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Uterine adenomyosis in the infertility clinic

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This review discusses uterine adenomyosis as a (co-)factor in female subfertility. The clinical presentation of adenomyosis uteri is reviewed as well as recent developments in non-invasive imaging modalities for the condition. Different treatment options are discussed, focusing on conservative management in patients who wish to maintain their childbearing capacity.

Key words: adenomyosis/endometriosis/infertility/ultrasound/uterus

Clinical presentation and histopathology of adenomyosis

Adenomyosis uteri is a common gynaecological disorder with unclear aetiology that is characterized by the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia.

Rokitansky first described the histopathological characteristics of the condition (Rokitansky, 1860). These include a poorly circumscribed area of smooth muscle cells, stroma and endometrial glands invading the uterine smooth muscle layers of the myometrium. The degree of invasion is variable and can involve the whole uterine wall up to the serosa. Most pathologists will not make a diagnosis of adenomyosis unless glandular extension below the endometrial-myometrial interface (EMI) is >2.5 mm (Uduwela *et al*., 2000), whereas adenomyosis sub-basalis can be defined as minimally invasive adenomyosis extending <2 mm beneath the basal endometrium (Bird *et al*., 1972). The posterior wall is more often affected than the anterior wall. A degree of hyperplasia of the smooth uterine musculature is often seen, resulting in the typical increase in uterine size. Several different diagnostic criteria and classifications have been proposed, based on the depth of the infiltration, leading to a wide range of reported prevalence figures of adenomyosis in uterine specimens (Bergholt *et al*., 2001). Other localizations of adenomyosis have been described, and the differential diagnosis with other conditions like endometriosis is not easy, especially for the rectovaginal localizations (Donnez *et al.*, 1995). The histological features are present in 20–35% of women undergoing hysterectomy for benign gynaecological disorders (Azziz, 1989; Kim and Strawn, 2000).

Uterine adenomyosis is relatively frequent as it is thought to affect about 1% of female patients; moreover, the diagnosis is more often made in multiparous patients, in their fourth and fifth decade of life.

The presenting symptoms include a soft and diffusely enlarged uterus with menorrhagia (40–50%), dysmenorrhoea (10–30%), metrorrhagia (10–12%), dyspareunia and dyschezia. These symptoms are non-specific and can occur as part of many other gynaecological disorders, such as dysfunctional uterine bleeding, fibroids and endometriosis (Azziz, 1989). Typically, the symptoms start one week prior to the menstrual flow. Infertility is a less frequent complaint, since uterine adenomyosis is usually diagnosed in the fourth and fifth decade of life. However, since more women delay their first pregnancy until later in their thirties or forties, adenomyosis is encountered more frequently in the fertility clinic during diagnostic work-up. In a series including 26 patients with infertility and menorrhagia or dysmenorrhoea, adenomyosis was found in 14 (53.8%) (de Souza *et al.*, 1995).

Importance of the EMI during the ovulatory cycle and in normal pregnancy

The EMI consists of basal endometrium and subendometrial myometrium (myometrial junctional zone) and can be regarded as a functional unit that is important for sperm transportation, embryo implantation, placental development and menstruation (Uduwela *et al*., 2000). Both parts of the EMI (endometrium and subendometrial myometrium) have a common embryological origin from the paramesonephric ducts and show cyclical changes during the menstrual cycle, whereas the outer myometrium is of non-paramesonephric mesenchymal origin (Noe *et al*., 1999; Uduwela *et al*., 2000). The EMI can be identified as a hyperechoic perimeter surrounding a hypoechoic functional endometrium at high-resolution endovaginal ultrasonography only during the early luteal days, since the entire endometrium has become echogenic 7 days after ovulation (Grunfeld *et al*., 1991).

The basal endometrium forms the inner surface area of the EMI, is approximately 1 mm in thickness, and consists of

branching lower segments and bases of glands and associated stroma. Distinct periglandular lymphoid aggregates include a core of B cells, surrounded by more numerous T cells and an outer halo of monocytes/macrophages (Yeaman *et al*., 1997). The number of T cells and of cells positive for HLA-DR and interferon-gamma is higher in secretory than in proliferative endometrium, especially in the basalis (Chiang and Hill, 1997). The physiological role of these lymphoid aggregates and immune cells is not very clear, but these and other data related to the endometrial expression of VLA-1, Ber-EP4, adhesion molecules and localized proliferative activity (Tabibzadeh, 1991; Tabibzadeh *et al*., 1994) suggest that the endometrium is a polarized tissue with gradual changes from surface (functionalis) to bottom (basalis) instead of abrupt differences between functional and basal endometrial layers (Uduwela *et al*., 2000).

