Symptoms and classification of uterine adenomyosis, including the place of hysteroscopy in diagnosis

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Where histology used the presence of glands and/or stroma in the myometrium as pathognomonic for adenomyosis, imaging uses the appearance of the myometrium, the presence of striations, related to the presence of endometrial tissue within the myometrium, the presence of intramyometrial cystic structures and the size and asymmetry of the uterus to identify adenomyosis. Preliminary reports show a good correlation between the features detected by imaging and the histological findings. Symptoms associated with adenomyosis are abnormal uterine bleeding, pelvic pain (dysmenorrhea, chronic pelvic pain, dyspareunia), and impaired reproduction. However a high incidence of existing comorbidity like fibroids and endometriosis makes it difficult to attribute a specific pathognomonic symptom to adenomyosis. Heterogeneity in the reported pregnancy rates after assisted reproduction is due to the use of different ovarian stimulation protocols and absence of a correct description of the adenomyotic pathology. Current efforts to classify the disease contributed a lot in elucidated the potential characteristics that a classification system should be relied on. The need for a comprehensive, user friendly, and clear categorization of adenomyosis including the pattern, location, histological variants, and the myometrial zone seems to be an urgent need. With the uterus as a possible unifying link between adenomyosis and endometriosis, exploration of the uterus should not only be restricted to the hysteroscopic exploration of the uterine cavity but in a fusion with ultrasound. (Fertil Steril® 2018;109:380–8. ©2018 by American Society for Reproductive Medicine.)

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Already described in 1860 by Karl Freiherr von Rokitansky (1) in the German literature as "fibrous tumors containing gland like structures that resemble endometrial glands," in 1920 by Cullen (2) as "endometriosis with predominantly presence of fibromuscular tissue," and in 1921 by Sampson (3) distinguishing three types of adenomyosis, adenomyosis received little attention in the later decades and remained for a long time the small appendix in books on endometriosis despite a high impact on women's health. As adenomyosis could only be diagnosed definitively on histological specimens obtained after hysterectomy, the estimated incidence in retrospective studies varied between 5%–70% (4) and differences in prevalence are due to the criteria used.

A classical histological definition for adenomyosis is the invasion of the myometrium by endometrial glands and/or stroma, deeper than 2.5 mm from the endometrial –myometrial junction, accompanied by adjacent smooth muscle hyperplasia. It should be noted, however, that there are still different options in the definition of the disease ranging from the simple disruption of the endometrial –myometrial junction to a depth more than 8 mm or even relating the necessary depth of invasion to the myometrial thickness (5).

With the introduction and evolution of new imaging tools, adenomyosis moved from a histological diagnosis to a clinical entity. Ultrasound and magnetic resonance imaging (MRI) heralded a real turning point in the appreciation of adenomyosis as an important disorder of the female reproductive tract. The systematic use of these technics enables visualization of the myometrial architecture's distortions in a non-invasive way, distinguishing also the pathology of the outer and the inner myometrium or junctional zone (JZ). In contrast to the outer myometrium the JZ is hormonal dependent and is not only structurally but also functionally different from the outer myometrium. In women cycle dependent contractions are originated from the JZ in the late follicular phase in a cervical-fundal direction and in the late luteal phase in a fundal-cervical direction (6). A dysregulation of these contractions has been described in patients with endometriosis and adenomyosis resulting in dysperistalsis and hyperperistalsis, constituting the main mechanism of uterine auto-traumatization (7).

Despite the high prevalence of adenomyosis, the possibility of a pre-histologic identification and the severity of the symptoms interfering

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with women's health, the pathogenesis of adenomyosis is not well understood (8). This lack of knowledge contributes to the lack of consensus on the classification. Like endometriosis, adenomyosis may present itself in various disguises, ranging from simple JZ thickening to focal, cystic, or diffuse lesions. However JZ thickening or hyperplasia and focal lesions of the junctional zone have to be interpreted carefully as changes of the JZ can be due to the cyclic hormonal variations and to the thickening of the JZ by aging (9, 10). Focal lesions are well circumscribed and can present either as a muscular or cystic lesion. Borders of diffuse lesions are not well circumscribed and can involve partially or entirely the posterior and/or anterior uterine wall resulting in an increased uterine and asymmetric volume.

