GYNECOLOGY

FIRSTT study: randomized controlled trial of uterine artery embolization vs focused ultrasound surgery

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BACKGROUND: Uterine leiomyomas (fibroid tumors) cause considerable symptoms in 30–50% of women and are the leading cause of hysterectomy in the United States. Women with uterine fibroid tumors often seek uterine-preserving treatments, but comparative effectiveness trials are lacking.

OBJECTIVE: The purpose of this study was to report treatment effectiveness and ovarian function after uterine artery embolization vs magnetic resonance imaging–guided focused ultrasound surgery from the Fibroid Interventions: Reducing Symptoms Today and Tomorrow study.

STUDY DESIGN: The Fibroid Interventions: Reducing Symptoms Today and Tomorrow study, which is a randomized controlled trial of uterine artery embolization vs magnetic resonance imaging–guided focused ultrasound surgery, enrolled premenopausal women with symptomatic uterine fibroid tumors; women who declined randomization were enrolled in a parallel observational cohort. A comprehensive cohort design was used for outcomes analysis. Our target enrollment was 220 women, of which we achieved 41% (n=91) in the randomized and parallel arms of the trial. Primary outcome was reintervention for uterine fibroid tumors within 36 months. Secondary outcomes were change in serum anti-Müllerian hormone levels and standardized measures of fibroid symptoms, quality of life, pain, and sexual function.

RESULTS: From 2010–2014, 83 women (mean age, 44.4 years) were treated in the comprehensive cohort design (43 for magnetic resonance imaging–guided focused ultrasound surgery [27 randomized]; 40 for uterine artery embolization [22 randomized]); baseline clinical and uterine characteristics were similar between treatment arms, except for higher fibroid load in the uterine artery embolization arm. The risk of reintervention was higher with magnetic resonance imaging–guided focused ultrasound surgery than uterine artery embolization (hazard ratio, 2.81; 95% confidence interval, 1.01–7.79). Uterine artery embolization showed a significantly greater absolute decrease in anti-Müllerian hormone levels at 24 months compared with magnetic resonance imaging–guided focused ultrasound surgery. Quality of life and pain scores improved in both arms but to a greater extent in the uterine artery embolization arm. Higher pretreatment anti-Müllerian hormone level and younger age at treatment increased the overall risk of reintervention.

CONCLUSION: Our study demonstrates a lower reintervention rate and greater improvement in symptoms after uterine artery embolization, although some of the effectiveness may come through impairment of ovarian reserve. Both pretreatment anti-Müllerian hormone level and age are associated with risk of reintervention. Clinical Trial Registration Number: NCT00995878, clinicaltrials.gov

Key words: focused ultrasound surgery, leiomyoma, randomized controlled trial, uterine artery embolization, uterine fibroid tumor

Uterine leiomyomas, also called fibroid tumors or myomas, are common benign neoplasms that can cause heavy menstrual bleeding, pelvic pain, or infertility. Fibroid tumors are the leading cause of hysterectomy in the United States and are associated with substantial direct and indirect healthcare costs for management of symptoms.[1,2]

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Minimally invasive alternatives to hysterectomy are attractive to many women because of shorter recovery time, preservation of the uterus, and avoidance of the long-term risks that are associated with hysterectomy.[3] However, comparative effectiveness trials are lacking. Clinical trials have been performed to compare either uterine artery embolization (UAE) or magnetic resonance imaging–guided focused ultrasound surgery (MRgFUS) with hysterectomy, but not to compare them with each other.[4–8]

In 2007, an Agency for Healthcare Research and Quality–funded systematic review concluded that "the dearth of high-quality evidence supporting the effectiveness of most interventions for uterine fibroids is remarkable, given how common this problem is."[9] Shortly thereafter, we began this randomized controlled trial (RCT) to compare the effectiveness of UAE and MRgFUS for women with clinically significant fibroid tumors. The aim of the current study was to compare the need for additional intervention for symptomatic fibroid tumors during the trial. Secondary aims were to compare standardized measures—quality of life, pain, and fibroid symptom scores—and to assess the effect of treatment on ovarian reserve.

Materials and Methods

Overview

The Fibroid Interventions: Reducing Symptoms Today and Tomorrow

AJOG at a Glance

Why was this study conducted?

We aimed to compare the effectiveness of 2 uterine-preserving fibroid therapies that can treat both heavy menstrual bleeding and bulk symptoms: magnetic resonance imaging–guided focused ultrasound surgery and uterine artery embolization.

Key findings

We found a lower reintervention rate and greater improvement in symptoms after uterine artery embolization compared with magnetic resonance imaging–guided focused ultrasound surgery. Both pretreatment anti-Müllerian hormone level and age are associated with risk of reintervention.

What does this add to what is known?

The study results will assist in shared decision-making between a patient and her healthcare provider regarding the best alternative to hysterectomy for uterine fibroid tumors.

(FIRSTT) study was a National Institutes of Health–funded RCT to evaluate the comparative efficacy and safety of UAE and MRgFUS (NCT00995878, clinicaltrials.gov).[10] The design of the FIRSTT study and its participants' baseline parameters, periprocedural outcomes, and adverse events have been reported previously.[10–12] The study protocol was approved by the institutional review boards at Mayo Clinic (#09-005095; last approval, June 5, 2018), Duke University, and the University of California, San Francisco; an external data safety monitoring board oversaw study activities. Protocol changes are documented in Table 1.