The subendometrial myometrium (myometrial junctional zone) forms the outer surface area of the EMI, constitutes the inner third of the myometrium, and is about 5 mm in thickness. It is less vascular than the outer myometrium and consists of compact bundles of longitudinally oriented smooth muscle fibres running parallel to the endometrium (Brown *et al*., 1991), with a higher size and number of nuclei (Scoutt *et al*., 1991) and lower water content (McCarthy *et al*., 1989) when compared with the outer myometrium. Subendometrial myometrium can be identified as a hypo-intense layer beneath the endometrium on T2-weighted images on magnetic resonance imaging (MRI) (Hricak *et al*., 1983). Subendometrial myometrium shows a cyclic pattern of estrogen and progesterone receptor expression that is not present in the outer myometrium (Noe *et al*., 1999). Subendometrial myometrial contractility is retrograde during the non-menstrual phase (role in sperm transport and in conservation of pre-implantation blastocysts in the uterus) and antegrade during the menstrual phase of the cycle (shedding of endometrium, control of menstrual flow) (de Vries *et al*., 1990; Lyons *et al*., 1991). Retrograde subendometrial contractility has been observed in women with endometriosis and could contribute to the quantity of retrograde menstruation (Salamanca and Beltran, 1995).

The unique structural and functional feature of the EMI is the lack of a protective submucosa when compared with other mucosal-muscular junctions in the human body, exposing the myometrium to invasion by proliferating endometrium (Emge, 1962). The normal EMI is very irregular over its entire surface, and the normal indentations of the basal endometrium cannot be discerned from abnormal invasion (Brosens *et al*., 1995b).

During pregnancy, trophoblastic cells invade the inner myometrium and breach uterine spiral arterioles, resulting in haemochorial placentation. It is not well understood how the interaction between trophoblast and the EMI may contribute to the control of this process. At early stages of pregnancy, a focal disruption of the EMI can be observed using MRI (Turnbull *et al*., 1995), and normal EMI imaging only reappears 2 weeks to 6 months after normal delivery (Barton *et al*., 1993).

Role of the EMI interface in the pathogenesis of adenomyosis

The aetiology of adenomyosis is not yet fully understood. Conventionally, it is believed that adenomyosis results from the abnormal in-growth and invagination of the basal endometrium into the subendometrial myometrium, because continuity between the basal endometrium and underlying adenomyosis is often seen in tissue sections (Parrott *et al*., 2001; Leyendecker *et al*., 2002). Recently, more precise descriptions of the microscopical architecture of endometrium and myometrium have led to the idea that an intact EMI may be important in the protection against adenomyosis (Brosens *et al.*, 1995a). A disruption of this protective barrier may lead to the development of adenomyosis and may occur after mechanical damage (Mori *et al*., 1984; Azziz, 1989; Levgur *et al.*, 2000). This hypothesis is supported by animal experiments as well as by the association of adenomyosis with a history of intra-uterine procedures such as pregnancy termination (Mori *et al.*, 1984; Azziz, 1989; Levgur *et al.*, 2000). As mentioned above, the EMI is also disturbed by invading trophoblast in early pregnancy, and the epidemiology of adenomyosis shows predominance in parous patients. More recent studies have supported the hypothesis that adenomyosis, like endometriosis, results from the dislocation of basal endometrium into the myometrial wall due to dysfunctional uterine hyperperistalsis and/or dysfunctional contractility of the subendometrial myometrium (Brosens *et al*., 1998; Kunz *et al*., 2000; Leyendecker *et al*., 2002). This hypothesis is supported by the observation that, with respect to expression of estrogen receptors and progesterone receptors, endometrium of adenomyotic and endometriotic lesions mimicked the cyclical pattern of the basalis layer, but not the functionalis layer of eutopic endometrium (Leyendecker *et al*., 2002). Recent experimental evidence in mice also suggests that discrete hormonal derangements, which produce defects in stromal and myometrial differentiation early in human neonatal life, may explain the predisposition to adenomyosis in adulthood (Parrott *et al*., 2001). Furthermore, adenomyosis, like endometriosis, is also associated with immunological activation (Ota *et al*., 1998); that is, strong expression of cell-surface antigens, heat shock proteins or adhesion molecules, increased number of macrophages or immune cells, deposition of immunoglobulins and complement components, and increased prevalence of auto-antibodies in peripheral blood (Ota *et al*., 1998). Similarly, aberrant expression of superoxide dismutase (Ota *et al*., 1999), glutathione peroxidase (Ota *et al*., 2000), cyclo-oxygenase-2 (Ota *et al*., 2001a) or xanthine oxidase (Ota *et al*., 2001b) has been reported in adenomyotic tissue when compared with eutopic endometrium. However, it is not known whether these immunological changes and biochemical abnormalities are a consequence or a cause of adenomyosis.

