Review Adenomyosis uteri: an update

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Key content:
• Adenomyosis uteri is defined by the presence of endometrium in the myometrium.
• The prevalence in asymptomatic women remains unknown.
• It is commonly associated with other pathologies.
• Hysterectomy remains the main surgical option for women whose families are complete.

Learning objectives:
• To understand the theories regarding the aetiology.
• To appreciate the clinical picture and complications.
• To learn about current treatment modalities.

Ethical issues:
• Counselling women with adenomyosis uteri is challenging when the clinical significance of the condition is uncertain.
• Are more expensive diagnostic tests, such as magnetic resonance imaging, justifiable?
• Is the risk–benefit weighted against invasive investigation?

Keywords endometrial–myometrial interface / endomyometrial ablation / hysterectomy / magnetic resonance imaging (MRI)
Introduction

Adenomyosis uteri is defined by the presence of endometrium within the myometrium. Microscopically, uterine adenomyosis is defined by ectopic, non-neoplastic endometrial glands and stroma, surrounded by hypertrophic and hyperplastic myometrium (Figure 1). The first descriptions of the condition were made by Rokitansky in 1860 and von Recklinghausen in 1896.

Definition

There is no consensus on the depth of endometrial penetration diagnostic of adenomyosis uteri (opinions range from one high power field to >25% of the myometrial thickness), which makes comparisons between different studies difficult. A cut-off point of >2.5 mm for glandular extension below the endometrial–myometrial interface is advocated. A characteristic feature of the endometrial–myometrial interface is the lack of submucosa. As a result, the endometrial glands and stroma lie in direct contact with the myometrium. In addition, the endometrial–myometrial interface is irregular over its entire surface. The term ‘adenomyosis sub-basalis’ is suggested for more superficial disease.

Adenomyosis uteri can involve the whole muscle thickness down to the serosa and can be either ‘focal’ or ‘diffuse’. In diffuse adenomyosis uteri, the uterus becomes enlarged and globular. Glandular foci may contain brown haemosiderin deposits. Focal lesions can resemble leiomyomas: hence the older term ‘adenomyoma’. Adenomyosis uteri has poorly defined margins and cannot be enucleated. Endometrial glands and stroma in adenomyosis uteri resemble the basalis endometrium and show limited changes throughout the menstrual cycle but secretory changes, including stromal decidualisation, may be seen during pregnancy and in women receiving exogenous progestogens.

The precise reason for myometrial hyperplasia/hypertrophy around deep, focal adenomyotic lesions is unknown but it may be an attempt at controlling endometrial invagination or it may represent smooth muscle bundles pushed aside by the ingrowing endometrium. Myometrial hypertrophy is often absent in postmenopausal women.

Associated pathology

Up to 80% of women with adenomyosis also have other lesions, the most frequent being leiomyomas. Endometrial polyps, hyperplasia (with and without atypia) and adenocarcinoma are more frequent in women with adenomyosis (Table 1). Pelvic endometriosis is observed in 6–24% of women with adenomyosis uteri. Women with endometrial carcinoma have also been reported to have a higher incidence (60%) of adenomyosis uteri compared with women without cancer (39%) but adenomyosis has no adverse effect on cancer survival. Adenocarcinoma may, rarely, involve foci of adenomyosis. Whether adenocarcinomas located in both the overlying endometrium and foci of adenomyosis represent separate entities, or the extension of the former into adenomyotic foci, is unknown. When carcinoma is limited to adenomyotic foci, it should be considered intramucosal, since it does not make the prognosis worse than if the carcinoma is confined to the endometrium proper.

Pathogenesis

Adenomyosis uteri is believed to result from abnormal ingrowth and invagination of the basal endometrium into the subendometrial myometrium at the endometrial–myometrial interface. During periods of regeneration, healing and re-epithelialisation, the endometrium can invade a predisposed myometrium or a traumatised endometrial–myometrial interface. Hormonal, genetic, immunological and growth factors possibly play a role in this sequence of events. In one series, seven cases were reported in which mothers and daughters were affected. Tamoxifen treatment is also associated with a higher incidence.