TABLE 1
Key events in the Fibroid Interventions: Reducing Symptoms Today and Tomorrow Study

Date	Event
September 3, 2009	Approval of initial study protocol
April 29, 2010	First patient enrolled in randomized controlled trial
January 19, 2011	Extension of study follow-up to 36 mo; addition of magnetic resonance imaging and biospecimen collection with long-term follow-up; change of minimum age of enrollment from 30 to 25 years, and addition of industry-funded safety net for payment of magnetic resonance imaging–guided focused ultrasound surgery treatment costs
March 24, 2011	Launch of parallel cohort 1
September 29, 2011	Treatment allowed for women with previously treated pedunculated myomas by hysteroscopy or laparoscopy
September 30, 2011	Launch of parallel cohort 2
January 23, 2013	Exclusion criterion of 1 leiomyoma >10 cm was replaced with >6 leiomyomas of >3 cm in maximal diameter, based on contemporaneous practice
June 14, 2013	Addition of University of California, San Francisco, site
November 1, 2013	End of sponsor payments for safety net at 1 site
January 20, 2014	Gadolinium nonenhancement at baseline was added as an explicit exclusion criterion
February 6, 2014	Interim analysis
March 18, 2014	Close of 1 site to enrollment
August 1, 2014	Close of enrollment at other 2 sites

From AbdElmagied AM, Vaughan LE, Weaver AL, et al. Fibroid interventions: reducing symptoms today and tomorrow: extending generalizability by using a comprehensive cohort design with a randomized controlled trial. Am J Obstet Gynecol 2016;215:338.e1–18. With permission.

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Study population

Full inclusion and exclusion criteria have been reported elsewhere[10] and are listed in the Box. Briefly, all participants were premenopausal women who had symptomatic fibroid tumors, with uterine size smaller than 20 gestational weeks, and were not actively pursuing pregnancy.[10–12] For women who met inclusion criteria but declined enrollment in the nonblinded randomized study, a parallel observational arm was offered. The RCT arm began enrollment April 29, 2010, followed by March 24, 2011, for the observational arm. The final study procedure was performed August 1, 2014, which allowed for 24–36 months of participant follow-up, as determined by an interim analysis.[11]

Analysis of our baseline data and short-term outcomes showed that a comprehensive cohort design (CCD) that combines the RCT and observational participants yields valid results and provides additional power and greater generalizability.[11,12] Randomization was stratified by site and calculated uterine volume ($\geq$700 vs <700 cm^3) and was performed with the use of a Web-based, dynamic allocation application.[11] After randomization, we attempted to treat the patients within 10 days to reduce the chances that the patients would not be able to return for the assigned treatment or would be lost to follow-up. Because the treatments are quite different, neither participants nor investigators were blinded to study assignments.

Study treatment and image analysis

UAE and MRgFUS were performed by following standardized clinical protocols described previously[12] and discussed

BOX
Inclusion and exclusion criteria

Inclusion criteria:
- Women who are able to give informed consent and are willing and able to attend all study visits
- Premenopausal women who are at least 25 years old
- No evidence of high-grade squamous intraepithelial lesions by Papanicolaou or human papilloma virus testing within institutional guidelines

Exclusion criteria:
- Women actively trying for pregnancy or currently pregnant
- Uterine size >20 weeks of gestation
- Previous myomectomy, uterine artery embolization, or magnetic resonance imaging–guided ultrasound surgery (women with previously treated pedunculated myomas by hysteroscopy or laparoscopy were *not* excluded[a])
- More than 6 fibroid tumors >3 cm in maximum diameter[a]
- Allergy to either gadolinium or iodinated contrast medium
- Implanted metallic device that prohibits magnetic resonance imaging
- Severe claustrophobia
- Active pelvic infection
- Intrauterine contraceptive device in place at the time of treatment
- Severe abdominal scarring that precludes safe magnetic resonance imaging–guided ultrasound surgery treatment
- Body mass index that prohibits patient from fitting in magnetic resonance imaging device
- Current use of gonadotropin-releasing hormone agonists or antagonists
- Unstable medical conditions that require additional monitoring during the procedure
- Bleeding diathesis that requires medical treatment
- Magnetic resonance imaging that is suggestive of malignant disease of uterus, ovary, or cervix
- Magnetic resonance imaging that shows only adenomyosis
- Magnetic resonance imaging that shows pedunculated submucosal or subserosal myoma with a stalk <25% of the maximal fibroid diameter
- No enhancement of leiomyoma with gadolinium at baseline[a]

[a] Protocol change from initial trial. Modified from Bouwsma EV, Hesley GK, Woodrum DA, et al. Comparing focused ultrasound and uterine artery embolization for uterine fibroids-rationale and design of the Fibroid Interventions: reducing symptoms today and tomorrow (FIRSTT) trial. Fertil Steril 2011;96:704–10. With permission.

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later in the article. The treating physician recorded key treatment variables, which were not disclosed to the participant. Number, location, and volumes of fibroid tumors were recorded at baseline by study radiologists who used magnetic resonance images (MRIs); uterine volume for purposes of randomization strata was calculated with the prolate ellipsoid formula. Total fibroid load was calculated as the sum of the volumes of all fibroid tumors >1 cm. Vitrea 2.2 segmentation software (version 3.0; Vital Images, Inc, Minnetonka, MN) was used for image analysis.[13]

UAE treatment protocol

Moderate sedation with antiinflammatory agents and antiemetics was used. Foley catheters and prophylactic antibiotics were used at all sites; at 1 site, oral antibiotics were continued for another 5 days. UAE was performed through the right common transfemoral artery with a 5F sheath. A 5F catheter was used to catheterize the left internal iliac artery. Arteriography was performed through this catheter to demonstrate the origin and the course of the uterine artery. Generally, a 5F catheter was advanced into the artery directly; however, a 3F microcatheter was used coaxially through the 5F catheter on some occasions, and final arteriography was performed before embolization. Spheric embolic agents, 500–700 μm in size, were used until stasis was achieved. If 3 vials of the smaller agents were used (ie, for larger uteri), 700- to 900-μm agents were used thereafter. The embolization endpoint was near stasis. At that point, a Waltman loop was formed or a Bookstein catheter was used to catheterize the right internal iliac artery. The right uterine artery was then embolized in the same manner as the left. Final aortography was performed to evaluate for any blood flow from alternate sources, such as the ovarian arteries. The catheter and sheath were removed, and hemostasis was achieved with the use of manual compression or a vascular closure device. The patient was then transferred to a recovery room, where she was observed for 60 minutes before admission to a hospital-based observation unit overnight for pain control. Patients were discharged to home the next morning.

