Management of Uterine Fibroids: A Focus on Uterine-sparing Interventional Techniques

Uterine fibroids occur in approximately 50% of women over the age of 40 years, and an estimated 50% of those are symptomatic. Menorrhagia is the most common symptom and the primary indication for treatment, although bulk symptoms often occur and can be treated. Pharmacotherapy is typically inadequate unless it can be expected to successfully bridge to menopause or allow for a less-invasive intervention. However, hormonal therapies have risks. Hysterectomy is still the most commonly performed procedure for symptomatic fibroids and has the lowest rate of reintervention (compared with myomectomy or uterine artery embolization [UAE]), but rates of more serious complications are higher and patient satisfaction and ability to return to normal activities may also be less favorable. Myomectomy is not necessarily less morbid than hysterectomy and may have a greater failure rate than UAE. Techniques and devices vary with little standardization, and operator experience is crucial to success. The largest studies of UAE show very low rates of serious complications and rapid recovery. UAE significantly improves symptoms related to uterine fibroids in 85%–90% of patients. Herein, this article will discuss the nature of fibroids and their diagnosis, pharmacotherapy, surgical treatment, and nonsurgical interventional treatment, including UAE and magnetic resonance–guided focused ultrasound.
Uterine fibroids (leiomyomas) are the most common benign neoplasm of the female genitourinary tract and are present in more than 50% of women 40 years of age, peaking in the 5th decade of life (1,2). Although an estimated 50% of women with fibroids experience symptoms (3), epidemiology studies demonstrate a two to nine times increased prevalence among African-Americans and a peak incidence occurring 5–10 years earlier as compared with Caucasians (2,4). Rates among Asians and Hispanics appear to be comparable to Caucasians (2). Fibroids are thought to arise from the myometrium following neoplastic transformation of a single smooth muscle cell (5), with subsequent development of a connective tissue component and a pseudocapsule (6). Fibroid pathogenesis remains to be elucidated and there is controversy over the contribution of proposed causes, including cytogenetic abnormalities, abnormal extracellular matrix expression, growth factors, cytokines, and chemokines (7). There is increasing evidence that progesterone receptors have a major impact on the growth of fibroids (8).

Factors associated with a reduced risk for fibroids include a later age of menarche, menopause, and child bearing. Increased risk for fibroids has been associated with use of estrogens, obesity, red meat consumption, a family history of fibroids, tubal ligation, prior pelvic inflammatory disease, prior intrauterine device expulsion, hypertension, and diabetes (2).

Clinical Features (Signs and Symptoms)

Symptomatic fibroids are most commonly associated with menorrhagia (9) and are the most common cause of abnormal menstrual bleeding (10). Uterine fibroids may also cause menometrorrhagia, anemia, dysmenorrhea, dyspareunia, chronic (pelvic and back) pain, bloating, pelvic fullness, constipation, tenesmus, infertility, hydronephrosis, and urinary frequency (9). The growth of fibroids appears to be hormonally driven (9), accounting for their peak occurrence during reproductive age, enlargement during pregnancy, and regression after menopause (6). Fibroids are susceptible to ischemia (11), which when it occurs, results in hyaline or myxoid degeneration (6).

There is controversy over the effect of fibroids on fertility. However, a meta-analysis showed lower pregnancy rates and a greater incidence of miscarriage in patients with submucosal fibroids (12). Similarly, removal of submucosal fibroids has resulted in an increased rate of pregnancy (13). Fibroids have been shown to increase pregnancy risks, including intrauterine growth restriction, placental abruption, preterm delivery, premature rupture of membranes, abnormal fetal lie, cesarean section, and blood loss (14).

Imaging Classification

Fibroids can be classified by their location: submucosal, intramural, and subserosal (9) (Fig 1). Pedunculated fibroids can be intracavitary or exophytic (9) and can undergo torsion or derive new blood supply from adjacent structures (parasitize) (6). Intramural fibroids are the most common type of fibroid, while submucosal fibroids are the least common type. However, a submucosal fibroid may be more symptomatic than a subserosal or small intramural fibroid, owing to its relationship with the endometrium. Bulk symptoms are more often seen with large intramural or subserosal fibroids (6).

Although a high-quality ultrasonography (US) examination may be sufficient for evaluation in patients with straightforward cases of fibroids (for instance to estimate the size of a dominant fibroid), imaging evaluation is most reliably performed with magnetic resonance (MR) imaging to determine...

Abbreviations:
FDA = Food and Drug Administration
FUS = focused ultrasound
GnRHa = gonadotropin-releasing hormone agonist
HIFU = high-intensity focused ultrasound
UAE = uterine artery embolization

Conflicts of interest are listed at the end of this article.
the characteristics, number, size, and location of fibroids and to assess for other pathologic conditions such as adenomyosis (15–17). The recognition of adenomyosis is important as it may alter the treatment approach (18), patient counseling, and expectations (19). Adenomyosis is a diffuse or focal endometrial basal layer invasion of the myometrium that can cause symptoms similar to fibroids, and it is best seen on MR images as a thickened junctional zone (>12 mm), with scattered T1- and T2-hyperintense foci of endometrial glands (6) (Fig 2). Studies reveal that pretreatment MR imaging evaluation may alter therapy in about 20% of patients with fibroids (16,20).

