Uterine Artery Embolization for the Treatment of Adenomyosis

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ABSTRACT

Adenomyosis is a benign uterine disorder that causes menorrhagia and dysmenorrhea. Although it was once considered a contraindication to uterine artery embolization, several authors have examined whether adenomyosis can be treated with uterine artery embolization. This article reviews the pathophysiology of adenomyosis, its imaging characteristics, as well as recent studies evaluating the efficacy of uterine artery embolization for treatment of adenomyosis.

KEYWORDS: Adenomyosis, uterine artery embolization

Objectives: Upon completion of this article, the reader should be able to explain the pathologic and imaging findings of adenomyosis, and evaluate the current data regarding the use of uterine artery embolization for the treatment of adenomyosis.
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Adenomyosis is a benign, non-neoplastic process characterized by the ectopic proliferation of endometrial tissue into the myometrium with smooth muscle hypertrophy. It is a common disorder with prevalence in hysterectomy specimens historically ranging from 5 to 70%.[1] A more recent study, which used stricter criteria, found its prevalence to range from 10 to 18%.[2] Its most common presenting symptoms include abnormal uterine bleeding and dysmenorrhea.

Surgical hysterectomy is considered the definitive therapy for adenomyosis.[3] In recent years, innovations in gynecology, particularly in the area of medical and minimally invasive therapy, have resulted in new therapeutic options for women with adenomyosis. Uterine artery embolization (UAE) is one of these medical advances that has the potential to eliminate the need for surgical intervention. Although initial results were promising, subsequent studies have shown mixed outcomes. The future of UAE as a primary therapy for adenomyosis remains uncertain at the present time.

PATHOLOGY

The presence of endometrial glands in the myometrium was first referred to as "cystomsarcoma adenoids uterinum," by Rokitansky[4]in 1860. It was not until 1972, when the term "adenomyosis" was defined by Bird[5] as the "benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium." Pathologists today still use this definition, but have clarified it by adding "the presence of endometrial

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glands and stroma located haphazardly and deep within the myometrium."[6]

Adenomyosis can be further characterized as being diffuse or focal within the uterus. On gross examination, a uterus diffusely involved by adenomyosis is typically enlarged and globular. Haphazardly distributed, hypertrophied muscular trabeculae surrounding foci of adenomyosis are seen on cross section. Because focal adenomyosis can resemble a leiomyoma, the term adenomyoma is often used. An adenomyoma typically has poorly defined margins that merge with surrounding normal myometrium. In contrast, a leiomyoma has well-circumscribed margins that compress the surrounding myometrium. In addition, a leiomyoma can be enucleated, adenomyomas cannot.

Histologically, the endometrial glands and stroma of adenomyosis resemble the basalis endometrium. Because these glands rarely respond to hormonal stimuli, it is unusual to see hemorrhagic morphology within foci of adenomyosis. Focal hemorrhage in deep adenomyotic foci is something that remains poorly understood.[7] The failure of these glands to respond to hormonal stimuli also accounts for the poor response of adenomyosis to medical (hormonal) therapy. This is in contrast to endometriosis and the cyclic changes seen in association with this entity. Importantly, the ectopic endometrial tissue of endometriosis is similar to cells in the functionalis layer of the endometrium, which is better vascularized than the basalis-type endometrium seen in adenomyosis. This may help explain the difference in menstrual changes between the two tissue types.

Adenomyotic tissue does retain its proliferative potential, which may explain why endometrial ablation is often ineffective. Samples of adenomyotic endometrium demonstrate increased microvascular density when compared with normal endometrium. Microvessel density is related to angiogenesis, a characteristic of invasive tissue types. Schindl et al[8] have postulated that adenomyosis may have invasive properties, based on this histologic characteristic.

It is not fully understood why patients with adenomyosis experience symptoms. The frequency and severity of symptoms in patients with adenomyosis has been shown to correlate with the extent and depth of muscle invasion[9,10]. Menorrhagia may be due to the poor contractibility of the adenomyotic uterus due to intramural fibrosis and compression of the endometrium by a submucosal adenomyoma or leiomyoma. Ota et al[11] found a significant increase in the number and surface area of the endometrial capillaries in adenomyosis. Insufficient vasoconstriction, mediated by prostaglandins, may contribute to increased blood loss during menstruation. Dysmenorrhea may be due to uterine irritability, secondary to the increased blood loss associated with this condition.

