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Diagnosing adenomyosis: an integrated clinical and imaging approach

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On behalf of the Society of Endometriosis and Uterine Disorders (SEUD) Forum Group on Adenomyosis

BACKGROUND: Adenomyosis is a benign uterine disorder where endometrial glands and stroma are pathologically demonstrated within the uterine myometrium. The pathogenesis involves sex steroid hormone abnormalities, inflammation, fibrosis and neuroangiogenesis, even though the proposed mechanisms are not fully understood. For many years, adenomyosis has been considered a histopathological diagnosis made after hysterectomy, classically performed in perimenopausal women with abnormal uterine bleeding (AUB) or pelvic pain. Until recently, adenomyosis was a clinically neglected condition. Nowadays, adenomyosis may also be diagnosed by non-invasive techniques, because of imaging advancements. Thus, a new epidemiological scenario has developed with an increasing number of women of reproductive age with ultrasound (US) or magnetic resonance imaging (MRI) diagnosis of adenomyosis. This condition is associated with a wide variety of symptoms (pelvic pain, AUB and/or infertility), but it is also recognised that some women are asymptomatic. Furthermore, adenomyosis often coexists with other gynecological comorbidities, such as endometriosis and uterine fibroids, and the diagnostic criteria are still not universally agreed. Therefore, the diagnostic process for adenomyosis is challenging.

OBJECTIVE AND RATIONALE: We present a comprehensive review on the diagnostic criteria of adenomyosis, including clinical signs and symptoms, ultrasound and MRI features and histopathological aspects of adenomyotic lesions. We also briefly summarise the relevant theories on adenomyosis pathogenesis, in order to provide the pathophysiological background to understand the different phenotypes and clinical presentation. The review highlights the controversies of multiple existing criteria, summarising all of the available evidences on adenomyosis diagnosis. The review aims also to underline the future perspective for diagnosis, stressing the importance of an integrated clinical and imaging approach, in order to identify this gynecological disease, so often underdiagnosed.

SEARCH METHODS: PubMed and Google Scholar were searched for all original and review articles related to diagnosis of adenomyosis published in English until October 2018.

OUTCOMES: The challenge in diagnosing adenomyosis starts with the controversies in the available pathogenic theories. The difficulties in understanding the way the disease arises and progresses have an impact also on the specific diagnostic criteria to use for a correct identification. Currently, the diagnosis of adenomyosis may be performed by non-invasive methods and the clinical signs and symptoms, despite their heterogeneity and poor specificity, may guide the clinician for a suspicion of the disease. Imaging techniques, including 2D and 3D US as well as MRI, allow the proper identification of the different phenotypes of adenomyosis (diffuse and/or focal). From a histological point of view, if the diagnosis of diffuse adenomyosis is straightforward, in more limited disease, the diagnosis has poor inter-observer reproducibility, leading to extreme variations in the prevalence of disease. Therefore, an integrated non-invasive diagnostic approach, considering risk factors profile, clinical symptoms, clinical examination and imaging, is proposed to adequately identify and characterise adenomyosis.

WIDER IMPLICATIONS: The development of the diagnostic tools allows the physicians to make an accurate diagnosis of adenomyosis by means of non-invasive techniques, representing a major breakthrough, in the light of the clinical consequences of this disease. Furthermore, this technological improvement will open a new epidemiological scenario, identifying different groups of women, with a dissimilar clinical and/or imaging phenotypes of adenomyosis, and this should be object of future research.

Key words: abnormal uterine bleeding / adenomyosis / dysmenorrhea / imaging / histopathology / junctional zone / MRI / pelvic pain / ultrasound / uterine disorders

Introduction

Adenomyosis is a benign gynecological disease, described in the last century (Hunter *et al*., 1947) by the presence of endometrial glands and stroma within the myometrium (McCluggage and Robboy, 2009). However, in recent years adenomyosis has turned from a histopathological entity into a clinical condition, diagnosed by imaging techniques, independently of surgical treatment (Dueholm *et al*., 2001). Adenomyosis is also considered a specific item among those listed in the PALM-COEIN FIGO classification of causes of abnormal uterine bleeding (AUB) (Munro *et al*., 2011).

In the last decade, imaging technologies, such as magnetic resonance imaging (MRI) and transvaginal ultrasound (TVUS), have become widely available and accessible. These advancements have contributed to change the epidemiological profile of adenomyosis. Adenomyosis has been always considered the typical disease identified in multiparous women, with heavy menstrual bleeding (HMB), aged more than 40 years, who have undergone hysterectomy (Taran *et al*.; 2012; Li *et al*., 2014). Recently, adenomyosis has become a multifaceted disease diagnosed by non-invasive techniques in young women (Pinzauti *et al*., 2015), with AUB, infertility or pelvic pain and even asymptomatic women (Abbott, 2017). Furthermore, adenomyosis is often diagnosed in association with gynecological comorbidities, such as endometriosis (Di Donato *et al*., 2014; Eisenberg *et al*., 2017) and uterine fibroids (Brucker *et al*., 2014). However, shared clinical and imaging diagnostic criteria are still lacking and data coming from previous studies are heterogeneous and not fully comparable. On the one hand, advancements in imaging techniques have allowed the identification of an increasing number of cases of adenomyosis. On the other, the controversies on pathogenic theories, classifications and imaging diagnostic criteria prevent a shared definition of adenomyosis, even after histopathological examination. Thus, nowadays the diagnostic process of adenomyosis is challenging, and this review aims to collect all of the available evidence for an accurate diagnosis, considering symptoms (i.e. history) and clinical signs as well as imaging features of adenomyosis.

Methods

PubMed and Google Scholar were searched for all peer-reviewed original and review articles related to diagnosis of adenomyosis published in English until October 2018. Literature searches were performed to

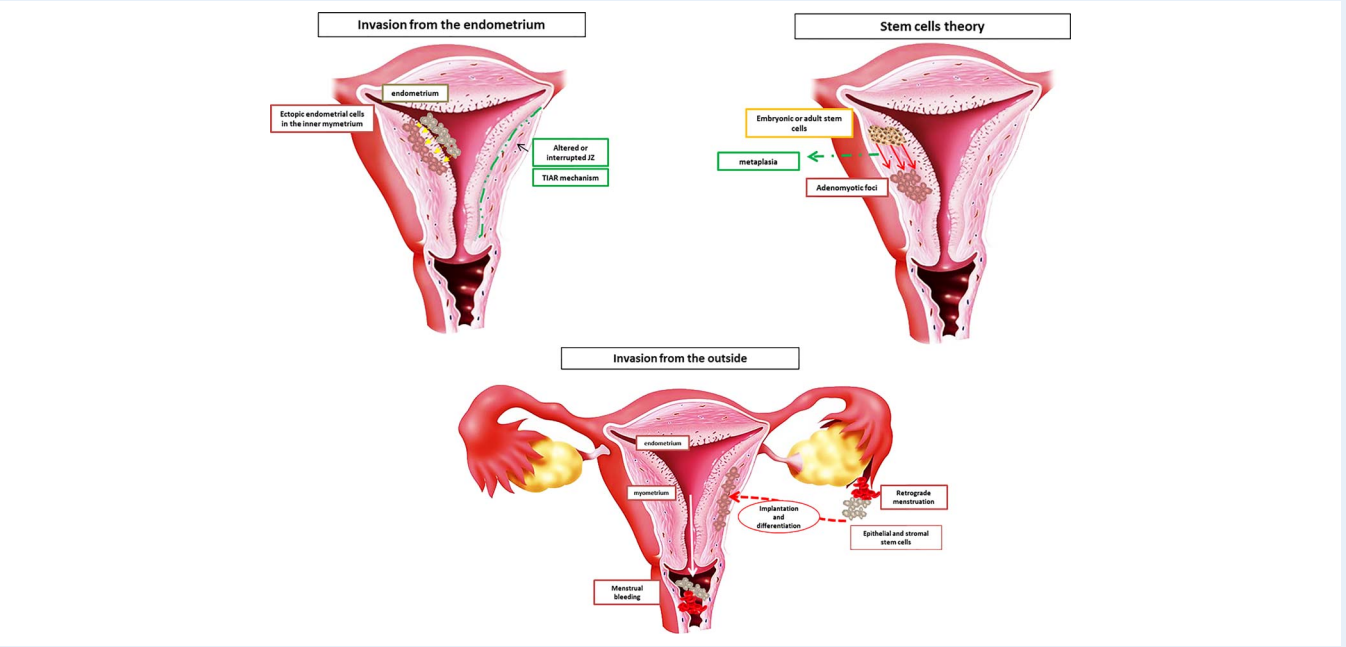


Figure 1 Pathophysiology of adenomyosis, different theories and potential mechanisms involved. (**A**) invagination of the endometrium into the myometrium through an altered or interrupted junctional zone (JZ) and the contribution of the mechanism of tissue injury and repair (TIAR); (**B**) metaplasia of intramyometrial embryonic or adult stem cells; (**C**) migration and differentiation of adult endometrial and stromal stem cells after retrograde menstruation through the invasion from outside.

identify all of the diagnostic criteria and techniques that have been applied so far in order to diagnose the disease. The main terms used were 'abnormal uterine bleeding', 'adenomyosis', 'diagnosis', 'dysmenorrhea', 'dyspareunia', 'imaging', 'heavy menstrual bleeding', 'histopathology', 'junctional zone', 'MRI', 'myometrium', 'pelvic pain', 'transvaginal ultrasonography', 'ultrasound', and 'uterine disorders'.

Pathogenic Correlates of Diagnostic Features of Adenomyosis

The precise adenomyosis pathogenesis is still poorly understood, and several hypotheses have been proposed (García-Solares *et al.*, 2018). Furthermore, in the last decade, an increasing number of studies have indicated the involvement of sex steroid hormone receptors, inflammatory molecules, extracellular matrix enzymes, growth factors and neuroangiogenic factors, as pathogenic mediators of adenomyosis (Vannuccini *et al.*, 2017).