**Pharmacotherapy**

Medical therapy is limited in the management of symptomatic fibroids. Oral contraceptive pills are a common first-line therapy (23) but are mainly used to regulate the menstrual cycle and may not reduce the volume of menstrual flow. Oral contraceptive pills carry side effects, including a 20%–40% increased risk of stroke in older smokers with hypertension (23), venous thromboembolism, liver adenomas, gallstones, weight gain, acne, breast tenderness, fluid retention, mood disturbances, and sexual dysfunction (9). Levonorgestrel-releasing intrauterine contraceptive devices have also been shown to decrease fibroid-associated menorrhagia (9,24). However, progestin-only treatments have not shown any benefit in reducing fibroid size (9). The Maine Women’s Health Study, which examined management of fibroids (380 patients) with any hormone regimen compared with management with hysterectomy (311 patients), showed that 25% of medically treated patients went on to undergo hysterectomy, while 25% of patients with abnormal bleeding and 50% with chronic pain still complained...
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of substantial symptoms after medical treatment (21).

Gonadotropin-releasing hormone agonists (GnRHAs), such as leuprolide (eg, Eligard; Sanofi-Aventis, Quebec, Canada), create a hypoestrogenic menopause-like state by means of competitive inhibition on the pituitary-hypothalamic axis (9,25). GnRHa therapy shrinks fibroids by 35% within 8 weeks on average, with induction of amenorrhea (9,25). Maximum effects are achieved after 24 weeks of therapy, with volume reductions up to 70% (1), but return of symptoms and original fibroid size recur in a similar timeframe after drug cessation (9,26). Long-term treatment is limited in 95% by side effects. As such, GnRHa therapy may be considered in perimenopausal women as a bridge to menopause (1). GnRHa therapy has also been recommended for short-term use (<6 months) to facilitate myomectomy, hysterectomy, or MR-guided focused ultrasound (FUS) therapy and allow for a preprocedure rise in hematocrit and shrinkage of the fibroid volume (1). However, these medications may be associated with more difficulty in surgical excision during myomectomy and higher recurrence rates. Therefore, presurgical GnRhA use is not universally accepted (14).

Surgical Treatment

Hysterectomy is a definitive therapy for uterine fibroids with the lowest re-intervention rates and the highest rate of symptom relief in a nonrandomized controlled study compared with uterine artery embolization (UAE), myomectomy, and control subjects (27). However, only 72% of women reported improvement of symptoms after hysterectomy in the Maine Women’s Health Study (9,21). Moreover, while patient satisfaction (28) and major complication rates have been comparable in some studies (29), a number of large trials have shown greater rates of major complications with surgery (30,31) and patient dissatisfaction (31) compared with UAE. While hysterectomy rates for symptomatic fibroids are decreasing, 25% of hysterectomies performed in women younger than 45 years in 2005 were for fibroids (approximately 200,000 per year) (32). Open hysterectomy still accounts for close to two-thirds of all hysterectomies performed (32).

In general, myomectomy is best suited for the treatment of one to three dominant fibroids in accessible locations (9). About one-fifth of patients who undergo myomectomy will require a second surgery at 5 years (33). A meta-analysis suggests that laparoscopic myomectomy results in fewer complications, less pain, and shorter recovery compared with open myomectomy (14,34).

A variety of techniques and devices may be used in the laparoscopic removal of fibroids, including dissection, enucleation, morcellation, and thermal myolysis (135–37). A recent controversy has arisen over the use of power morcellation with laparoscopic hysterectomy and myomectomy due to the potential risk of disseminating unsuspected uterine sarcoma. A retrospective report of 1091 uterine morcellations found a 0.09% rate of unexpected sarcoma and 1.2% incidence of unsuspected neoplasms, with dissemination occurring in two-thirds of these cases (38). A smaller review found one case (1% risk) of unsuspected atypical tumor after uterine morcellation in a low-risk population (39). Retrospective reviews of surgical specimens in 1332 patients and 923 patients found a 0.23% rate of uterine sarcoma (with a 0.27% rate in the subset with rapidly growing fibroids) (40) and a 0.4% rate of unsuspected malignancy in hysterectomy specimens, respectively (41).

As such, a 2014 U.S. Food and Drug Administration (FDA) safety communication discourages the use of laparoscopic power morcellation, estimating a one in 350 risk for an unsuspected sarcoma and potential pelvic dissemination (42). The American Congress of Obstetricians and Gynecologists issued a special report on the use of power morcellation in May 2014, suggesting an incidence of two in 1000 for unsuspected sarcoma (43).

Endometrial thermal ablation is an option for the treatment of menorrhagia in patients with fibroids and minimal bulk symptoms who are finished with child-bearing since the endometrial cavity develops synechiae (9). However, results are inconsistent and not always enduring (44). Uterine artery ligation, performed either laparoscopically or transvaginally, has not been well studied (9). A small randomized trial of UAE versus laparoscopic uterine artery occlusion showed superiority of UAE: 17% symptom recurrence and 100% rate of complete fibroid infarction at MR imaging with UAE, compared with 48% symptom recurrence and 23% fibroid infarction with ligation (45). Another study comparing 225 laparoscopic uterine artery occlusion and 112 UAE patients reported equivalent fibroid volume reductions of 41.2% and 49.2%, respectively, without reporting on symptom improvements (46).

Uterine Artery (Fibroid) Embolization

Procedure History

UAE was first performed in France in 1994 by Merland, a neuroradiologist, who subsequently collaborated with Ravina, a gynecologist, to reduce blood loss prior to myomectomy (47). Subsequently, in 1997, Goodwin et al reported on a series of UAE patients in the United States with fibroid-related menorrhagia, demonstrating successful reduction of fibroid-related symptoms (48). The procedure has since been validated as a safe, efficacious, and cost-effective treatment option for symptomatic fibroids. About 14,000 UAEs are estimated to be performed per year in the United States (49).

