With the use of modern high-resolution imaging, small foci of endometrial glands are increasingly being visualised. 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 relation between localized lesions, infertility, menstrual abnormalities and dysmenorrhoea.

Some fifteen 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 the outline of available
evidence and consider whether this supports the existence and description of distinct types of adenomyosis.

2. **CLASSIFICATIONS BASED ON HISTOLOGIC CRITERIA**

A number of 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 affection is diffuse or localized. The latter encompasses focal or nodular lesions where 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; Siegler 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. Add to this, the fact that the incidence of adenomyosis was shown to vary in relation to the number of histologic sections examined and the lack of agreement on a cut-off point for defining the condition (Table 1) and the situation becomes really 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). 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’ (1-3 glands per LPF), ‘moderate’ (4-9 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. There was an equal incidence in the anterior and the posterior wall. Interestingly, adenomyosis sub-basalis was found to correlate with the presence of menorrhagia. It is notable, that despite undertaking detailed histologic examination, these authors have made no comment referring to 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 <280 grams 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 found 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 4 categories, based on the depth of glands within the myometrium, namely: <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. However, they provided no details of how this was standardized. The number of slides per specimen was determined based on the 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). But in line with the proposal by Levgur et al. (2000), they added the criterion of 2.5mm 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 and also considered lesion configuration, depending on whether the affection 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 presented particular difficulty to grasping and suturing 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 is that 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 where foci of endometrial mucosa are scattered throughout the uterine musculature from ‘focal adenomyosis’, where the affection is restricted to a localized area within the myometrium. They included adenomyommas 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, worth of notice is the study by Hulka et al. (2002) who 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 affection of the inner third of the myometrium (excluding the innermost 2-3mm), but also includes cases with microscopic affection of the uterus. Category 3 refers to affection of the outer two thirds of the myometrium or the entire uterus.

3. CLASSIFICATIONS BASED ON IMAGING CRITERIA

The use of US 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 standardised 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 US imaging. In 2018, they proposed that reporting of adenomyosis should take the following into account (van den Bosch et al., 2018): Identification of adenomyosis based on MUSA criteria.

1. Location of the disease: anterior, posterior, left lateral, right lateral, fundal.
2. Classification of the lesions as focal or diffuse.
3. Presence or absence of intra-lesion cysts.
4. Involvement of the myometrium: limited to the inner portion, invading the body of the uterus, reaching the serosa.
5. Extent of the disease: affecting <25%, 25-50%, >50% of the uterine volume).
6. Size of the lesions.

Previous attempts to evaluate disease severity based on the presence of a number of US features including by 3 Dimensional US (Naftalin et al., 2014, 2016) were hindered because of the difficulty in quantifying the lesions and related symptoms. It is recognized that symptoms do not necessarily correlate with US observed features, or with the extent of adenomyosis in histological sections, since 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. However, image-based diagnosis can enable better understanding of the importance of identified lesions and their natural history.

It is to be considered that, 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 JZ) ranged from substantial to almost perfect (Cohen k= 0.658 – 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 JZ regions into three separate US-based categories: ‘adenomyosis of the inner myometrium’; ‘JZ disease’, characterized by a ‘serrated’ appearance of the JZ and ‘linear JZ’.

Studies carried out a decade ago, using trans-abdominal US indicated high specificity, but low sensitivity. The pooled sensitivities, specificities and positive likelihood ratios for trans-vaginal US are 0.72-0.82, 0.85-0.81, and 4.67-3.7, respectively (Meredith et al., 2009; Champaneria et al., 2010). But the heterogeneity between the studies 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 JZ, it appears as a localized or diffuse thickening of the JZ (Togashi et al., 1988).

Three dimensional (3D) 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 3D TVS compared with 2D TVS. Recently, also the MUSA expert group concluded that in the evaluation of adenomyosis, the additional value of 3D-imaging, i.e. to examine the coronal plane, requires future studies (Van den Bosch et al., 2019).