Associated pathology is very common. Up to 80% of women with adenomyosis have another uterine abnormality. Leiomyoma occur in up to 53% of women with adenomyosis. Pelvic endometriosis and endometrial polyps also are reported in 2 to 20% of patients with adenomyosis. Endometrial hyperplasia, as well as adenocarcinoma, also appear more frequently in patients with adenomyosis.[1,5,6]

DIAGNOSIS

As many as 35% of patients with adenomyosis are asymptomatic.[9] The most frequent symptoms associated with adenomyosis include menorrhagia (50%), dysmenorrhea (30%), and metrorrhagia (20%). Dyspareunia is also an occasional complaint seen in these patients. Because these symptoms are nonspecific and commonly seen in association with other pathologic entities, such as leiomyomata, the clinical diagnosis of adenomyosis is difficult. Nikkanen and Punnonen[12] found that 136 patients with adenomyosis had variable, nonspecific symptoms, which could be related to associated pathologies, including leiomyomata and endometriosis. In another study, Kilkku[13] failed to show a difference in frequency or severity of dysmenorrhea and pelvic pain between 28 women with adenomyosis and 157 controls.

Historically, a definitive diagnosis of adenomyosis has required histology. Currently, transvaginal ultrasound (US) and magnetic resonance imaging (MRI) are being used to definitively diagnose adenomyosis and have been shown to correlate well with pathologic and histologic findings.

TRANSVAGINAL ULTRASOUND

On ultrasound imaging, uterine contour is more likely elliptical and not globular. Adenomyosis most commonly appears as focal or diffuse areas of myometrial hypoechogenicity. Heterogeneity in the myometrium may be seen as well. Within the myometrium, small (< 5 mm) cysts may be seen in $\sim$50% of patients; echogenic nodules may be seen as well. The focal lesions of adenomyosis typically have poorly defined borders and there is usually a relative lack of mass effect. This contrasts with the appearance of fibroids, which is typically well defined and fibroids tend to compress the normal myometrium. Linear striations may be seen radiating out from the endometrium, sometimes giving the appearance of pseudowidening of the endometrium.

MAGNETIC RESONANCE IMAGING

MRI of the pelvis is now considered to be the most definitive noninvasive means of diagnosing adenomyosis. Imaging with T2-weighted sequences will often show widening of the low signal inner myometrium,

otherwise known as the junctional zone. The normal maximal thickness of the junctional zone is 12 mm. A thickness >12 mm is consistent with a diagnosis of adenomyosis. Subendometrial high signal intensity may be present as well. Other findings on MRI that suggest adenomyosis include bright foci within the low signal myometrium, high signal linear striations radiating out from the endometrium, pseudowidening of the endometrium, and poor definition of the endomyometrial junction. As in US, lesions of adenomyosis demonstrate poorly defined borders with relative absence of mass effect. An elliptical contour of the abnormality helps to define the presence of adenomyosis. Cystic adenomyosis is characterized by well-circumscribed, cystic myometrial lesions with different stages of hemorrhage.[14]

In 1996, Reinhold et al[15] prospectively imaged women scheduled for elective hysterectomy with MRI and US and subsequently compared the imaging findings with the postoperative histologic findings. Of the 119 patients included in this study, 28 (24%) had adenomyosis on histopathologic examination. US correctly depicted adenomyosis in 25 patients, and excluded it in 81 patients. The sensitivity and specificity of US in the diagnosis of adenomyosis is 89%. Pelvic MRI correctly depicted adenomyosis in 24 patients and excluded it in 78 patients. The sensitivity and specificity of MRI in the diagnosis of adenomyosis is 86%. These results show no significant difference between the two modalities. Ascher et al[16] and Dueholm et al[17] prospectively compared the two modalities as well and both found MRI to be superior to US for diagnosing adenomyosis. After excluding indefinite cases, as well as very large uteri, Dueholm's group showed the sensitivity and specificity of MRI to be 81% and 82%, respectively. The sensitivity and specificity of US in their series was 72% and 62%, respectively. In these studies, a measurement of junctional zone thickness was found to provide objective and distinct results, enabling them to detect most cases of adenomyosis. Pelvic MRI is especially helpful at identifying adenomyosis when numerous leiomyomas are present and in large uteri. As minimally invasive therapies for adenomyosis evolve, these diagnostic tools will prove invaluable in providing accurate diagnoses.