Pelvic Arterial Anatomy and Pitfalls

The internal iliac (hypogastric) artery is classically described as having anterior and posterior divisions, with the uterine artery arising from the anterior division, but this appears to occur only 51% of the time (50). Alternatively, four angiographic patterns of uterine artery branching have been described from the superior gluteal, inferior gluteal, and the internal iliac (hypogastric)
arteries, 90% of the time either trifurcating with the superior gluteal and inferior gluteal arteries or arising as a first branch from the inferior gluteal artery (with near equal frequency) (51) (Fig 3).

The uterine artery has descending, transverse, ascending, and multiple intramural segments. The cervicovaginal branch typically arises from the mid- to distal portion of the transverse segment, and the vaginal artery can have a common trunk with the uterine artery (10). These vessels should be delineated and avoided if possible during UAE to minimize the risk for vaginal mucosal ulceration, loss of sexual function (52), and dyspareunia (53,54) (Fig 4).

Utero-ovarian anastomoses may also be present, which can increase the risk of nontarget ovarian embolization, such as with type I anastomoses

Figure 3: Illustration of an angiographic classification of uterine artery branching patterns (IGA = inferior gluteal artery, SGA = superior gluteal artery, UA = uterine artery). Type I: Uterine artery as first branch of inferior gluteal artery. Type II: Uterine artery as second or third branch of inferior gluteal artery. Type III: Trifurcation. Type IIIA: Uterine artery and superior gluteal artery bifurcation with inferior gluteal artery as a branch of the latter. Type IV: Uterine artery as a first branch of the internal iliac artery. Type I and III comprise about 90% of cases with equal frequency.

Figure 4: Angiographic images before and after UAE. (a) Digital subtraction angiogram with a reverse curve catheter in the contralateral internal iliac artery opacifying type I or type III branching anatomy and a hypertrophied uterine artery (UA) and perifibroidal plexus. Note the cervicovaginal branch arising from the proximal uterine artery (arrows). (b) Postembolization image with evidence of successful embolization through a catheter tip (arrow) distal to the level of the cervicovaginal branch to avoid embolizing that artery.
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Spherical polyvinyl alcohol particles have shown comparatively unacceptable rates of failure in three randomized controlled trials (59,65,66). Gelatin sponge embolization has been successfully used, although considered less precise, and has recently been studied in Korea with superior results compared with embolization using polyvinyl alcohol (61). Polyzene F-coated hydrogel microspheres (67,68) and a pingyangmycin lipiodol emulsion and silk-segment embolic (69) have shown good results.

The arteriographic end point of embolization was initially described as a static column of contrast material in the uterine artery based on the use of polyvinyl alcohol particles. However, with calibrated microspheres, it is sufficient to observe sluggish antegrade flow in the uterine artery (53) (visualization of contrast material for at least five cardiac cycles) (59). The use of microspheres greater than 500 microns theoretically helps avoid nontarget passage of the embolic agent through these anastomoses (56). Additionally, a type II utero-ovarian anastomosis may be a cause of UAE failure due to partial or complete arterial supply of the fibroid directly from the ovarian artery (3.9% incidence) (55) (Fig 1). Ovarian artery catheterization and embolization may be required (53) (Fig 7).

Many operators forgo an initial aortography examination and perform a completion aortography examination (10). However, aortography increases the estimated radiation dose by 20% and has an 18% sensitivity for detecting collateral ovarian artery supply (57). The effects on dose of cone-beam computed tomography to identify regions of persistent perfusion within fibroids remains unclear (58).

**Technical Details and Cost**

Most UAE procedures are performed with intravenous sedation (29) by means of a right common femoral approach with a reverse curved 4- or 5-F catheter to access the contralateral internal iliac artery followed by formation of a Waltman loop to access the ipsilateral internal iliac artery (48,59–61) (Fig 5). Some investigators suggest the routine use of a microcatheter, for example, a 2.7-F Progreat (Terumo, Somerset, NJ) to preserve flow in the uterine artery and facilitate access to distal branches (48,59,61–64).

Perifibroidal plexus vessels are generally 500–800 microns in caliber (56), which is the basis for the selection of either 500–700 or 700–900-micron–sized particles (59). In the United States and Europe, particulate material is by far the most common embolic agent used for UAE. Several embolic materials are FDA-approved for UAE of uterine fibroids, including tris-acryl gelatin spheres (Embospheres, Merit, South Jordan, Utah) and polyvinyl alcohol particles (various manufacturers). Spherical polyvinyl alcohol particles have shown comparatively unacceptable rates of failure in three randomized controlled trials (59,65,66). Gelatin sponge embolization has been successfully used, although considered less precise, and has recently been studied in Korea with superior results compared with embolization using polyvinyl alcohol (61). Polyzene F-coated hydrogel microspheres (67,68) and a pingyangmycin lipiodol emulsion and silk-segment embolic (69) have shown good results.

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appearance of the perifibroidal plexus (54) (Fig 8).

Preprocedure administration of 1 g cefazolin (eg, Ancef; GlaxoSmithKline, Philadelphia, Pa) intravenously is a widely accepted prophylactic antibiotic of choice. However, this has not been validated and the risks of a side effect from the antibiotic may be greater than those of an infection (10). The presence of an intrauterine device, or IUD, does not appear to increase the risk of endometritis (70). Abstention from use of tampons, swimming, bathing, or sexual intercourse is likely only necessary for 7–10 days.