Local, but not systemic, hyperestrogenism may be involved and may also account for the
hypertrophy/hyperplasia in the surrounding myometrium and overlying endometrium. Several studies in animal models support a role for hyperprolactinaemia (either induced by pituitary transplantation or drug therapy) in the pathogenesis of adenomyosis uteri but it is unclear if a similar mechanism is involved in humans. Other studies in rodent models have described in utero or neonatal dosing with tamoxifen or diethylstilbestrol to induce adenomyosis uteri and all showed marked myometrial disruption and pathology. These models raise the possibility of in utero developmental events leading to uterine adenomyosis.

Prevalence

The majority of cases are diagnosed following histological examination of hysterectomy specimens but this introduces selection bias when estimating the prevalence of the disease. The percentage of hysterectomy specimens containing adenomyosis varies from 5–70%. This wide variation may be partly explained by the histological criteria used and/or by the number of tissue blocks examined. The exact prevalence in the ‘normal’ population is unknown. The specificity of preoperative diagnosis based on the clinical picture is poor, ranging from 2.6–26%. The sensitivity and specificity of magnetic resonance imaging (MRI) and ultrasound is highlighted in Table 2.3–16

Using MRI criteria, Hauth et al.16 identified uterine adenomyosis in 12 out of 100 healthy women. In another study,20 the diagnosis was suggested by MRI in 19 of 204 (9.1%) women following term deliveries and in 16 of 104 (15.4%) women following preterm delivery; the overall incidence was 11.3%. In 1931, Lewinski27 reported an incidence of 54% in 54 autopsies.

Clinical correlates

Despite lack of agreement on the histological criteria, adenomyosis uteri is frequently reported following hysterectomy. As the incidence of the disease in the general population remains unclear, and because of its common association with other pathologies such as fibroids, the clinical significance remains uncertain.

The majority of cases are reported in women aged 40–50 years and there is a positive association with parity. Adenomyosis occurs relatively frequently in pregnancy. It has been reported in 27 out of 151 (17%) caesarean hysterectomy specimens1 and was diagnosed using MRI in 11.3% of women postpartum.20 There is no relation to age at first childbirth and prior caesarean section does not seem to be a predisposing factor. Four large studies23–26 failed to demonstrate an increased incidence with caesarean delivery. The average incidence of caesarean section delivery in women with adenomyosis uteri was 6–6.4%.4,25 Older women tend to be more symptomatic, whilst symptoms in younger women are relatively mild or absent. The relative importance of parity and age remains unanswered, as parous women also tend to be older. No association is seen with age at menarche, menopausal status, or age at hysterectomy or its indication.

Spontaneous miscarriage has been observed more frequently in women with adenomyosis uteri. Sharp curettage during termination of pregnancy or following early pregnancy loss increases the risk possibly by disrupting the endometrial–myometrial interface and facilitating embedding of the endometrium within the myometrium.23–30 This practice has largely been superseded by suction curettage. Interestingly, sharp curettage of the nonpregnant uterus does not increase the risk of uterine adenomyosis. This differential effect may be related to disruption of the endometrial–myometrial interface by invading trophoblasts.

Women who smoke tend to be at reduced risk of adenomyosis uteri. Oral contraceptives, intrauterine contraceptive devices and tubal sterilisation do not appear to be associated with increased risk.

Adenomyosis has been reported in 60% of postmenopausal women on long-term tamoxifen therapy, perhaps because tamoxifen reactivates pre-existing adenomyosis. Kunz et al.22 found a high incidence in their cohort of infertile women with endometriosis (28%). A summary of clinical correlates is presented in Table 3.22–30

Menstrual disorders

About 35% of women with adenomyosis uteri are asymptomatic. Symptomatic women mostly