The most accepted theories consider that the disease develops through the down growth and invagination of the endometrium basalis into the myometrium through an altered or absent junctional zone (JZ) (Parrott *et al.*, 2001; Bergeron *et al.*, 2006) (Fig. 1A). The increased invasiveness of endometrial cells through bundles of weak smooth muscle fibres, which have loosened their tissue cohesion, may result in the development of adenomyosis (Kolioulis *et al.*, 2017).

The JZ is a highly specialised structure, identified in MRI studies of the uterus as the subendometrial halo or in US as the hypoechoic tissue identified beyond the endometrial basal layer (Brown *et al.*, 1991; Brosens *et al.*, 1998; Exacoustos *et al.*, 2013). No uniform terminology exists for JZ, as it has been called as inner myometrium, archimyometrium or endomyometrial junction (Uduwela *et al.*, 2000), but it identifies a structurally and functionally different tissue from the outer myometrium (Brosens *et al.*, 1995). The endometrial–myometrial interface does not rely on any particular histological feature. The JZ observed at MRI does not have any histological correlate, which may explain why the JZ concept has a poor traction among pathologists. The lower limit of the endometrium is not delineated from the underlying inner myometrium by any microscopic junction or membrane. Furthermore, this interface is often microscopically ill-defined and not straightforward or apparent. Instead, some endometrial glands and stroma penetrating the inner myometrium is a common histopathological finding and should be considered as a normal variation of the endometrial–myometrial interface, without any pathological significance *per se*.

Another theory supports uterine auto-traumatisation and the mechanism of tissue injury and repair (TIAR) as the primary event in the initiation process of adenomyosis (Leyendecker *et al.*, 2009; Leyendecker and Wildt, 2011). Specifically, the process of chronic proliferation and inflammation is induced at the level of JZ by chronic uterine auto-traumatisation (tissue injury), and subsequently tissue repair is ensued (Leyendecker *et al.*, 2015). Peristaltic myometrial contractions promote repeated cycles of autotraumatisation, damaging the JZ. Thus, the TIAR mechanism in response to increased intrauterine pressure due to hypercontractility leads to migration of fragments of basal endometrium into the myometrium (Shaked *et al.*, 2015) (Fig. 1A). However, uterine peristalsis is seemingly universal in women of reproductive age, and it is unclear why some women, but not the others,

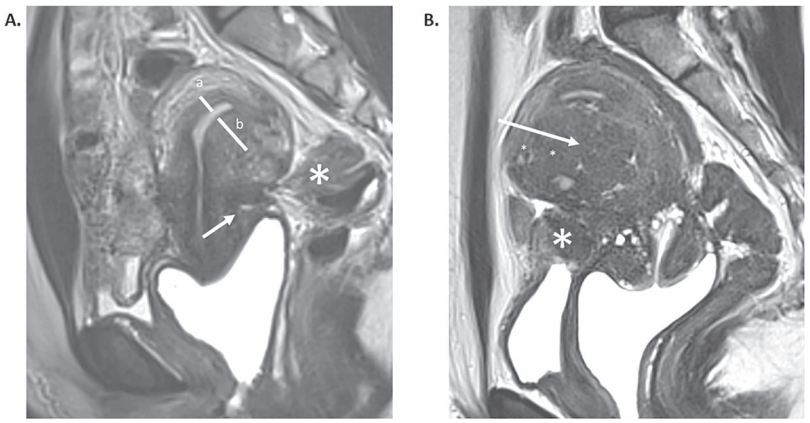


Figure 2 MRI sagittal T2-weighted images of focal adenomyosis and endometriosis. (**A**) posterior focal adenomyosis of the outer myometrium (FOAM) (white arrow). The lesion is contiguous to a deep infiltrating endometriosis (DIE) nodule affecting the uterine torus and the rectal wall (white star). Significant increased focal thickness of posterior junctional zone (b) (JZ) compared to the anterior JZ (a), suggesting a diffuse internal adenomyosis. (**B**) Anterior FOAM (white arrow) with the presence of intramyometrial cysts (small white stars). The lesion is contiguous to a bladder nodule of deep infiltrating endometriosis (DIE) (big white star).

apparently undergo peristalsis with much greater magnitude, leading to the autotraumatisation which, in turn, eventually yields adenomyosis.

Another pathogenic theory of adenomyosis supports the role of embryonic or adult stem cells which may undergo metaplasia into the myometrium, as a de-novo process (Gargett *et al*., 2016). The theory proposes that the adenomyotic foci may originate from metaplastic changes of intramyometrial embryonic pluripotent Müllerian remnants, leading to establishment of *de novo* ectopic endometrial tissue within the adult myometrial wall process (Gargett, 2007). Nevertheless, permanent populations of adult stem cells have also been reported in the endometrial basalis, as playing a critical role for cyclic repair of endometrium (Fig. 1B). However, those cells may allow an uncontrolled growth also beyond the endometrial–myometrial interface, maybe activated after tissue injury at level of JZ (Vannuccini *et al*., 2017). Alternatively, adult endometrial and stromal stem cells may be displaced into the myometrium after retrograde menstruation, undergoing further cellular differentiation and forming adenomyotic islands (Garcia-Solares *et al*., 2018) (Fig. 1C). Accordingly, Chapron *et al*. (2017) described the migration of ectopic endometrial cells from deep infiltrating endometriosis (DIE) nodules into the myometrium, supporting the 'from outside to inside invasion' theory. After retrograde menstruation, ectopic endometrial cells may have the potential to infiltrate not only pelvic organs, but also the uterine walls. The hypothesis is supported by the increased prevalence of a specific phenotype of adenomyosis, the posterior focal adenomyosis of the outer myometrium (FOAM), in patients with endometriosis nodules in the posterior compartment, diagnosed by MRI (Chapron *et al*., 2017) (Fig. 2A). Similarly, the intraperitoneal seeding of endometrial cells after menstruation may cause invasion of the vesicouterine pouch, generating both a bladder nodule and anterior FOAM, thorough a common 'outside-in' trans-serosa invading process (Marcellin *et al*., 2018) (Fig. 2B). This theory is supported by the finding of a 50% association between anterior FOAM and endometriosis bladder nodules at MRI evaluation. Of course, the final proof or refutation of this theory will come from studies that establish the phylogenetic relationship between DIE and FOAM lesions.

However, all of the existing theories may not fully explain the different phenotypes of the disease and the elucidation of how the disease may originate and develop in different forms may also help to better understand clinical signs and symptoms and imaging presentations. Most importantly, no theory has ever been experimentally proven so far, nor has a theory made useful, previously unknown, predictions.

Histopathological Aspects of Adenomyosis

Adenomyosis is defined as the presence of ectopic endometrial tissue (endometrial stroma and glands) within the myometrium (Bergeron *et al*., 2006; McCluggage and Robboy, 2009; Zaloudek *et al*., 2011; Nucci and Quade, 2011) (Fig. 3A). In severe adenomyosis, the pathological diagnosis is straightforward, with evident disease at both gross and microscopic examinations. However, in more limited disease, the diagnosis may be difficult, with poor inter-observer reproducibility. This concern leads to extreme variations in the prevalence of adenomyosis among different pathologists, ranging from 10 to 88% (Seidman and Kjerulff, 1996).

In severe adenomyosis, the disease is usually grossly apparent (Fig. 3B). The uterine corpus is enlarged, even globular in more extreme forms. The enlargement may be diffuse, may predominate in one uterine wall, usually the posterior wall (Ferenczy, 1998; Zaloudek *et al*., 2011), or may be more focal resulting in ill-defined intramural nodule(s). This enlargement is mainly the consequence of the myometrial smooth-muscle hyperplasia/hypertrophy that accompanies adenomyosis foci. This hyperplasia appears grossly as areas of hyperfasciculation of the myometrium, with a swirl trabeculated pattern. Differently from uterine fibroids, this smooth-muscle hyperplasia has indistinct limits without bulging at cutting. The

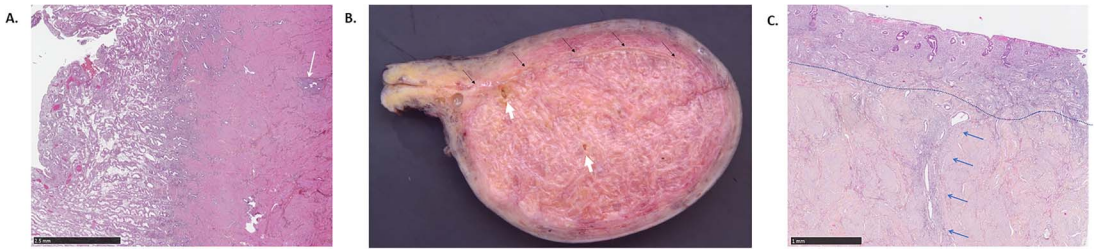


Figure 3 Histopathological images of adenomyosis. (**A**) Microscopic features: presence of ectopic endometrial tissue (endometrial stroma and glands) (white arrow) within the myometrium. (**B**) Gross features of severe adenomyosis: diffuse enlargement of uterine corpus with smooth-muscle hyperplasia/hypertrophy appearing as hyperfasciculation of the myometrium with a swirl trabeculated pattern and indistinct limits. Note also the presence of haemorrhagic cysts within the myometrium (white arrows). Black arrows indicate the eutopic endometrium. (**C**) Microscopic features of early adenomyosis. The adenomyotic process (arrows) originates from the endometrial-myometrial interface (dotted line), extending into the myometrium from 'inside to outside'.

ectopic endometrium may be grossly unapparent, or appear as gray-white foci, usually with some hemorrhagic dots or petechia. Small glandular cysts may be observed, more frequently in younger patients (Brosens *et al*., 2015).

The different microscopic aspects of adenomyosis are well described in pathology textbooks (McCluggage and Robboy, 2009; Nucci and Quade, 2011; Zaloudek *et al*., 2011). The ectopic endometrial tissue is constituted by glands and stroma and is present as foci of variable sizes, haphazardly located in the myometrium (Fig. 3A).

The endometrioid glands are usually inactive, as the basalis glands of the eutopic endometrium (Ferenczy, 1998). However, secretory changes may sometimes appear during pregnancy or under progestin treatments. Glands vary in size and configuration and may by cystic (Pistofidis *et al*., 2014) in 5% of cases, filled with cell debris and/or iron-laden macrophages. Epithelial metaplasia is an uncommon finding and is usually of ciliated or tubal types. In the 'gland-poor variant', which can be observed in post-menopausal women, endometrioid glands are sparse, only present in rare adenomyotic foci (Goldblum *et al*., 1995).