Aggressive postprocedure pain management allows same-day discharge with a medication regimen consisting of a narcotic analgesic, a nonsteroidal anti-inflammatory drug, and an antiemetic, tapering these medications over the course of 7 days. Patients should be educated about postembolization syndrome (pyrexia, pain, and nausea) and how to manage it. This syndrome occurs in at least half of patients (28,29) and lasts approximately 72 hours (10).

Multiple studies have demonstrated significantly shorter mean hospital stays with UAE when compared with surgical treatment (from one-half to one-fifth of the time), with an associated cost savings (28–30,71) and a greater net hospital income with UAE (72). However, there may be no long-term savings given the higher rates of reintervention with UAE (73).

Radiation dose for UAE is directly in the middle range for interventional radiology procedures, including elective and emergency procedures (74). Mean effective dose associated with UAE has been reported to be 77.8 mSv, which can be decreased to 11.3 mSv after intense dose reduction (including avoiding digital subtraction angiography), with doses as low as 3.3 mSv in one study (the equivalent of three abdominal radiographs) (75). Calculated absorbed skin doses have been reported as representing only 2.2% of the risk from medical radiation (75), rarely approaching thresholds for transient erythema (76). A review of radiation dose studies concludes that standard UAE “is very unlikely to cause any significant increases in radiation-induced cancer” and that it is “high unlikely that the radiation dose from UAE alone would directly cause infertility” (75).

**Patient Selection**

Indications for UAE include uterine fibroids causing symptoms, primarily menorrhagia, anemia, and bulk-related symptoms (77). Contraindications to UAE include pelvic inflammatory disease, uterine malignancy, or pregnancy. Relative contraindications include severe renal insufficiency not managed by dialysis or a refractory coagulopathy (10). Pedunculated subserosal fibroids...
Recent studies have demonstrated equivalent safety and efficacy of UAE even in patients with large (>10 cm) fibroids or uterine volumes (>700 mL) compared with those with smaller volumes (81,82). Efficacy has even been shown in 22 patients with “megauter- us” (>1600 mL), 80% of whom avoided hysterectomy (83).

Figure 7: 

(a) Opacification of the left perifibroidal plexus from a catheter tip in the distal left uterine artery. Note the relatively small arteries feeding the cranial portion of the fibroid (arrow). 

(b) Digital subtraction flush aortogram demonstrates a hypertrophied left ovarian artery (arrow). 

(c) Digital subtraction aortogram of a subselected left ovarian artery demonstrates a type II utero-ovarian anastomosis with partial supply of the fibroid (arrow) directly from the ovarian artery, which can be a cause of treatment failure unless a separate ovarian embolization is performed. Note the peri-ovarian plexus (arrowhead) also supplied by the ovarian artery, which should be avoided with embolization.

The role of endometrial biopsy and Papanicolaou test to exclude cancer prior to UAE has not been defined. Unfortunately, malignancy is not reliably distinguished from leiomyomata, either by means of symptoms or imaging. Reports that diffusion-weighted imaging and apparent diffusion coefficient characterization of presumed fibroids may be used to predict risk of underlying leiomyosarcoma have yet to be substantiated (80). Moreover, two retrospective studies of patients with rapid fibroid growth suggest no increased risk for malignancy and that premenopausal women with symptoms and imaging findings consistent with fibroids can be treated without undue consideration for sarcoma (38,40). However, a discussion should occur with the patient about the small risk (approximately one in 350–1000 or less) (38,40,43) that a malignancy could be present, understanding that this risk is probably less in younger patients.

Adenomyosis (with or without fibroids) can be treated with UAE, although the patient should be counseled that the results might not be as durable as with symptoms due to fibroids alone. Small studies have shown substantial short-term symptom improvement in 84% (84) and 92.3% (85). However, 2-year results from another small study showed higher recurrence rates compared with UAE for fibroids (19). Better outcomes may be seen in adenomyosis with lower T2 signal intensity on MR images, focal areas of adenomyosis (18,86), and use of smaller particles (18) and hydrogel-coated microspheres.
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Diffuse adenomosis with generalized thickening of the junctional zone seems to be a useful predictor for recurrence after UAE (68). Outcomes

A fibroid-specific self-administered uterine fibroid symptom and quality of life (UFS-QoL) questionnaire has been developed to assess symptom resolution and quality of life, including a menorrhagia questionnaire and sexual function scale (87). Its initial development and validation showed the ability of this questionnaire to discriminate between UAE patients and normal volunteers as well as between UAE patients with different outcomes and has proved to very important in the assessment of quality of life after UAE and for the FIBROID registry (87–89).

A number of landmark studies have shown greater safety and shorter hospital stays (on average by 4 days) with UAE compared with hysterectomy (9,28,30,90). A 2012 Cochrane review of five randomized controlled trials of UAE compared with hysterectomy and myomectomy concluded that UAE has a similar patient satisfaction rate compared with surgical treatments, while being associated with shorter length of hospital stay and disability (91). However, UAE had more minor complications and a higher likelihood of surgical reintervention within 2–5 years (91). While overall complication rates are higher with UAE in some studies (25%–50%), at least half of the reported complications are due to postembolization syndrome and are rarely serious (28,30). In contrast, hysterectomy complications are more often severe (28). Reported rates of clinical success after UAE are high, ranging from 82% to 90% (28,30,31,73,88,92–94) for menorrhagia after a year and from 77% to 86% with dysmenorrhea and bulk symptoms (93,94).

