REVIEW

Therapeutic options for adenomyosis: a review

Michael Levgur

Abstract

Background To review the literature on various therapeutic modalities for uterine adenomyosis.

Methods Reviews, case-controlled studies and reports from November 1949 until August 2006 written in English or summarized in English abstracts retrieved from Medline and Pubmed using the key words: adenomyosis and adenomyosis therapy.

Results Symptoms of adenomyosis may be alleviated by antiprostaglandins, sex hormones, danazol and GnRH analogs. Minor surgical procedures for therapy include endomyometrial ablation, laparoscopic myometrial electrocoagulation and adenomyoma excision. Patient's age and symptoms, desired fertility, site and extent of lesion and surgeon's skills should be considered in choosing the appropriate procedure. Endomyometrial ablation is effective for lesions deeper than the endometrial–myometrial junction whereas the efficacy of hysteroscopic ablation is limited to foci 2–3 mm deep. Focal and diffuse disease may be managed by laparoscopic electrocoagulation or myometrial excision with preservation of fertility but risk of recurrence exists. Uterine artery embolization assumingly invokes infarction and necrosis. Encouraging results reported in some cases warrant expanding its use for more experience. Hysterectomy is the ultimate solution for women with deep myometrial involvement or if future fertility is not desired.

Conclusions Various therapeutic options for adenomyosis, including few minimally invasive procedures became available in the last two decades but need evaluation and improvement.

Keywords Medical management of adenomyosis · Endometrial ablation and myometrial excision for adenomyosis · MRI guided focus ultrasound surgery for adenomyosis · Laparoscopic myometrial reduction for adenomyosis · Uterine artery embolization for adenomyosis

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Introduction

Adenomyosis is a disorder characterized by presence of endometrial islets within the myometrium. By definition, they consist of epithelial as well stromal elements and situated at least 2.5 mm below the endometrial–myometrial junction. The disease appears in two forms, diffuse and focal, and involves mostly the posterior uterine wall [1–5]. In the past the diagnosis relied on clinical manifestations but the last two decades witnessed remarkable development in imaging modes to enhance diagnostic accuracy. Indeed the efficacy of vaginal sonogram and MRI has been confirmed by several studies [1, 4–8]. Of the minimally invasive diagnostic methods myometrial biopsy has been used by several authors and seems promising [3, 9–11].

Parallel to the development of improved diagnostic methods for adenomyosis, innovative modalities were

introduced as alternatives therapies for women for whom hysterectomy would not be considered an option [12, 13].

The purpose of this review is to summarize and evaluate the accrued experience with these methods. A Pubmed search and cross-referencing were used in order to retrieve all manuscripts on the treatment of adenomyosis, written or abstracted in English and published from November 1949 to August 2006, using the key words adenomyosis and adenomyosis treatment.

Medical therapy

Over the last two decades, drug regimens have been tried in cases of symptomatic adenomyosis as alternatives for uterine extirpation. Since dysmenorrhea is a manifestation of myometrial contractions that are caused by PGI_2 produced by adenomyosis tissue, antiprostaglandins have been use extensively for the relief of this symptom [14].

Sex hormones, progestins, danazol and GnRH-a alleviate menorrhagia and dysmenorrhea. However, none have been evaluated in controlled studies or have demonstrated notable impacts on disease process [12, 15]. Sex hormone receptors in adenomyosis foci respond to sex hormones less than normal endometrium. In non-pregnant women only 30–50% of foci displayed secretory changes and only 57% of foci in cesarean section specimens had decidual reaction. Thus their response to progesterone is relatively uncommon and is lagging behind the response of normal endometrium. This is in agreement with the fact that basalis cells, in spite of being the predominant component of all endometrial layers in adenomyosis foci are the least sensitive to progesterone. Indeed, estrogen, progesterone and androgen receptors in the foci are fewer than in surrounding myometrium [16–18]. Interestingly, in some cases the number of progesterone receptors was slightly higher in the foci than in the myometrium whereas in others these receptors were not detected at all [19]. As pointed out in the classic review by Azziz [17] the measurements of these receptors must be viewed with caution as they are carried out in tissue minces that, besides myometrium, contain ectopic endometrium and blood vessels [16, 17, 19–21].

Progestins

The suppression incurred on foci by the progestin levonorgstrel released from an IUD (LNG-IUD) was the topic of two studies [22, 23]. The first evaluated efficacy of the device in 25 women complaining of recurrent menorrhagia and diagnosed sonographically [22]. A LNG-IUD, releasing 20 µg of levonorgestrel per day was inserted 7 days after the onset of menses. Blood loss was determined monthly and sonographic imaging was performed quarterly. In 23 women completing the follow-up the average uterine volume diminished from 948 ± 171 ml to 914 ± 139 ml ($P < 0.01$), a statistically significant finding that bears no clinical relevance. Twelve months after insertion normal menstrual flow resumed in roughly two-thirds of women whereas the rest had amenorrhea, spotting or oligomenorrhea. The average blood loss dropped concurrently from 211 ± 61 to 44 ± 18 ($P < 0.001$) as hemoglobin, serum iron and ferritin levels raised [22]. The other paper was a case report of adenomyosis diagnosed sonographically. The uterine volume dropped 27% and both menorrhagia and dysmenorrhea resolved 12 months after LNG-IUD insertion [23]. The ensuing endometrial atrophy in these cases stemmed from decidualization or from downregulation of estrogen receptors in the endometrium [22, 23]. LNG levels measured in the endometrium were 1,000-fold higher than serum levels indicating a selective action of the hormone on endometrium and adenomyosis foci [23]. Breakthrough bleeding occurred, in general, in the first 3 months and was regarded as inconsequential considering the clinical benefits. However, the authors acknowledged that side effects of prolonged exposure to progestin such as headache, breast tenderness, seborrhea, acne and weight gain may ameliorate patient satisfaction [22, 23].