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

Interest in promoting a classification for adenomyosis may help distinguish between JZ hyperplasia and adenomyosis. Although the existence and importance of JZ hyperplasia is not uniformly agreed, it was defined as partial or diffuse thickening of the JZ from ≥8mm to <12mm in the absence of additional imaging signs of adenomyosis. In recognition of the known age-related increased JZ thickness, it was also suggested that this category be limited to women ≤35 years (Gordts et al., 2018). For two decades a maximum thickness of the junctional zone (JZmax) ≥12 mm, was considered as highly suggestive of adenomyosis, but this has been recently 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 authors 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 <1/3, <2/3, > 2/3 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 JZ; 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 (Gordts et al., 2018;
Tellum et al., 2018; Bazot and Daraï, 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).

It should also be taken into account that the 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. Thus, although MRI is more precise compared to TVS, it has limitations (Bazot and Daraï, 2018).

A recent metanalysis compared MRI and 2-D or 3-D TVS and recommended that TVS be used as a first-line method and MRI as a second-line method, if TVUS is inconclusive (Tellum et al., 2019). Another recent retrospective study compared MRI with TVS done 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).

4. RECENT EFFORTS

Following some years with little progress, a few years ago the International Federation of Gynecology and Obstetrics (FIGO) renewed its efforts to develop a classification for adenomyosis in 2015 under the auspices of the FIGO ‘Menstrual Disorders Group’. Related information has been published (Abbott 2017). But challenges 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. However, full reliance on imaging 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 the deepest or the most widespread affections. A major objective will be to accommodate complex patterns without this becoming unduly cumbersome.

A number of proposals have recently been put forward. 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 US-guided hysteroscopic biopsies with histologic confirmation. Biopsies obtained using the Spirotome™ can be performed under US guidance, are probably safer compared to true cut needle biopsies and the risk to adjacent organs is small. But, although hysteroscopic biopsies cause only minimal uterine trauma, their use remains limited outside research. Endo-myometrial biopsies have a specificity of 78.46% with a low sensitivity of 54.32% due 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 JZ. 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 is tabled into 4
different scores based on the number and size of identified lesions and into Grades according to extent into the myometrium. They demonstrated a high degree of interobserver agreement using stored 2D and 3D ultrasound images. The problem with this proposal is that a classification should be simple, reproducible and being related to surgical or histologic data and, it does not seem that these conditions have been met.

5. **IS THERE A RELATIONSHIPS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS?**

Despite this question has been debated for decades, disagreements remain. A number of similarities exists between adenomyosis and endometriosis (Larsen et al., 2011) and, for this reason, a modern classification of adenomyosis should aim at enabling a better understanding of any link or shared pathophysiology particularly for affections of the pouch of Douglas (PoD) or the utero-vesical pouch (UVP). 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 JZ in 79% of women, 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 >150g and reported coexisting endometriosis in 26.3% vs. 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 2/3 of the uterine cavity in only 2% of cases. Depending on the cut-off point for diagnosing adenomyosis, its 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%. They suggested a correlation between adenomyosis affecting the JZ and inner myometrium and peritoneal endometriosis. No comment was made of rectovaginal affection or of ‘extrinsic’ adenomyosis. Here again, caution should be exercised in interpreting the findings: Firstly, there could be bias, as suspicion of adenomyosis was an inclusion criterion in the study population; secondly, because the clinical significance of some of the focal adenomyotic lesions identified is not known; and thirdly, 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 (81.1%) cases and deep infiltrating endometriosis (DIE) was diagnosed in a large number of these (n=166, 70%). Adenomyosis was present in 175 (59.9%) of the total group. Based on MRI, isolated ‘diffuse adenomyosis’ or ‘focal adenomyosis of the outer myometrium’ (FAOM) was present in 53 (18.2%) and 74; (25.3%) or cases respectively. But 48 (16.4%) of cases had both ‘diffuse and FAOM’. Diffuse adenomyosis was defined by the association of two criteria: (i) JZ max of at least 12 mm and (ii) ratio max
(e.g. $Z_{\text{Jmax}}$/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 JZ by interposing healthy muscular tissue. Thus, 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, the majority (66\%) of women with DIE had FOAM and for women with FOAM ($n=122$) the vast majority (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 generalisability 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 to 19.4\% of the control group. DIE was present in 75.8\% of patients suspected with the disease and 34.5\% of these had adenomyosis but adenomyosis was present in 35.1\% of the group without recto-vaginal endometriosis ($p > 0.05$). These findings do not support a link between rectovaginal affection and adenomyosis beyond the increased risk linked to endometriosis at any site. However, similar to other studies in the field, 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 JZ and no comment is made referring to involvement of the sub-serosal myometrium. Vercellini et al.
(2014), reviewed published literature on the pregnancy rate following surgical resection of rectovaginal and DIE. 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 relation between adenomyosis and endometriosis, it is important to remember that endometriosis itself has distinct phenotypes (Nisolle and Donnez, 1997) and also that deep endometriotic nodules may be distinct from superficial peritoneal endometriosis (Donnez et al., 1996).