Role of the EMI and adenomyosis in uterine bleeding disorders and infertility

Clinically, dysfunctional contractility of the outer myometrium and/or EMI during menstruation in women with adenomyosis could account for a proportion of cases with menorrhagia (Bird *et al.*, 1972; McCausland, 1991; Brosens *et al*., 1995b), whereas minimally invasive adenomyosis basalis (invasion of basal endometrium into the myometrium less than 2 mm below the basal endometrium) could be related to dysfunctional uterine bleeding (McCausland, 1991).

The reason why adenomyosis impedes fertility has not been thoroughly examined. Traditionally, investigators have hypothesized that the abnormal structure of the EMI and myometrium—especially in fundal localizations—could interfere with normal implantation. However, the present evidence from recipients of

sibling oocytes in IVF suggests that adenomyosis by classical ultrasound criteria (see below) has no impact on the rate of embryonic implantation (Camargo *et al*., 2001).

Imaging features of adenomyosis

Adenomyosis remains a difficult diagnosis and is often only established at pathological examination of a hysterectomy specimen. Recently, different non-invasive techniques were described which enable the clinician to at least suspect the diagnosis prior to any treatment. Due to these developments, the use of more invasive diagnostic methods such as percutaneous or laparoscopic uterine biopsy can therefore generally be avoided (Vercellini *et al.*, 1996). Ideally, imaging techniques should aim at three goals:

- To diagnose the condition with sufficient sensitivity, specificity and predictive power in a non-invasive manner. An obvious problem here is that most studies obtained positive predictive values comparing their technique and criteria with presence or absence of adenomyosis on histological preparations from the hysterectomy specimens, which implicates that the figures obtained are not necessary valid in patients with impaired fertility.
- To determine the extent of the pathological zone and the depth of the infiltration, as this not only correlates with the symptoms but will also influence the treatment modality (McCausland and McCausland, 1996).
- Especially important for infertility patients, non-invasive imaging should enable a careful follow-up of patients during conservative management. The different non-invasive imaging modalities for adenomyosis have recently been reviewed in depth (Reinhold *et al.*, 1998).

Hysterosalpingography

Hysterosalpingography (HSG) was the first imaging modality used for the diagnosis of adenomyosis. The characteristic findings on HSG are multiple small (1–4 mm) spicules extending from the endometrium into the myometrium with saccular endings. Alternatively, a local accumulation of contrast material in the myometrium can sometimes provide a honeycomb appearance. Due to its low sensitivity and specificity, HSG is no longer used in the evaluation of patients with suspected adenomyosis. However, HSG remains part of routine diagnostic work-up in many fertility clinics and the findings described above should be recognized when present even in infertile patients.

Transabdominal sonography

Transabdominal ultrasonography (TAS), using probes with a frequency varying from 3.5 to 5 MHz, offers sufficient penetration to visualize organs posterior to the bladder. Due to the limited spatial resolution of TAS it is difficult consistently to make a differential diagnosis between adenomyosis and fibroids. Studies using only abdominal access for the diagnosis of adenomyosis reported relatively poor sensitivities (Bohlman *et al.*, 1987; Siedler *et al.*, 1987). Although spatial resolution obtained with more modern transabdominal probes has improved since these studies were conducted, it remains true that transvaginal ultrasonography is usually required to demonstrate the more subtle sonographic features of adenomyosis in a reproducible and consistent way.