Although efficacy of oral contraceptives, progestins or androgens was demonstrated in few symptomatic adenomyosis patients some anecdotal case reports suggested actually the opposite, namely stimulation of foci, thus providing clinical evidence for the presence of both estrogen and progesterone receptors in adenomyosis foci [17, 19–21]. In fact, by one report, 16 months of combined estrogen and progestin therapy exacerbated symptoms, increased the uterine weight to 726 g and prompted a pseudodecidual reaction in the foci [24].

Danocrine

The aversion of endometrial proliferation by the antigonadotrophin danocrine (danazol) prompted its utilization in cases of adenomyosis. Given for 25 days to 335 women with menorrhagia prior to hysteroscopic endometrial laser ablation danazol, at a daily dose of 800 mg elicited atrophy of the endometrium but was ineffective clinically [25]. Other authors employed this

drug locally, by an IUD as a vehicle or by intra-cervical injection [26, 27]. A device that released a total of 175 mg of danazol was used in four individuals diagnosed by symptoms, uterine enlargement and sonography. The uterus decreased in size as long as the IUD remained in situ but upon its removal this process reversed and ended in two conceptions [26]. Released amounts of danazol ranged from 0.21 to 0.72 mg/day and were too small to affect ovulation or raise blood levels to detectable values, unlike the oral daily dose of 400 mg that suppresses ovulation and elevates blood levels. Since the diagnosis in this particular study did not rely on accepted sonographic criteria, no conclusion as to treatment efficacy can be drawn. The only valid point this study makes is that danazol elicits a direct action on endometrial cells, a finding that was also supported by observations on endometrial cells in tissue cultures [26, 28].

GnRH-a

GnRH-a therapy for adenomyosis was first reported in 1991 [29]. The diagnosis was confirmed by multiple myometrial biopsies from a soft posterior uterine mass. After 6 months of daily subcutaneous injections of 1 mg leuprolide acetate (lupron, LA), amenorrhea was noticed together with general clinical improvement. The uterus decreased in size by 65%, from 440 to 150 cm^3 and on histology the foci were decidualized. Not unexpectedly, discontinuation of therapy prompted re-growth of the uterus to 420 cm^3 and resulted in recurrence of symptoms [29]. This report was followed by others in pursue of alternatives to hysterectomy [13, 30–34]. In one case, two infiltrative uterine cystic masses identified as adenomyomas were partially removed. Six monthly injections of LA were employed and repeated twice more due to recurrence of severe pelvic pain [13]. After each of the 4- and 3-month courses the symptoms subsided with a temporary decrease in uterine size following which the patient conceived. Another symptomatic and infertile woman underwent a wedge resection biopsy from the uterine fundus showing disease [30]. After 6 months of nafarelin acetate (synarel) nasal spray therapy the patient conceived but miscarried in the first trimester leading the authors to postulate that in addition to shrinking the uterus, GnRH-a also promoted uterine and endometrial receptivity.

A similar case associated with a 10 years of secondary infertility, severe symptoms and diffuse uterine enlargement attributed to leiomyomas was managed by wedge biopsy from the posterior wall revealing severe adenomyosis penetrating to the serosa [31].

After five monthly courses of GnRH-a conception ensued and the patient delivered a 3,400 g newborn, the first live birth after GnRH-a therapy for severe adenomyosis.

The fourth case described severe adenomyosis proven by a sagittal T2-weighted MRI in a 16 weeks size uterus. The symptoms improved with a GnRH-a but recurred after its cessation [32]. A longer, 24 weeks course resulted in a normal-size uterus with improved MRI findings. A small, well-defined residual adenomyoma was excised and the patient conceived after 12 additional weeks of danazol and delivered at term by cesarean section.

A short course of 3 months of Buserelin by nasal spray was administered to two women with adenomyosis [33]. The disease was documented by histology of a wedge biopsy obtained from the uterine fundus and was suspected as the cause of infertility. Both patients were relieved from symptoms and the uterine size diminished almost 50% and both conceived within 6 months after cessation of therapy and delivered at term. Reporting the shortest regimen of GnRH-a for adenomyosis described so far, the authors point out its advantage in cost reduction without affecting efficacy.

Four other infertile women reported favorable results with GnRH-a [34]. Adenomyosis was diagnosed by a non-specified method. Three women underwent removal of a posterior wall adenomyoma and all four received 6-month courses of triptorelin or goserelin during which they remained amenorrheic as the enlarged uteri attained normal size. The three conceptions that followed lend further support to the facilitating impact of agonists on endometrial receptivity even though its correlation to the diminished uterine size or symptom relief is not clear [34].

Surgical therapy

For decades hysterectomy was the only therapeutic option available to women with adenomyosis, and this diagnosis was verifiable only at tissue examination of the removed uterus. However, as imaging and minimally invasive diagnostic methods were pursued and developed, new and less aggressive therapeutic options were introduced including endomyometrial ablation, laparoscopic myometrial electrocoagulation and simple excision of adenomyomas [12, 35]. As pointed out in a recent review there are no evidence-based guidelines to treat adenomyosis by minimally invasive methods [36]. Actually, our knowledge from the case reports is based mostly on management that was not intended for adenomyosis but rather aimed at leiomyomata.

Another reason for lack of such guidelines is the non-unified definition of adenomyosis [36]. This is reflected by the outcome of these therapeutic modalities. Diffuse disease is frequently ill defined and therefore complete excision of involved sites is seldom achievable. Indeed, early reports reported suboptimal efficacy of these methods, hovering around 50%. In addition, the scarring process following these procedures may reduce uterine volume and jeopardize future fertility [12]. A problem encountered by most studies evaluating these methods is the relatively short follow-up, thus does not allow assessment of long-term benefits. Factors that should play roles in selecting the appropriate procedure include patient's age and symptoms, desire for future fertility, site and extent of disease and operative skills of the surgeon [12].