UTERINE ARTERY EMBOLIZATION

UAE has been shown to be an effective treatment for women with symptomatic uterine fibroids.[18–20] First described in 1995 by Ravina et al,[21] the procedure has stood the test of time with long-term results showing significant and persistent symptom and quality of life improvements, as well as fibroid and uterine volume reductions.[22,23]

Despite the success of UAE as a minimally invasive treatment option for patients with symptomatic fibroids, it has not been as remarkable as a treatment option for patients with adenomyosis. In fact, much of the early data surrounding UAE and adenomyosis has been to attribute treatment failure after UAE to adenomyosis. One of the first to describe this was Smith et al in 1999.[24] In this report, a patient with menorrhagia and pelvic pain underwent UAE with polyvinyl alcohol (PVA) particles measuring 355 to 500 microns in diameter after physical examination and ultrasound both demonstrated uterine fibroids. This patient had persistent abnormal bleeding and pain 5 months after embolization and ultimately underwent a hysterectomy. At pathology, all of the fibroids in the uterus were completely infarcted, but viable islands of adenomyosis were found. In light of this finding, the authors attributed the failure of the embolization procedure to the presence of adenomyosis. Goodwin et al[19] described 6 patients who required hysterectomy after unsatisfactory response to UAE and adenomyosis was found in 50% of these patients.

Other investigators have continued to evaluate the causes of UAE treatment failure after these initial reports. In 2002, Walker and Pelage[25] evaluated the outcomes of 400 women undergoing UAE for uterine fibroids. Twenty-three women had symptoms that did not respond or recurred within the first year and 9 of these patients went on to have a hysterectomy. Histology was obtained on 6 of these specimens and adenomyosis was found in 50%. Three women had adenomyosis associated with fibroids. One additional woman in the clinical failure group had adenomyosis diagnosed by transvaginal biopsy. This was similar to McLucas and colleagues[26] finding that up to 39% of patients who go on to have hysterectomy after failed treatment for fibroids have adenomyosis at pathology. In 2006, Huang et al[27] retrospectively evaluated the outcomes of 233 consecutive UAE patients. In this series, 16 patients had a hysterectomy within 13 months of treatment. Histopathologic examination revealed adenomyosis in 25% of the hysterectomy specimens. In 2007, Gabriel-Cox et al[28] reported on a series of 529 women undergoing UAE to treat uterine fibroids. In this series of patients, 100 received a hysterectomy within one year of treatment with embolization. In this group, 21% contained adenomyosis at pathology, including 5 patients without any evidence for leiomyomata. Given the potential for treatment failure, these reports have led some to feel that adenomyosis should be considered as a contraindication to UAE.

Recent pathologic studies have attempted to understand why UAE may fail in the setting of adenomyosis. In 2005, Weichert et al[29] evaluated hysterectomy specimens from 2 women with adenomyosis who were treated with tris-acryl gelatin microspheres (Embosphere Microspheres, Biosphere Medical, Inc., Rockland, MA) measuring 500 to 700 and 700 to 900 microns in diameter. At 34 and 48 weeks postprocedure, they found

that foci of adenomyosis remained unaltered following embolization. Additionally, no changes were seen in the morphology of the endometrium. Particles were found to be randomly distributed throughout the outer half of the myometrium. In light of these findings, they attributed treatment failure to the lack of a defined arterial supply and the diffuse distribution of endometrial glands and stroma throughout the myometrium. Similarly, Dundr et al[30] looked at three hysterectomy specimens from women with adenomyosis who underwent UAE. Again, particles were found in a random distribution throughout the myometrium, with no morphological changes seen in areas of adenomyosis.

Since these reports were published, others have conducted studies evaluating the efficacy of UAE for the treatment of adenomyosis. These studies focused more on the clinical success seen after UAE in patients with adenomyosis as opposed to explaining causes of treatment failure after UAE performed in patients with leiomyomata. In 2001, Siskin et al[31] described their experience treating 15 women with adenomyosis based on MRI findings. Six women had adenomyosis without uterine fibroids and 9 women had adenomyosis with fibroids. Embolization was performed with PVA particles measuring 355 to 500 microns in diameter. Short-term clinical and imaging follow-up was obtained at a mean of 8.2 and 5.9 months, respectively. They found significant improvement in patients' quality of life and symptoms although one patient was noted to have persistent heavy bleeding 4 months after UAE. This patient had diffuse adenomyosis and multiple uterine fibroids at presentation. Objectively, uterine volume and junctional zone thickness were decreased in those patients undergoing follow-up MRI. In 2003, Jha et al[32] examined the clinical and imaging outcomes in 30 women undergoing UAE for adenomyosis. Clinically, 25 of 30 patients reported improvement in their presenting symptoms at 3 months. Twenty of 20 patients completing follow-up at one year reported stability or improvement in their symptoms. At 3 months and one year after UAE, significant decreases in mean uterine volume were seen on follow-up MRI. Of note in these patients, the junctional zone thickness decreased 22% in 3 months, with an additional 15% decrease after one year. Contrast enhanced MRI findings after UAE demonstrated devascularized areas of adenomyosis with findings suggestive of hemorrhagic infarction. Also in 2003, Toh et al[33] retrospectively evaluated the outcomes of 13 patients undergoing UAE for dysmenorrhea attributed to adenomyosis. In these patients, embolization was performed with PVA particles measuring 400 to 600 microns in diameter. The mean follow-up time was 10.9 months. Although only 25% of women experienced complete resolution of their dysmenorrhea; another 58% reported partial improvement. In the follow-up period, no patients required surgery. The uterine volume reduction in these patients with adenomyosis was 42%.