The endometrioid stroma vary in abundance and are usually inactive and non-mitotic, made of monotonous blue ovoid cells. Focal or extensive stromal decidualisation may occur during pregnancy or under progestin treatment. In menopause or under some hormonal treatments, the stroma may undergo atrophic changes, leading to difficulties in recognising its endometrioid nature under the microscope. In those cases, CD10 immunohistochemistry, a marker on the endometrial stroma, can be helpful. Extensive fibrotic changes, instead of the endometrioid stroma, are present in about 10% of cases, with or without surrounding smooth muscle hyperplasia (Pistofidis *et al*., 2014).

The smooth muscle hyperplasia/hypertrophy is visible as nodules around the ectopic endometrial foci. These nodules usually feature hyperfasciculation, with ill-defined borders with the adjacent myometrium. Smooth muscle cells can appear enlarged when compared to the adjacent myometrial cells. Smooth muscle hyperplasia may however be minimal or even lacking in post-menopausal women (Bazot *et al*., 2001).

The adenomyotic lesions also display an increased microvessel density (MVD), as shown by immunostaining for CD34, a glycosylated transmembrane protein present on endothelial cells. MVD has reported to be significantly more represented in ectopic endometrium of women with adenomyosis than in eutopic endometrium of both pathological and healthy women (Schindl *et al*., 2001). This histological finding of the role played by angiogenesis in adenomyosis is further supported by the observation at immunohistochemistry that adenomyotic lesions show an increased vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1alpha (HIF-1alpha) expression, particularly in the epithelial cells, associated with an increase of MVD, compared to eutopic endometrium and healthy controls (Goteri *et al*., 2009).

The topographic distribution of adenomyotic lesions is variable. In most instances, the disease appears to originate from the endometrial–myometrial interface with subsequent centrifugal extension towards the outer myometrium (Benagiano and Brosens, 2006) (Fig. 3C). The depth of myometrial infiltration is also variable, from cases limited to the more inner myometrium to those involving the whole myometrial thickness (Bazot *et al*., 2001). The positive histopathological diagnosis of adenomyosis is difficult in cases of minimal myometrial infiltration. In such cases, additional sampling should be performed and the presence of a clear smooth-muscle hyperplasia around the ectopic endometrial foci constitutes a diagnostic clue. A false positive diagnosis of adenomyosis can be made because of a tangential sampling of the endometrial–myometrial interface. Thus, a diagnosis of adenomyosis from hysteroscopy specimens should be carefully performed, as during both the hysteroscopic procedure and the paraffin inclusion of the tissue chips tangential artefacts are very frequent.

However, there are currently no formally agreed guidelines about sampling of adenomyotic uterus. Furthermore, a general consensus is lacking for defining robust histological criteria for the microscopic diagnosis of adenomyosis. To avoid false positive diagnosis of adenomyosis, the ectopic endometrium should be observed at least at some distance from the endometrial–myometrial interface. Proposed cut-off values are variable (Vercellini *et al*., 2006; Benagiano *et al*., 2015), for instance: one half of a low-power field (≈2.5 mm) (Zaloudek *et al*., 2011); one low-power field (≈4 mm) (Vercellini *et al*., 1993); two low-power fields (≈8 mm) (Sandberg and Cohn, 1962); one-third of the uterine wall thickness (Shaikh and Khan, 1990; Hendrickson and Kempson, 1987); and a quarter of the uterine wall thickness (Ferenczy, 1998).

The 2.5-mm cut-off value however appeared to be the most commonly accepted criterion (Vercellini *et al*., 2006). This cut-off value is

purely arbitrary and might lead to underdiagnosis of mild disease, which could still cause symptoms (Benagiano *et al.*, 2015).

Histopathological classification

Sampson differentiated adenomyomas into three groups according to the origin, including the invasion from within the uterus, the invasion from outside the uterus and the growth of misplaced endometrial tissue in the uterine wall (Sampson, 1921). Later, several attempts at classifying adenomyosis were performed by using the depth of myometrial penetration of adenomyotic foci at histological examination (Bird *et al.*, 1972), by grading the severity according to adenomyotic involvement of the inner third (superficial adenomyosis), two thirds, and entire myometrium (deep adenomyosis) (Siegler and Camilien, 1994), or according to the 'penetration ratio', (depth of penetration/myometrial thickness) representing the extent of the disease (Sammour *et al.*, 2002).

Vercellini *et al.* (2006), based on the proposal of Siegler and Camilien (Siegler and Camilien, 1994), proposed to consider three different parameters: (i) depth of penetration (up to one-third, mild disease; between one- and two-thirds, moderate disease; more than two thirds, severe disease), (ii) degree of spread defined by the number of foci per low-power field (1–3 islets, grade I; 4–10 islets, grade II, >10 islets, grade III), and (iii) configuration (diffuse versus nodular/focal). If the number of foci per slide appeared to be associated to the depth of penetration, it remains unclear whether this classification is correlated to the clinical severity of the disease.

Diagnostic Process for Adenomyosis

Adenomyosis is associated with a wide variety of symptoms which may or may not be directly due to the disease: no pathognomonic symptomatology is distinctive of adenomyosis (Peric and Fraser, 2006). Common symptoms include pelvic pain (in the forms of dysmenorrhea, dyspareunia and chronic pelvic pain), AUB and impaired reproductive potential (Gordts *et al.*, 2018) (Table I). However, those symptoms may be reported also in other benign gynecological conditions (Lippman *et al.*, 2003; Munro *et al.*, 2011; Fuldeore and Soliman, 2017). In fact, approximately 30% of women with adenomyosis are asymptomatic (Peric and Fraser, 2006). Mechanisms of symptoms generation are not well understood in this condition, and little is known about differences in the histology or pathogenesis in these asymptomatic women. The pathology has really only been described by study of hysterectomy symptoms, hence most of these women must have presented with symptoms requiring a surgical cure; thus, the samples may not accurately reflect the characteristics of the entire female population of interest. In addition, imaging and pathology data have demonstrated that uterine and pelvic comorbidities (uterine fibroids, endometriosis, endometrial polyps, endometrial hyperplasia) are very common in women with adenomyosis (60–80%) (Kunz *et al.*, 2005; Taran *et al.*, 2010; Di Donato *et al.*, 2014; Brucker *et al.*, 2014; Genc *et al.*, 2015; Eisenberg *et al.*, 2017).

The diagnostic process of adenomyosis should start, as usual, with the suspicion of disease, supported by the clinical presentation of relevant symptoms and signs, and their impact on quality of life, leading to complaint to a health professional. The interpretation of the presence of AUB and/or chronic pelvic pain should take into account also the possible combination with other benign gynecological pathologies. Therefore, the heterogeneity of the disease and non-specificity of symptoms often make the accurate diagnosis more challenging, but may guide the clinician to a suspicion of the disease. Then, the confirmation of the presence of adenomyosis should be performed by the imaging techniques, identifying a range of agreed and acceptable features and assessing the extent of the adenomyosis process. Imaging may help also to defining the presence of comorbidities. Moreover, a number of cases of adenomyosis may be identified as an incidental finding on imaging performed for other indications in asymptomatic women.

Table I Symptoms of adenomyosis.

Symptoms possibly associated with or caused by adenomyosis
1. Abnormal uterine bleeding (AUB)
a. Heavy menstrual bleeding
b. Prolonged menstrual bleeding
c. Inter-menstrual bleeding
d. pre-menstrual spotting
2. Gynecological pain symptoms
a. Dysmenorrhea
b. Dyspareunia
c. Chronic pelvic pain
3. Infertility and recurrent miscarriage
4. Local pressure symptoms
5. Bladder and gastrointestinal symptoms
a. Dysuria
b. Dyschezia

Risk factor profile

Several risk factors for adenomyosis have been evaluated. However, most of the studies have not been correctly designed to identify significant increases in relative risk. Vercellini *et al.* (1995) observed that adenomyosis, diagnosed at hysterectomy, was directly associated with the number of births and tended to be higher in cases of miscarriages and induced abortions. The result was confirmed by a second cross-sectional study, where adenomyosis was identified as a typical disease of parous middle-aged women (40–50 years) (Parazzini *et al.*, 1997). However, a recent ultrasound study on women aged from 18 to 30 years showed that adenomyosis features were present in more than 30% of young women, correlating with dysmenorrhea and AUB (Pinzauti *et al.*, 2015). Similarly, an MRI study on women aged less than 42 years showed that isolated diffuse adenomyosis occurred in one-third of the study population (34.6%) (Chapron *et al.*, 2017). Previous uterine surgical trauma, such as dilatation and curettage, increases the odds for adenomyosis, through the mechanical endometrial invasion of the myometrium (Levgur *et al.*, 2000; Panganamamula *et al.*, 2004), with an increasing trend in risk with increasing number of abortions. Similarly, the history of a previous cesarean section seems to be another risk factor according to the review of a surgical dataset (Vavilis *et al.*, 1997), even though the results are controversial (Bergholt *et al.*, 2001).

Clinical symptoms

AUB

All early studies (Benson and Sneeden 1958; Bird et al., 1972) indicated that women, who underwent hysterectomy and had adenomyosis, had a high presenting incidence of heavy menstrual bleeding (HMB), of the order of 50% of these women. Fairly high proportions of these women also had prolonged or irregular bleeding and smaller numbers had intermenstrual bleeding or pre- or post-menstrual spotting. However, the high frequency of comorbidities in most early and subsequent adenomyosis case series (60 to 80%) means that there is great controversy about which symptoms were attributable to adenomyosis per se and which to the comorbidity (Benson and Sneeden 1958; Bird et al., 1972).