Hysterectomy

For many years, uterine extirpation was the only therapy that offered complete resolution of adenomyosis symptoms. It has been also the only mode by which the clinical suspicion of the disorder could be verified. Abdominal or vaginal hysterectomies have both been performed. However, concerns were raised as to possible recurrence in the cervical stump or recto-vaginal septum after subtotal hysterectomy [12, 17, 37, 38]. In spite of recent emergence of less invasive modalities, hysterectomy is still the method of choice if future fertility is not an issue, if other less invasive modalities failed or if extensive disease precludes endometrial ablation [12, 37, 39, 40–42]. In many occasions hysterectomy is performed for other indications and adenomyosis is an incidental finding on histologic evaluation. This was the case with a uterus weighing 475 g, the largest containing adenomyosis only that was removed by vaginal hysterectomy for uterus prolapse [43].

Hysteroscopic procedures

Endometrial ablation/resection

Over the last two decades, hysterocopy has become a major diagnostic and therapeutic tool for uterine disorders. For abnormal uterine bleeding, particularly menorrhagia, destruction of the endometrium via hysteroscopy is considered an accepted therapeutic modality. In cases of adenomyosis, especially superficial disease, hysterocopy is advantageous, both in identifying endometrial openings of adenomyosis foci and in targeting ablation or excision to affected areas [12, 35, 39, 44–54].

In their review from 1998, McCausland and McCausland [35] summarized steps in the development of the three major tools for hysteroscopic endometrial ablation: the YAG laser, the urologic resectoscope and the roller-ball electrode. They underlined the relative refractoriness to any mode of ablation in the presence of adenomyosis, due to leaving some foci intact during the procedure [55, 56]. Most studies, however, encountered one common problem: While adenomyosis was diagnosed in many patients with poor response to the procedure, the number of those with good response and thus spared from surgery could not be determined as pathologic confirmation was lacking.

The experience with the YAG laser in more than 2000 patients treated for abnormal bleeding was summarized in six manuscripts published from 1981 to 1995. The risk of failures in adenomyosis cases, early as well as late, was underlined by all six publications [57–62]. In many cases, particularly if foci penetration exceeded 2.5 mm, hysterectomy was unavoidable [57, 59–62].

Hysterocopic resection was introduced in 1983 and followed by number of trials [44, 46, 55, 56, 63–68]. In one trial, three of the 62 women who had the procedure failed and subsequently needed hysterectomy, of which one specimen proved adenomyosis [65]. Better results were reported a year later in 26 patients undergoing myometrial shaving [66]. Of the 15 women with adenomyosis only one failed therapy. In a series reported 2 years later the outcome was less encouraging, possibly owing to the larger number of patients treated and the longer follow-up period that averaged more than 2 years [67]. One-third of the 196 women in this series experienced recurrent bleeding and many of the 22 women that eventually underwent hysterectomy had proven adenomyosis.

Other authors limited endometrial resections to adenomyosis patients. Of 15 symptomatic women reported by Wood et al. [46] in 1993, eight were suspected with this condition by vaginal ultrasound alone whereas five were also confirmed by a transcervical myometrial biopsy. In seven of the 15 procedures an additional 1 cm myometrial strip provided histological diagnosis whereas two others had also laparoscopic myometrial reductions. Four of the seven had a 2 years relief from menorrhagia and dysmenorrhea and thus considered cured [46] (Table 1). However, the study is inconclusive as the number of patients was small and the diagnosis was not reached in a uniform fashion. These flaws were corrected a year later in an expanded study of 31 participants, all diagnosed sonographically as well as by myometrial biopsies [44]. Ten of the biopsies were percutaneous with sonographic guidance, nine were

performed transcervically with an electrosurgical loop and the other 12 were obtained by needle through laparotomy or laparoscopy. Ten of the 15 women undergoing endometrial resection and myometrial stripping reported remarkable improvement of menorrhagia and partial relief from dysmenorrhea [44] (Table 1). It is not clear, however, if these ten women included those two that underwent also laparoscopic myometrial reductions. Nevertheless, most importantly this procedure leads to abolishing two-thirds of the planned hysterectomies.

Summarizing therapeutic options and their 24-month follow-up periods Wood [12] reported symptom relief after endometrial resection in 10 of the 18 women treated (Table 1). This extensive review from 1998 also discussed the technical aspects of endometrial ablation and resection and advocated adding laparoscopic myometrial excision for deeper penetrating disease [12].

Hysteroscopic ablation by the roller-ball was incorporated into clinical practice in 1989 [69]. Main advantages are the low risk for uterine perforation and the ease of technique, especially in less accessible areas such as the fundus and the cornua [47]. However, like other modalities, roller ball ablation has been repeatedly difficult in patients with adenomyosis. Indeed, among 15 treated by roller-ball ablation the only failure occurred in a woman with severe adenomyosis who eventually needed a hysterectomy [69]. In another series, 42 women with either adenomyosis or leiomyomas underwent roller-ball ablation of the fundal and cornual areas after an initial endometrial resection [47]. Adenomyosis was suspected in four women sonographically and confirmed by the resection specimens. Two other specimens were positive even though not suspected by sonography. All six women reported diminished menstrual flow but one required hysterectomy later for persistent pain (Table 2). Also, of 64 women in the series of Daniell et al. [70] out of the four that needed hysterectomy two had adenomyosis. Such

suboptimal results of roller ball ablation in patients with adenomyosis were echoed in other reports. One showed no change in outcome after preoperative employment of goserilin and danazol to promote endometrial-thinning [71]. Similarly, a 4-year follow-up of 42 women undergoing ablation in 1996 disclosed that of the 14 who needed hysterectomy for recurrent symptoms six had adenomyosis [72]. By another account from the same year, this therapy failed in one-fourth of all treated patients [73]. A fourth study utilized posterior wall biopsies to diagnose adenomyosis in 50 women with menorrhagia and normal hysterocopic evaluation [45]. Six women harbored disease and eventually all needed hysterectomy that confirmed deep penetrating disease. The seventh hysterectomy revealed diffuse disease although the biopsy alluded only to minimal invasion (Table 2). Thus, for disease deeper than 2 mm the chance for symptom relief by ablation is bleak [45, 47].

In contrast to these results, roller ball ablation in 50 women had no failures. However, the number of proven disease was not reported and the post therapy follow-up was relatively short [74].