The 2008 FIBROID registry, which involved 3160 UAE patients from 72 sites, found relatively low rates of reintervention. At 3 years of follow-up in 1278 patients, further treatment with hysterectomy, myomectomy, or repeat UAE was estimated to be 9.79%, 2.82%, and 1.83%, respectively (88). Similarly, further treatment was required in 10.5% of 200 patients (92) and 6% of 400 patients (93) in other studies. In a study of 200 UAE patients, two of three patients with partial infarction showed regrowth of the residual fibroid at imaging follow-up. Both of these patients had recurrent symptoms, suggesting that percent of fibroid infarction rather than volume reduction is important for predicting outcomes (95).

Pelvic pain is by far the most common symptom after UAE and is expected to last 48–72 hours, but it can last for up to a month (10). Vaginal discharge associated with the procedure typically resolves after 1 month (10). Major complications have been reported in 4.5% of UAE patients in the HOPEFUL trial compared with 14.8% in the surgical arm (31) and in 1.3% in the EMMY trial compared with 14.5% of surgery patients (29). A 400-patient
patients but a greater rate of re-intervention (36.7% compared with 6.1%) without a significant difference in total symptomatic relief (98).

The need for hysterectomy due to a complication of UAE occurs in less than 1% of patients (14). The Society of Interventional Radiology quality improvement guidelines from 2010 suggested complication thresholds of 20% for prolonged vaginal discharge, 3% for permanent amenorrhea in patients younger than 45 years and 15% in those older than 45 years, 15% for transcervical expulsion of fibroids, 3% for septicemia, less than 1% for thromboembolic disease, and less than 1% for nontarget embolization (99).

Three fatalities have been reported after UAE (14), including fatal pulmonary embolism (100), lethal sepsis from pyometrium (10), and death from ovarian cancer (101).

**Fertility and Pregnancy**

Fertility after UAE has not been conclusively established, although most studies suggest ovarian failure is rare (77), and data suggest that fertility rates are likely similar after myomectomy (53). However, while successful pregnancies after UAE have been reported, UAE may have a negative impact on subsequent pregnancy, including greater rates of spontaneous abortion (46), failed pregnancy attempts (102), abnormal placental position (103), and Cesarian section (31,100).

A small study showed no difference in rates of conception after UAE and laparoscopic uterine artery occlusion but a significantly greater rate of spontaneous abortion in the UAE group (36% compared with 10.5%), without a significant difference in preterm deliveries, cesarean sections, or malpresentation (46). A prospective randomized trial of UAE versus myomectomy in 121 women showed better reproductive outcomes for myomectomy after 2 years (102), with greater rates of pregnancy and labor and fewer spontaneous abortions, but similar perinatal and obstetrical results (102). A dedicated ongoing trial (FEMME) measuring quality of life and pregnancy after UAE versus myomectomy in the United Kingdom has yet to report results.

**Focused Ultrasound Therapy**

FUS or high-intensity focused ultrasound (HIFU) technology has existed since the 1940s. It was first used clinically in the liver in 1942 (104), for neurologic disease in the mid-1950s (105), and for tumor treatment in 1995 (106). FUS has been used in the treatment of breast, brain, eye, prostate, bladder, renal, pancreatic, metastatic bone, liver, and uterine tumors (107). However, the need for image guidance to facilitate precise targeting and to provide temperature feedback initially limited its clinical use (108). Early US-guided FUS therapy has been slow to affect clinical practice due to the limited ability to visualize the target lesion (109), assess outcome during a session, and perform thermometry (110). A six-patient series from China in 2002 demonstrated the feasibility of MR-guided FUS fibroid treatment, with symptomatic improvement in five patients (111). Since then, small phase I, II, and III trials have been performed, demonstrating the safety, feasibility, and efficacy of MR-guided FUS therapy for uterine fibroids (105–109).

The ExAblate 2000 device (InSightec, Haifa, Israel) is an MR-guided system that received U.S. FDA approval in 2004 for uterine fibroid ablation. Various other commercial systems are available but not FDA approved, including the Sonalleve (Philips Healthcare, the Netherlands) volumetric ablation system (31,100), as well as US-guided systems (eg, Ablatherm, FEP-BY02, and Sonoblate) (114). The MR technologies can be used with 1.5- and 3-T MR imaging units and require a special MR imaging–compatible table with the embedded US transducer in a sealed degassed water bath (to improve acoustic coupling) (107) (Fig 10).

FUS/HIFU therapy causes destruction of tissue by thermal injury from absorption of sound wave energy and vibratory effects and secondarily by cavitation through the generation of microbubbles. The high-intensity ultrasound...
waves bypass nontarget structures and are focused on a target to cause thermally induced protein denaturation and coagulative necrosis, leading to cell death (107,114). The ablation volume of a sonication varies from a few millimeters up to a centimeter with the ExAblate and 16 mm × 40 mm with the Sonalleve system (113), depending on the energy applied, the type of tissue being treated, and the attenuation of the sound waves by intervening tissue (107). During and after each sonication, using the shift in proton resonance frequency that occurs with rises in temperature, a dynamic thermal map is created (107). The temperature-dependent proton frequency shift is linear over a wide temperature range (including above the coagulation threshold); therefore slight elevations in adjacent tissues can safely be used to monitor for nontarget damage (108).