In the Benson series (1958), a correct preoperative diagnosis of adenomyosis based solely on symptoms of HMB, with or without pelvic pain, was only made in 9.3% of women undergoing hysterectomy at a later date. AUB may be due to increased uterine volume, increased vascularisation, improper uterine contractions and/or increased production of estrogen and prostaglandins (Vannuccini et al., 2017). A recent study (Naftalin et al., 2014) evaluated menstrual symptoms in a large prospective case series of 714 women attending a general gynecology clinic and undergoing a transvaginal ultrasound (TVUS). The semi-quantitative assessment of HMB showed no significant association between the presence of adenomyosis and HMB, but did find a strongly significant correlation between the severity of adenomyosis on US and a complaint of HMB. Similarly, a study of hysterectomy specimens which correlated with symptoms (Levgur et al., 2000) found no significant association between the presence of adenomyosis and HMB or other AUB.

It is clear that there are no symptoms which are pathognomonic of adenomyosis (Peric and Fraser, 2006), but quality data are surprisingly scanty. It is probable that the common occurrence of a complaint of HMB by women who are later found to have adenomyosis is due to the simultaneous presence of another pathology, especially uterine fibroids. However, we cannot exclude that in a proportion of women with adenomyosis, HMB or any other symptoms of AUB is caused exclusively by the adenomyosis itself.

Pain

Original descriptions of adenomyosis reported an association between the disease and a 'great deal of pain' (Benson and Sneeden, 1958). Several studies later confirmed this finding (Bird et al., 1972; Sammour et al., 2002; Li et al., 2014), while others have not shown significant differences in terms of pain symptoms (Weiss et al., 2009).

Two recent prospective studies analysed a group of women attending a gynecology clinic and a positive correlation between two specific US features of adenomyosis and the pain score was observed (Naftalin et al., 2014; Naftalin et al., 2016). Furthermore, an MRI study of women with severe dysmenorrhea lasting more than 11 years showed a significantly higher frequency of adenomyosis (Kissler et al., 2008). In addition, chronic pelvic pain was significantly more likely to persist after surgical removal of endometriotic lesions if the JZ thickness was more than 11 mm on preoperative MR imaging (Parker et al., 2006).

Previous evidence reported that the severity of dysmenorrhea worsened as the depth and degree of invasion of adenomyosis into the myometrium increased (Bird et al., 1972; Sammour et al., 2002). Similarly, two studies on women undergoing hysterectomy showed that the histopathological features of adenomyosis, including the depth and the number of adenomyotic foci, correlated with the severity of dysmenorrhea (Nishida, 1991; Levgur et al., 2000).

In 15–57% of the cases, uterine fibroids and adenomyosis coexist in the same uterus and women with both conditions are more likely to experience pelvic pain (Ates et al., 2016). Results from a case–control study on women undergoing hysterectomy showed that women with uterine fibroids and adenomyosis were more likely to report various types of pain compared to women with fibroids only. In the presence of coexisting adenomyosis, pain with menses, pain during intercourse and non-cyclic pelvic pain were significantly more frequent than in cases of uterine fibroids alone (Taran et al., 2010; Taran et al., 2012; Boeer et al., 2014). Also DIE is associated with the presence of adenomyosis (Lazzeri et al., 2014; Perelló et al., 2017; Chapron et al., 2017). A preoperative and postoperative evaluation of clinical symptoms and a TVUS evaluation of women with DIE revealed the coexistence of adenomyosis in around 40% of women (Lazzeri et al., 2014). In such cases, bladder and gastrointestinal pain symptoms, such as dysuria and dyschezia, should also be considered. In addition, in those with DIE and adenomyosis, dysmenorrhea, dyspareunia and AUB remained significantly higher after surgical treatment than in those without adenomyosis. Thus, the presence of adenomyosis explains in part the persistence of pain symptoms and heavy bleeding after surgical treatment (Parker et al., 2006; Lazzeri et al., 2014).

Reproductive failure

The presence of adenomyosis is discovered at a high frequency in patients consulting with fertility problems (Maheshwari et al., 2012; Harada et al., 2016; Dueholm, 2017). In the presence of a dysregulation of the myometrial structure and altered endometrial function, a negative impact of adenomyosis on fertility could be expected (Campo et al., 2012). The incidence of adenomyosis in patients with dysmenorrhea, HMB and infertility was reported to be as high as 50% (Brosens et al., 1995). A disturbed utero-tubal transport was also reported (Kissler et al., 2004). Necropsy in baboons with long-term infertility showed the presence of adenomyosis in all of them with co-occurrence of endometriosis in 43% of them (Barrier et al., 2004). Lower pregnancy rates were reported after colorectal surgery for endometriosis in the presence of adenomyosis (Ballester et al., 2012). Although genes involved in implantation seem not to be altered (Martínez-Conejero et al., 2011), a higher miscarriage rate was reported in adenomyosis patients undergoing oocyte donation. Maubon et al. described the negative impact of uterine adenomyosis in patients after *in vitro* fertilisation (IVF) (Maubon et al., 2010). Results after IVF seem to be controversial with some publications not showing any difference in pregnancy rates (Costello et al., 2011; Benaglia et al., 2014) while others do show a difference (Salim et al., 2012; Yan et al., 2014; Vercellini et al., 2014; Mavrelos et al., 2017; Younes and Tulandi, 2017), and miscarriage rates seem to be elevated (Chiang et al., 1999; Salim et al., 2012; Younes and Tulandi, 2017). Conflicting results are due to the heterogeneity of the ovarian stimulation protocols used and to a mixing up of the different forms of adenomyosis without proper description of the type of adenomyosis. Understanding adenomyosis is greatly hampered by a lack of agreed-upon terminology or consensus on the classification of the lesions (Gordts et al., 2008).

In a meta-analysis, Vercellini et al. (2014) reported a negative impact of adenomyosis on pregnancy and miscarriage rates. Another recent meta-analysis reported also a negative effect of adenomyosis on IVF

clinical outcomes with a reduction of pregnancy rates, a 41% decrease in live birth rates and an increased miscarriage rate (OR 2.2, 95% CI 1.53–3.15) (Younes and Tulandi, 2017). Although most of the retrieved studies did not state the severity of the adenomyosis, it appeared that the negative impact of diffuse adenomyosis was more pronounced compared with the focal forms (Park *et al*., 2016).

In a retrospective study, the impact of adenomyosis in patients with endometriosis on perinatal outcome was evaluated (Scala *et al.*, 2018). The incidence of small for gestational age (SGA) babies in women with endometriosis alone was 10.8% as compared to 40% in patients with endometriosis and diffuse adenomyosis, whereas no statistically significant difference was observed in the comparison with those affected by focal adenomyosis (Scala *et al.*, 2018). Another study, looking at pre-pregnancy images of ultrasound and/or MRI, found a 1.84-fold (95% CI 1.32–4.31) risk increase for preterm delivery in patients with adenomyosis and a 1.98-fold (95% CI 1.39–3.15) risk increase for preterm premature rupture of membranes (PPROM) (Juang *et al.*, 2007). Furthermore, increasing evidence has been published on the impact of adenomyosis on adverse late pregnancy outcomes, such as preterm birth, SGA babies, cesarean section and postpartum hemorrhage (Mochimaru *et al*., 2015; Tamura *et al*., 2017; Hashimoto *et al*., 2018; Yamaguchi *et al*., 2018). A number of mechanisms seem to be implicated in the link between adenomyosis and obstetric complications, including activation of local and systemic inflammatory pathways, increased myometrial prostaglandin production, altered uterine contractility and defective myometrial spiral artery remodelling at the basis of an altered placentation (Vannuccini *et al*., 2016).

As there are well-documented differences for focal and diffuse forms of adenomyosis in terms of reproductive outcome (Park *et al*., 2016; Younes and Tulandi, 2017), there is a need for a comprehensive, clear and user-friendly, categorisation of adenomyosis including the pattern, location, histological variants and the myometrial zone.

Clinical examination

Women who present with gynecologic symptoms undergo bimanual examination of the pelvis in a large number of cases, as the first clinical step during gynecological consultation. The bimanual examination can help to estimate uterine or pelvic pain, pain localisation, uterine size and mobility and adnexal masses, and to raise the suspicion of the presence of DIE in the retrocervical region. Uterine size estimation by bimanual pelvic examination has been found to correlate well with preoperative ultrasound assessment in women undergoing hysterectomy (Condous *et al.*, 2007). However, the clinical examination alone cannot adequately detect uterine adenomyosis, although it may raise the suspicion of the disease. In some cases, the uterus might be larger than normal, but the alterations of the uterine tissue cannot be diagnosed without imaging techniques (Krentel *et al.*, 2017). In fact, as a next step, the clinical history and gynecological examination should be combined with imaging.

Benign gynecological comorbidities: uterine fibroids and endometriosis

Adenomyosis frequently coexists with other gynecological diseases, such as endometriosis and uterine fibroids (Di Donato *et al.*, 2014), which are commonly associated with pelvic pain and HMB. In a retrospective review of a consecutive cohort of 710 premenopausal women with adenomyosis who underwent hysterectomy, it was found that 343 (48.3%), 158 (22.3%), 129 (18.2%) and 80 (11.3%) patients, respectively, had adenomyosis alone, adenomyosis and endometriosis, adenomyosis and uterine fibroids, and all three conditions combined (Li *et al*. 2014). Among these patients, 580 (81.7%, 95% CI = 78.8–84.6%) of them complained of dysmenorrhea, and 352 (49.6%, 95% CI = 45.8–53.3%) and 116 (16.3%, 95% CI = 13.5–19.1%) complained of AUB and chronic pelvic pain, respectively (Li *et al*., 2014). Hence, it is important to differentiate adenomyosis-related symptoms from those caused by other conditions (Peric and Fraser, 2006; Taran *et al.*, 2013). Unfortunately, most of these studies used retrospective analysis of women who underwent hysterectomy for a wide range of benign gynecological pathologies, thus the reported results are biased because of non-homogeneous sampling. Furthermore, without more accurate diagnostic tools, the diagnosis of adenomyosis is rarely established prior to hysterectomy, and therefore the preoperative diagnosis based on clinical findings is very poor (Vercellini *et al.*, 2006).