It seems that patients with focal adenomyosis would be ideal candidates for hysteroscopic resection as demonstrated in a recent case report of a cystic mass in the posterior uterine wall seen on transvaginal sonogram that was resected by a bipolar loop [75]. On histology the mass was identified as an adenomyotic cyst. On the other hand, ablation may not be as useful in or an enlarged with diffuse and deep adenomyosis. A possible solution in such cases may be the curved microwave applicator [76]. Indeed, such an applicator emitting frequency of 2.45 GHz was inserted into a 12-cm-long uterus with deep adenomysis. The menorrhagia subsided thereafter and a post-operative MRI demonstrated a subendometrial low-signal zone corresponding to necrotic tissue that disappeared a year after surgery. Although the authors admitted that this method still might fail to destroy deep disease they suggested its use

Table 1 Outcome of endometrial resection in the treatment of adenomyosis

Authors	Ref.	Year	No. of patients	No. of improved (%)	No. of not improved (%)	Follow-up (months)
Wood et al.	[46]	1993	7	4 (57)	3 (43)	12–24
Wood et al.	[44]	1994	15	10 (67)	5 (33)	24
Wood	[12]	1998	18	10 (55)	8 (45)	24

Table 2 Outcome of endometrial ablation in the treatment of adenomyosis

Authors	Ref.	Year	No. of patients	No. of improved (%)	No. of not improved (%)	Follow-up (months)
Wood	[47]	1992	6	5 (83.3)	1 (16.6)	12–24
McCausland et al.	[45]	1996	7	0	7 (100)	>42

to achieve as at least improvement of menorrhagia and thus avoiding or postponing hysterectomy.

As mentioned earlier, the main problem posed by these ablation methods is a relatively high failure rates. However, few additional concerns were expressed as to their use in cases of adenomyosis. One is the possible progression of disease induced by endometrial resection as tissue fragments, being under pressure, may lodge within transected myometrial blood vessels [77]. This phenomenon had been demonstrated in a woman with no previous pathology that, following combined endometrial resection and roller-ball ablation developed adenomyosis de novo [78]. Furthermore, such progression may also be the result of an incomplete destruction that may not only lead to failure but, like any other insults to endometrial tissue, may actually stimulate uninjured cells for further growth and enhancement of disease process [45]. This may be avoided by prior administration of a GnRH-a to thin the endometrium and avert myometrial penetration [12, 70]. Another potential problem is extension of tissue damage beyond 2–3 mm and involvement of surrounding tissue that may prompt bleeding from foci that otherwise would have been controlled by myometrial contraction [45, 47]. The potential for a concealed malignant process has been another concern as the ablative procedure may delay manifestations by covering incompletely destroyed endometrium with a scarred layer, particularly in cases of deep disease, that is less amenable to complete eradication [35, 79]. Another important concern is the uncertainty of future fertility leading some authors to limit the procedure to cases where fertility is not an issue [15, 80].

For the sake of completion, the fourth hysteroscopic method should be mentioned here. Total uterine mucosal ablation (TUMA) was introduced in 1996 by Semm [68] but its specific utilization for women with adenomyosis has not been established.

Magnetic resonance-guided focused ultrasound surgery (MRgFUS)

This newly developed non-invasive procedure has been performed only in few centers. Sequential ultrasound beams are precisely focused on a target under the real-time magnetic resonance (MR) guidance [81]. The ultrasound beams cause thermal coagulation and necrosis within the predefined lesion. Done in an outpatient setting, the procedure requires only conscious sedation and with minimal to moderate post-procedural pain the patient may return to normal activities immediately. In the treatment of uterine leiomyomas, MRgFUS has demonstrated precision in targeted damage while avoiding the surrounding myometrium and thus preserving fertility. These virtues led some authors to use it in a case of a single adenomyoma, but only after accumulating vast experience with 700 women with leiomyoma that desired future fertility and only after establishing the accuracy of tissue destruction by MRgFUS [81]. Six weeks after the procedure the menorrhagia improved considerably and the volume of the lesion decreased by 50%. The patient conceived spontaneously 3 months after the procedure. Both pregnancy and delivery were not affected by the procedure. Remnants of the adenomyotic lesion could be visualized by ultrasound during the pregnancy and on manual exploration of the uterine cavity after the spontaneous delivery no structural abnormalities could be detected.

Open abdominal procedures

Myometrial excision

This procedure refers to the removal of diseased tissue from the otherwise normally functioning uterus. The wedge defect it creates in the myometrium is repaired by metroplasty that, pending on size, may be approached by laparoscopy, mini-laparotomy or laparotomy [12, 39]. The accrued experience with myometrial excision is based on limited number of cases. An early paper from 1993 by Wood et al. [46] reported on three women only. They had this procedure via laparotomy after diagnosis by TVS, confirmed in two cases by myometrial biopsy. One case of adenomyoma that was started with laparoscopy was converted to laparotomy for uncontrollable bleeding. Improvement of symptoms was noted after 12–24 months in all three women [46] (Table 3). A year later, the same authors reported on eight patients, all diagnosed by sonography and myometrial biopsy and undergoing laparotomy [44]. After 2 years, seven were free of symptoms whereas one needed hysterectomy (Table 3). In a summary of the various therapies for the disease Wood [12] reported symptom relief in 20 of the 25 women (80%) 6 months after myometrial excision, dropping to 16 (64%) after 24 months [12] (Table 3).

This procedure may encounter several problems. First, as clinical improvement may be only temporary the likely recurrence may pose difficulty for future procedures due to subsequent adhesions [39]. Another issue is removal of more tissue than necessary because of unclear demarcation from surrounding normal myometrium. That may lead to future uterine deformities, intrauterine adhesions, reduced uterine capacity and compromised fertility [12, 39, 44]. Yet another late

Table 3 Outcome of myometrial excision in the treatment of adenomyosis

Authors	Ref.	Year	No. of patients	No. of improved (%)	No. of not improved (%)	Follow-up (months)
Wood et al.	[46]	1993	3	3 (100)	0 (0)	12–24
Wood et al.	[44]	1994	8	7 (87.5)	1 (12.5)	24
Wood	[12]	1998	25	16 (64)	9 (36)	24

complication is subsequent uterine scars that may conceal more adenomyosis foci and result in reduction of tensile strength.