Transvaginal sonography

The technical progress of transvaginal ultrasonography (TVS) in the mid-1980s led to renewed interest in the diagnosis of adenomyosis. The higher frequencies (5–7 MHz) reduce artefacts while improving the spatial resolution, making it invaluable in the diagnosis and follow-up of most gynaecological disorders. Leading authors support the use of routine real-time TVS with a detailed depiction of the myometrium in both patients with suspected adenomyosis as well as in the routine diagnostic work-up of patients with long-lasting subfertility (Reinhold *et al.*, 1998).

The ultrasound features of adenomyosis are often subtle and extremely variable; the different diagnostic criteria described in the literature are summarized in Table I. The most common findings on TVS in the patient with adenomyosis are poorly marginated hypoechogenic and heterogeneous areas (Figure 1). One group (Atri *et al.*, 2000) compared ultrasound and histological findings and demonstrated that the decreased echogenicity of the myometrium is due to the smooth muscle hypertrophy accompanying the heterotopic endometrial tissue. In about 50% of the cases (Reinhold *et al.*, 1995), small (1–6 mm) myometrial cysts are present (Figure 2). The timing of the ultrasound in the cycle is important, as the uterine size has been shown to increase substantially during the menstrual period in patients with adenomyosis. Several authors have compared the accuracy of different sonographic criteria for the prediction of adenomyosis. Although numbers are relatively small and inclusion criteria vary widely, overall good performance is obtained when diagnostic criteria are combined and real-time examination is used (Fedele *et al.*, 1992a,b; Asher *et al.*, 1994; Brosens *et al.*, 1995b; Hirai *et al.*, 1995; Reinhold *et al.*, 1995). These data are summarized in Table II. Results of other studies are more difficult to interpret due to incomplete description of the study population (Bromley *et al.*, 2000) or histological criteria used (Koçak *et al.*, 1998).

The sonographic features of adenomyosis can exhibit overlap with those of leiomyomas, especially in cases of focal adenomyosis. In such cases, additional imaging using magnetic resonance may be necessary. Arguments in favour of adenomyosis include (Figures 3 and 4):

- Echo texture is not uniform, with poorly defined borders.
- Minimal mass effect on the endometrium or the serosa relative to the size of the lesion.
- Elliptical rather than globular shape.
- Lack of edge shadowing; ‘shaggy’ or whorled appearance of the endometrium.
- Small myometrial cysts or spaces scattered throughout the myometrium.
- Echogenic nodules or linear striations radiating out from the endometrium into the myometrium.
- Absence of circular vascularization at the border of the lesion (contrary to myomas).

The TVS appearance of adenomyosis can mimic the features of endometrial carcinoma, and a coexistence of adenomyosis may lead to over-staging of endometrial carcinoma. Pulsed and colour Doppler may be helpful to distinguish between both conditions (Hirai *et al.*, 1995). Furthermore, it is sometimes difficult to

Table I. Sonographic criteria for adenomyosis

Reference	Sonographic criteria for adenomyosis
Brosens *et al.* (1995b)	Uterine enlargement in the absence of leiomyomas
Asher *et al*. (1994) Brosens *et al.* (1995b) Hirai *et al.* (1995)	Asymmetric enlargement of the anterior or posterior myometrial wall
Brosens *et al.* (1995b)	Lack of contour abnormality or mass effect
Fedele *et al.* (1992a) Asher *et al.* (1994) Brosens *et al.* (1995b) Hirai *et al.* (1995)	Heterogeneous, poorly circumcised areas within the myometrium
Atri *et al.* (2000)	Hyperechoic islands or nodules, finger-like projections or linear striations
Hirai *et al.* (1995) Reinhold *et al*. (1995) Fedele *et al.* (1997)	Anechoic lacunae or cysts of varying size
Asher *et al.* (1994) Hirai *et al.* (1995)	Increased echo texture of the myometrium