These initial preliminary studies prompted others to evaluate the role of UAE in the care of patients with adenomyosis. In 2004, Kim et al[34] reported a series of 43 women with adenomyosis without fibroids who underwent UAE with PVA particles ranging in diameter from 250 to 710 microns. Short-term clinical and imaging follow-up was obtained at 3.5 months. Menorrhagia and dysmenorrhea were improved in 95% of affected patients. Bulk-related symptoms, pelvic heaviness and urinary frequency, were improved by 78% and 48%, respectively. MRI findings showed complete necrosis of focal adenomyosis in 44% of patients, with partial necrosis seen in 27.9%. In 25.6% of patients, the uterine volume decreased despite the absence of necrosis. Only one patient showed no changes at all on MRI. Overall, 93% of patients were satisfied with the outcome of their procedure, but this study failed to evaluate the long-term outcomes after UAE in this patient population. Pelage et al[35] studied 18 patients with adenomyosis treated with UAE performed with tris-acryl gelatin microspheres ranging in size from 500 to 900 microns in diameter, PVA particles ranging in size from 355 to 500 microns in diameter, or Gelfoam (Pfizer, Inc., New York, NY). Overall, 28% of the patients ultimately hysterectomy required a hysterectomy up to 27 months after UAE. Viable foci of adenomyosis were present on surgical specimens. Two other patients required medical therapy or endometrial ablation to control recurrent symptoms. Ultimately, they reported that 50% of patients had persistent symptom improvement after 2 years of follow-up. In 2006, Kitamura et al[36] reported on 19 women undergoing UAE for adenomyosis. Follow-up at 3 and 12 months showed 16 of 18 patients and 10 of 11 patients reporting symptom improvement, respectively. MRI findings showed significant decreases in uterine volume and junctional zone thickness. However, areas of devascularization did not seem to correlate with successful outcomes, as some patients without any visible areas of devascularization had symptom improvement and some patients with areas of devascularization did not have symptom improvement.

Several of the more recent studies provide additional insight into UAE in patients with adenomyosis. Lohle et al[37]prospectively evaluated 38 women undergoing UAE for adenomyosis. Fifteen patients had adenomyosis as their only presenting uterine abnormality. The remaining patients had both fibroids and adenomyosis. Embolization was performed with tris-acryl gelatin microsphere ranging in size from 500 to 900 microns in diameter. Although all patients reported at least some resolution of symptoms initially after UAE, 6 women required surgery at 8 to 34 months post UAE. Of the women shown to have adenomyosis as their only uterine abnormality, 20% went on to have

surgery to address recurrent symptoms. On imaging, all patients showed a decrease in total uterine volume and junctional zone thickness; 44% showed infarction of their areas of adenomyosis. Also in 2007, Kim et al[38] followed 54 women undergoing UAE for adenomyosis using PVA particles measuring 250 to 710 microns in diameter. The mean follow-up after UAE was 4.9 years (3.5 to 5.8 years). Of the 50 patients with initial clinical improvements, 19 (38%) had symptomatic recurrence with additional follow-up. The mean interval between UAE and symptom recurrence was 17.3 months (4 to 48 months). Recurring symptoms resulted in hysterectomy for 5 patients. MRI follow-up was performed at 3 months in 22 patients and after a mean of 4.9 years in 29 patients. At short-term follow-up, MRI findings showed complete necrosis in 65.2% of the patients with focal adenomyosis and in none of the patients with diffuse adenomyosis. Partial necrosis was seen in 68.8% of the patients with diffuse adenomyosis. The rates of complete necrosis were significantly higher in the group receiving 250 to 355 and 500 to 710 micron PVA particles than in the groups receiving only 355 to 500 or 250 to 355 micron particles.