A concomitant diagnosis of adenomyosis and uterine fibroids was encountered in 22.8% of women attending a gynecological clinic and undergoing a TVUS (Naftalin *et al.*, 2012). Women undergoing hysterectomy with both adenomyosis and uterine fibroids have a number of different clinical features compared to those with only fibroids, including more pelvic pain, less fibroid burden, higher parity and lower body mass index (Taran *et al*., 2010; Taran *et al*., 2012). In women with both adenomyosis and fibroids (for example, Fig. 4), severe forms of pelvic pain (dysmenorrhea, dyspareunia, chronic pelvic pain) were more frequently observed (Taran *et al*., 2010) and higher scores of distress were reported (Brucker *et al*., 2014).

On the other hand, the presence of endometriosis in patients with adenomyosis has been reported to be as high as 80.6% (Di Donato *et al*., 2014; Leyendecker *et al*., 2015; Chapron *et al*., 2017; Eisenberg *et al*., 2017), while adenomyosis was present in 79% of patients with endometriosis diagnosed by MRI, with a clear relationship between the thickness of the JZ and the severity of endometriosis (Kunz *et al.*, 2005). Furthermore, an US sign, the so-called 'question mark sign', is commonly found in women with adenomyosis and endometriosis, in particular those with posterior compartment involvement: the corpus uteri is flexed backwards, the fundus of the uterus faces the posterior compartment, and the cervix is directed frontally toward the bladder (Di Donato and Seracchioli, 2014). The dynamic evaluation of the pelvis and, notably, the negative sliding sign may be very helpful to raise the suspicion of adenomyosis due to invasion from outside, particularly if it is associated with posterior compartment nodules (Guerriero *et al*., 2019; Arion *et al*., 2019).

In addition, in women with DIE, focal adenomyosis of the outer myometrium (FOAM) was significantly more frequent, supporting the hypothesis of a different pathogenesis between the inner and outer myometrium forms of adenomyosis (Chapron *et al.*, 2017) (Fig. 2A and B). However, the inconsistencies in term of prevalence of adenomyosis and gynecological comorbidities highlight the need to identify uniform diagnostic criteria in imaging.

Imaging

The development of the imaging diagnostic tools has allowed accurate non-invasive diagnosis of adenomyosis (Dueholm and Lundorf, 2007), representing a major breakthrough in the light of the clinical

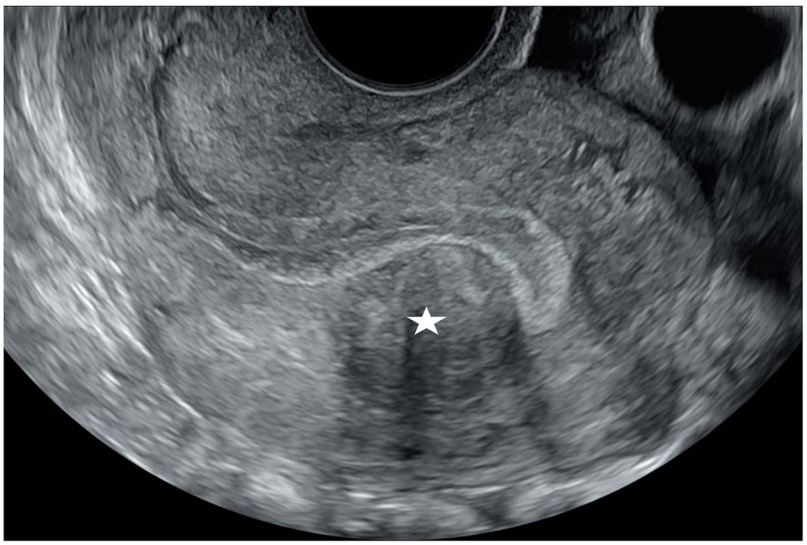


Figure 4 TVUS image of coexistence of uterine adenomyosis and fibroid. The area of coexistence is indicated (white star).

consequences of this disease. Imaging is essential for an accurate diagnosis and a tailored management including medical (Vannuccini *et al.*, 2018) or surgical conservative treatment (Osada, 2018). Currently, most women with adenomyosis are treated medically, without histological proof of the disease. Therefore, imaging techniques are crucial to make a diagnosis and to enable future studies assessing changes in adenomyosis appearance during the menstrual cycle, hormonal therapies, fertility treatment and pregnancy. Nowadays, a 2D (and eventually 3D) TVUS is the first-line diagnostic tool for diagnosing adenomyosis, while more expensive techniques, such as MRI, have a more complementary role (Andres *et al.*, 2018).

US

Ultrasound has become the first-line technique in the gynecological patient work-up, as it is easily available in the outpatient setting, is relatively less expensive than other imaging techniques, allows a dynamic examination (exploring organ mobility and site specific tenderness) and is very accurate in the diagnosis of gynecological pathologies, if performed by a trained sonographer (Van den Bosch, de Bruijn *et al.*, 2019). This mainly refers to transvaginal ultrasonography (TVUS), which allows an optimal view of the uterus, by using a 2-dimensional (2D) and 3D setting and Power/Colour Doppler.

Transabdominal ultrasonography is of limited value but may be of use when the vaginal route is not possible or in case of grossly enlarged uteri (Bazot *et al.*, 2002). The transabdominal ultrasound signs typical for adenomyosis are a large uterus, with regular external contour, asymmetrical myometrial walls and a heterogeneous myometrium, with intramyometrial cysts (Levy *et al.*, 2013). Although these signs have a good specificity of greater than 95%, the sensitivity is very poor, around 30% (Levy *et al.*, 2013). On the contrary, the sensitivity of TVUS to detect adenomyosis ranges from 65% to 81%, and the specificity ranges from 65% to 100% (Dueholm, 2006). A meta-analysis in 2009 on the accuracy of ultrasound in the diagnosis of adenomyosis demonstrated a sensitivity of 82.5% (95% confidence interval (CI), 77.5–87.9) and a specificity of 84.6% (95% CI, 79.8–89.8), with a positive likelihood ratio of 4.7 (3.1–7.0) and negative likelihood ratio of 0.26 (0.18–0.39), which is comparable to MRI (Meredith *et al.*, 2009). A more recent meta-analysis showed similar results for TVUS 2D for the diagnosis of adenomyosis with a sensitivity and specificity of 83.8% and 63.9%, respectively (Andres *et al.*, 2018).

Several ultrasonographic criteria have been utilised for the diagnosis of adenomyosis, including uterine enlargement, asymmetry of anterior and posterior uterine wall thickness, presence of heterogeneous myometrial areas, findings of anechoic areas in the myometrium (known as myometrial cysts), the presence of echogenic striations in the sub-endometrium, sub-endometrial echogenic nodules, irregular endometrial–myometrial interface, poor definition and thickening of the JZ (Kepkep *et al.*, 2007; Levy *et al.*, 2013; Shwayder and Sakhel, 2014; Graziano *et al.*, 2015).

Ultrasound reports from the 1980s proposed an enlarged uterus as the only sign to identify the condition, but with a very poor accuracy (Bohlman *et al.*, 1987; Murao *et al.*, 1986; Siedler *et al.*, 1987). In the 1990s the improvement of TVUS techniques allowed a better performance in detecting diffuse adenomyosis (Fedele *et al.*, 1992). The diagnosis was mainly based on the presence of ill-defined myometrial heterogeneity (Brosens *et al.*, 1995). Also the peak systolic velocity and the resistance index of intralesional vessels were proposed to differentiate between adenomyosis and fibroids (Hirai *et al.*, 1995). Therefore, already in the 1990s clinicians realised that a non-invasive diagnosis of adenomyosis was possible, by using either TVUS or MRI (Ascher *et al.*, 1994; Arnold *et al.*, 1995). Adenomyosis was identified based on an abnormal myometrial echotexture (decreased or increased echogenicity, heterogeneous echotexture, myometrial cysts). Those features correlated with histopathological findings (Reinhold *et al.*, 1995; Vercellini *et al.*, 1998; Reinhold *et al.*, 1999). The diagnostic accuracy of adenomyosis by TVUS improved if the presence of subendometrial linear striations, subendometrial echogenic nodules or asymmetric myometrial thickness were added (Atri *et al.*, 2000). In women undergoing TVUS, MRI and hysterectomy, the presence of myometrial cysts was the most sensitive and specific TVUS diagnostic criterion (Bazot *et al.*,

2001). In 2007, Kepkep *et al.* (2007) found that subendometrial linear striations were the most specific sonographic feature (95.5%) with the highest PPV (80.0%) for the diagnosis of adenomyosis. According to Dueholm's review published in 2006, TVUS was highly observer-dependent, but showed an adequate diagnostic accuracy if performed by an experienced sonographer (Dueholm, 2006). However, in 2008 Gordts *et al.* (2008) made a plea for a common terminology and a shared classification and suggested the crucial role of the JZ.

Colour flow Doppler imaging improves adenomyosis evaluation by assessing the location, amount and type of vascular flow (Valentini *et al.*, 2011; Exacoustos *et al.*, 2014). This technique can be used to differentiate adenomyosis from uterine fibroids and the overall diagnostic accuracy of the use of TVUS with colour Doppler for adenomyosis is 93.8% (Andres *et al.*, 2018). Typically, 'translesional flow' is seen in adenomyosis, as opposed to the circular flow seen in fibroids (Bazot and Darai, 2018), and power Doppler US displays vessels perpendicular to the endometrial interface (Perrot *et al.*, 2001). Furthermore, it has been suggested that in cases of posterior adenomyosis associated with DIE, the outer posterior myometrial border appears heterogeneous and myometrial cysts and radial vessels can be seen (Bazot and Darai, 2018).