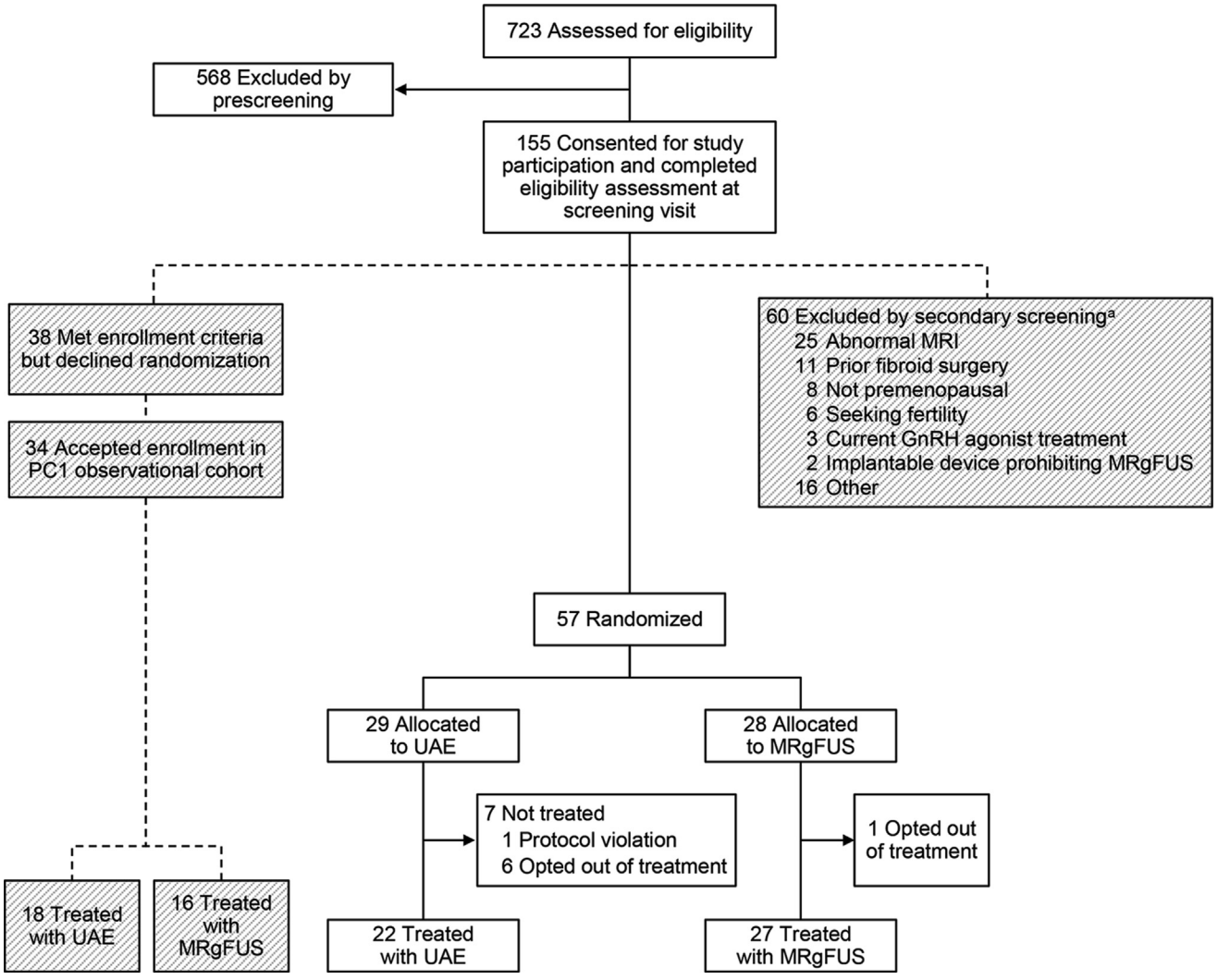
MRgFUS treatment protocol

Treatments were performed with a clinical MRgFUS system (ExAblate 2000; InSightec Ltd, Tirat Carmel, Israel) that incorporates real-time MRI-thermometry feedback and volumetric planning. Light conscious sedation was used, thus allowing women to give feedback to the treating physician. A Foley catheter was placed, and a nurse regularly monitored vital signs.

The patient was positioned prone over the transducer, which was embedded inside a water tank within the MRI table, with a flexible, custom-made, receive-only, pelvic coil (USA Instruments, Aurora, OH) wrapped around her pelvis. Acoustic coupling between the patient and the water tank was achieved by the use of a layer of degassed water and thin gel pad (Parker Laboratories, Fairfield, NJ).

Anatomic T2-weighted images in 3 orthogonal planes were acquired and transferred to the MRgFUS workstation

FIGURE 1
Flow diagram of participants in comprehensive cohort design



Solid lines and *white boxes* show disposition of randomized controlled trial participants. *Dashed lines* and *shaded boxes* indicate participants who were not assigned randomly and entered the parallel cohort. [a]Eleven patients had 2 exclusion criteria. From AbdElmagied AM, Vaughan LE, Weaver AL, et al. Fibroid interventions: reducing symptoms today and tomorrow: extending generalizability by using a comprehensive cohort design with a randomized controlled trial. Am J Obstet Gynecol 2016;215:338.e1–18. With permission.

GnRH, gonadotropin-releasing hormone; *MRgFUS*, magnetic resonance imaging–guided focused ultrasound surgery; *MRI*, magnetic resonance imaging; *PC1*, parallel cohort; *UAE*, uterine artery embolization.

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for detailed treatment planning. The focal spot ranged from approximately 4.5–6.0 mm in diameter and approximately 18.0–35.0 mm in length. All sonications were evaluated in advance for safe beam passage in all 3 dimensions. Interactive modification during the treatment took place to obtain sufficient thermal dose (derived from MRI-thermometry) and complete coverage of the target volume.

Initial low-energy tests were used to ensure accurate targeting. Subsequently, for therapeutic sonications, the pulse duration was generally 12–24 seconds, with an interval between pulses of 45–90 seconds to allow for tissue cooling. After completion of the treatment, gadolinium contrast medium was administered, and a set of T1-weighted images was acquired for assessment of the treated (nonperfused) volume. After MRgFUS treatment, women were typically observed for 1 hour after their last dose of sedation and discharged with an escort.