In 2008, Bratby and Walker[39] retrospectively reviewed the outcomes of 27 women with adenomyosis treated with UAE using PVA particles measuring 355 to 500 microns in diameter. Fourteen of the patients also had uterine fibroids. One woman received unilateral therapy due to unfavorable anatomy and went on to have a hysterectomy 2 months later due to persistent symptoms. Clinical follow-up was obtained 6 and 12 months after embolization; 88% of women reported either complete or partial improvement in menorrhagia at 6 months. This number dropped to 79% at one year. In those patients who had adenomyosis without fibroids, 80% reported improvement in menorrhagia at one year. One woman had a hysterectomy at 8 months due to poor response. This study also provided 3-year follow-up on 14 patients, 6 of whom had adenomyosis without fibroids. Of these patients, 63% reported complete resolution of their dysmenorrhea and 54% reported complete resolution of their bulk-related symptoms. These numbers increased to 81% and 80% when women with partial improvement were included. Only 18% reported complete resolution of their menorrhagia, with 36% reporting partial improvement; 54% of patients reported worsening of their menorrhagia. Imaging demonstrated decreased uterine volume in all patients ($n = 12$) imaged at one year.

CONCLUSION

From reviewing the above-presented data, it is clear why questions remain about the role of UAE in the treatment of patients with adenomyosis. In these studies, most patients do very well initially, with symptom improvement and favorable changes seen on postprocedure imaging studies. However, the recurrence rate in studies providing data on long-term follow-up is higher than that seen in association with UAE and uterine fibroids. Therefore, the primary question that needs to be answered when evaluating the efficacy of UAE for adenomyosis is "What should be considered a good or acceptable response?" The highest recurrence rate reported has been 50% in 2 years reported by Pelage et al in 2005.[35] In light of this data, many in the interventional radiology community have turned away patients, expressing concern about the probability of symptomatic recurrence. This is likely due to comparisons being made between the outcomes after UAE seen in patients with adenomyosis and the outcomes seen in patients with uterine fibroids.

Although the clinical presentation of these two disorders may be similar, the disease entities are not the same. Adenomyosis is a disease process that has historically been difficult to treat without turning to hysterectomy for definitive management. The addition of UAE as a potential treatment option should potentially be seen as a good thing for patients looking to avoid surgical management for adenomyosis. Is it perfect? The above data shows that UAE for adenomyosis is not perfect, but more than half of the patients who undergo this treatment report either partial or complete resolution of their symptoms after follow-up as long as 3 years. It appears ironic that many interventional radiologists remain divided about UAE for adenomyosis while many gynecologists would enthusiastically support any procedure that has the potential to treat 50% of patients with this disorder.[40]

Given the questions that exist surrounding the use of UAE in patients with adenomyosis, the next step in the evolution of this therapy is to determine what role, if any, UAE should have in the treatment of these patients. Additionally, we need to determine if and how outcomes can be improved after UAE. From one perspective, all evaluations of therapy for adenomyosis have been either retrospective or case control studies. A prospective study would be important to perform to better evaluate outcomes. Attention should also be paid toward optimizing technique for UAE in patients with adenomyosis. Pathologic studies have failed to demonstrate good penetration of particulate embolic agents into areas of adenomyosis. Additionally, we must consider the potential invasive nature of adenomyosis. Does this make the tissue more resistant to the effects of embolization? Perhaps there is a role for using smaller particles for UAE in these patients, even though that may be associated with an increased risk of uterine necrosis or ovarian failure. Finally, understanding when UAE is most appropriate will help with patient selection and optimizing outcomes. It is possible that UAE could be used to potentiate the effects of other therapies

currently in use (e.g., levonorgestrel, intrauterine device [IUD], endometrial ablation). Perhaps UAE is best used as an option for women with adenomyosis who desire future fertility because there are few other appropriate treatment options for these patients.

In conclusion, UAE has shown promise in the treatment of adenomyosis by providing symptomatic improvement in this difficult patient population. However, when comparing outcomes after UAE in these patients with the outcomes seen after treating patients with uterine leiomyomata, it is apparent that the rate of recurrence is higher in patients with adenomyosis, especially in long-term follow-up. This fact alone warrants caution and more investigation into the role of UAE in these patients. Even though few options exist for women desiring nonsurgical treatment alternatives, questions exist as to whether or not a procedure with a recurrence rate approaching 50% is appropriate to offer to these patients. Perhaps avoiding surgery in 50% of symptomatic patients is sufficient. Alternatively, we could employ existing experience as a starting point to try to improve outcomes after UAE. Either way, the controversy continues and will continue until more data becomes available.

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