<table>
<thead>
<tr>
<th>Increased risk</th>
<th>Decreased risk</th>
<th>No risk</th>
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<tbody>
<tr>
<td>Parity</td>
<td>Smoking</td>
<td>Age at menarche</td>
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<td>Spontaneous miscarriage</td>
<td>Menopausal status</td>
<td>Age at first childbirth</td>
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<tr>
<td>Endometriosis</td>
<td>Oral contraceptives</td>
<td>Intrauterine contraceptive devices, tubal sterilisation</td>
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<td>Menorrhagia</td>
<td>Surgical termination</td>
<td>Indication for and age at surgery</td>
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<td>Infertility</td>
<td>Curettage in pregnancy</td>
<td>Endometrial carcinoma</td>
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<td>Endometrial hyperplasia</td>
<td>Caeasarian section</td>
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<tr>
<td>Preterm birth</td>
<td>Preterm birth</td>
<td>Dilatation and curettage</td>
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Table 3: Summary of risk factors and symptoms of adenomyosis22–30
present with menorrhagia (40–50%), dysmenorrhoea (10–30%) and metrorrhagia (10–12%) and, occasionally, dyspareunia or dyschezia. Menorrhagia may be due to dysfunctional contractility of the myometrium. Mefenamic acid administration can reduce blood loss, suggesting that prostaglandins may be involved. Other factors that may be involved are anovulation or endometrial hyperplasia. The extent and spread of adenomyosis uteri may correlate with pelvic pain and dysmenorrhoea and, to a lesser degree, with menorrhagia and dyspareunia.

Endometriosis
Pelvic endometriosis coexists with adenomyosis uteri in 2–24% of cases, suggesting that the two conditions may be linked. Using MRI in a cohort of infertile women, 126 out of 160 (79%) women with endometriosis and 19 out of 67 (28%) women without endometriosis had adenomyosis. Kunz et al. hypothesise that pelvic endometriosis and uterine adenomyosis are variants of the same disease, involving dislocation of the basal endometrium both in the underlying myometrium and the peritoneal cavity. They postulate that chronic uterine dysfunctional peristalsis and hyperperistalsis are important causal factors. Women with endometriosis displayed a marked uterine hyperperistalsis that differed significantly from the peristalsis of the controls during the early- and mid-follicular and midluteal phases. During the late follicular phase of the cycle, uterine peristalsis in women with endometriosis became dysperistaltic, arrhythmic and convulsive in character while, in controls, peristalsis continued to show long and regular cervicofundal contractions.

Infertility
Because of its association with multiparity, scant attention has been paid in the past to a possible relationship between adenomyosis uteri and infertility. Adenomyosis uteri is linked to lifelong infertility in baboons. Advances in imaging and delayed pregnancy may contribute to the condition being encountered more frequently in fertility clinics. Reported studies include a cohort of infertile women with poorly defined demographics and a high incidence of endometriosis. The authors suggest that adenomyosis impairs uterine sperm transport, an effect that could not be confirmed in the absence of endometriosis.

It has been proposed that the abnormal structure of the endometrial–myometrial interface and myometrium in adenomyosis uteri, especially at the fundus, could interfere with normal fertilisation and implantation. One putative mechanism is the production of excess nitric oxide by the enzyme endothelial nitric oxide synthase, which could affect human sperm function, fertilisation, implantation and embryo development. Overexpression of endothelial nitric oxide synthase in adenomyosis uteri may be triggered by an immune response stimulating macrophages to attack endothelial cells or by endometrial cells. Evidence from recipients of sibling oocytes via in vitro fertilisation (IVF), however, suggests that adenomyosis uteri, as diagnosed by ultrasound, has no impact on implantation rate.

Imaging and diagnosis
Management of adenomyosis uteri is hindered by the lack of a reliable, noninvasive diagnostic test. No serum markers are currently available. The role of invasive hysteroscopic or laparoscopic biopsy remains limited, with only small series reported. The small number and size of biopsies obtained may be insufficient to rule out the disease, especially given that the diagnosis may be influenced by the numbers of uterine sections examined.

Hysterosalpingography
Hysterosalpingography was an early imaging modality used for the diagnosis of adenomyosis uteri but it has low sensitivity and specificity. Features suggestive of adenomyosis include multiple, small (1–4 mm) spicules extending from the endometrium into the myometrium, with saccular endings. A local accumulation of contrast material in the myometrium may produce a honeycomb appearance.