Outcomes

The primary study outcome was additional intervention, including hysterectomy, myomectomy, UAE, or MRgFUS, for symptomatic fibroid tumors within 36 months. The need for additional

TABLE 2
Baseline characteristics of treated study participants

Characteristic	Comprehensive cohort design		*P* value
	Magnetic resonance imaging–guided ultrasound surgery (n=43)	Uterine artery embolization (n=40)	
Demographic data			
Age at treatment, y[a]	44.0±5.0	44.9±5.0	.45
Race, n (%)			.41
White	28 (65)	31 (78)	
Black	5 (12)	4 (10)	
Asian	4 (9)	1 (3)	
Hispanic or Latina	4 (9)	1 (3)	
Other	2 (5)	3 (8)	
Body mass index, kg/m^2[a]	26.7±5.5	27.8±6.4	.41
Age at fibroid diagnosis, y[a]	39.9±7.1	40.9±7.1	.49
Uterine characteristics			
Fibroid tumors ≥3 cm, n (%)			.17
0	2 (5)	1 (3)	
1	18 (42)	21 (53)	
2	4 (9)	11 (28)	
3	11 (26)	3 (8)	
≥4	8 (19)	4 (10)	
Calculated uterine volume, cc[b]	586 (395–707)	540 (382–837)	.90
Total fibroid load, cc[a,c]	249.2±159.9	362.5±292.3	.03

From Barnard EP, AbdElmagied AM, Vaughan LE, et al. Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis. Am J Obstet Gynecol 2017;216:500 e1–11. With permission.

[a] Data are given as mean±standard deviation; [b] Data are given as median (interquartile range); [c] Calculated based on all fibroid tumors >1 cm.

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intervention was based on clinical decision-making between the participant and her physician. Secondary outcomes included onset of menopause (defined as 1 year without menstrual bleeding); disease-specific (uterine fibroid symptom quality of life [UFS-QOL] health-related quality of life and symptom severity subscales [SSS]) and general quality-of-life (36-Item Short Form Health Survey; RAND Corporation, Santa Monica, CA); pain scores using a visual analog scale (VAS) and the short-form McGill Pain Questionnaire (MPQ) total score; sexual function measured by the Female Sexual Function Index; and assessment of ovarian reserve by measuring serum anti-Müllerian hormone (AMH). Patient self-reported outcomes were confirmed through medical record review, when available. Participants completed questionnaires and telephone follow-up at baseline and 6, 12, 24, and 36 months.

AMH assay

Serum was obtained before treatment and at yearly follow-up visits for up to 3 years for the measurement of AMH. Samples were processed and stored centrally by the Mayo Clinic Biospecimens Accessioning and Processing laboratory at −80°C. At study completion, all samples were thawed for assay with the Ansh Labs (Webster, TX) AMH assay kit by Mayo Medical Laboratory (Rochester, MN).[14] The lower level of detection for the assay was 0.1 ng/mL.

Statistical analysis

Analyses were conducted with both the RCT and CCD cohorts; reported results are from the CCD.[11] Baseline characteristics, AMH levels, and patient-reported measures were summarized and reported with the use of frequency (percentage) for categoric variables and mean±standard deviation (SD) or median (interquartile range [IQR]) for continuous variables. Comparisons between treatment arms (MRgFUS vs UAE) for these variables were evaluated with the use of the χ^2 test for categoric variables, the 2-sample *t* test or Wilcoxon rank sum test for continuous variables, and paired *t* tests for paired data.

The initial sample size calculations were conducted on the basis of single-arm studies in the published literature to detect differences between the 2 treatment arms for the need for reintervention for symptomatic fibroid tumors over the course of the follow-up period and the mean decrease in UFS-QOL SSS (compared with baseline). Given the lack of published data on 36-month outcomes for MRgFUS at that time, calculations were based on the following published outcomes at 24 months: (1) 20% and 37.5% of patients needing reintervention after UAE and MRgFUS, respectively, and (2) mean±SD decreases in SSS of 40.1±25.2 and 28.1±23.6 from baseline scores for UAE and MRgFUS, respectively.[15–17] The study was designed to recruit 99 women per treatment arm, which provided statistical power of 78% and 93%, respectively, to detect the anticipated differences in outcomes 1 and 2. These calculations were based on a 2-sided χ^2 test and *t* test with a type I error of .05.

The cumulative incidence of reintervention (with menopause as the competing risk) was estimated for each treatment arm with a nonparametric approach. Follow-up for all patients who were not in menopause was censored at the end of their study participation. Univariate and multivariable Fine and Gray[18] competing risk regression models were fit

TABLE 3
Baseline and longitudinal validated patient-reported measures among treated comprehensive cohort design patients (n = 83)

Measure	Baseline			Follow-up								
				6-Month			12-Month			24-Month		
	Magnetic resonance imaging–guided focused ultrasound surgery (n=43)	Uterine artery embolization (n=40)	*P* value[a]	Magnetic resonance imaging–guided focused ultrasound surgery (n=33)	Uterine artery embolization (n=34)	*P* value[a]	Magnetic resonance imaging–guided focused ultrasound surgery (n=26)	Uterine artery embolization (n=29)	*P* value[a]	Magnetic resonance imaging–guided focused ultrasound surgery (n=19)	Uterine artery embolization (n=22)	*P* value[a]
Uterine Fibroid Symptom and Quality of Life instrument												
Symptom Severity subscale subscore[b,c]	53.9±19.8	53.1±19.8	.85	31.3±18.7	13.2±10.2	<.001	34.1±24.7	13.8±12.8	<.001	32.1±22.9	14.2±16.5	.006
Health-related quality of life subscore, total[b,d]	52.5±18.4	51.0±23.0	.76	77.0±20.5	91.2±10.7	<.001	72.8±22.5	93.0±8.9	<.001	71.8±25.3	92.4±13.5	.002
36-Item Short Form Health Survey[e]												
Physical component score[b]	43.7±9.1	46.3±9.1	.20	49.1±8.5	52.1±8.3	.15	48.9±7.6	53.8±6.5	.01	47.6±9.9	54.1±5.1	.01
Mental component score[b]	41.6±9.7	44.5±11.5	.21	49.1±9.9	52.6±7.6	.10	44.1±12.6	52.3±8.6	.007	49.5±10.5	53.5±7.7	.17
Short-form McGill Pain Questionnaire total score[f,g]	10.0 (6.0–17.0)	7.0 (2.0–12.0)	.08	3.0 (1.0–9.0)	1.0 (0.0–3.0)	.008	4.0 (1.0–13.0)	1.0 (0.0–3.0)	.01	3.0 (0.0–15.0)	1.0 (0.0–4.0)	.18

