

Differential diagnosis of adenomyosis: the role of hysteroscopy and laparoscopy

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Summary

Adenomyosis is defined as the heterotopic presence of endometrial mucosa (glands and stroma) abnormally implanted within myometrium with a range of clinical presentations, the most common being heavy menstrual bleeding and dysmenorrhoea; nevertheless, patients can also be asymptomatic. This review describes the state of the art of role of hysteroscopy and laparoscopy in the diagnosis of adenomyosis according to recent literature findings. Hysteroscopy offers the advantage of direct visualization of the uterine cavity, and nowadays is performed in the office. It is immediately preceded by a physical exam and a transvaginal ultrasound (TVUS) to evaluate uterine characteristics. It offers the possibility of obtaining endometrial/myometrial biopsies under visual control. Laparoscopy is not traditionally considered a diagnostic tool for adenomyosis, but it can have a complementary role in the differential diagnosis of this insidious pathology.

Key words: Adenomyosis; Laparoscopy; Hysteroscopy.

Introduction

Uterine adenomyosis and/or adenomyoma are characterized by uterine enlargement secondary to areas of the endometrium, both the endometrial glands and stroma, located deep within the myometrium. The diagnosis is based on a myometrial depth > 2,5 mm or more on one microscopic field at 10-times magnification from the endometrium-myometrium junction, and a variable degree of adjacent myometrial hyperplasia, causing globular and cystic enlargement of the myometrium, with some cysts filled with extravasated, hemolysed red blood cells and siderophages [1]. The exact prevalence of this condition in asymptomatic women is unclear, and the reported prevalence in surgical series varies widely due to the differences in histological diagnostic criteria used and number of tissue sections analyzed. Estimated prevalence of histologically confirmed adenomyosis in surgical series varies between 5% and 70% [2]. Different pathologies such as leiomyoma (80%), endometriosis (6.3%-24%), endometrial polyps (2.3%-14.7%), endometrial hyperplasia (3.5%-13.6%), and adenocarcinoma (2.2%-5.3%) may be associated with adenomyosis [3]. The etiology of adenomyosis is unknown, and various theories have been proposed. Support for the various theories comes from commonly identified risk factors such as exposure to estrogen, parity, and prior uterine

surgery. It is thought that increased estrogen exposure may contribute to the disease. Adenomyosis is most commonly diagnosed in women during their 40s and 50s, which is in keeping with clinical practice in which hysterectomies are common in this age group and adenomyosis is then diagnosed at histology. However, the increased rate of adenomyosis in this age group may also be caused by prolonged exposure to hormones over a woman's lifetime [4]. Templeman *et al.* found that increasing parity, early menarche (≤ 10 years of age), short menstrual cycle (24 days on length), elevated body mass index, and oral contraceptive (OCP) use were all statistically significant findings in patients with adenomyosis, thus suggesting an association between adenomyosis and estrogen exposure [5]. Additionally, studies have shown increased rates of adenomyosis in patients who have received tamoxifen treatment. Tamoxifen binds to selective estrogen receptors and can stimulate both normal and ectopic endometrial tissue, fostering the development of adenomyosis [6-8]. Parity may be a risk factor because studies have shown an increased frequency of adenomyosis in multiparous patients [5]. Some authors described an increased risk of adenomyosis in women with history of dilatation and curettage [9]. Riggs *et al.* described a strong association between adenomyosis and previous cesarean section [10]. The clinical presenta-

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tion of adenomyosis is heterogeneous; abnormal uterine bleeding (AUB) and dysmenorrhea are two of the most commonly described symptoms in 65% of patients with adenomyosis [11, 12].

Heavy menstrual bleeding is present in 40%-60% of patients with adenomyosis and it may be caused by the increased endometrial surface of the enlarged uterus, or it may be the result of the increased vascularization of the endometrium lining [13]. Uterine adenomyosis may be asymptomatic in about 35% of the cases, whereas 50% of women with symptoms have menorrhagia, 30% have dysmenorrhea, and 20% have metrorrhagia [11]. Furthermore, the association of uterine adenomyosis with infertility is still debated. It was thought that adenomyosis was a typical condition of parous women [13]. However, in the last years adenomyosis has become more relevant in the setting of infertility and assisted reproductive technologies due to the better imaging techniques, and to the growing number of women delaying their first pregnancy [13-15]. Commonly, the diagnosis of adenomyosis is made histologically; however, the use of imaging can help to guide the differential diagnosis. The two most common modalities are transvaginal ultrasound (TVUS) and MRI [1-10]. They characterize adenomyosis by identifying myometrial cysts (1-7 mm round anechoic areas), a distorted and heterogeneous myometrial echotexture, and poorly defined foci of an abnormal myometrial echo texture. Findings on MRI include a large asymmetric uterus without leiomyomas, thickening of the junctional zone to 8-12 mm, or an abnormal ratio (> 40%) of junctional zone to myometrial thickness. [15-17].