Pelvic ultrasonography
Transvaginal ultrasound (TVS) is superior to transabdominal ultrasound in demonstrating the subtle features suggestive of adenomyosis uteri. The normal myometrium has three distinct sonographic layers. The middle layer is the most echogenic and is separated from the thin outer layer by the arcuate venous and arterial plexuses. The inner layer is hypo-echoic relative to the middle and outer layers (the subendometrial or myometrial halo). The presence of adenomyosis uteri can alter or distort the sonographic appearance of these zones (Box 1).

Studies on the accuracy of TVS reported variable accuracy indices, with sensitivity and specificity varying between 53–89% and 50–99%, respectively (Table 2). The reported studies were conducted on selected women prior to surgery.
and caution is needed when TVS is used for other groups with a lower prevalence of uterine adenomyosis.

Three-dimensional ultrasonography offers advantages in determining organ volume and uterine pathology, including endometrial tumours. There are some reports on the use of 3D-TV5 and 3D power Doppler in adenomyosis, including vessel distribution and branching, and differences in perfusion patterns in affected areas.11,41

Magnetic resonance imaging
In women of reproductive age, three different zones can be identified within the uterus by MRI. The normal endometrium and endometrial secretions appear as a high signal intensity-type stripe on T2-weighted sagittal images. Immediately underneath this is a band of low signal intensity, which represents the innermost layer of the myometrium: the junctional zone.41 The outer layer of the myometrium is of intermediate signal intensity. There is considerable variation in the normal junctional zone thickness, ranging from 2–8 mm.19,45 The appearance of diffuse or focal widening of the junctional zone on MRI is suggestive of adenomyosis uteri. Areas of low signal intensity corresponding to smooth muscle hyperplasia can also be seen, together with high signal intensity foci or linear striations representing the ectopic endometrial tissue (Box 2).

There is growing evidence to support the role of MRI in the diagnosis of adenomyosis uteri. The high cost and limited availability, however, hinder its routine use. Several studies have compared the accuracy of TVS and MRI (Table 2). Although the sensitivities and specificities of both techniques were comparable, MRI proved to be superior to TVS in women where associated leiomyomas or additional pathologies were suspected.19,46

<table>
<thead>
<tr>
<th>Box 2</th>
<th>MRI criteria suggestive of adenomyosis uteri</th>
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<tr>
<td>• Focal or diffuse thickening of the junctional zone</td>
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<tr>
<td>• Low signal intensity uterine mass with ill-defined border</td>
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<tr>
<td>• Junctional zone thickness &gt; 12 mm</td>
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<tr>
<td>• Poor definition of junctional zone border</td>
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<tr>
<td>• Localised high signal foci within an area of low signal intensity</td>
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<tr>
<td>• Linear striations of increased signal radiating out from the endometrium into the myometrium</td>
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<tr>
<td>• Bright foci in endometrium of similar intensity to the myometrium (T1-weighted)</td>
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<tr>
<td>• Ratio of maximal junctional zone thickness to myometrium thickness (ratio-of-max) &gt;40%</td>
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Medical
Nonhormonal therapy, including mefenamic and tranexamic acid, may be effective for the symptomatic relief of menorrhagia associated with uterine adenomyosis19 but there are no studies specific to adenomyosis uteri. Hormonal treatments for symptomatic relief include progestogens, the combined oral contraceptive pill and gonadotrophin-releasing hormone (GnRH) analogues. The aim of medical therapy is to suppress the cyclical changes of ovarian steroids, inhibiting pituitary gonadotrophins or preventing the mid-cycle estrogen surge. Overall, the effect of these treatments is limited to a variable and unpredictable degree of symptomatic relief, usually restricted to the duration of treatment.

Low-dose, continuous combined oral contraceptives with withdrawal bleeds every 4–6 months may be effective in relieving menorrhagia and dysmenorrhoea but, again, there are no specific studies on adenomyosis uteri.

GnRH analogues have also been used in the treatment of adenomyosis uteri.49 They reduce uterine volume and result in symptomatic relief but their use is limited because of skeletal and general side-effects.