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(continued)

TABLE 3
Baseline and longitudinal validated patient-reported measures among treated comprehensive cohort design patients (n=83) *(continued)*

Measure	Baseline			Follow-up								
				6-Month			12-Month			24-Month		
	Magnetic resonance imaging–guided focused ultrasound surgery (n=43)	Uterine artery embolization (n=40)	*P* value[a]	Magnetic resonance imaging–guided focused ultrasound surgery (n=33)	Uterine artery embolization (n=34)	*P* value[a]	Magnetic resonance imaging–guided focused ultrasound surgery (n=26)	Uterine artery embolization (n=29)	*P* value[a]	Magnetic resonance imaging–guided focused ultrasound surgery (n=19)	Uterine artery embolization (n=22)	*P* value[a]
Visual analog scale pain score[f,h]	38.0 (21.0–66.0)	24.5 (4.5–54.0)	.09	15.0 (4.0–34.0)	3.0 (0.0–11.0)	.004	16.0 (2.0–34.0)	3.0 (0.0–12.0)	.008	5.0 (2.0–32.0)	3.5 (0.0–9.0)	.21
Female Sexual Function Index full scale score[i,b]	19.6±10.6	19.3±9.8	.91	24.4±9.8	24.3±9.7	.96	25.8±8.7	24.3±10.2	.58	24.1±9.3	19.9±12.9	.25

[a] *P* values for continuous variables were derived using equal variance *t* tests and Wilcoxon rank sum tests; [b] Data are given as mean±standard deviation; [c] Higher scores indicate greater symptom severity; [d] Higher scores indicate better quality of life; [e] Higher scores indicate better functioning; [f] Data are given as median (interquartile range); [g] Higher scores indicate more pain; [h] Scale of 0, no pain, to 100, worst pain possible; [i] Higher scores indicate better sexual functioning.

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to evaluate the association of treatment and potential risk factors with the cumulative incidence function; associations were summarized with hazard ratios (HRs) and 95% confidence intervals (CIs) estimated from the model parameters.

Sensitivity analyses for patient-reported measures were performed after the use of multiple imputation with Markov chain Monte Carlo and last-observation-carried-forward methods to account for missing data in the longitudinal measures. All calculated probability values were 2-sided, and $P<.05$ was considered statistically significant. Analyses were performed with SAS software (version 9.3; SAS Institute Inc, Cary, NC) and R (version 3.3.1).

Results

Baseline data

Among 83 women who underwent MRgFUS or UAE in the CCD (49 were RCT participants; Figure 1), mean age was 44.4±5.0 years at enrollment, and most participants were white (71%) and overweight (mean body mass index, 27.2±5.9 kg/m^2; Table 2).[12] Uterine and fibroid characteristics were similar between treatment arms, except higher total fibroid load in the UAE arm (mean fibroid load, 362.5±292.3 cc vs MRgFUS, 249.2±159.9 cc; $P=.03$).[12]

Validated measures were similar between treatment arms at baseline (Table 3). The mean UFS-QOL SSS score was 53.9±19.8 for MRgFUS and 53.1±19.8 for UAE,[12] which is consistent with other published trials and indicates substantial fibroid symptoms.[19–21] VAS and MPQ scores were higher at baseline in the MRgFUS arm than the UAE arm, but the differences were not statistically significant.[12] Female Sexual Function Index scores at baseline were low for both treatment arms and were similar to scores in women with sexual arousal disorder.[22]

Primary outcome

Among the 43 women in the MRgFUS arm, 13 (30%) underwent a second fibroid procedure during the study period, compared with 5 of the 40 women (13%) in the UAE arm (Table 4). All subsequent procedures after UAE were hysterectomies,

TABLE 4
Outcomes of participants who were treated in the study

First event or censoring reason	Comprehensive cohort design, n (%)	
	Magnetic resonance imaging–guided ultrasound surgery (n=43)	Uterine artery embolization (n=40)
Second fibroid procedure	13 (30)	5 (12.5)
Hysterectomy	8	5
Myomectomy	3	0
Uterine artery embolization	2	0
Magnetic resonance imaging–guided ultrasound surgery	0	0
Onset of menopause	4 (9)	5 (12.5)
Completed study per protocol	16 (37)	23 (57.5)
Lost to follow-up	7 (16)	5 (12.5)
Withdrew from study	2 (5)	0 (0)
Other[a]	1 (2)	2 (5)

[a] Women who completed the study to 2 years, but the trial ended before they completed the study protocol.

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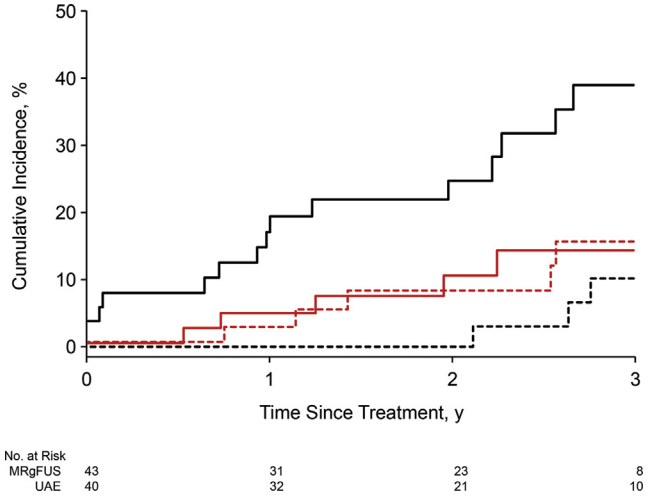
whereas secondary procedures after MRgFUS included hysterectomy, myomectomy, and UAE. In a Fine and Gray[18] competing risk model with menopause as the competing event, the risk of a second fibroid procedure was higher after MRgFUS than after UAE (HR, 2.81; 95% CI, 1.01–7.79; *P*=.047; Figure 2).