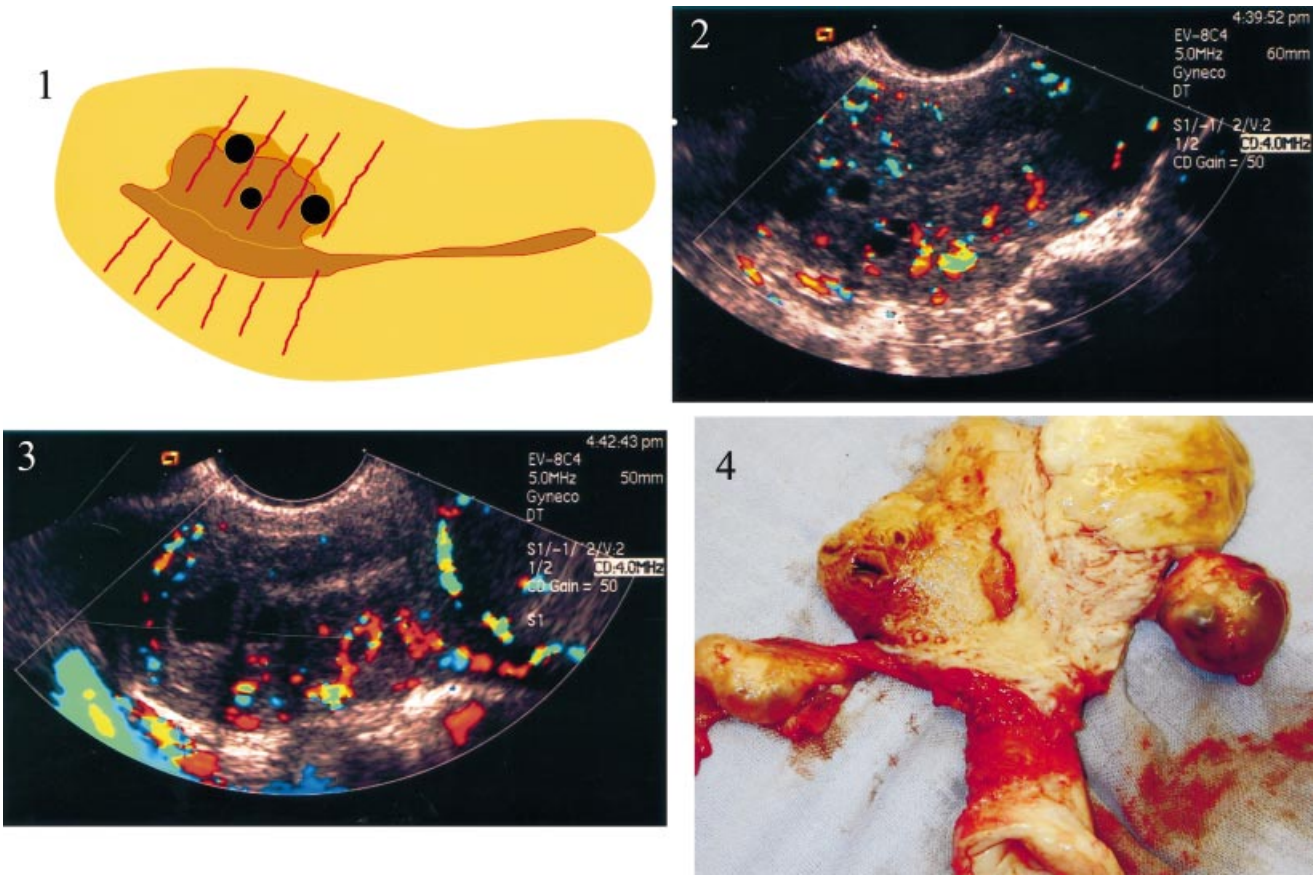

Figure 1. Schematic diagram summarizing the most common ultrasound findings in adenomyosis: poorly marginated hypoechogenic and heterogeneous areas, small myometrial cysts, absence of circular vascularization at the border of the lesion
Figure 2. Transvaginal ultrasound image of small myometrial cysts in a uterus with adenomyosis.
Figure 3. Ultrasonographic appearance of a uterus with a leiomyoma (right) and adenomyosis (left).
Figure 4. Macroscopic appearance of the same uterus (Figure 3) after hysterectomy. Note the chocolate-like fluid in the adenomyotic cysts.