6. INTERNAL AND EXTERNAL (also named INTRINSIC AND EXTRINSIC) FORMS OF ADENOMYOSIS

Several authors argued that ‘internal’ and ‘external’ adenomyosis are distinct. ‘Internal adenomyosis’ being defined as the presence of focal or multifocal intra-myometrial tiny cystic structures on MRI. This may be accompanied by an increased JZ 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 Daraï, 2018). Lesions can affect the posterior, anterior, or lateral uterine wall and be associated with either posterior, anterior or lateral deep endometriotic lesions.

Some authors view this distinction to entail consequences to our understanding of the relation 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, or – on the contrary – 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 relation 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 classify DIE lesions in the PoD and lesions in the UVP.

6.1. 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, 6 had no other endometriosis lesions, 6 also had rectovaginal adenomyotic nodules (including 2 with other pelvic of endometriosis), the remaining 5 had pelvic endometriosis (but no rectovaginal lesions). None of this group with bladder endometriosis was identified with uterine adenomyosis. Excised lesions exhibited active endometrial glands, but 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 them to conclude that primary bladder endometriosis is a retroperitoneal adenomyotic nodule and the consequence of metaplasia of Müllarian rests. A point worth of mention is that whilst the metaplasia theory has not been refuted, accepting it is 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. (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 those with rectovaginal affection 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 ≥3cm 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 JZ was thickened in 27 of these cases and the rectosigmoid was involved in 95. 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. There appear to be a discrepancy 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 to the earlier report that describes PoD 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). Whilst these could be interpreted as supporting an origin from cervical adenomyosis (Figures 5 and 6), 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. In order to clarify this distinction, Batt et al (2014) referred to this structure as the ‘rectocervical septum’ and argued that previous studies which refer to rectovaginal lesions (e.g. 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 towards 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 result of the reaction of this mucosa to menstruation. But he added that 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 the theory of an adenomyotic origin of DIE, is that a large number of 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. It is interesting to note that Cullen (1920) described some cases with fibroids, but no cases of adenomyoma of the uterus in association with his cases where 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 2/3 of the uterus in only 2% out 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 3-4mm. Finally, in most of the publications mentioning DIE and adenomyosis, the adenomyotic lesion and location or extent is not specified.

6.2. 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. Based on MRI they differentiated cases into 4 subtypes based on MRI appearance:

Subtype I: termed “intrinsic” adenomyosis, involves lesions directly connected to the eutopic endometrium and is characterized by a thickened JZ.

Subtype II: termed “extrinsic” adenomyosis, represents cases where lesions are noted in the outer myometrium. The JZ appears intact on MRI.
Subtype III: labelled “intramural” adenomyosis, is the variant where foci are separate from the JZ and from the serosa.

Subtype IV: coined “indeterminate” adenomyosis, includes cases that do not fit any of the above criteria.

In this study 38.8% (58/152) were classed as subtype I and 33.5% (51/152) were classed as subtype II. 14.4% (22/152) were subtype III and 13.1% (20/152) was indeterminate or subtype IV. They proposed that subtype I best fitted the classic definition of adenomyosis. However, it is clear that the features in the classical descriptions by Cullen 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 JZ thickness on MRI does not exclude adenomyosis. Thus, there is arguably insufficient evidence 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 – where there is no evidence of 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). But the finding of differences is staining characteristics 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). But whilst the description provided of these lesions is incomplete, the relation 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 1930’s. It was also pointed out that 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.

