The Clinical Features and Diagnosis of Adenomyosis

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As early as 1920, Cullen [1] described adenomyosis as "endometriosis with predominantly presence of fibromuscular tissue," and in 1921 Sampson [2] distinguished three types of adenomyosis. However, adenomyosis remained little known in the later decades and written only as an appendix in books on endometriosis, not knowing that adenomyosis has a great adverse impact on women's health. For a long time, adenomyosis could only be diagnosed on histological specimens after hysterectomy in reproductive age women with heavy menstrual bleeding or pelvic pain [3]. Therefore the incidence rate in retrospective studies was seriously underestimated, and the prevalence rate varies due to the criteria used. Over the last 10 years, adenomyosis has become a condition diagnosed in young reproductive age women [4] because of the recent advancements in imaging techniques. Despite the new diagnostic tools, the awareness of the disease is still poor among the doctors with consensus on definition, and classification is still lacking [5]. Furthermore, adenomyosis is often associated with other gynecological conditions, such as endometriosis and fibroids. This chapter will discuss the clinical features and diagnosis of adenomyosis.

The diagnosis of adenomyosis should first be based on the patient's history, clinical symptoms, and signs. Imaging examination is an important basis for the diagnosis of adenomyosis, but the gold standard for the diagnosis is still pathological diagnosis.

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4.1 Pathology Diagnosis

The diagnosis of adenomyosis has always been from the histological examination of hysterectomy specimens [6, 7] in the past. The disease is commonly confirmed histologically by the presence of endometrial glands and stroma located deep within the myometrium, associated with smooth muscle hyperplasia [8] (Fig. 4.1). It is the invasion of the myometrium by basal glands and stroma with the destruction of normal myometrium architecture [7, 9]. Nevertheless, the incidence of adenomyosis can vary widely, depending on the diagnostic criteria among different pathologists, because there are no uniform criteria regarding the depth of invasion and number of foci to make a diagnosis, especially when the disease is not diffuse. For example, to make a diagnosis of adenomyosis, an invasion of more than one-third thickness of the myometrium is used as a criterion, whereas in others, a myometrial invasion >4 mm is diagnostic [10–12].

Histologically, adenomyosis is defined as focal when a nodular area of the endometrial glands and stroma are surrounded by normal myometrium. This focal lesion can present either as a muscular or cystic lesion. On the other hand, in diffuse adenomyosis, endometrial glands and stroma are recognized throughout the myometrium of the uterus. Diffuse adenomyosis is not well circumscribed and can involve either the posterior and/or anterior uterine wall partially or wholly, resulting in asymmetric enlargement of the uterus.

4.2 The Clinical Diagnosis

Adenomyosis affects the physical and mental health of patients. But only a small group of women undergo non-conservative surgical treatments for adenomyosis, because the introduction of new medications has allowed clinicians to treat the disease conservatively. Patients need early diagnosis of adenomyosis, so that early treatment and intervention can ensure her a better quality of life and reproductive outcomes. Many experts agree that adenomyosis requires a lifelong management plan, including pain, bleeding control, fertility support, and pregnancy outcome.

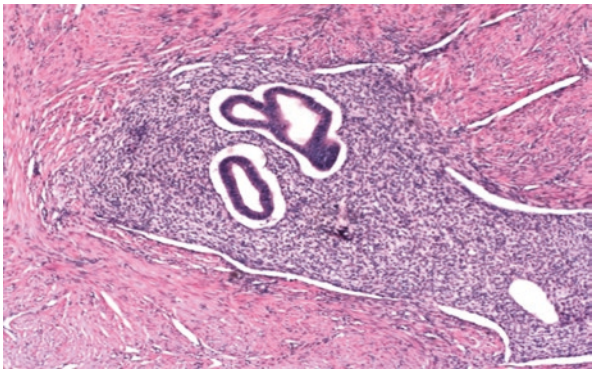

Fig. 4.1 Hematoxylin and eosin staining of adenomyosis (40 X). It shows a nodular area of the endometrial glands and stroma surrounded by a normal myometrium

Thus, a realistic treatment background cannot be established only from histopathology, which is often unavailable. Therefore the patient's history, clinical symptoms, and signs together with imaging examination are important for the diagnosis of adenomyosis.

4.3 History

4.3.1 Age

It had been reported that 70–80% of women undergoing hysterectomy for adenomyosis are in their fourth and fifth decade of life [13–15]. However, newer studies suggest that the disease may cause dysmenorrhea and chronic pelvic pain in adolescents and women of younger reproductive age by using MRI criteria for diagnosis [16, 17]. The age at their clinical presentation may be much earlier, and it may be a different clinical phenotype compared to adenomyosis of late onset.