Materials and Methods

This paper is a review synthesizing the findings of literature retrieved from searches of computerized databases. The database PubMed (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA) was used. Key research words were “adenomyosis”, “differential diagnosis of adenomyosis”, “adenomyosis and hysteroscopy,” “adenomyosis and laparoscopy,” “uterine adenomyosis surgery,” “laparoscopy in adenomyosis,” and “diagnosis of adenomyosis.” The authors focus their discussion on role of hysteroscopy and laparoscopy for diagnosis of adenomyosis. They searched for all original articles published in English through the end of 2017 and decided to extract every notable item of information concerning definition, symptoms, clinical features, and differential diagnosis.

Results and Discussion

Historically, the definitive diagnosis of adenomyosis has been made by histologic findings after a hysterectomy; on microscopic examination, adenomyosis is identified when endometrial tissue is found inside the myometrium.

A histological diagnosis of adenomyosis can also be obtained from hysteroscopic or laparoscopic myometrial biopsies [16-19]. Although hysteroscopy is not suitable to

allow a pathognomonic sign for adenomyosis, some authors have reported the hysteroscopic uterine framework of women with adenomyosis; findings such as irregular endometrium with endometrial defects, hypervascularization, strawberry pattern or cystic haemorrhagic lesions are possibly associated with adenomyosis. As in hysterosalpingography, which occasionally highlights sac-like mucosal defects or multiple spiculations that forward from the endometrial cavity into the myometrium, during hysteroscopy, small openings at the endometrial surface can be seen. The available data on the hysteroscopic appearance of adenomyosis show an irregular endometrial vascular distribution in more than half of the patients. Ota and Tanaka utilized morphological analysis of the endometrium to establish that the mean surface area, total surface area, and total number of capillaries enhanced in women with adenomyosis, either in the proliferative and secretory phase. These findings highly strengthen the notion that endometrium is functionally abnormal in patients with adenomyosis. However, it should be underlined that the superficial vascularization can be examined adequately only decreasing the intracavitary pressure at the moment of hysteroscopic visualization [18]. In addition to the direct visualization of the uterine cavity, hysteroscopy allows the possibility to perform uterine biopsies for histological examination under visual control and enable correlations between images and histopathology [19]. Biopsies of the endometrium and underlying myometrium can be performed, either with the mechanical-punch technique or with electrical-loop resection. Furthermore, the visual appearance before, during, and after the loop resection also can highlight typical signs for adenomyosis [19, 20].

McCausland first reported the technique of myometrial biopsy through the hysteroscope with loop resection and described a prevalence of adenomyosis of 66% in patients with AUB [21]. That analysis also demonstrated a correlation between the depth of the lesion and the severity of the menorrhagia. The same study reported that a single myometrial biopsy of the posterior wall is not only diagnostic of adenomyosis but also represent the area most severely involved [21]. He supported this conclusion by literature studies utilizing histopathology, ultrasonography, or MRI, which demonstrated that the posterior wall is the most severely affected part of adenomyosis. Darwish *et al.* defined the value of the hysteroscopic myometrial biopsy comparing two hysteroscopic techniques (rigid biopsy forceps versus resectoscopic myometrial biopsy). Resectoscopic myometrial biopsy was better in harvesting myometrial biopsies. This highly difference can be clarified by the fact that the blades of the forceps are too small to achieve adequate biopsies and to go deep inside the myometrium [22]. At the moment, there is no consensus on the diagnosis of adenomyosis by hysteroscopic resectoscopic biopsy with respect to handling, orientation of the resected pieces, and depth of penetration. However, adenomyosis may be highly

suspected when the following findings are seen: irregular subendometrial myometrium, absence of typical myometrial architecture during the resection, and intramural endometriomas. Hysteroscopy endometrial ablation can be used as a treatment option in patients who have completed childbearing and report AUB [22, 23]. Resection is often limited to superficial lesions because there is risk of causing significant bleeding from arteries present approximately 5 mm below the myometrial surface. McCausl and examined 50 patients diagnosed with adenomyosis up to 3,5 years after endometrial ablation and found that patients with superficial adenomyosis (inferior to 2 mm) had good results, whereas patients with deep adenomyosis (superior to 2 mm) had poor outcomes after ablation. They reported that rollerball electrode has a coagulation effect approximately 2 to 3 mm into the myo-metrium and can therefore destroy the endometrium and surrounding hypertrophic dysfunctional smooth muscle. However, as the ectopic endometrium penetrates further into the myometrium, there is less complete destruction of the tissue [21-23]. More recently, Gordts *et al.* published an article on two patients with cystic adenomyosis and described the role of hysteroscopy in both the diagnosis and excision of myometrial cystic adenomyosis by using mechanical dissection and ablative bipolar current [25].

They explained that at hysteroscopy, the cystic adenomyosis may appear as a bulge not the cavity, or one may see abnormal vascularization or fibrosis in the endometrium overlying the cyst. Visualization of the cystic structures is improved by lowering the intrauterine pressure. In addition to being able to visualize the cavity directly, another benefit of this approach is that it allows for biopsies under direct visualization at hysteroscopy. They concluded that hysteroscopy allowed for direct visualization of the cavity and the ability to treat cystic adenomyosis by mechanical dissection or bipolar ablative surgery, while causing minimal tissue damage, leaving the outer myometrium intact, preserving fertility, and avoiding an abdominal scar. However, it is noted that this approach is not an option for diffuse adenomyosis, and when patients have larger cystic adenomyotic structures localized in the outer intramural third, a laparoscopic approach is better [18-25].