The accuracy of the ultrasound in the diagnosis of adenomyosis is high with a mean sensitivity of 0.72 (95% confidence interval [CI] 0.65-0.79), specificity of 0.81 (95% CI 0.77-0.85), and area under the curve (AUC) of 0.85 (11); however, its diagnostic performance is biased by the experience of the examiner. With a higher diagnostic accuracy having a sensitivity of 77% (95% CI 67–85%), specificity of 89% (11), and AUC of 0.93, MRI, although more costly, has the advantage that it is less operator-dependent and diagnosis is based on objective image findings. MRI shows an excellent soft tissue differentiation with a clear identification of the junctional zone.

SYMPTOMS

It is hard to allocate one pathognomic symptom to the presence of adenomyosis. Symptoms associated with adenomyosis are pelvic pain (in the forms of dysmenorrhea, dyspareunia, and chronic pelvic pain), abnormal uterine bleeding, impaired reproductive potential, and feeling of swelling; however, approximately 30% patients with adenomyosis are asymptomatic (12). Furthermore, concomitant diseases with similar symptomatology are frequently present, masking the causal relationship between the disease and the symptoms; most frequent coexisting morbidities are endometriosis and fibroids. The incidence of adenomyosis as an isolated pathology is not clear, ranging from 38% to 64% (13).

Pain

Although a strict consensus on the association of adenomyosis and dysmenorrhea is debatable, the incidence of dysmenorrhea was reported between 50% and 93.4% (14–17). Women with leiomyomas and adenomyosis had an odds ratio of 3.4 (95% CI 1.8-6.4) to have more dysmenorrhea than women with only fibroids (17). A linear correlation between the extent of the adenomyosis and the severity of dysmenorrhea was described (16, 18). The problem of dysmenorrhea and pelvic pain in women with adenomyosis is not well understood, but prostaglandins may play an important role (19). In contrast with deep endometriosis, the presence of nerve fibers as a possible explanation for pain were described (20), the presence of nerve fibers in uterine adenomyosis is still a matter of debate (21, 22). Post hysterectomy specimens showed absence of nerves in areas of adenomyosis at the endometrial-myometrial nerve plexus. Focal proliferation of small-diameter nerve fibers was observed at the margins of adenomyosis in some uteri (21). Uterine hyperperistalsis and the increased expression levels of oxytocin receptor in patients with adenomyosis may contribute to the severity of the dysmenorrhea (14).

Bleeding

In the presence of co-existing morbidity like uterine fibroids and inclusion of multiparous women, the causal effect of adenomyosis is hard to prove. However a higher incidence of abnormal uterine bleeding in nulliparous women with diffuse adenomyosis suggested by ultrasound examination was described by Pinzauti et al. (16). Naftalin et al. (13) reported a significant 22% increase in menstrual loss for each additional feature of adenomyosis [OR 1.21 (95% CI: 1.04–1.40). McCausland (23) in an attempt to estimate the amount of blood loss quantified the clot size in four categories. He found a statistically significant correlation between the depth of adenomyosis and the severity of abnormal uterine bleeding (AUB).

Although the genesis of abnormal uterine bleeding in cases of adenomyosis is difficult to prove, the PALM-COEIN classification (24) included adenomyosis as a cause of AUB in women of reproductive age. In hysterectomy specimens of patients with AUB, the prevalence of adenomyosis was 34.3%–49% (25, 26). In the absence of concomitant pathology, adenomyosis caused AUB in 27%–65% of patients (Table 1). AUB can be due to an increased uterine volume, increased vascularization, improper uterine contractions and increased production of estrogen and prostaglandins. In a series of 111 specimens Levgur et al. (27) found that there was no correlation between the number of adenomyotic foci and the severity of AUB, but that heavy menstrual bleeding correlated with the depth of penetration. There is no clear consensus in the literature on the correlation between adenomyosis and heavy menstrual bleeding. Meticulous recording of concomitant pathology (fibroids, high body mass index, presence of endometrial polyps) and of the different features visualized at ultrasound will be important to identify the most plausible explanation responsible for AUB.

Reproductive Potential

With the introduction of the concept of archimetra (28) and the use of more sophisticated techniques of direct imaging

TABLE 1

Adenomyosis proven by histology as the only pathology in presence of abnormal uterine bleeding.

Study	AUB
Owolabi et al. (85) (1977)	65
Bird et al. (68) (1972)	51.2
Ozkan et al. (86) (2011)	35
Weiss et al. (87) (2009)	27
Benson and Sneeden (88) (1958)	38.4

Note: Data presented as percent. AUB = abnormal uterine bleeding.

Gordts. Clinical aspects uterine adenomyosis. Fertil Steril 2018.