Table II. Accuracy of ultrasonography in the prediction of adenomyosis

Reference	Studied population	Prevalence	Sensitivity (%)	Specificity (%)
Fedele *et al*. (1992b)	Hysterectomy for symptomatic uterine masses	23/405	87	99
Fedele *et al.* (1992a)	Surgery for menorrhagia	22/43	80	74
Asher *et al.* (1994)		17/20	53	75
Brosens *et al.* (1995b)		28/56	86	50
Reinhold *et al.* (1995)	Consecutive hysterectomies for various reasons	29/100	86	86
Koçak *et al.* (1998)	Hysterectomy for benign uterine pathology	18/95	89	88
Bromley *et al.* (2000)	Ultrasound suspicion of adenomyosis over 10 year period	51/ ?	84	84

Table III. Criteria for adenomyosis using magnetic resonance imaging (MRI)

Reference	MRI criteria for adenomyosis
Togashi *et al*. (1989)	Focal or diffuse thickening of the junctional zone (T2)
Togashi *et al.* (1989) Mark *et al.* (1987)	Low signal intensity uterine mass with ill-defined borders (T2)
Asher *et al.* (1994) Reinhold *et al.* (1996)	Junctional zone thickness >5 mm (T2)
Kang *et al.* (1996)	Junctional zone thickness >12 mm (T2)
Reinhold *et al*. (1997) Reinhold *et al*. (1996)	Poor definition of junctional zone borders (T2)
Togashi *et al.* (1989)	Localized high signal foci within an area of low signal intensity (T2)
Togashi *et al.* (1989)	Linear striations of increased signal radiating out from the endometrium into the myometrium (T2)
Reinhold *et al.* (1997)	Bright foci in endometrium isointense with myometrium (T1)

differentiate between adenomyosis and myometrial contractions, hypertrophy and vascular calcifications.

While TVS is inexpensive, readily available and well tolerated, the accuracy of diagnosis of adenomyosis is highly dependent on the experience and interest of the ultrasonographer. This limitation can hamper the acquisition of standardized images for sequential follow-up. Therefore, some authors recommend the use of MRI in the follow-up of conservatively treated patients with adenomyosis. During recent years technical advances in ultrasound equipment have significantly improved the resolution and overall image quality. Thus, it is not surprising that older studies reported lower accuracies.

Magnetic resonance imaging

MRI—especially with T2-weighted images—has become an important imaging modality for uterine pathology because of its excellent soft tissue differentiation. It is less operator-dependent compared with TVS and the images are standardized and reproducible, especially in the presence of intramural leiomyomas. Several studies have shown MRI to be highly accurate in the diagnosis of uterine adenomyosis, with sensitivity and specificity ranging from 86 to 100% in a symptomatic patient population (Reinhold *et al.*, 1999).

Diagnostic tools used in these studies are shown in Table III. In general, adenomyotic lesions appear as a low intensity area on T2-weighted images, which frequently gives the appearance of diffuse or focal widening of the so-called junctional zone, the band of lower signal intensity representing the inner layer of the myometrium. The differential diagnosis with leiomyomas, uterine contractions or uterine muscular hypertrophy is sometimes difficult (Reinhold *et al.*, 1998). In infertility patients with symptoms suggestive of uterine pathology, MRI can be useful in differentiating the nature of the condition (de Souza *et al.*, 1995) or in evaluating conservative management (Siskin *et al.*, 2001).

Several authors have compared the accuracy of TVS and MRI in the diagnosis of adenomyosis on the same patient population. As pathology of hysterectomy specimens was used as the 'gold standard', these comparative studies did not focus on an infertile population. Asher and colleagues (Asher *et al.*, 1994) found MRI to be superior in a small series with a high prevalence of adenomyosis (17/20), while Reinhold and co-workers found no differences between the sensitivities and specificities for both modalities in 119

Table IV. Successful pregnancies following treatment with GnRH agonists for adenomyosis and infertility