In sum, as concluded by Wood [12] myometrial excision may not be completely curative except in cases of a well-defined lesion such as adenomyoma.

A relatively new approach reported in 2004 is the transverse H technique for removal of adenomyosis-involved myometrium [82]. The technique consists of one vertical and two crossing horizontal incisions that allow easy removal of considerable amount of adenomyosis tissue with good exposure of a wide area in the uterine wall. In addition, it enables palpation and identification of diseased tissue, easy hemostasis and assessment of endometrial perforation. This method was used in six women after chromopertubation [82]. If the incision was too deep or close to the endometrium a second chromopertubation was done after the procedure. Comparing these six patients with five patients who had the old classical reduction revealed that the time of surgery was longer the blood loss was larger in the transverse H group. On the other hand this group had smaller volume of tissue removed. However, due to the small size of each group of patients, none of these differences were significant. Uterine perforation occurred in one patient from the transverse H incision group and in two from the conservative group. The mean follow-up of all 11 women was 45.6 ± 15.3 months. Subjective symptom improvements were more apparent in the transverse H technique. During the follow-up time, only one patient from the transverse H group had recurrence compared to four in the classical treatment group. As to long-term benefits, two women from the transverse H group conceived spontaneously after 4 and 6 months whereas none of the women treated by the classical reduction did [82].

Laparoscopic procedures

Myometrial reduction or coagulation

This procedure is carried out by laparoscopic insertion of a needle electrode into the affected myometrium. Coagulation with a 50-W current to the depth of 1–3 cm results in necrosis and shrinkage [12, 46]. Both the focal and the diffuse forms of the disease may be subjected to this therapy. However, the outcome was found to be inferior to surgical excision due to imprecision in electrical conduction through the abnormal tissue rendering it to incomplete desiccation, the extent of which may not be assessed at the time of procedure.

The earliest myometrial reductions reported in 1993 were performed in four women with sonographic evidence of adenomyosis, two of whom proven by biopsy as well [46]. Two women reported considerable relief but since they also underwent endometrial resection this favorable result could not be attributed to either procedure, making the report inconclusive (Table 4). A larger study published by the same authors a year later reported on myometrial reduction in seven women with disease proven by sonography and myometrial biopsies [44]. Four were cured whereas the other three needed hysterectomy (Table 4). Satisfactory results were also reported from Russia, including, in addition to symptom relief, four conceptions within 1 year [83]. This procedure was also carried out in ten women with adenomyoma diagnosed by MRI and preceded by three monthly injections of GnRH-a [40]. The injections reduced the mean uterine volume by 27.7% and the subsequent coagulation diminished it further by an average of 73.9% from baseline. A year later, seven women were relieved of menorrhagia and dysmenorrhea whereas two needed an endometrial resection and one had a hysterectomy (Table 4). In his

Table 4 Outcome of laparoscopic myometrial reduction or coagulation in the treatment of adenomyosis

[a] Patients had also endometrial resection

Authors	Ref.	Year	No. of patients	No. of improved (%)	No. of not improved (%)	Follow-up (months)
Wood et al.	[46]	1993	3	3 (2[a]) (66.6)	1 (33.3)	12–24
Wood et al.	[44]	1994	7	4 (57.1)	3 (42.9)	
Phillips et al.	[40]	1996	10	7 (70)	3 (13)	12
Wood	[12]	1998	11	6 (2[a]) (55)	5 (45)	24

thorough evaluation Wood [12] found improvement in six of 11 patients (55%) 24 months after myometrial reduction. This outcome was not different from the one reported for endometrial resection but the number of patients in the two series was different (6 vs.18) (Tables 1, 4). Of the five women who reported no improvement three harbored extensive disease in both anterior and posterior walls. Massive electro-coagulation relieved symptoms in two for 2 years whereas in the third patient the procedure failed again. After GnRH-a therapy had no effect either, this patient subsequently conceived spontaneously and presented with uterine rupture at 12 weeks gestation [12].

A preliminary report on myometrial adenomyomas by laparoscopic excision in three women with localized adenomyosis was published in 2004 [84]. The lesions were delineated with MRI in all three women who then received several doses of a GnRH-agonist as preoperative preparation. Enucleating the lesion was similar to myomectomy but was more difficult due to unclear boundaries from adjacent normal tissue. Bleeding was minimized by local injection of vasopressin. The masses were morcellated to enable removal and the myometrial defects were sutured laparoscopically. No intra-operative complications were encountered. The symptoms disappeared by the first menstrual period after surgery. The authors pointed out the accuracy in the preoperative localization of the lesions and the meticulous complete removal of all the lesions as key factors in the success of the procedure. However, concern as to the wisdom in placing a suture to close the myometrial gap after removing the adenomyoma was raised in a letter to the editor in response to the paper [85]. In this regard, adenomyoma should not be analogous to leiomyoma since closing the gap may burry myometrial tissue that harbor adenomyosis.

Although the issue of future pregnancies was not addressed by these authors, two recent reviews expressed concern of increased risk of uterine rupture after laparoscopic myometrial electro-coagulation [15, 80]. Such concern may be valid as successful restoration of fertility was achieved by laparoscopic excision of an adenomyoma in two infertile women. The two, diagnosed with local adenomyosis conceived spontaneously, 30 and 21 months after the laparoscopic removal of this lesion and delivered by cesarean section [86].

Surgery combined with medical therapy

An interesting concept emerged in review the treatment of infertility in women with adenomyosis; the cyto-reductive method is followed by hormonal therapy [87]. It was hypothesized that surgical procedures improve blood supply to adenomyosis foci and thus facilitate the local effect of the medication, in addition to improving the immune function of the host [87, 88].

In four cases reported by two papers few years ago successful pregnancies were achieved with this combined methods [88, 89]. The surgical component in the three cases reported by the second paper consisted of a microsurgical procedure in order to minimize the damage to the uterus [89].