FIGURE 2
Cumulative incidence of second uterine fibroid procedure and menopause accounting for competing risk events



Cumulative incidence curves estimate the incidence of a second fibroid procedure (*solid lines*) or onset of menopause (*dashed lines*) for those in the magnetic resonance imaging–guided focused ultrasound surgery group (*black lines*) or the uterine artery embolization group (*red lines*).

MRgFUS, magnetic resonance imaging–guided focused ultrasound surgery; *UAE*, uterine artery embolization.

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Secondary outcomes

Menopause and ovarian reserve

Five women (13%) in the UAE arm and 4 women in the MRgFUS arm (9%) reached menopause during the study period without needing reintervention. The risk of menopause was not significantly different between treatment arms when a second fibroid procedure was considered to be the competing event (MRgFUS vs UAE: HR, 0.67; 95% CI, 0.19–2.34; *P*=.5). Although menopausal events occurred slightly earlier in the UAE subgroup (Figure 2), the mean age at menopause was similar between the 2 groups (UAE, 50.8±2.2 years vs MRgFUS, 49.3±1.4 years).

Baseline AMH samples were obtained in 76 women (92%; Table 5). Both treatment arms had a median baseline AMH level of 0.3 ng/mL; 27% and 31% of women who underwent MRgFUS and UAE, respectively, had undetectable baseline AMH levels. All 9 women who reached menopause during the study period had undetectable baseline AMH levels. As expected, median AMH levels decreased with time (Table 5). At 12 months, the median (IQR) absolute change in AMH was −0.2 (−0.3–0.0) in the MRgFUS arm and 0.0 (−0.3–0.0) in the UAE arm (*P*=.82). At 24 months, median (IQR) absolute change in AMH was significantly larger for the UAE arm (−0.6 [−1.2– −0.4]) than the MRgFUS arm (−0.2 [−0.4–0.4]; *P*=.03). Percentage change was not significant at either timepoint.

Validated patient-reported outcomes

Both treatments resulted in improved fibroid symptoms and health-related quality of life by 6 months on the 2 UFS-QOL subscales, which persisted throughout follow-up (Table 3). However, both subscale scores were significantly better for women who underwent UAE at each posttreatment timepoint (all *P*≤.006). These differences between treatment arms persisted even after adjustment for baseline UFS-QOL scores

TABLE 5
Baseline and longitudinal anti-Müllerian hormone values among treated comprehensive cohort design patients with serum samples[a]

Variable	Baseline			12 Months			24 Months		
	Magnetic resonance imaging–guided ultrasound surgery (n=41)	Uterine artery embolization (n=35)	*P* value[a]	Magnetic resonance imaging–guided ultrasound surgery (n=24)	Uterine artery embolization (n=25)	*P* value[a]	Magnetic resonance imaging–guided ultrasound surgery (n=10)	Uterine artery embolization (n=8)	*P* value[a]
Samples with undetectable anti-Müllerian hormone, n (%)	11 (27)	11 (31)	.66	9 (38)	16 (64)	.06	4 (40)	3 (38)	.91
Anti-Müllerian hormone, ng/mL[b]	0.3 (<0.1–1.1)	0.3 (<0.1–0.9)	.64	0.15 (<0.1–0.6)	<0.1 (<0.1–0.3)	.09	0.15 (<0.1–0.9)	0.15 (<0.1–0.35)	.68
Absolute change from baseline, units[b,c]	—	—		−0.2 (−0.3–0.0)	0.0 (−0.3–0.0)	.82	−0.2 (−0.4–0.4)	−0.6 (−1.2–0.4)	.03
Percentage change from baseline, units[b,d]	—	—		−17.6 (−63.0–0.0)	−10.0 (−66.7–0.0)	.93	−60.8 (−82.0–13.3)	−73.5 (−84.2–61.1)	.17

[a] *P* values were derived with the use of the χ^2 test for the dichotomous variable and the Wilcoxon rank sum test for the continuous variables; [b] Data are given as median (interquartile range); [c] Absolute change calculated as value−baseline value; [d] Percentage change calculated as ((value−baseline value)/baseline value)×100.

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and baseline pain scores (data not shown). Change from baseline to 6 months within each treatment group was also evaluated for each patient-reported measure in additional analyses that used paired *t* tests. Results showed significant improvement in both treatment groups for all measures ($P<.05$ for all; data not shown).

36-Item Short Form Health Survey scores also improved significantly during follow-up for both treatments (Table 3). Patient-reported physical and mental component measures were significantly higher in the UAE arm than MRgFUS at 12 months and for the physical component at 24 months. Regression models that adjusted for score at baseline for each questionnaire were also fit and yielded similar results (data not shown).

Pain scores were also improved at follow-up for both treatment arms (Table 3). The MPQ and VAS scores were significantly lower at 6 and 12 months among women who underwent UAE, compared with MRgFUS; however, the difference was no longer significant after adjustment for baseline pain scores (data not shown). Results were attenuated at 24 months.

At the 6-month and 12-month follow-up, there was similar improvement in sexual function for both treatment arms (Table 3). However, scores decreased for the UAE arm at the 24-month follow-up, with sexual function scores similar to those at baseline.

Multivariate analysis

Additional analyses were performed to assess the effect of baseline predictors on the risk of reintervention. In univariate competing risk models, the risk of a second fibroid procedure was 46% higher with a doubling of pretreatment AMH (HR, 1.46; 95% CI, 1.17−1.82) and 12% lower per 1-year increase in age (HR, 0.88; 95% CI, 0.80−0.97; Table 6).