At the time of FDA approval of MR-guided FUS in 2004, the manufacturer’s indications for use for the ExAblate 2000 system allowed for a maximum of 33% of the fibroid volume to be treated, due to concerns for injury to the normal uterine tissue. In 2006, the FDA allowed for up to 50% of the fibroid volume to be treated (108). In 2009, the FDA allowed for the treatment of 100% of the fibroid volume, with the stipulation that the treatment focal spot should not be within 10 mm of the serosal surface of the uterus (115,116). Therefore, studies employing MR-guided FUS using the FDA standards prior to 2009 were biased toward less than optimal results.

Use of MR-guided FUS therapy is limited by the time required to perform quality assurance, synchronize the ultrasound transducer and MR imaging scanner coordinates, create a treatment plan, acquire the MR images, perform each acoustic ablation (termed sonication), allow for cooling of the technology, and reposition the treatment focal spot. While cooling time has the greatest impact on procedure time, advances have been made in the efficiency of treatment by increasing sonication sizes and decreasing sonication times. In a 2008 study with the ExAblate system, the number of sonications performed for a typical ablation ranged from six to 31, with MR occupancy times ranging from 3 hours 19 minutes to 4 hours 55 minutes per case (117). In contrast, a 2013 retrospective study of 115 patients had a mean of 74 sonications during a treatment session (115). The Sonalleve system’s larger sonication size allows for greater treatment efficiency as compared with the InSightec unit. Average treatment time with the Sonalleve system has been reported as 3.67 hours with 99 sonications performed (requiring an average of 54.6 minutes of sonication) (112) and 4.07 hours with 432 sonications (with an average of 2.33 hours of sonication time) (113).

**Patient Selection**

Indications for treatment are similar to the indications for UAE and myomectomy. The number, size, location, and characteristics of the fibroids will be used to determine if a patient is a candidate. In addition, if the patient has an abdominal scar or intestines in the acoustic path, the patient is at risk for a skin burn or intestinal perforation, respectively. Placing vitamin E capsules on an abdominal scar during the MR imaging is helpful in determining if the scar is in the acoustic path, although scars are often readily recognized on MR images. If the targeted fibroid tissue is too deep, the acoustic energy is unlikely to be effective (as the transducer is unable to focus the energy at that depth); if the patient has a large amount of subcutaneous fat, the need to use higher ultrasound energies increases the risk of a skin burn (107,118). Obtaining a pretreatment MR imaging study with the patient in the prone position to define the anatomy prior to FUS therapy is helpful in treatment planning (108).

Currently, patients with more than four fibroids or fibroid volumes greater than 500 mL are not considered to be good candidates for MR-guided FUS therapy (107). Maximal fibroid size that can be treated with MR-guided FUS has not been established, but a retrospective study showed the best results in fibroids less than 50 mL in volume (115). Many studies have used a maximum diameter...
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of 10 cm (approximately 520 mL) for a fibroid as the limit for inclusion, although an ongoing comparison study of UAE and MR-guided FUS has a limit of 3 cm (119). Some studies have used no limitations on proximity to the endometrium (108), while others maintained a 1.5 cm distance from the endometrium and 1 cm distance from the junctional zone (120). GnRHa pretreatment has been attempted in one small study to reduce fibroid volume prior to ablation of fibroids 10 cm or larger with good results (121). Increased fibroid vascularity has been suggested as a predictor of treatment failure with greater perfusion on dynamic contrast-enhanced MR images correlating with worse treatment efficacy (122,123). In addition, homogeneously T2-hypointense fibroids without infarction or areas of cystic degeneration on MR images have shown better response rates with FUS/HIFU therapy than heterogeneous and T2-hyperintense fibroids (118,124). However, a retrospective study of 282 patients undergoing MR-guided FUS found smaller, but adequate, nonperfusion volume ratios (used as a surrogate for the percentage of ablated tissue) in patients with heterogeneous fibroids (120). Similarly, a retrospective study from the United States of 115 patients showed no significant difference in nonperfusion volume based on T2 signal intensity or homogeneity (115). However, higher rates of skin burns (12.5%) and technical failures have been suggested with T2-hyperintense fibroids (as well as subcutaneous fat thickness > 20 mm), likely due to the need for higher acoustic energies, which also resulted in more terminations of procedures (33%) owing to pain during treatment (118).

Contraindications to MR-guided FUS include pedunculated fibroids, lower abdominal wall scarring in the acoustic path, potential malignancy, pelvic infection, pregnancy, calcified fibroids, fibroids too close to the sacral nerve roots, and loops of bowel within the acoustic path. Unfortunately, anatomic limitations may not be discovered until the patient is on the procedure table. In a study of 333 patients seeking to undergo MR-guided FUS treatment and 103 clinically eligible patients, only 25% were eligible anatomically (based on MR imaging findings) and only 14% were ultimately eligible due to feasibility and safety concerns (125). A 2013 retrospective study of 123 patients had a 6.5% technical failure rate due to the presence of bowel (115). Various maneuvers have been used to increase the number of patients who can be treated with FUS. A study of 21 patients showed the feasibility of using a degassed water-filled balloon placed beneath a prone patient to successfully displace bowel from the acoustic path (117). Similarly, a 230-patient study showed significant decrease in screening failures after use of a bowel displacement technique: sequential normal saline bladder filling, ultrasound coupling gel rectal filling, followed by bladder emptying (120).