Reference	*n*	Medication	Pregnancy outcome	Duration of infertility	Interval from cessation of treatment to conception
Hirata *et al.* (1993)	1	Nafarelin acetate nasal spray 800 µg/day for 6 months	Spontaneous abortion at 10 weeks gestation	4 years	4 months
Nelson and Corson (1993)	1	Leuprolide acetate 0.5 mg s.c. daily for 6 months followed by leuprolide acetate i.m. injection 3.75 mg/month for a total of 20 months over 3-year period	Viable first-trimester pregnancy	No infertility	1 month
Silva *et al.* (1994)	1	Leuprolide acetate i.m. injection 3.75 mg/month for 5 months	Caesarean section at term; 3400 g healthy infant	10 years	5 months
Huang *et al.* (1999)	2	Buserelin acetate nasal spray 600 µg/day for 3 months	(1) Vaginal delivery of 3550 g infant at 39 weeks gestation	(1) 2 years	(1) 4 months
			(2) Caesarean section at 38 weeks gestation; 2700 g infant	(2) 4 years	(2) 6 months
Lin *et al*. (2000)	2	(1) Goserelin 3.6 mg s.c. monthly for 6 months	(1) Vaginal delivery of 3150 g infant at 38 weeks gestation	(1) 6 years	2 to 4 months
		(2) Triptorelin acetate 2.75 mg i.m. monthly for 6 months	(2) Reportedly normal pregnancy until 28 weeks of gestation	(2) 3 years	

patients undergoing hysterectomy (Reinhold *et al.*, 1996). The high cost and limited availability of MRI makes it an impractical tool for the initial evaluation of patients with non-specific gynaecological complaints suggestive of adenomyosis. It has however its place as an adjunctive tool in the assessment of patients with clinically significant adenomyosis, especially in the presence of leiomyomas and the follow-up of patients receiving hormonal therapy.

Treatment options in the patient with subfertility

The classical treatment for debilitating adenomyosis consists of endoscopic endometrial ablation or hysterectomy. However, endometrial ablation in patients presenting with adenomyosis can lead to intracavitary adhesions, haematometrium and increased pain. Furthermore, an increasing number of patients delaying childbearing wish is expected to be confronted with the condition. Indeed, the trend in civilized countries is to delay the first pregnancy, and the condition is typically observed when the woman is in her late thirties and forties. Additionally, the condition is interfering with the normal implantation function of the uterus and can therefore be a cause of subfertility. In recent years, a number of conservative treatment options for these patients have been described, but the total number of patients treated and subsequently conceiving remains extremely small. The conservative options in the treatment of uterine adenomyosis can be divided into three categories: vessel embolization; hormonal treatment; and combined surgical and hormonal treatment.

Vessel embolization

Interventional radiological techniques to embolize the uterine vessels selectively in case of adenomyosis have been described recently. The reported series are small, and so far no successful pregnancy was described following embolization for this indication. On the other hand, at least 10 successful outcomes have been reported in 11 pregnancies in patients previously diagnosed with uterine vascular malformations for which an embolization of the uterine arteries had been performed (Timmerman *et al.*, 2000). One group (Siskin *et al.*, 2001) reported on 15 cases of adenomyosis diagnosed with MRI in which embolization led to improvement in quality of life in 12 out of 13 patients. However, in this retrospective review the follow-up was incomplete (only 9/15 patients underwent MRI during follow-up) and 12 patients included in the study had concurrent fibroids, for which embolization is an established treatment option.

Hormonal treatment

Hormonal treatments for symptomatic relief include progestagens, continuous oral contraceptive pills, anti-estrogens and GnRH agonists. Overall, the effect of these treatments is limited to a variable and unpredictable degree of symptomatic relief, usually restricted to the duration of treatment. GnRH agonists and anti-estrogens such as danazol have been the most studied hormonal therapeutic options. GnRH analogues create a pseudo-menopausal, hypoestrogenic environment. They have been successful in the treatment of other diseases dependent on ovarian steroidogenesis, such as endometriosis and uterine leiomyomas. The use in the treatment of adenomyosis is less well established. The main restrictions of the use of these drugs are the menopausal side effects that include hot flushes, mood swings and bone demineralization. These can be countered only partially by so-called 'add back' estrogen substitution. In a description of the first case to be treated with GnRH agonists for adenomyosis, the

patient showed uterine size reduction and subsequent symptomatic improvement, but remained infertile (Grow and Filler, 1991). More recently, several authors reported on successful pregnancies or live births following treatment with GnRH agonists for adenomyosis and infertility; these are summarized in Table IV. The results obtained by one group using short-course treatment are interesting but await future confirmation (Huang *et al*., 1999). In this study, treatment did not protect against serious psychological side effects in one of the patients.