Adding an adjuvant medication may allude to incompleteness of the surgical procedure alone. It has been suggested, however, that a combined approach of surgery and subsequent GnRH-a administration should be reserved only for patients who failed to respond to GnRH-a alone or those who need effective contraception for at least 6 months [87].

Summary of surgical procedures

All three methods, endometrial resection, myometrial excision and myometrial coagulation are aimed at the relief of symptoms while preservation of fertility. However, as 55% of patients were relieved of symptoms by 24 months after resection and coagulation, 64% improved after excision [12]. Meaningful conclusions, however, are hampered by a relatively small number of patients treated with each method and by short follow-up periods [12] (Tables 1, 2, 3, 4). Furthermore, as more than one method were used in some cases, the efficacy of a single method could not be assessed objectively and it is clear that some of these procedures may actually hamper fertility or complicate future pregnancies. It is also important to keep in mind that these methods may be ineffective sometimes and hysterectomy is the only feasible solution.

Other surgical procedures

Uterine artery embolization

Since the symptomatology of adenomyosis and uterine leiomyomas is similar it is not surprising that attempted have been pursued to manage both conditions in the same fashion. Thus uterine artery embolization (UAE), popularized in recent years for leiomyomas, has been recently attempted in cases of adenomyosis with some success [90–97]. Necrosis and hyaline degeneration, histologic changes observed in leiomyomas subsequent to the procedure may be expected in adenomyosis by virtue of diminished blood-flow and thrombosis [97, 98]. Like in cases of leiomyomas, UAE has to accomplish complete occlusion of the arterial supply to a point of stasis or near stasis [99]. Not unlike

leiomyoma, foreign body reaction around the embolized polyvinyl particles may also incite platelet aggregation and thrombosis in adenomyosis-affected sites [100]. Devascularization of regions of adenomyosis may predict a long-term success of UAE in treating adenomyosis but it is difficult to assess the efficacy UAE in cases of combined leiomyomas and adenomyosis [99]. Studies that did not delineate the two conditions are therefore not conclusive [95, 96]. Also, as one group pointed out, midterm follow-up after UAE is crucial because improvement noticed early indicates desired effects on leiomyomas whereas midterm failures are generally due to adenomyosis [99]. This may be explained by resistance to blockage of the blood vessels supplying adenomyotic foci and thus casts some doubt as to efficacy of this procedure in these cases [101].

In the first publication from 1999, 60 women underwent UAE but only three were suspected with adenomyosis, all responding well [102]. However, in addition to the small number of patients with disease, this study has also been flawed with high false negative rate. Indeed, inaccurate diagnosis should be blamed on reliance on symptomatology as well as unspecified sonographic criteria. Of the six women that were considered negative for adenomyosis and for some reasons had a hysterectomy, only three had histological proof of disease (Table 5).

The second series from the same year included 20 women undergoing UAE. Only one failed therapy and complained of continuing pain and menorrhagia that ended 5 months later with a vaginal hysterectomy [103]. On examination of the specimen, more than 20 completely degenerating leiomyomas mixed with areas of adenomyosis were detected. Ischemic changes or infarctions in these areas were not seen, thus implying that UAE had no effect on adenomyosis in this case, leading the authors to postulate that the 10% failure rate reported for this procedure in leiomyomas may be attributed, at least partially, to coexistence of unresponsive adenomyosis [103]. Thus the importance of reaching accurate pre-procedure diagnosis cannot be over emphasized. It seems prudent, however, that for most cases of adenomyosis, with or without leiomyomas, this low-risk procedure should be warranted and attempted before seeking more extensive operative modes [97] (Table 5). Indeed in the 5 years UAE use for adenomyosis has been expanded and results were assessed not only clinically but also histologically.

A cohort of 224 women undergoing UAE was included 209 with uterine leiomyomas, six with adenomyosis diagnosed by MRI and nine women with both conditions [97]. All 15 patients with adenomyosis presented with abnormal bleeding, 11 had dysmenorrhea and seven complained of bulk-related symptoms. The procedure in three women was preceded by the employment of a GnRH-antagonist. During a follow-up period that averaged 8.2 months (3–16 months), quality of life improved considerably in 12 of 13 (92.3%) patients whereas menorrhagia persisted in one patient [97] (Table 5). Imaging studies demonstrated a 42% reduction in mean uterine volume in nine patients, from 455.4 to 230.6 cm^3 ($P < 0.05$), concomitant with a 33% reduction in the average thickness of the junctional zone (JZ), from 31 to 20 mm ($P < 0.05$). Drop in size was even more impressive in six of the 11 leiomyomas reaching an average of 71% (18.7–100%) ($P < 0.05$) [97]. Although encouraging, this experience in a limited number of patients warrants expansion in future studies.

The outcome was also satisfactory in 23 Chinese women undergoing UAE for symptomatic adenomyosis [104]. Dysmenorrhea disappeared altogether with two later recurrences and uterine size diminished significantly in 19 patients (Table 5).

The study from 2003 assessed not only symptom relief but also the post-operative MRI appearance [90]. Of 30 women with adenomyosis, 27 had also leiomyomas but six demonstrated dominance of adenomyosis by MRI. All nine patients, six with dominant and three

Table 5 Outcome of uterine artery embolization in the treatment of adenomyosis

Authors	Ref.	Year	No. of patients	No. of improved (%)	No. of not improved (%)	Uterine size	Follow-up (months)
Goodwin et al.	[102]	1999	3	3 (100)	0 (0)		
Smith et al.	[103]	1999	20	19 (95)	1 (5)		
Siskin et al.	[97]	2001	13	12 (92)	1 (8)	⇓42%	8.2
Chen et al.	[104]	2002	23	19 (83)	4 (17)		
Jha et al.	[90]	2003	9	9 (100)	0 (0)		
Toh et al.	[91]	2003	12	3 (25)	9 (75)		
Kim et al.	[92]	2004	43	40 (93)	3 (7)	⇓ 32.5%	3.5
Pelage et al.	[99]	2005	18	10 (55)	8 (45)		24
Kitamura et al.	[106]	2006	18	16 (89)	2 (11)	⇓ 25.1%	

with pure disease reported improvement following the procedure and in all except one the post-procedure MRI showed considerable reduction in the JZ thickness, ranging from 19.8 to 61.4%. Twelve patients, all with a JZ wider than 20 mm (normal < 12) had also regions of devascularization, a direct result of the procedure (Table 5).