Currently, the U.S. FDA advises precaution with use of MR-guided FUS after UAE because it has not been studied. Interactions with embolic agents may limit results or lead to complications with beam scattering. Additionally, the effects of MR-guided FUS on fertility have not been well studied (107). Currently, the recommendation from InSightec is that an intrauterine device should be removed if it is in the direct treatment pathway but may be otherwise left in place, although this has not been well studied. Procedural timing with respect to phases of the menstrual cycle has not shown significant differences in outcomes (117).

Treatment of adenomyosis with FUS has been studied at multiple institutions in Asia, with reported benefit in 89.9% at 18 months (127), 89% at 6 months (128), and 77% at 12 months (129). There is also a case report of term vaginal delivery after MR-guided FUS treatment of focal adenomyosis in a 33-year-old woman with an inability to conceive (130).

Patient Preparation and Procedure

Efforts to minimize bowel activity during a treatment session include a low residue diet, bowel cathartics, 6-hour fasting, and glucagon. The lower abdominal wall is shaved and cleansed to prevent trapped air and contaminants from interfering or absorbing the FUS beam that could predispose to a skin burn. Prophylaxis to prevent deep venous thrombosis is recommended (107,120).

Successful positioning of the fibroid over the FUS transducer is confirmed with rapid gradient-echo localizer sequences, followed by a baseline triplanar T2-weighted planning study. The radiologist manually outlines the treatment target area in a single plane, and software then interpolates the three-dimensional fibroid treatment volume (107). Electronic barriers to sound are manually placed in orthogonal planes to prevent any portion of the individual acoustic waves from traversing key anatomic structures (bowel, pubic bone, and skin scars). Additional electronic barriers are placed adjacent to nerve roots emanating from the sacral foramina to minimize the heating of nerves. A focal spot distance of at least 4 cm from the sacrum should be maintained to avoid sacral heating and nerve damage or pain. Electronic fiducial markers are also placed as a reference to monitor movement during the treatment session. If too much movement occurs, treatment replanning is required. Subtherapeutic test sonications are performed in the coronal plane (perpendicular to the ultrasound beam) and sagittal (parallel) plane to assess targeting accuracy, and adjustments are made to synchronize the FUS transducer coordinates with the MR imaging unit. MR images can also be used to scrutinize the abdomen surface for air bubbles overlying the skin. Skin heating can be assessed on thermal mapping images (131).

Treatment proceeds with gradually increasing ultrasound energy (107) (Fig 11). Acoustic power, spot size, and sonication frequency and duration can be adjusted with a desire to generate targeted tissue heating to 65°C for the ExAblate system (107) and 60°–62°C for the Sonalleve system (112). Each treatment sonication lasts about 20–30 seconds, with an 80–100-second cooling period interspersed for both the ExAblate and Sonalleve systems (107,112). Patients are instructed to use a “stop sonication” button device if they experience severe

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A cumulative electronically calculated thermal map of the treatment foci provides a prediction of the ablated volume. A triplanar fat-saturated T1-weighted unenhanced and gadolinium-enhanced MR imaging study is performed to assess and calculate the degree of ablation and nonperfused volume (Fig 11). A second session may be performed for inadequate treatment but not until the gadolinium-based contrast agent has effectively been eliminated, as the FDA has cautioned that the high-energy beam may release toxic free gadolinium. However, a study of MR-guided FUS treatment of breast pain, internal heating, skin burning, or pain radiating down their legs (107).

Figure 11: Images of MR-guided FUS treatment with the ExAblate system. (a) Sagittal T2-weighted MR image shows planned sonication path (blue) and treatment zones for each sonication (green rectangles). The radiologist manually outlines the fibroid and the volume is interpolated by the computer (red). The patient’s bladder has been filled to displace anterior bowel cranially out of the ultrasound beam path. (b) Coronal T2-weighted MR image shows planned treatment sonication zones en face (green circles) and electronic fiducials to track motion (red). (c) Intraprocedural thermometry (measuring water proton resonance frequency shift) obtained every 2–4 seconds throughout sonication (blue path), with the portion of the focal spot reaching the desired temperature threshold (depicted in red). The last image shows the accumulated thermal dosimetry that reached the desired threshold during sonication (green), with the prior accumulated foci of sonication (dark blue) that reached the threshold temperature. (d) Real-time sonication thermometry is plotted with temperature measurements over time. (e) Coronal T2-weighted MR image and accumulated dosimetry after sonication. Additional sonications could be planned at this point before administration of gadolinium-based contrast agent if the predicted ablation zone is inadequate. (f) Coronal fat-saturated T1-weighted postcontrast MR image shows the nonenhancing, nonperfused ablated tissue. Note how the nonperfused volume corresponds to the dosimetry map.
cancer is using gadolinium-enhanced images to guide therapy and no adverse events have been reported (107). In addition, a study of HIFU treatment of gadolinium-enhanced rat tumor and muscle showed no dissociation of gadopentetate dimeglumine (132).

Following the procedure, patients are monitored for 30–60 minutes, although early study patients were monitored for up to 3 hours (120,133,134). The majority of patients require only nonsteroidal anti-inflammatory analgesics (117). In one study, only 10% of patients required any analgesics in the first 72 hours (acetaminophen or nonsteroidal anti-inflammatory drugs), with the most common symptom being mild to moderate generalized discomfort (in 23% of patients) (117). Women can often return to work the following day (107).