Two reports have been published on the use of the levonorgestrel-releasing intra-uterine system (LNG-IUS) in the treatment of uterine adenomyosis outside the context of infertility. In a series of 25 patients with adenomyosis-associated menorrhagia, the authors reported a modest 9.8% mean decrease in uterine size after 12 months of treatment. Menorrhagia, surprisingly present in only 15 patients, disappeared in all cases leading to an improvement of the anaemia (Fedele *et al.*, 1997). The second study reported a successful treatment of both menorrhagia and dysmenorrhoea with the LNG-IUS in a patient with a grossly enlarged uterus and a contraindication for surgery. Interestingly, the uterine size decreased (from 501 to 366 ml) during the 12 months of treatment, which could be attributed to the high concentrations of levonorgestrel obtained locally in the uterus (Fong and Singh, 1999). The use of a LNG-IUS during a certain time period could therefore (in theory) be a treatment option in the case of adenomyosis and infertility, but no successful subsequent pregnancies have been reported so far.

In a preliminary uncontrolled study, treatment of 12 women with adenomyosis using a danazol-loaded intra-uterine device resulted in three pregnancies (Igarishi *et al.*, 2000). In this study, danazol serum levels were undetectable and both menstrual and ovulatory function were preserved. The authors' hypothesis was that high intra-uterine danazol concentrations are released directly to the pathological EMI, which might give better results than oral danazol towards symptomatic control and fertility.

Combined surgical and hormonal treatment

Microsurgical complete resection of the visible adenomyotic area followed by treatment of GnRH agonists (goserelin acetate 3.6 mg, two to six courses) resulted in the birth of healthy newborns in four cases (Huang *et al.*, 1998; Wang *et al*., 2000). It is suggested that this cytoreductive surgery results in an increased sensitivity to hormonal treatment due to improved blood supply to the adenomyosis tissue and an improved immune function of the host. The rationale for medical adjuvant therapy is the assumption that surgical resection of the pathological area without damage to the uterine cavity is incomplete. This approach seems attractive, but one must be aware of the surgical and obstetric consequences. Indeed, all babies were delivered by Caesarean section and in some cases, a midline uterine incision had been performed to remove the adenomyosis by careful dissection and coagulation. One case was complicated by ante-partum bleeding and threatened pre-term labour (Huang *et al.*, 1998). Furthermore, the authors describe the presence of intra-abdominal adhesions, although minimal. No information is given on the recurrence of symptoms or uterine size following the post-partum period. In a report of obstetric complications (Lin *et al.*, 2000), one of the patients underwent laparoscopic removal of a deep adenomyotic nodule in the posterior uterine wall. She was treated post-operatively with triptorelin 3.75 mg monthly for 6 months and conceived within 4 months of cessation of the GnRH agonist. An emergency Caesarean section was needed at 30 weeks of gestation for threatened uterine rupture, exposing both mother and baby to significant risks. In another study (Ozaki *et al.*, 1999) a persistent, well-localized area of adenomyosis was observed after two courses (3 and 8 months respectively) of leuprolide acetate. The nodule was removed operatively, and adjuvant therapy with danazol administered for 3 months. The patient conceived rapidly and was delivered after an uneventful pregnancy by Caesarean section.

In the light of these reports, a combined approach should be considered only in patients in whom GnRH agonists alone were not effective and effective contraception for a minimal duration of 6 months following uterine surgery seems advisable.

Future treatment options

In the near future, new developments such as high-intensity focused ultrasound (HIFU) may play a role in the conservative management of adenomyosis. Indeed, this technique permits the combination of coagulation and tissue destruction in a non-invasive, bloodless manner. Most of the clinical experience in this burgeoning field has been obtained in the treatment of prostate tumours, thereby confirming the feasibility and safety of transrectal application (ter Haar, 2001). A spectacular tumour reduction was obtained in rats when using this technique on uterine leiomyomas, with a mean 82.5% tumour mass reduction being reported after a single application (Vaezy *et al*., 2000). The safety of transvaginal HIFU is currently being assessed.

In summary, uterine adenomyosis remains a fairly frequent and debilitating disease that will be encountered with increasing incidence in the infertile female population. While spectacular advances have been made in recent years in the non-invasive diagnosis of the condition, non-surgical treatment options arise but need to be confirmed in larger series.

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