The following variables were evaluated univariately and in combination for their effect on reintervention: treatment arm, age, AMH levels, VAS scores, and total fibroid load at baseline. Because of the limited number of events, the number of factors was restricted to those with

TABLE 6
Hazard ratios in 12 separate competing risk models using 83 patients in the comprehensive cohort design[a]

Model	Terms included in each model	n	Hazard ratio (95% confidence interval) of predictor[b]				
			Treatment (magnetic resonance imaging–guided ultrasound surgery vs uterine artery embolization)	Log_2 (anti-Müllerian hormone)[c]	Age	Baseline visual analog scale	Log_2 (total fibroid load)
Univariate analysis							
1. Treatment	1	83	2.81 (1.01–7.79)[d]	—	—	—	—
2. Log_2 (anti-Müllerian hormone)	1	76	—	1.46 (1.17–1.82)[d]	—	—	—
3. Age	1	83	—	—	0.88 (0.80–0.97)[d]	—	—
4. Baseline visual analog scale	1	79	—	—	—	1.16 (0.99–1.37)	—
5. Log_2 (total fibroid load)	1	81	—	—	—	—	1.01 (0.69–1.47)
Multivariable analysis of treatment arm and other predictors							
6. Treatment+age	2	83	2.38 (0.82–6.93)	—	0.89 (0.80–0.99)[d]	—	—
7. Treatment+baseline visual analog scale	2	79	3.70 (0.93–14.69)	—	—	1.10 (0.92–1.32)	—
8. Treatment+log_2 (total fibroid load)	2	81	3.43 (1.13–10.48)[d]	—	—	—	1.08 (0.71–1.66)
9. Treatment+log_2 (anti-Müllerian hormone)	2	76	3.36 (0.92–12.28)	1.40 (1.13–1.75)[d]	—	—	—
Multivariable analysis of other predictors without treatment arm[e]							
10. Log_2 (anti-Müllerian hormone)+age	2	76	—	1.32 (1.01–1.73)[d]	0.93 (0.82–1.06)	—	—
11. Log_2 (anti-Müllerian hormone)+baseline visual analog scale	2	73	—	1.52 (1.18–1.95)[d]	—	1.25 (1.01–1.56)[d]	—
12. Log_2 (anti-Müllerian hormone)+log_2 (total fibroid load)	2	75	—	1.48 (1.20–1.84)[d]	—	—	0.95 (0.63–1.45)

[a] Event was considered any second fibroid procedure; competing risk was onset of menopause; [b] Hazard ratio is for magnetic resonance imaging–guided ultrasound surgery vs uterine artery embolization, per a doubling in anti-Müllerian hormone levels (nanograms/milliliters) and total fibroid load (cubic centimeters), per 1-year change in age, and per 10-unit increase in baseline pain on a scale of 0 (no pain)–100 (worst pain possible); [c] Undetectable levels were recoded to 0.09 before applying the log_2 transformation; [d] Denotes significance at the $P<.05$ level; [e] Interaction terms between anti-Müllerian hormone and baseline predictors were tested for all main effects models that contained both terms; none were significant.

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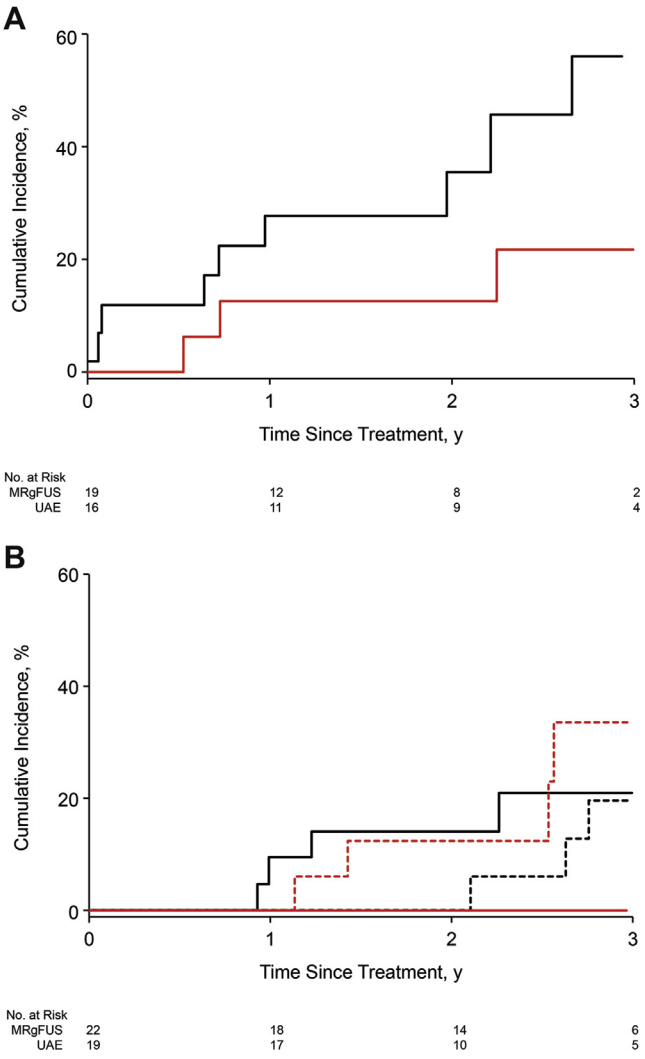
FIGURE 3
Cumulative incidence of second leiomyoma procedure or menopause accounting for competing risk events by anti-Müllerian hormone level



Patients were stratified into **A,** high anti-Müllerian hormone level (>0.3 ng/mL) and **B,** low anti-Müllerian hormone level (≤0.3 ng/mL), based on median anti-Müllerian hormone levels, among all comprehensive cohort design participants with baseline anti-Müllerian hormone levels. Cumulative incidence curves estimate the incidence of a second leiomyoma procedure (*solid lines*) or onset of menopause (*dashed lines*) for those in the magnetic resonance imaging–guided focused ultrasound surgery group (*black lines*) or the uterine artery embolization group (*red lines*).

MRgFUS, magnetic resonance imaging–guided focused ultrasound surgery; *UAE*, uterine artery embolization.