Complications
Severe skin burns requiring skin grafting can occur at the site of a scar without patients experiencing pain during the procedure (presumably due to scar denervation). Most studies have not excluded patients simply because of lower abdominal scarring and have made exclusion decisions based on the extent of scarring and expected ultrasound beam path. It has been suggested that evaluation for persistence of skin sensation is an important determinant for patient inclusion (107). First-degree burns in two patients occurred in a retrospective of 115 patients, both which resolved after 1 week (115). No burns were reported in a 2007 multicenter prospective trial of 160 patients (108). A 2007 study of 35 patients reported one first-degree burn (2.9%) that resolved within 2 weeks (134).

In a 2007 study, one of 35 patients (2.9%) reported sciatic nerve pain, which subsided after a week (134), and one of 160 patients (0.6%) in a phase III study reported sonication-related leg pain that resolved after 2 days (108). However, sciatic nerve damage can take months to resolve. The same study reported pain or discomfort related to procedure positioning or uterine cramping in 47%–54% of patients. Vaginal discharge was reported in 9% of patients (108). Additional soft-tissue damage includes focal abdominal wall edema and deep vein thrombosis (reported in one patient in the FDA Manufacturer and User Facility Device Experience adverse event database) (107). Thermal damage to the bowel is a serious complication and several cases have been reported on the FDA database.

Outcomes
Pelvic pain and pressure improve soon after the procedure, with a decrease in menorrhagia and uterine volume taking approximately three menstrual cycles to occur. There is a correlation between the nonperfused volume and symptom resolution, with enduring symptom relief and a lower likelihood of needing additional treatments with nonperfused volumes greater than 50%–60% (118). Patients with greater than 30% nonperfused volume, compared with those with less, are three times more likely to have a 10-point improvement on the uterine fibroid symptom and quality of life questionnaire (UFS-QoL) symptom severity scale (108). Moreover, with nonperfused volume of 80% or more, the reduction in fibroid volume is significantly greater than with less than 80% nonperfused volume (135).

In a 2011 study of 130 women, 85.7% reported symptom improvement at 3 months, 92.9% at 6 months, and 87.6% at 12 months (136). However, in an update of this report, patients with lower nonperfused volume (on average, 45.5%), younger age, and heterogeneously bright fibroids on T2-weighted images were more likely to require additional treatment: 19% at 36 months and 23% at 48 months (137). Phase III trials have shown significant reductions in symptoms in 78%–80% of women after 6–12 months (14,108). Short-term studies have also corroborated significant decreases in symptom severity scores among nearly all patients (115,138–140). A multicenter randomized UAE-controlled trial, the FIRSTT trial, is currently recruiting patients (119), and a 3-year, 1000-patient international registry began to collect data on MR-guided FUS in 2013 (141).

Pregnancy after MR-guided FUS has not been well studied, although there are reports of successful child bearing after the procedure as well as use of the treatment to address infertility (130,142–145). A registry maintained by the ExAblate manufacturer reported 54 pregnancies in 51 women with a mean time to conception of 8 months, 41% resulting in live births, 64% delivering vaginally, 28% experiencing spontaneous abortion, 11% electing abortion, and 20% with ongoing pregnancies at the time of the report (146).

United States and British studies in 2009 modeled cost-effectiveness of MR-guided FUS compared with other treatments, predicting total costs and quality-adjusted life-years (147,148). Quality-adjusted life-years were similar for UAE, MR-guided FUS, myomectomy, hysterectomy, and pharmacotherapy (in decreasing order of added quality of life) in the U.S. study (147), while MR-guided FUS had only a small gain in quality-adjusted life-years and cost savings in the British study (148). Myomectomy was more costly and less effective than both MR-guided FUS and UAE (147).

Future Directions
Another percutaneous image-guided fibroid treatment technique being studied is radiofrequency ablation. A 2012 Danish study of 43 patients who underwent US-guided radiofrequency ablation for symptomatic fibroids showed significant mean symptom severity score reduction of 48.6%, mean fibroid volume reduction of 69.7%, no adverse events, and a 4.7% rate of subsequent hysterectomy after 9 months. Success rates with larger fibroids have been shown in some studies, while incomplete ablation was seen in others. Further study is still required to determine the safety precautions needed to protect adjacent structures, such as intraperitoneal saline instillation and normal tissue margins (149).

Conclusion
Various techniques are available and are being investigated for the treatment of symptomatic uterine fibroids. Treatment approach in many cases depends
on the likelihood of success given the nature, size, and distribution of the fibroids; the patient’s anatomy; and treatment goals. UAE is a highly effective, safe, and cost-effective approach. While there is risk of failure requiring reintervention, patient satisfaction may be higher and major morbidity lower compared with surgical techniques. In select patients, MR-guided FUS is proving to be an even safer approach, with an extremely short recovery period and low morbidity.

Disclosures of Conflicts of Interest: J.E.S. disclosed no relevant relationships. D.K.P. disclosed no relevant relationships. A.H.M. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: grants from W.L. Gore, Medtronic, and Cook; member of data safety monitoring board for Trivascular, Bolton Medical, and W.L. Gore; member of advisory board for Tenex Medical and BrightWater; consultant for Medicines Co; Stockholder, advisory board for Tenex Medical and BrightWater; member of scientific advisory board for Boston Scientific; member of data safety monitoring board for Trivascular, Bolton Medical, and W.L. Gore; member of advisory board for Tenex Medical and BrightWater; consultant for Medicines Co; Stockholder, Volcano Medical. Other relationships: disclosed no relevant relationships. J.B.S. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: consultant, Boston Scientific and Merit Medical. Other relationships: disclosed no relevant relationships.

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