4.3.2 Multiparity

Among women with adenomyosis, many are multiparous [3, 15, 18, 19]. As early as 1995, Vercellini et al. [20] reported in the Milan epidemiological study on adenomyosis that the frequency of adenomyosis was directly associated with the number of births and tended to be higher with spontaneous and induced abortions. The odds ratio of adenomyosis in women with one and more than two births was 1.3 and 1.5, respectively, compared with nulliparous women ($P < 0.05$). But in their study, there was no relationship between the risk of adenomyosis and age during surgery, age at menarche, indication for surgery, menopausal status at intervention, and the presence of endometriosis. In a cross-sectional study conducted on 707 consecutive women who underwent hysterectomy between 1993 and 1994 [21], the incidence of adenomyosis was higher in parous women, in comparison with nulliparae; the odds ratios of adenomyosis were 1.8 (95% CI 0.9–3.4) and 3.1 (95% CI 1.7–5.5), respectively, in women reporting one and more than two births ($P < 0.01$).

Pregnancy might facilitate the formation of adenomyosis due to the invasive nature of the trophoblast extending into the myometrial fibers, thus allowing ectopic endometrial foci from the endometrial-myometrium junctional zone to be included in the myometrium [18, 19]. Besides, adenomyosis has high-level estrogen receptors; thus, pregnancy with its hormonal milieu may favor the development of islands of ectopic endometrium [13].

4.3.3 History of Uterine Surgery

The history of operations involving the uterine cavity may be one of the risk factors of adenomyosis, even though there are still controversies. The assumption that

surgical disruptions of the endometrial-myometrial border could result in endometrial glands invading the myometrial layer, with increasing risk of adenomyosis formation [14, 22]. In a cohort study of 1850 women with hysterectomy in over 4 years, Curtis et al. 2002 [23] analyzed the surgical disruption of the endometrial-myometrial junctional zone by sharp curettage as a risk factor for adenomyosis. For women who had a history of suction evacuation for termination of pregnancy, those with more than three abortions had an increased risk of adenomyosis of 5.9 (95% CI 1.5–23.3), and the risk increased with the number of abortions. Repeated sharp curettage during early pregnancy at the time of abortion may greatly increase the risk of adenomyosis by disrupting the endometrial-myometrial border and facilitating implantation, embedding, and survival of endometrium within the myometrial wall. Based on the understanding of wound healing, the endometrial-myometrial interface disruption (EMID) is proposed to cause adenomyosis resulting from iatrogenic trauma to endometrial myometrial interface (EMI) [24]. The EMID hypothesis includes many mechanisms, as presented in Fig. 4.2, i.e., hypoxia at the wounding site, platelet aggregation, angiogenesis, that enhanced survival of endometrial cells dispersed and displaced due to iatrogenic operations. This EMID hypothesis predicts that the risk of adenomyosis can be reduced if certain perioperative interventions are performed.

Interestingly, in the non-pregnant status, sharp curettage might not increase the risk. Panganamamula et al. studied 412 adenomyosis in 873 women (47%) who underwent hysterectomy for benign conditions within 8 years [22]. When individual types of surgery were analyzed separately, there were no significant differences between women with and without adenomyosis relating to previous cesarean delivery, myomectomy, endometrial ablation, dilatation and evacuation. However, after pooling all procedures, the history of any prior uterine surgery significantly increased the risk of adenomyosis (49% versus 41%; OR 1.37, 95% CI 1.05–1.79).

On the other hand, some studies reported no increased cesarean section or any other uterine surgical procedure in women with adenomyosis [3, 25, 26]. Therefore, it is still controversial that uterine surgery is a risk factor for adenomyosis. Moreover, the majority of the studies were conducted 10 years ago; the results from any new studies may well be different because of the advance in imaging technology and classification of adenomyosis.

4.3.4 Smoking

There are different views on the relationship between smoking and adenomyosis. Parazzini et al. 1997 [27] reported that smokers were less likely to have adenomyosis in comparison with women who never smoked. Adenomyosis is an estrogen-dependent lesion [8, 9, 28], and decreased serum levels of estrogen have been reported in smokers [29, 30]. Therefore this finding might explain the correlation. On the other hand, two studies reported a higher rate of women smokers with adenomyosis than in controls [3, 31]. Thus, we need further investigations to study the association between adenomyosis and smoking.

4.4 Symptoms

The clinical presentation and symptoms of adenomyosis are not discussed in detail here, because they are in other chapters of this book. This chapter only addressed the relationship between clinical manifestations and clinical diagnosis.