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biologic implications (age and AMH levels) and those that were imbalanced between the treatment arms at baseline (VAS scores and total fibroid load). In multivariate analysis, treatment arm (MRgFUS vs UAE) had a similar magnitude of effect on reintervention as in the unadjusted model but was no longer significant after separate adjustment for AMH level (Table 6, model 9: HR for treatment, 3.36; 95% CI, 0.92–12.28) or age (Table 6, model 6: HR for treatment, 2.38; 95% CI, 0.82–6.93). However, both AMH level and age remained significant after separate adjustment for treatment effect. Interaction terms were not significant in any of the models (data not shown). Competing risk models were also fit with the use of race as a predictor (data not shown); race was not significant in either the unadjusted model or the model separate adjustment for treatment and AMH.

AMH was associated with reintervention in univariate analysis and after separate adjustment for treatment arm, age, and baseline VAS scores (Table 6). When the competing risk analysis was stratified by median AMH value, no participants with a baseline AMH >0.3 ng/mL reached menopause naturally during the study. However, cumulative incidence of reintervention at 3 years was 56.9% in the MRgFUS arm and 23.0% in the UAE arm for women with baseline AMH level higher than median (Figure 3, A). In contrast, in the stratum of low AMH, the cumulative incidence of reintervention was lower (22.1% for MRgFUS and 0.0% for UAE at 3 years; Figure 3, B).

Sensitivity analyses

Of the 83 women who were treated in the CCD, data were missing for the UFS-QOL measures in 15 women (18%) at the 6-month follow-up, 27 women (33%) at the 12-month follow-up, and 41 women (49%) at the 24-month follow-up. Similar patterns were observed in the other validated measures. Multiple imputations of these missing follow-up surveys based on baseline demographic, uterine, and validated measures potentially associated with the missing data and UFS-QOL follow-up measures yielded results that were consistent with the main analysis of these secondary outcomes (data not shown).

Comment

In this comparative effectiveness study, the proportion of women who underwent a second fibroid procedure was higher among those who underwent MRgFUS than those who underwent UAE. However, treatment arm was not the only determinant of outcome. In separate models that were adjusted for treatment, AMH and age were each independent predictors of reintervention (Table 6); younger women and women

with higher AMH levels were more likely to undergo reintervention. Thus, our data suggest that pretreatment AMH level could be used as a tool to help women decide between uterine-sparing procedures or hysterectomy.

In contrast, no baseline uterine or fibroid parameter appeared to affect the need for reintervention. The only observed baseline difference, a higher mean total fibroid load in the UAE arm, was unlikely to have biased the results because all fibroid tumors are treated simultaneously during UAE. Because MRgFUS is a more targeted treatment, having multiple fibroid tumors in the uterus could make complete treatment more difficult. The women with >3 fibroid tumors in our study had similar outcomes as women in the overall study, which indicates that higher fibroid number was not a limitation in this study.

AMH as a predictor of outcome is important for 2 reasons. First, mechanistically, it suggests that fibroid treatment may be mediated both directly by fibroid treatment and indirectly by impairment of ovarian reserve. Second, understanding this relationship in younger women is important because fibroid tumors develop in many women, especially African American women, at younger ages, before they have started or completed childbearing.[23,24] The small changes in AMH levels seen in this study leave open the possibility that the treatment effect may not be clinically significant in younger women with more robust ovarian reserve. In addition, diminished ovarian function after UAE could be contributing to the return to baseline levels of sexual function that was seen at 24 months. The initial improvement in sexual function that was seen at 6 and 12 months is similar to that seen in a previous study,[25] but 1 longer-term study also found improvement out to 2 years, contrary to our findings.[26]

Among the patients who completed the study protocol, symptoms, quality of life, and pain scores remained stable posttreatment within treatment arms, which indicates that improvement at 6 months may predict durability at 2 years. However, it appears that only women who are treated with UAE reach the health-related quality of life levels that were seen in women without fibroid tumors.[27,28]

Our trial provides much- needed information for women with fibroid tumors who prefer a uterine-sparing procedure. There have been no previous prospective comparative effectiveness trials between UAE and MRgFUS; previous studies have used placebo or surgery only as a comparator.[5,7,8,19] Women who elect uterine-sparing procedures are generally different from those who elect to undergo hysterectomy, and long-term comparisons are not equivalent because there is no need for reintervention after hysterectomy. The 1 retrospective cohort study to compare women who underwent UAE and MRgFUS showed similar results to our trial.[20] Interestingly, the average age of women in the MRgFUS group in that study was 6.5 years younger than in the UAE group; thus, the higher reintervention rate in the MRgFUS arm might also be influenced by age and ovarian function, as we found.[20]

This trial also suggests that a CCD may be more feasible and generalizable than a strict RCT for women with fibroid tumors. The genesis of the CCD analysis was the differential dropout rate before treatment in the RCT for the more invasive arm (UAE); thus, allowing women to select a therapy may be more appealing to reproductive-aged women than being assigned randomly.[11]

Limitations of our study include low enrollment (41% of our initial sample size: 91 women were enrolled in the randomized arm or parallel observation arm with a target enrollment of 220 women), which was most likely due to the reproductive-aged women declining randomization. Also, because African American women are more likely to have fibroid tumors, we added sites to increase diversity in our population, but we still did not achieve our targeted enrollment. A second limitation was that not all patients completed questionnaires during follow-up visits, which could have affected our conclusions. Last, the MRgFUS device used throughout the study has now been superseded by newer technology and may not represent the potential of current MRgFUS devices. After the completion of our study in October 2015, the US Food and Drug Administration approved the ExAblate 2100 (InSightec Ltd), which has several advantages over the ExAblate 2000 and new features leading to significantly larger treated volumes while maintaining safety.[29] In a recent study of 252 women who were treated with the ExAblate 2100, the reintervention rate at 19 months was 12.7%,[30] which is comparable with the reintervention rate of UAE in this study.

In this comparative effectiveness trial, a second fibroid procedure was more common after MRgFUS than after UAE, and the magnitude of symptom reduction was less with MRgFUS. However, both UAE and MRgFUS offered substantial short-term fibroid relief and low reintervention rates when women were older or had low AMH levels. ■

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