Following the introduction of 3D TVUS, high frequencies probes and more advanced modalities, such as volume contrast imaging (VCI), JZ became more easily visible on US. The main advantage of 3D TVUS is that it enables assessment of the lateral and fundal aspects of the JZ and it provides a clearer visualisation of endometrial protrusions into the myometrium. 3D TVUS offers the additional advantage of allowing the rendering of the coronal plane of the uterus, so that the physician can evaluate the JZ (Naftalin and Jurkovic, 2009; Exacoustos *et al.*, 2014; Senturk and Imamoglu, 2015). In 2011, Exacoustos *et al.* (2011) evaluated by 2D and 3D TVUS the JZ in 72 premenopausal women before hysterectomy. Through the multiplanar view, they obtained the JZ measurements including the maximum (JZmax) and minimum (JZmin) JZ values and the difference between them (JZdif). Results showed that JZdif $\geq$4 mm and JZ infiltration and distortion had a high sensitivity (88%) and the best accuracy (85% and 82%, respectively) for the diagnosis of adenomyosis (Exacoustos *et al.*, 2011). Furthermore, in a study comparing morphologic alterations in the myometrium and JZ by US with histopathologic features of targeted biopsy specimens of the uterus, 3D TVS demonstrated high diagnostic accuracy in detection of site and position of adenomyosis in the uterine walls (Exacoustos *et al.*, 2013). Overall, the sensitivity and specificity of all combined imaging characteristics of TVUS 3D evaluation of adenomyosis were 88.9 and 56.0%, respectively. However, the sensitivity of TVUS gradually decreased to as low as 33% when fibroids were present (Dueholm *et al.*, 2001), in particular when the volume of the uterus was greater than 300 mL (Dueholm and Lundorf, 2007).

In the last 5–6 years, the increasing use of imaging techniques has allowed estimates of the prevalence of adenomyosis not only in those undergoing hysterectomy but also in those attending an ultrasound gynecology unit. The diagnosis of adenomyosis is often performed based on US features, even though no agreement on US features for adenomyosis exists. In 2012, Naftalin *et al.* (2012) estimated a prevalence of US signs of adenomyosis of 20.9% in symptomatic women seeking medical attention. Furthermore, adenomyosis was independently and significantly associated with the severity of menstrual pain, and the higher the number of US features, the higher was the pain score (Naftalin *et al.*, 2016). The severity of adenomyosis on US correlated also with the amount of menstrual loss estimated using pictorial blood loss assessment charts in a cohort of premenopausal women attending a general gynecology clinic (Naftalin *et al.*, 2014). Similarly, in 2015 Pinzauti *et al.* (2015) reported a significant association between the number of 2D-TVUS adenomyosis features and the score for dysmenorrhea and HMB in a cohort of nulliparous women, aged 18–30 years. In this population the prevalence of diffuse adenomyosis was 34%, of whom 83% were symptomatic (Pinzauti *et al.*, 2015).

MUSA terminology and a new reporting system for adenomyosis

The Morphological Uterus Sonographic Assessment (MUSA) consensus published in 2015 (Van den Bosch, Dueholm *et al.*, 2015) aimed to provide a standardised terminology for describing ultrasound images of normal and pathological myometrium. A shared identification and reporting system is essential both in clinical and research settings, in order to minimise interoperator variability during myometrial evaluation, to optimise diagnostic accuracy for uterine pathology and to evaluate myometrial changes after medical or surgical treatments (Gordts *et al.*, 2008). Furthermore, without common terminology and diagnostic criteria, the comparison between different studies is akin to building the tower of Babel and any meta-analysis attempt would be futile.

MUSA provides a list of 2D and 3D US features associated with adenomyosis (Fig. 5). The US examination should start with a 2D scan with measurements of the uterus, especially the anterior and posterior uterine walls in sagittal view. An asymmetry of uterine walls thickness (ratio above or below 1 or subjective impression) is considered a 2D US feature of possible adenomyosis (Fig. 6A). Similarly, an enlarged globular uterus with a regular contour shape is suggestive of adenomyosis. However, it is advisable to exclude the presence of transient uterine contractions, because they may modify the uterine walls thickness and change the myometrial echotexture, making the uterus appearing more globular.

The evaluation of myometrial appearance should be performed, defining the presence of intramyometrial cysts, hyperechoic islands, fan-shaped shadowing, echogenic subendometrial lines and buds (Van den Bosch, Dueholm *et al.*, 2015). Myometrial cysts are defined as round-shaped lesions within the myometrium, with anechoic, low-level echogenicity, ground-glass appearance or mixed echogenicity of intracystic content. Typically there is a hyperechogenic rim surrounding the cyst (Fig. 6B). The presence of regular, irregular of ill-defined hyperechogenic areas within the myometrium are called hyperechogenic islands (Fig. 6C). Fan-shaped shadowing is defined as alternating hypoechogenic and hyperechogenic linear stripes crossing the uterine wall (Fig. 6D). This acoustic effect is caused by the alternation of acoustic enhancement and shadowing behind the liquid content of the cyst and side wall respectively. Hyperechogenic subendometrial lines or buds refer to structures perpendicular to the endometrial cavity, but in continuum with the endometrium (Fig. 6E). In fact, the invasion of the endometrial glands into the subendometrial tissue induces a hyperplastic reaction that appears as echogenic linear striations fanning out from the endometrial layer. These latter features may be a sign of JZ disruption (Van den Bosch, Dueholm *et al.*, 2015).

The JZ normally appears as a dark subendometrial brim visible both on 2D and 3D US. However, the multiplanar view of the uterus by 3D US examination, by assessing also the coronal view, allows a better

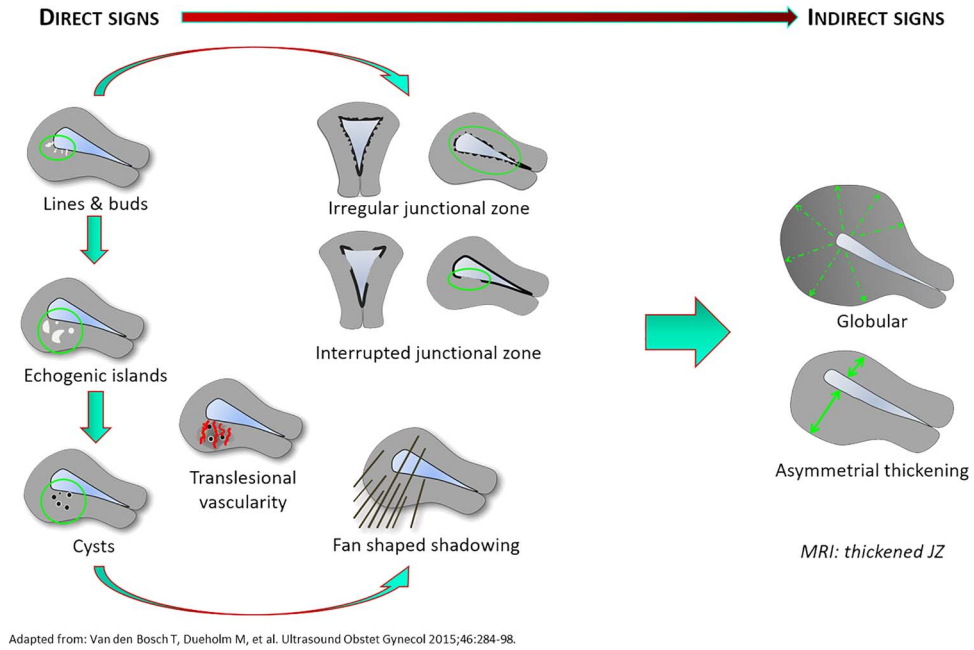


Figure 5 Two-dimensional (2D) and three-dimensional (3D) transvaginal ultrasound sonography (TVUS) features of adenomyosis, according to Morphological Uterus Sonographic Assessment (MUSA) protocol. Direct signs and indirect signs. Adapted from: Van den Bosch T, Dueholm M, *et al*. Ultrasound Obstet Gynecol 2015;46:284–98.

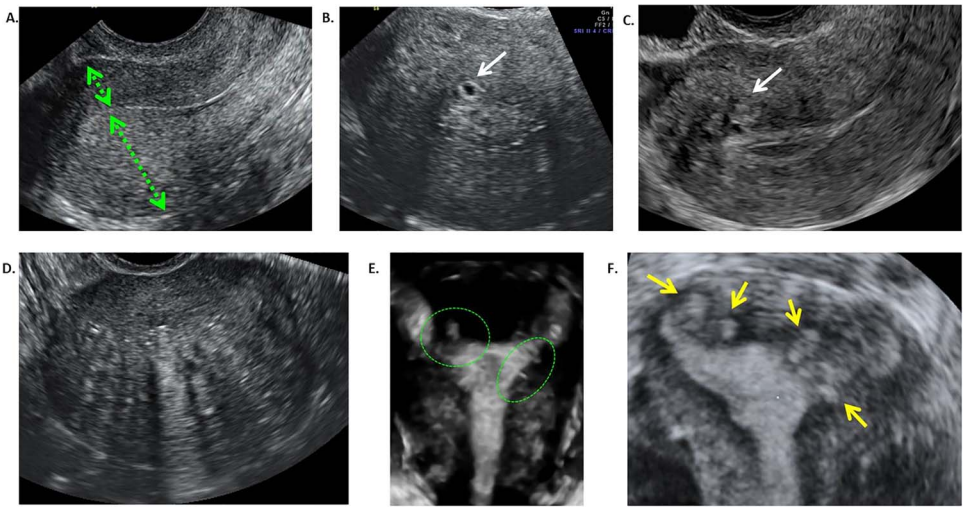


Figure 6 Two-dimensional (2D) and three-dimensional (3D) transvaginal ultrasound sonography (TVUS) signs of adenomyosis. (**A**) asymmetry of uterine walls thickness; (**B**) intramyometrial cysts; (**C**) intramyometrial hyperechogenic islands; (**D**) myometrium with fan-shaped shadowing; (**E**) hyperechogenic sub-endometrial lines of buds in 3D coronal view of the uterus, as signs of junctional zone (JZ) interruption; (**F**) JZ interruption in multiple sites visible at 3D coronal view.

evaluation of the JZ. In adenomyosis, the JZ may be reported as irregular, interrupted, not visible or not measurable (Fig. 6F) (Van den Bosch, Dueholm *et al*., 2015). For a more meticulous assessment of the uterus, VCI and other post-processing modalities, such as TUI (also called multislice imaging), may be helpful. Tables II and III summarise the pooled sensitivity and specificity for some of the criteria listed above (Andres *et al*., 2018).

Although it has been shown that 2D and 3D features are associated with adenomyosis, the importance of each item or their combination in the diagnosis of adenomyosis and in terms of pain and bleeding, or fertility and pregnancy outcome, has yet to be defined. However, the MUSA consensus represents a good start toward uniform terminology in describing myometrial lesions, with the aim of sharing a common language both in daily clinical

Table II Sensitivity and specificity of different 2D TVUS for the diagnosis of adenomyosis.