4.4.1 Pain

Progressive dysmenorrhea is a typical clinical symptom of adenomyosis; the incidence of dysmenorrhea was reported between 50 and 93.4% [3, 4, 32]. Women with adenomyosis and fibroids had an odds ratio of 3.4 (95% CI 1.8–6.4) to experience dysmenorrhea than women with only fibroids [3]. Some researchers described a linear correlation between the extent of the adenomyosis and the severity of dysmenorrhea [4, 33]. The mechanism of dysmenorrhea and pelvic pain is likely due to an increase in prostaglandins and increased nerve fibers in the adenomyosis [34, 35]. The focal proliferation of small-diameter nerve fibers was observed at the margins of adenomyosis in some uteri [35]. Another mechanism of pain is due to uterine hyperperistalsis and the increased oxytocin receptors in patients with adenomyosis; these all contribute to the severity of dysmenorrhea [36].

4.4.2 Abnormal Uterine Bleeding

Abnormal uterine bleeding has been described with enlarged uterus due to diffuse adenomyosis. Not only is there increased menstrual loss [37] but also there is a statistically significant correlation between the extent of adenomyosis and the severity of abnormal uterine bleeding [38, 39]. The PALM-COEIN (polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified, International Federation of Gynecology and Obstetrics) classification [40] includes adenomyosis as a specific entity of abnormal uterine bleeding in reproductive aged women, and it is strictly associated with heavy menstrual bleeding. In hysterectomy specimens of patients with abnormal uterine bleeding, the prevalence of adenomyosis was 34.3–49% [41, 42]. The abnormal vaginal bleeding can be due to an increased uterine volume, increased vascularization, abnormal uterine contractions, and increased production of estrogen and prostaglandins.

4.4.3 Infertility

Adenomyosis has an adverse effect on women's fertility. The mechanism mainly includes the dysfunction of the endometrial-myometrial junctional zone, the change of endometrial receptivity, the imbalance of estrogen receptor and

progesterone receptor regulation, the abnormal level of oxygen free radicals in the uterine cavity, and the disorder of immune regulation. Adenomyosis also has adverse effects on the outcome of in vitro fertilization embryo transfer (IVF-ET) [43], such as the decrease of implantation rate, clinical pregnancy rate, continuous pregnancy rate, and live birth rate and the increase of abortion rate and adverse obstetric outcomes, such as premature delivery and premature rupture of membranes [43–45]. In two recent meta-analyses, adenomyosis was associated with a 30% decrease in the likelihood of pregnancy [43, 45]. By delaying pregnancy to a later reproductive age span, this group of women will be associated with greater risks of adenomyosis, requiring advice for fertility problems [38].

Patients with adenomyosis, in terms of clinical symptoms, have the following typical clinical presentations: ① progressive and gradually increasing dysmenorrhea; ② menorrhea (and/or prolonged menstruation); ③ infertility; ④ adverse pregnancy history, such as repeated abortion and premature delivery; ⑤ gynecological examination can often feel the increase of uterine uniformity, spherical shape, or localized nodule bulge, posterior position, and poor uterine motility. Then, the diagnosis of adenomyosis should be considered. However, it also should be reminded that some patients with adenomyosis are asymptomatic [46].

4.4.4 Imaging

MRI and transvaginal ultrasonography (TVUS) imaging technology have allowed clinicians to make a non-invasive diagnosis of adenomyosis in women suffering from dysmenorrhea, abnormal uterine bleeding, and infertility. The accuracy of the transvaginal ultrasound in the diagnosis of adenomyosis is high with a mean sensitivity of 72% (95% confidence interval [CI] 65–79%), specificity of 81% (95% CI 77–85%) and area under the curve (AUC) of 0.84 [5, 47]. However, its diagnostic performance could be biased by the experience of the examiner [5]. MRI has the advantage that it is not operator-dependent, and diagnosis is based on objective image findings. The sensitivity could reach 77% (95% CI 67–85%), specificity of 89% (95% CI 84–92%) [47, 48], and AUC of 0.92. Then MRI appears to be more accurate than transvaginal ultrasound and also has an excellent soft tissue differentiation with a clear identification of the junctional zone. However, MRI is more expensive than ultrasound. The technology progress of MRI not only greatly offers an early diagnosis of adenomyosis but also become the basis of clinical classification of adenomyosis. Among clinical types based on MRI, there are several representative classifications. Kishi et al. classified adenomyosis into four subtypes according to the localization of adenomyosis in the inner or outer myometrium, i.e., intrinsic, extrinsic, intramural, and indeterminate1 [49]. Grimbizis et al. 2014 [50] suggested a clinico-histological classification, identifying them as diffuse, focal, and cystic adenomyosis. More recently, Bazot and Daraï 2018 [51] proposed more

complex subtypes of type A to K, according to MRI features. However, a shared classification system has not been developed yet, as further research is needed to better understand the physiopathology of adenomyosis, its onset and progression, and the interpretation of imaging signs according to the pathogenic theories [7].