The use of danazol has largely been superseded because of its side-effects. A more recently-developed danazol-loaded intrauterine device was used to treat 12 women with adenomyosis uteri.49 Three pregnancies were reported following discontinuation of the treatment. Danazol serum levels were undetectable and both menstrual and ovulatory functions were preserved.49 In another study,50 there was a significant decrease in dysmenorrhea.

Reports have been published on the use of the levonorgestrel-releasing intrauterine system (Mirena®: Schering Health, Berks, UK) in women with adenomyosis uteri outside the context of infertility. Menorrhagia disappeared in all cases, leading to improvement of anaemia. Reduction in uterine size was, however, modest (9.8%). Other studies42,51 reported an improvement in...
Dysmenorrhea. The levonorgestrel-releasing intrauterine system has also been successfully used for adenomyosis-associated menorrhagia when inserted immediately after endometrial ablation.  

Mifepristone (RU486) has been used for the treatment of endometriosis. Long-term, low-dose mifepristone causes anovulation, a reduction in painful symptoms and improved endometriosis scores. When given for up to 30 days, mifepristone has been shown to suppress markedly the development of adenomyosis uteri in mice but it has not been used in humans. There is a case report on the concomitant use of the aromatase inhibitor anastrozole with a GnRH agonist in a woman with severe symptomatic uterine adenomyosis.

### Surgical

Laparoscopic myometrial electrocoagulation induces localised coagulation and necrosis of adenomyosis uteri. Needle punctures are made at 1–2 cm intervals to deliver a unipolar or bipolar coagulation current. Electrocoagulation can be difficult to apply with precision and can reduce the strength of the remaining myometrial tissue. Furthermore, there is a risk of emergency hysterectomy for uncontrollable bleeding during the procedure, as well as a high incidence of adhesion formation following the procedure. Although not recommended, this technique may be best suited for women > 40 years of age who have completed their families but who wish to avoid hysterectomy.

Localised excision of affected myometrium can be performed in localised adenomyosis uteri if the extent of the disease can be accurately defined. The approach is similar to myomectomy and may be useful for women seeking to preserve their fertility, provided the remaining myometrium is sufficient to allow uterine expansion. Complete microsurgical resection of the visible adenomyotic areas, followed by GnRH agonists, has been suggested to improve symptom control and fertility. Published series are small, with limited success. The surgical and obstetric complications of myometrial excision must be considered. Excision of a large part of the myometrium, as may be needed to remove all affected areas, may lead to difficulty in wound apposition, decreased expansive capacity of the uterus and weakening, leading ultimately to uterine rupture.

Reduction of the uterine blood flow by uterine artery embolisation has been shown to reduce the symptoms associated with adenomyosis uteri and to improve the quality of life. Many women, however, had concurrent fibroids, for which uterine artery embolisation is a recognised treatment option. The chances of a subsequent successful pregnancy are unclear. Laparoscopic uterine artery ligation has been studied in 20 women with symptomatic uterine adenomyosis. Only 15% of women, however, rated the treatment as satisfactory at 6-month follow-up, suggesting that this approach may not be effective.

Endometrial ablation or resection may be an option for women with superficial disease complaining of menorrhagia but, clearly, desire for a future pregnancy is a contraindication. In addition, it should be considered that deep adenomyosis uteri has been associated with an increased failure rate of endometrial ablation, proportionate to the depth of endometrial penetration. Hysterectomy remains the main surgical option for women not wishing to preserve their fertility.

### Conclusion

Adenomyosis uteri remains one of the most common pathological findings in hysterectomy specimens. This clearly argues for better diagnosis and specific therapy aimed at reducing hysterectomy rates. With better imaging modalities, such as MRI and modern ultrasound, accurate diagnosis is becoming increasingly possible. Preoperative diagnosis raises the possibility of specific therapy and can be useful for counselling prior to interventions such as endometrial ablation. Wider use of imaging will enable better recognition of the impact of adenomyosis uteri. There remains a need for specific therapy based on a better understanding of the pathophysiology of the disease.

### References


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