Another study published in the same year included 43 women undergoing UAG but only 12 had adenomyosis [91]. Three of these 12 were completely relieved from their symptoms (Table 5). The other study of 43 women with adenomyosis but no leiomyomas included pre-procedure MRI evaluations [92]. Significant improvement in dysmenorrhea was noted in 40 of 42 (95.2%) women and in 38 of the 40 (95%) complaining of menorrhagia. Pelvic heaviness and urinary symptoms were better in 78.1 and 48.4% of the patients, respectively. Altogether, 40 patients (93%) were satisfied with the procedure. A follow-up MRI performed 1–8 months after the procedure disclosed coagulation necrosis in 31 patients (72.1%), diminished uterine size without necrosis in 11 patients (25.6%) and no change in one patient (2.3%) only. The mean reduction in uterine volume was 32.5% [92] (Table 5).

A prospective study, presented in 2005 included 18 women diagnosed with adenomyosis based on the heterogenous appearance of the uterus on sonography or on widened JZ on MRI [99]. As patients with uterine leiomyomas were excluded, this study is the largest one to include patients with adenomyosis only. In spite its flaw, being still too small, as acknowledged by the authors too and omitting contrast enhancement from the post-operative imaging studies, this study is important for its information on the long-term outcome of these patients [99]. Diffuse disease was diagnosed in 14 women and adenomyoma in four. UAE was successful in 17 patients and failed in one that underwent hysterectomy 4 months later. All subjects had ultrasound or MRI follow-up imaging at 6, 12 and 24 months after the procedure. At 6 months all women resumed menstruation: seven of 16 (44%) had improvement and eight (50%) had complete resolution of their menorrhagia [99]. At 1 year only 11 of the 16 women still reported benefits (73%) including eight that were completely cured. Uterine volume decreased by a mean of 15% in 17 of the 18 women (94%). Of nine women that completed the 24 months follow-up, five reported complete resolution of menorrhagia. A total of eight women of the 18 initially undergoing UAE (44%) required additional therapy, including five hysterectomies (28%) (Table 5). Thus, although the short-term results of UAE were satisfactory, the midterm results were somewhat disappointing as only 55% of women

were clinically improved after 2 years. However, others viewed a 55% success in a more positive way as a subset of women with disease, especially those desiring fertility can be offered a reasonable option [105]. At any rate, this paper highlighted the fact that short-term favorable results do not reflect long-term efficacy.

MRI evaluations were conducted 4 months after UAE in 19 women and compared to the pre-procedural images [106]. Compared parameters included width of the JZ, JZ–mymetrial ratio, uterine size and presence of avascular areas. Uterine size diminished by a mean of 25.1%. JZ width decreased significantly ($P < 0.001$) but the decrease in JZ–myometrial ratio was not significant. Devascularization within the lesion was evident in 14 women (73.7%). Clinical improvement was reported in 16 of the 18 patients that completed the questionnaires (88.9%) including 11 with devascularaized areas (Table 5).

In summary, UAE was performed so far in 156 women suffering from symptoms of uterine adenomyosis. Of those, 131 women reported improvement in symptoms. As mentioned earlier, since the procedure carries a very low risk these results from few years of experience underline the need to popularize the use of UAE in women with adenomyosis.

Uterine artery ligation

In a prospective study, 20 symptomatic women, suspected with adenomyosis by TVS or MRI underwent laparoscopic occlusion of the uterine and ovarian arteries by electro-coagulation or hemoclips application [107] After 6–11 months, menorrhagia improved in 81% and dysmenorrhea in 75%, (13/16 and 12/16, respectively). However, among the 12 dysmenorrheic women nine developed ischemic uterine pain that was severe enough to mandate hysterectomy in three patients. Two of the nine women initially complaining of mass effect got better. The authors speculated that positive clinical outcomes and regression of adenomyosis foci were actually attributed to change in estrogen status rather than reduced blood perfusion and diminishing uterine size. However, their results pointed to the opposite as uterine volume dropped only by $11.9 \pm 16.5\%$ on average and evidence for the so-called change in estrogen status was lacking [107]. On the other hand the fact that the three hysterectomy specimens showed no evidence of necrosis or ischemia does not lend support to the direct correlation of clinical improvement to interruption of blood supply. Still, the mechanism by which this procedure exerts its clinical benefits is obscure. As 40% of the patients were not satisfied with the procedure and as many as 89% would

have refused it if offered again, the authors recommended, and correctly so, to remove this procedure from the list of therapeutic options for adenomyosis [107].

Future fertility after surgery

As mentioned, the surgical therapy for patients with adenomyosis was limited to hysterectomy for many years. Exclusion of women who desired future fertility as candidates for this definitive therapy was, no doubt, an important factor for recent trend to promote more conservative methods to treat adenomyosis. Indeed some of these methods, conservative as well as minimally invasive led to few pregnancies but all were described as case reports or series. As the causative relation between adenomyosis and infertility has not been clarified and since the incidence of infertility in these series was not specified, these reports are merely anecdotal and thus inconclusive. Except one report on IUD delivering 175 mg of danazol that helped four women and resulted in two conceptions [26] all other conservative therapies, leading to eight conceptions included the administration of a GnRH-a agent (Table 6).