7. DISCUSSION
Renewed interest in producing a classification of the multiple phenotypes of adenomyosis reflects the increased recognition of the importance of this disease, as well as the increased availability of non-invasive US- and MRI based diagnosis. It was previously believed that imaging-diagnosis should be based on the single criterion of a JZ thickness above 12mm. Today, however, a ‘sole criterion’ based diagnosis has been called into question and a broader approach has been proposed (Bazot and Darai, 2018). The advantages of an agreed classification cannot be overstated, since 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 impact of the disease. MRI provides a means of disease mapping within the affected uterus without requiring a hysterectomy. MRI is becoming increasingly available and although still expensive, is less labour
intensive compared to systematic histologic examination of the uterus. MRI is recognized as the most accurate imaging diagnostic modality and available literature suggests good sensitivity and specificity. But published literature comes from specialist centres with highly selected patient groups and have a high level of specialised expertise. In addition, the cited sensitivities and specificities relate only to the diagnosis of adenomyosis, not to its location or mapping. Thus, there is no indication as to how imaging-based mapping correlates with histology which has traditionally been considered the gold standard. There also remains disagreement 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 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’ (Mehasseb et al., 2010; Benagiano et al, 2016; Kishi et al, 2017; García-Solares et al., 2018; Khan et al., 2019). But supporting evidence is still fragmentary and incomplete and the factors that enable glands and stroma to be aberrantly located within the myometrium or the POD 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 opposite 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. MRI imaging and immunohistochemical features that suggested similarities or differences between tissues obtained from different locations have been used by proponents to advance their viewpoints. But there remain unresolved questions related to MRI mapping, 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.

key message

There is, as yet, no widely agreed classification for adenomyosis. 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.

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**Figure 1:** MR imaging examinations in a 30-year woman with sagittal 2D-T2-w (A) and 3DT1-weighted (B) MRI showing a huge globular uterus containing multiple endometrial foci related to deep diffuse internal adenomyosis.
Figure 2: MR imaging examination in a 29-year woman, G1P0 (abortion retrieved by curettage) with two consecutives sagittal 2DT2-weighted MR images showing a hypointense lesion (A) containing small tiny spots (curved arrows) and located in the posterior wall, adjacent to the endometrial cavity related to focal adenomyosis. Note the linear aspect of the lesion (arrows) suggestive of uterine perforation during curettage (B).
**Figure 3:** MR imaging examination in a 43-year woman with sagittal 2DT2 (A) and 3DT1-weighted (B) MRI. Anteverted uterus displaying an ill-defined mass located in anterior wall and endometrial cavity (large arrows). This mass containing small high intense tiny cysts on T2-w and T1-w images is related to submucous adenomyoma.
Figure 4: MR imaging examinations in a 35-year woman, with previous myomectomy showing on sagittal 2D-T2-w (A) and axial 3D-T1-weighted MRI (B) a huge globular uterus with extensive thickening of anterior junctional zone containing multiple high intensity spots (arrows) related to deep diffuse internal adenomyosis. 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).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnostic cut-off point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owolabi and Strickler (1977)</td>
<td>&gt;1 LPF</td>
</tr>
<tr>
<td>Novak and Woodruff (1979)</td>
<td>&gt;1 HPF</td>
</tr>
<tr>
<td>Hendrickson and Kempson (1980)</td>
<td>&gt;1/4 of total uterine wall thickness</td>
</tr>
<tr>
<td>Gompel and Silverberg (1985)</td>
<td>&gt;1 medium-power field (x100)</td>
</tr>
<tr>
<td>Parazzini et al (1997)</td>
<td>&gt;0.5 LPF (2.5mm)</td>
</tr>
<tr>
<td>Vercellini et al (1995)</td>
<td>Prevalence varied when ≥1, ≥2, or ≥3mm from the endometrial-myometrial junction was used as a cut-off point</td>
</tr>
<tr>
<td>Bergholt et al (2001)</td>
<td></td>
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</table>