4.4.5 Laboratory Test

CA125 is a well-known tumor marker of ovarian cancer. However, its levels may also be elevated in several relatively benign gynecological conditions, such as endometriosis and adenomyosis. Several studies have reported that elevated CA125 levels are associated with adenomyosis [52]. Besides, Kil et al. 2015 [53] reported that the differential diagnosis of adenomyosis and myoma could be based on a cut-off value if 19 U/mL for CA125 to provide improved diagnostic performance. They also suggested that serum CA125 testing can be performed during the initial screening of women with possible adenomyosis to differentiate it from myoma. However, the diagnostic accuracy of using CA125 testing alone is limited.

4.4.6 Hysteroscopy

Hysteroscopy, a diagnostic procedure, which allows the direct visualization of the uterine cavity, is also useful in the diagnosis of adenomyosis. It is the use of a rigid hysteroscope, via the transcervical route and distending medium to examine the endometrial cavity. The procedure is well-tolerated in an out-patient environment. El-Toukhy et al. 2016 [54] demonstrated that hysteroscopy found 26% of unsuspected uterine pathology in patients with recurrent implantation failure and normal ultrasound examination. Hysteroscopy can become a useful diagnostic method in the diagnosis of adenomyosis. It can allow the biopsy of the endometrial-myometrial junction zone under direct hysteroscopic vision. Because the field of vision is limited to the surface of the endometrium, and it is an invasive procedure by biopsy, hysteroscopy cannot often be used as a definitive diagnosis.

Hysteroscopic adenomyotic images can become obvious after a surgical subendometrial exploration during hysteroscopic resection (Fig. 4.2). The following hysteroscopic features may also indicate the diagnosis of adenomyosis: irregular endometrium, small openings between the surfaces; clear hyperplastic blood vessels; the “strawberry sign” of the endometrium; deep blue- or chocolate-colored cystic hemorrhage on the surface; and fibrocystic changes in the intrauterine focus. In adenomyosis, the abnormal distribution of endometrial blood vessels can be seen in both proliferative and secretory phases. This phenomenon can be enhanced and fully visible by reducing the inflation pressure of the distending medium, thus confirming the hypothesis of “dysfunction of endometrium in adenomyosis.”

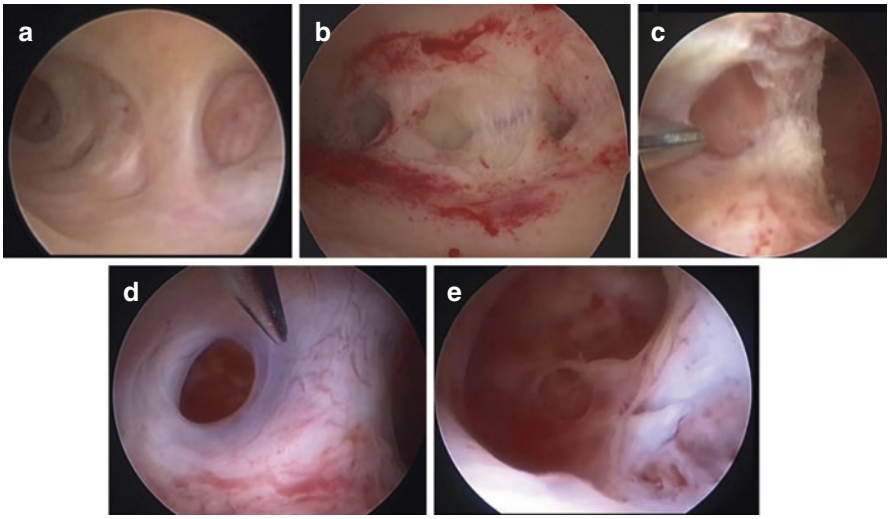

Fig. 4.2 (**a**) Visible endometrial defects; (**b**) after incision, different structures appear, showing adhesion and cystic opening; (**c**) after incision, an adenomyotic cystic opening becomes obvious; (**d**) other small cyst openings over the endometrial wall (**e**) a large cystic cavity is revealed after surgical incision of the cyst (reproduced with permission from Gordts's paper in Fertil Steril 2018)

4.5 Conclusion

Adenomyosis should be considered a chronic disease, which has an adverse impact on the physical and mental health of patients. Early and correct diagnosis, together with early intervention, can alleviate the suffering of patients, improve the quality of life, and improve the outcome of fertility. Despite controversies in the diagnosis and classifications of adenomyosis, the present information will serve as the direction of future research efforts.

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