As to surgical options, the yield of various methods was 13 pregnancies, including one following MRgFUS (Table 7). However, it should be remembered that the goal of most therapies was alleviation of symptoms rather than conception. The experience gathered so far with UAE has not shown effect on fertility. However, one study focused specifically on this issue reporting on eight pregnancies in 94 women undergoing the procedure for leiomyoma or adenomyosis; six were in women planning pregnancy and two in whom contraception failed [108]. Among the six, three had adenomyosis, two delivered vaginally and one by cesarean section. One patient had both leiomyoma and adenomyosis and delivered vaginally. As 88 of the 94 women

were excluded for different reasons the number of women interested in fertility was too small and therefore no definite answer could be offered to the question of future fertility in patients undergoing UAE for adenomyosis.

Conclusions

The last two decades witness a considerable accumulation of information on therapeutic options other than hysterectomy for adenomyosis. All studies published, some very informative, are flawed by their design, as none were randomized or controlled. Another drawback is lack of a unified methodology in reaching the diagnosis of adenomyosis and the common appearance of other conditions, mainly leiomyomas in many cases. A third obstacle is the lack of standardized assessment of the outcome of therapy. As most authors considered symptom relief as the endpoint, this was assessed mostly by patient response that by nature is subjective. And lastly all studies were flawed by small number of subjects and relatively short follow-ups.

In spite of all these shortcomings, the emergence of various medical and surgical managements of a condition that for decades could be solved only with hysterectomy is most gratifying. Indeed this limited experience encourages further pursuit of these modalities. All medical therapies are symptomatic only and were not followed long enough to allow meaningful conclusions. At present anti-prostaglandins, combined estrogen–progestin, progestins, danazol and GnRH-a are the medications available.

As to surgical options, hysterectomy may still be appropriate in severe cases where more than one-third of the myometrium is involved or if future fertility is not desired. However, in milder conditions or if future pregnancies are planned, minimally invasive procedures, hysteroscopic or laparoscopic are at the sur-

Table 6 Pregnancies after conservative therapy for adenomyosis

Authors	Ref.	Year	No. of patients	Treatment	Route	Length (months)	Outcome
Hirata et al.	[30]	1993	1	Nafarelin acetate	Nasal spray	6	Spontaneous abortion
Silva et al.	[31]	1994	1	Leuprolide acetate	Intramuscular	5	Term C/S
Ozaki et al.	[32]	1999	1	Leuprolide acetate + Danazol	Subcuteous + Oral	6 + 3	Term SVD
Huang et al.	[33]	1999	2	Buserelin	Nasal spray	3	Term SVD / Term SVD
Lin et al.	[34]	2000	3 of 4	Triptorelin or Goserelin acetate		6	Term C/S / C/S at 30 weeks / On going pregnancy

Table 7 Pregnancies after operative therapy for adenomyosis

Authors	Ref.	Year	No. of patients	Treatment	Time to conception (months)	Outcome
Strizhakov et al.	[83]	1995	4	Myometrial reduction	<12	?
Wood	[12]	1998	1	Electrocoagulation × 2 + GnRH	?	Uterine rupture (12 weeks)(12 w)
Huang et al.	[89]	1998	1	Myometrial reduction + GnRH	?	?
Wang PH et al.	[88]	2000	2	Myometrial reduction + Goserelin acetate	12	Term C/S
					3	Term C/S
Fujishita et al.	[82]	2004	2 of 6	Transverse H suture	4	Term C/S
					6	Ongoing pregnancy
Rabinovici et al.	[81]	2006	1	MRgFUS	3	Term SVD
Wang CJ et al.	[86]	2006	2	Laparoscopic excision	30	Term C/S
					21	Term C/S

geon's disposal. Their disadvantages include partial efficacy and compromised fertility due to incomplete excision, scarring and reduced uterine volume. Selection of the appropriate procedure depends on age, symptoms, site and extent of disease, desire for future fertility and surgical skills. Hysterocopic procedures include endometrial ablation and endomyometrial resection. Both can be carried out with the YAG laser, the urologic resectoscope and the roller-ball electrode but the latter is easier to manipulate. As relief of symptoms can be achieved in two-thirds of women undergoing endomyometrial resection and removal of a 0.5–1 cm myometrial strip and thus averting a planned hysterectomy, this option seems valid. Complemented with laparoscopic myometrial excision, hysteroscopy may be useful for deeper disease. Poor outcome is more likely if disease penetration exceeds 2.1 mm. In general, the coexistence of adenomyosis with other menorrhagia-causing conditions hampers success of endometrial ablation. The side effects of this procedure are several. Not only that destruction may be incomplete and the results suboptimal but the procedure may actually lead to cell proliferation and enhance disease progression. It may also create adenomyosis de novo and incite bleeding from foci by impaired contractions of the damaged surrounding myometrium. Other concerns are concealed malignant transformation of foci and delayed diagnosis of pre-existing malignancy.

In myometrial excision the diseased portion of the uterine wall is removed laparoscopically or through minilaparotomy or laparotomy. However, normal myometrium removed in the process may lead to unnecessary reduction of uterine volume. In addition, ensuing uterine scars may harbor concealed adenomyosis lesions and diminish myometrial tensile strength rendering repeat procedures difficult.

Myometrial reduction or coagulation refers to laparoscopic desiccation and subsequent necrosis and shrinkage of the affected myometrium. Preoperative employment of GnRH-agonist may enhance efficacy but results may be inferior to surgical excision due to imprecise electrical conduction and incomplete desiccation. However, favorable outcome achieved in 55–70% of patients is comparable to endometrial resection and myometrial excision.

The experience with MRgFUS in adenomyosis is currently limited to one case report but employment of this technique in cases of uterine leiomyoma suggests further exploration of this option.

Experience with UAE is still limited but it seems that the outcome in patients undergoing this procedure is less favorable for patients with adenomyosis than in those with leiomyomas. The main problems in evaluating this method are difficult delineation of adenomyosis from other uterine pathologic conditions and the fact that the former is more resistant to blockage of blood vessels. Thus longer follow-up periods are necessary to assess the efficacy of this procedure. Furthermore, as MRI is becoming crucial in the diagnosis of adenomyosis, it seems that it should also be included in the follow-up assessments. UAE carries a very low risk and therefore it may be chosen as the first line treatment for adenomyosis with or without leiomyomas.

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