As mentioned previously, the most common symptoms of adenomyosis are AUB and dysmenorrhea. Other symptoms include dyspareunia and chronic pelvic pain. On physical examination, patients often have an enlarged uterus that may be tender to palpation. Traditionally adenomyosis was only diagnosed after hysterectomy. In many situations, a firm diagnosis of adenomyosis is not possible due to overlap of adenomyosis signs and symptoms with other disorders. The differential diagnosis, based on typical symptoms may include endometriosis (pelvic pain, dyspareunia, dysmenorrhea, infertility, subfertility), fibroids (menorrhagia, metrorrhagia, pelvic pain, dyspareunia, uterine enlargement), ovarian masses (pelvic pain, dyspareunia), and en-

dometrial cancer (similar age range for at-risk women, menorrhagia, metrorrhagia) [26]. Imaging methods TVUS and MRI) play an important role in the diagnosis. In addition, several other methods have been investigated (laboratory testing, biopsies, and laparoscopy). Laparoscopy is a common instrument for the diagnosis of menstrual symptoms and chronic pelvic pain. However, the pathologies that are looked-for during laparoscopy are uterine fibroids, endometriosis, adhesions or ovarian cyst [27]. Basak *et al.* demonstrated that clinicians very rarely consider adenomyosis in the differential diagnosis of AUB with or without chronic pelvic pain and rarely they consider the possibility of adenomyosis even when a diffusely enlarged uterus is encountered at laparoscopy. Of the 16 patients who underwent diagnostic laparoscopy, only three cases were suspected to have a bulky uterus and ten cases were reported with a normal-sized uterus. The diagnostic suspicion of adenomyosis was very low [28]. Laparoscopy is not traditionally considered in the diagnosis of adenomyosis, because the lesions rarely involve the external surface of the uterus causing marked pathological changes. However, Graziano *et al.* described characteristic findings such as the gross deformation of the uterus (adenomyomas or hemorrhagic cysts), the “blue sign” (the typical colour acquired by the adenomyotic uterus during the tubal patency test with methylene-blue solution due to the alteration in the myometrial tissue and junctional zone). They also described decreased resistance of the uterus during manipulation with endoscopic instruments [29].

Different studies investigated the role of myometrial biopsies obtained during laparoscopy for the diagnosis of adenomyosis [4]. Popp *et al.* performed 70 myometrial biopsies during laparoscopy in 34 patients with clinical symptoms of adenomyosis and found that the sensitivity of a single myometrial sample taken at laparoscopy ranged from 8% to 18.7% [29].

Brosens *et al.* also found that myometrial needle biopsy has low sensitivity and it is dependent on the number of biopsies and the depth of adenomyosis. They took eight needle biopsies from 27 hysterectomy specimens with adenomyosis. The calculated sensitivities of two biopsies, taken at random, were between 2.3% and 56% [30].

Vercellini *et al.* performed myometrial needle biopsy on 72 women undergoing laparoscopy for infertility and/or chronic pelvic pain using a 14-gauge Tru-cut needle. Adenomyosis was diagnosed in eight of the 42 (19%) subjects with menstrual pain and five of the 30 (17%) asymptomatic ones and pelvic endometriosis in 27 and 10, respectively (64% vs. 33%, $p = 0.02$) [31]. In conclusion, there was no benefit in this technique for the diagnosis of adenomyosis and the role of laparoscopic biopsy remains limited. However, since in the last years adenomyosis has become more relevant in the setting of infertility and assisted reproductive technologies, laparoscopy can play an important role in the differential diagnosis for ruling out the presence of

pelvic unfavorable conditions such as endometriosis, adhesions, and confirming the diagnosis of adenomyosis.

The enlarged irregular uterus with decreased resistance of the uterus during manipulation with endoscopic instruments should be taken into considerations in the confirmation of a presurgical suspicion of adenomyosis.

Conclusions

Adenomyosis is a still largely under-diagnosed condition that is asymptomatic in one-third of cases, while in the remainder, it can cause dysmenorrhoea and/or menometrorrhagia. Its incidence in patients with infertility is unclear. An earlier diagnosis of adenomyosis of uterus requires complete enquiry of pelvic symptoms in women with AUB and/or pelvic pain but at present, there is no reliable method to detect this condition. Ultrasonography and MRI are still the most important diagnostic tool in symptomatic patients. Nevertheless, hysteroscopy and laparoscopy can be very important in the diagnostic work-up of adenomyosis. Moreover, in some cases of focal/cystic diseases, they can play an important role even in the minimally invasive treatment of this enigmatic condition. A presurgical attention to the possibility of association of adenomyosis with deep infiltrating endometriosis is warranted in order to inform the patients that even if a complete excision of endometriosis nodules has been correctly performed, dysmenorrhea should persist after surgery [32].

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