TVUS feature	Sens	Spec
Asymmetry myometrial wall	57.2	71.9
Myometrial cysts	72.0	62.7
Hypoechoic linear striations	71.3	79.7
Heterogeneous myometrium	86.0	61.3
Poor definition junctional zone	58.6	71.5
Globular uterus	55.0	80.2
Question mark sign	75.0	92.3

TVUS: transvaginal ultrasonography; Spec: specificity (%); Sens: sensitivity (%)
Adapted from Andres *et al*, Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2018;25:257–264.

Table III Sensitivity and specificity of different 3D TVUS for the diagnosis of adenomyosis.

TVUS feature	Sens	Spec
Asymmetry myometrial wall	59.2	53.4
Myometrial cysts	58.2	54.3
Hypoechoic linear striations	52.8	61.1
Heterogeneous myometrium	82.7	41.4
Poor definition junctional zone	87.8	56.0

TVUS: transvaginal ultrasonography; Spec: specificity (%); Sens: sensitivity (%)
Adapted from Andres *et al*, Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2018;25:257–264.

practice and for research purposes (Van den Bosch, Dueholm *et al*., 2015).

Very recently, a more detailed uniform reporting system of US findings of adenomyosis has been proposed, to be used in future studies on prevalence, clinical symptoms, efficacy of medical/surgical treatment, impact on fertility and pregnancy outcome (Van den Bosch, de Bruijn *et al*., 2019). According to this reporting system (Fig. 7), adenomyosis should be described in its location (anterior, posterior, lateral left, lateral right or fundal), differentiating between the focal and diffuse types. Focal adenomyosis is identified when more than 25% of the lesion is surrounded by normal myometrium (Van den Bosch, de Bruijn *et al*., 2019). When a focal lesion is completely surrounded by hypertrophic myometrium, this condition is named 'adenomyoma'. Furthermore, the same uterus can present with focal and diffuse lesions. In that case, the condition is called 'mixed type adenomyosis'. Another aspect to consider is the definition of adenomyosis as 'cystic' or 'non-cystic'. Intramyometrial cysts are reported as measurable if the largest diameter is more than 2 mm (Van den Bosch, de Bruijn *et al*., 2019).

Adenomyosis may involve one or more of the three uterine layers. Adenomyosis is defined as type 1 when only the JZ is involved, type 2 when the middle myometrium (the layer between the JZ and the vascular arcade) is involved, and type 3 if adenomyotic lesions are found in the outer myometrium (Van den Bosch, de Bruijn *et al*., 2019). Moreover, the severity of adenomyosis may be classified according to the extent of the disease in terms of percentage of affected myometrium (mild <25%; moderate 25–50%; severe >50%).

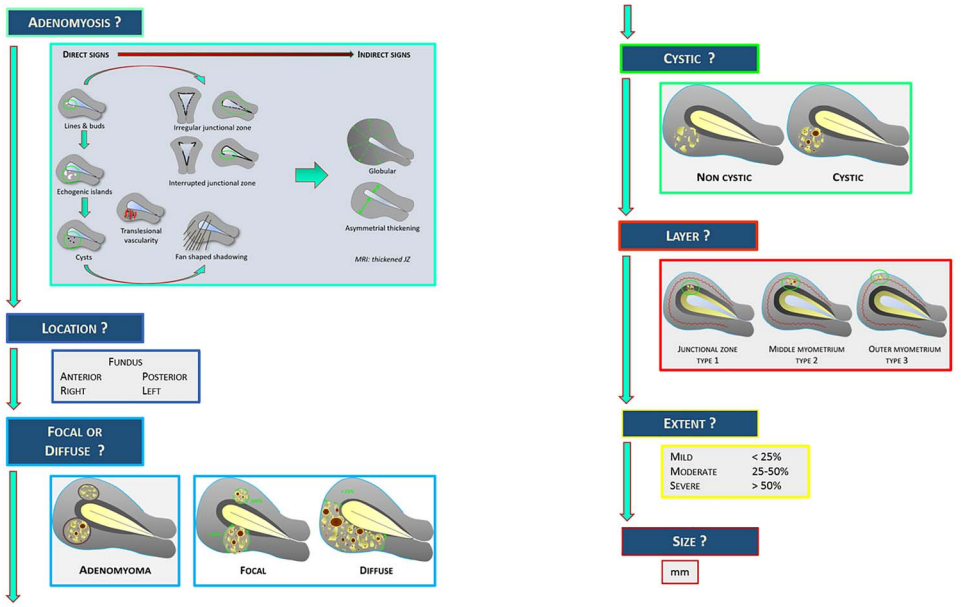
This is the first US adenomyosis classification and reporting system proposed by a panel of expert sonographers. However, it needs to be further validated in future prospective studies. The accuracy of the evaluation of localisation, extent and size of adenomyotic lesions, as well as the myometrial layer involved, should be tested in large series, in order to adequately define and differentiate focal versus diffuse forms. Furthermore, the relationship between the suggested US criteria and the clinical presentations of adenomyosis is still unknown and needs to be investigated, as well as the extent of adenomyotic lesions versus the severity of symptoms.

MRI

MRI is an accurate and non-invasive technique usually used as a second-line examination for the diagnosis of adenomyosis (Bazot and Darai, 2018). The sensitivity and specificity of MRI in diagnosing adenomyosis range from 88 to 93% and 67 to 91%, respectively (Kinkel *et al*., 1999; Dueholm and Lundorf, 2007; Champaneria *et al*., 2010; Exacoustos *et al*., 2014; Shwayder and Sakhel, 2014; Graziano *et al*., 2015).

Although there is some overlap in the features used for adenomyosis diagnosis between TVUS and MRI, at least three objective parameters have been identified for MRI diagnosis of adenomyosis, linked to JZ evaluation on T2-weighted sequences (Agostinho *et al*., 2017): the thickening of the JZ at least 8–12 mm, the ratio of junctional zone maximum/total myometrium over 40%, and the difference between the maximum and the minimum thickness of the JZ (JZmax – JZmin) more than 5 mm (Fig. 8A and B). A thickness exceeding 12 mm seems to be highly predictive of adenomyosis (Bazot *et al*., 2001; Champaneria *et al*., 2010), while a JZ less than 8 mm generally allows the presence of adenomyosis to be excluded (Reinhold *et al*., 1999).

It is important to be aware that JZ thickness varies with: the phase of the menstrual cycle (thickest between Day 8 and Day 16 and variable during menstruation), reproductive status (thinner or possibly absent during menopause and during pregnancy), use of medication (thinning with oral contraceptives or GnRHa) and age (thickens up to the age of 50 and then thins) (Novellas *et al*., 2011; Levy *et al*., 2013; Graziano *et al*., 2015; Bazot and Darai, 2018). Furthermore, a common pitfall to be aware of is the JZ thickness variation caused by transient uterine contractions, that can mimic either T2-weighted hypointense bands perpendicular to the JZ or focal thickening of the JZ (Togashi *et al*., 1993; Tamai *et al*., 2005). In such cases, it is useful to repeat MRI acquisition in order to differentiate a physiological condition from adenomyosis (Fig. 9A and B). Because of those modifications of the JZ, the first two diagnostic criteria have been criticised. In fact, a JZ measurement between 8 and 12 mm identifies the condition of adenomyosis only if other criteria are fulfilled, such as maximal JZ thickness to myometrium thickness ratio over 40% or a relative thickening of the JZ in a localised area. Conversely, the criteria of JZmax – JZmin more than 5 mm seems to be more independent from hormonal status and other interfering factors (Dueholm *et al*., 2001; Exacoustos *et al*., 2014). However, adenomyosis may be identified also in case of a poorly defined JZ or in presence of linear striations of high T2 signal radiating from the endometrial zona basalis into the myometrium.



Adapted from: Van den Bosch T, Dueholm M, et al. Ultrasound Obstet Gynecol 2015;46:284-98 and adapted from Van den Bosch T, de Bruijn AM, et al. Ultrasound Obstet Gynecol 2019;53:576-582.

Figure 7 Reporting system of ultrasound findings of adenomyosis, considering also location, type, involved layer, extent and size of the adenomyotic lesions. Adapted from: Van den Bosch T, Dueholm M, *et al*. Ultrasound Obstet Gynecol 2015;46:284–98 and adapted from Van den Bosch T, de Bruijn AM, *et al*. Ultrasound Obstet Gynecol 2019;53:576–582.

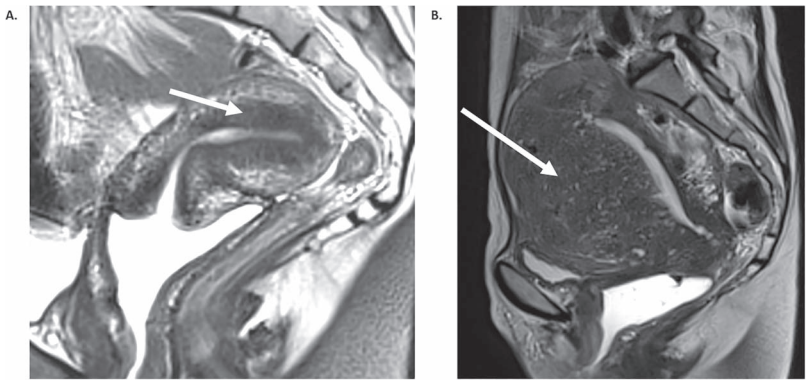


Figure 8 MRI sagittal T2-weighted images of adenomyosis. (**A**) Thickening of the junctional zone (JZ) (white arrow). Ratio of JZ maximum/total myometrium over 40%. (**B**) Severe adenomyosis of the anterior uterine wall (white arrow), with intramyometrial cysts (hyperechoic in T2 sequences).