Table (1): Proposed histological cut-off points for the diagnosis of adenomyosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Classification</th>
</tr>
</thead>
</table>
| Bird et al (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: 1-3 glands per LPF  
Moderate: 4-9 glands per LPF  
Marked: 10 or more glands per LPF |
| Siegler and Camilien (1994) | A) According to depth of penetration from the basal layer of endometrium: Grades 1-3.  
B) Degree of involvement: mild (1-3 islands/LPF), moderate (4-10 islands/LPF), severe (>10 islands/LPF).  
C) Configuration: diffuse, discrete (nodular/focal). |
| Levger et al (2000) | 2.5mm depth from the endo-myometrial border as a cut-off point  
Superficial: <40% uterine wall thickness  
Intermediate: between 40-80% wall thickness  
Deep: >80% wall thickness |
| Sammour et al (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 et al (2002) | Category 1 (mild): Only microscopic foci or only affection of the...
inner 1/3 of myometrium excluding innermost 2-3mm.  
Category 2 (focal lesions).  
Category 3 (severe): Affections of the outer 2/3 of the myometrium

| Vercellini et al (2006) | >2.5mm 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 (1-3 islet/LPF; 4-10 islets/LPF, >10 islets/LPF).  
Configuration: diffuse, focal or nodular

| Grodts et al (2008) | JZ hyperplasia: ≥8 but <12mm on MRI in women aged ≤35 years.  
Adenomyosis: JZ ≥12mm; 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

Subtype II: Extrinsic: Outer uterine layer (normal JZ)  
Subtype III: Solitary adenomyosis no connection to the JZ or to the serosa.  
Subtype IV: Indeterminate

| Pistofidis et al (2014) | Included assessment of gross appearance at time of surgery:  
- Sclerotic  
- Nodular  
- Cystic

- Focal: affection of a restricted are (includes adenomyoma and cystic variety)  
- Polypoid (typical and atypical)  
- Special (rare forms)

Table (2): Histological based classification of adenomyosis in different studies.
Diffuse adenomyosis

Focal adenomyosis

Adenomyoma

<table>
<thead>
<tr>
<th>Score</th>
<th>1 wall affected, ≤20 mm thick</th>
<th>2 walls affected, ≤20 mm thick. Or; 1 wall affected, between &gt;20 to ≤30 mm thick</th>
<th>JZ\text{max} &gt;6 to ≤8 mm. Or; JZ\text{dif} &gt;4 to ≤6 mm. Or; Diffuse JZ infiltration ≤20 mm in length</th>
<th>1 lesion ≤10 mm</th>
<th>1 hyperechoic lesion Or; Cystic areas ≤10 mm</th>
<th>1 lesion ≤20 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 2</td>
<td>2 walls affected, ≤20 mm thick. Or; 1 wall affected, between &gt;20 to ≤30 mm thick</td>
<td>JZ\text{max} &gt;8 mm. Or; JZ\text{dif} &gt;6 mm. Or; Diffuse JZ infiltration ≤20 mm in length or &lt;50% of the uterus</td>
<td>≥2 lesions ≤10 mm. Or; 1 lesion &gt;10 to ≤20 mm</td>
<td>≥2 lesions ≤10 mm. Or; 1 lesion &gt;10 to ≤20 mm</td>
<td>2 lesions ≤20 mm. Or; 1 lesion &gt;20 to ≤30 mm</td>
<td></td>
</tr>
<tr>
<td>Score 3</td>
<td>1 wall affected, &gt;30 mm thick. Or; 2 walls affected, &gt;20 to ≤30 mm thick</td>
<td>Diffuse JZ infiltration &gt;50% to ≤80% of uterus</td>
<td>≥2 lesions &gt;10 to ≤20 mm. Or; 1 lesion &gt;20 mm</td>
<td>≥2 lesions &gt;10 to ≤20 mm. Or; 1 lesion &gt;20 mm</td>
<td>2 lesions &gt;20 to ≤30 mm. Or; 1 lesion &gt;30 to ≤40 mm</td>
<td></td>
</tr>
<tr>
<td>Score 4</td>
<td>2 walls affected, &gt;30 mm thick. Or; All uterus affected and globally enlarged</td>
<td>80% total JZ infiltration</td>
<td>≥2 lesions &gt;20 mm</td>
<td>≥2 lesions &gt;20 mm</td>
<td>≥1 lesion &gt;40 mm</td>
<td></td>
</tr>
</tbody>
</table>

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\text{max}= Maximum JZ thickness. JZ\text{min}= Minimum JZ thickness. JZ\text{dif}= JZ_{\text{max}}- JZ_{\text{min}}.