MRI diagnosis of adenomyosis is essentially linked to the characteristics of the JZ, but it includes also direct and indirect signs of the presence of endometrial glands within the myometrium and smooth muscle cell hypertrophy (Tamai *et al.*, 2006; Exacoustos *et al.*, 2014). Typical adenomyosis appears as an ill-demarcated low-signal-intensity area on T2-weighted images, representing the smooth muscle hyperplasia and the heterotopic endometrial tissue (Fig. 8B). In addition intramyometrial cysts and small high-signal-intensity areas referring to ectopic endometrium may also be detected on T2-weighted MRI (Fig. 8B). Similarly, T1-weighted sequences contribute to the diagnosis of adenomyosis, allowing the identification of high-signal intensity foci representing areas of hemorrhage, that has a high positive predictive value (95%), however, with a low sensitivity (47.5%) (Bazot *et al.*, 2001).

After the introduction of the imaging techniques, in particular the MRI, the localisation of adenomyotic lesions was used to classify the disease, introducing also the concept of inner and outer myometrium thanks to the identification of the JZ. In 2012, Kishi *et al.* (2012) classified adenomyosis in four subtypes according to the localisation of MRI lesions: intrinsic, extrinsic, intramural and indeterminate. Subtypes 1 and 2 occur in the uterine inner and outer myometrial layer, respectively and, according to their theory, they originate from direct endometrial invasion and endometriotic invasion from the outside, respectively. Subtype 3 arises from de novo metaplasia and it has

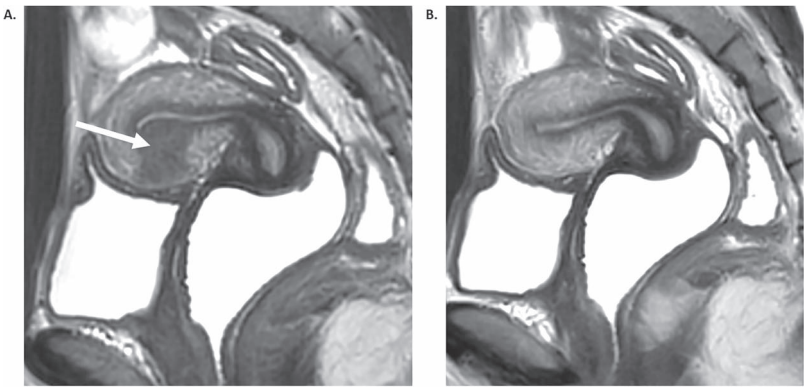


Figure 9 MRI sagittal T2-weighted images of a transient uterine contraction. The contraction mimics (**A**) a focal thickening of the JZ, that (**B**) disappears in the sequence acquired 7 min later.

no relationship with structural components, while subtype 4 is a heterogeneous mixture of advanced disease. In 2014, Pistofidis *et al.* (2014) identified four types of adenomyosis according to laparoscopic and histological findings: diffuse, sclerotic, nodular and cystic, and these correlated with clinical presentation. The same year, Grimbizis *et al.* (2014) elaborated a clinical histological classification, identifying (i) diffuse adenomyosis, with inner myometrium thickening and outer myometrium extensive disease; (ii) focal adenomyosis, including adenomyomas and cystic adenomyosis; (iii) polypoid adenomyomas, including typical and atypical forms; and (iv) some special categories, like those of adenomyomas of the endocervical type and retroperitoneal adenomyosis.

More recently, Bazot (2017) proposed a classification of adenomyosis according to MRI features, which allow identification of three main types: internal adenomyosis, external adenomyosis and adenomyoma. Internal adenomyosis may be focal, superficial or diffuse, specifying the symmetry of the lesion, while the external adenomyosis may be anterior or posterior. Regarding the adenomyoma, there are subtypes according to the localisation of the lesion and the content (Bazot and Darai, 2018). Very recently, the first attempt of a reporting and classifying system of adenomyosis based on US findings was published (Van den Bosch, de Bruijn *et al.*, 2019); however, a shared classification system has not been developed yet and the use of different technique does not help in providing comparable results. Further research is needed in order to better understand the physiopathology of adenomyosis, its onset and progression: this would allow interpretation of imaging and pathology signs according to the pathogenic theories, explaining all of the different phenotypes.

Other techniques and emerging technologies

Sonohysterography

In case of adenomyosis, the installation of a saline infusion into uterine cavity for a sonohysterography may show continuity between the subendometrial cystic spaces characteristic of the disease and the endometrial cavity. Flame-shaped or lollipop diverticula extending from the endometrium layer to the myometrial wall may be demonstrated (Verma *et al.*, 2009; Reeves *et al.*, 2010). However, this technique cannot depict the overall uterine condition, thus it may not be considered a single complete diagnostic method for adenomyosis. In case it is performed for other indications, it may provide proof of the loss of continuity between the endometrium and the myometrium in those phenotypes of adenomyosis where the JZ is involved.

Hysteroscopy

Hysteroscopy allows the direct visualisation of the uterine cavity and a list of endometrial signs suggestive of adenomyosis may be identified, such as endometrial hyper-vascularisation, strawberry pattern, endometrial defects and submucosal hemorrhagic cysts (Molinas *et al.*, 2006; El-Toukhy *et al.*, 2016; Di Spiezio *et al.*, 2017; Gordts *et al.*, 2018). This technique does not allow a definitive diagnosis of adenomyosis, and it is not considered as one of the standard methods to identify the disease, but some recent evidence describes the use of hysteroscopy to assess also the inner myometrium. The hysteroscopic exploration of the sub-endometrial myometrial area may help to identify signs of adenomyosis, such as neovascularisation or chocolate dye filled cysts with endometrial implants (Gordts *et al.*, 2014).

In the last few years, a new fusion technique, integrating US and hysteroscopy, has been introduced and it offers the possibility of obtaining endometrial and/or myometrial biopsies by using a utero-spirotome device under US guidance, in order to histologically evaluate suspicious area for adenomyosis (Gordts *et al.*, 2018). Endo-myometrial biopsy showed a specificity of 78.5% with a low sensitivity of 54.3%, due to the high incidence of false negative because of deep adenomyosis (Dakhly *et al.*, 2016). The histological evaluation of suspicious endomyometrial areas at US may open the possibility of further research on the correlation between imaging and pathology. However, the use of a utero-spirotome device under US guidance certainly increases costs and patient distress, and it is an invasive technique. Additionally, it is still under investigation whether the application of this technique would allow more effective treatments. Only a few studies have indicated that adenomyosis can be diagnosed using intrauterine modalities, such as hysteroscopy. The test performance of these techniques is far from clear and, currently, the applicability in everyday clinical practice still appears poor.

Elastography

The principle of elastography involves light external tissue compression that produces strain or displacement within the tissue, similar to palpation. Algorithms calculating the strain profile along the axis of compression produce the elastography image. The stiffness of the tissues examined by elastography is displayed in a range of false colours from red (components with the greatest strain or displacement in strain elastography; in shear-wave elastography it would be the hardest component i.e. the softest components) to green (components with average strain) to blue (components with no strain, or the hardest components). Elastography, when applied to TVUS, has been used to discriminate fibroids from adenomyosis. The findings as to the lesion stiffness reflected by elastography are conflicting. Some studies (Stoelinga *et al*., 2014; Frank *et al*., 2016; Stoelinga *et al*., 2018) report that adenomyosis is associated with softer tissue characteristics, while others (Acar *et al*., 2016; Liu *et al*., 2018) found a higher lesion stiffness. Liu *et al*. (2018) observed that transvaginal elastosonography was superior to conventional TVUS in the differential diagnosis of adenomyosis and uterine fibroids. In the latter study, lesional stiffness correlated closely with both the extent of lesional fibrosis, and with the severity of symptoms in patients with adenomyosis. More remarkably, the lesional stiffness, which is a proxy for the extent of lesional fibrosis, was reported to correlate closely with the expression levels of hormonal receptors. However, other studies have reported that adenomyotic tissues have a lower stiffness at elastography and the results were consistent with MRI findings (Stoelinga *et al*., 2014; Stoelinga *et al*., 2018).

The reasons for these strikingly inconsistent findings are unclear, but may indicate different types of adenomyosis. Future studies comparing elastography findings with strict ultrasonographic criteria and with histology are warranted, before introducing elastography into clinical practice.

Future Perspective for Diagnosis

In the last two decades, our understanding on adenomyosis has significantly improved and the awareness of this condition among clinicians has increased (Lone *et al*., 2006). In addition, the development of non-invasive diagnostic tools has made possible an accurate diagnosis of adenomyosis, without any surgical intervention. The introduction of MRI and 2D-3D Doppler TVUS has represented a major breakthrough, considering the clinical consequences of this disease. However, there are still many controversies in terms of diagnostic criteria. Most of imaging features have not been correlated yet with the clinical presentation of adenomyosis, thus their diagnostic and prognostic value is still unknown. Furthermore, suspicious signs and symptoms reported by the patient sometimes may not give any help to the diagnostic process, as a third of adenomyosis patients are asymptomatic or have a gynecological comorbidity that biases the diagnosis. The current available classifications proposed different phenotypes of adenomyosis but, once more, there is no shared language, neither uniformity in terms and definitions. For inclusion in a classification system, potentially important parameters could be: the affected area (inner or outer myometrium), the localisation (anterior, posterior or fundus) and the pattern and size (diffuse or focal specified as muscular or cystic). From a clinical perspective, an ideal imaging technique should not only diagnose adenomyosis accurately but also be helpful in deciding the best treatment modality, be it surgical, medical or otherwise no or minimally invasive procedures, such as radiofrequency and microwave ablation or ablation by high-intensity focused ultrasound (HiFu). The integration of non-invasive diagnostic tools is warranted by combining the risk factor profile, signs and symptoms and imaging techniques, in order to follow a common diagnostic approach to easily and early identify adenomyosis. This, of course, will call for more global collaboration and concerted research, preferably using standardised terminology and procedures.

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Authors' roles

C.C. and F.P. developed the original design, and each author contributed to the first drafting according to the area of expertise: pathogenesis (C.C., S.W.G., P.S.), clinical presentation (F.P., I.S.F., S.G.), imaging (T.V.D.B., S.V., M.S.A., F.C.), histology (P.A.J., J.C.N.) and classification (G.P.). S.V. and P.S. wrote the first integrated manuscript. C.C. and F.P. critically revised the manuscript for important intellectual content. All authors contributed to the writing of the final manuscript and approved it to be published.

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Conflict of interest

The authors declare no conflict of interest.

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