

# A Physician's Guide to ExAblate® 2000 Magnetic Resonance guided Focused Ultrasound (MRgFUS) for the Treatment of Uterine Fibroids

By Eric Fassler, MD, Focused Ultrasound Northwest, Seattle, WA, USA

## Introduction

ExAblate® 2000 utilizes Magnetic Resonance-guided Focused Ultrasound (MRgFUS) to non-invasively treat symptomatic uterine fibroids (UF). It uses high intensity focused ultrasound energy to ablate tissue in combination with on-going magnetic resonance imaging (MRI), which helps guide and control the treatment. The system provides constant MR thermal feedback, which allows the physician to control and adjust the treatment in real time to ensure that the targeted tumor is fully treated and surrounding tissue is spared.

ExAblate received FDA approval for the treatment of symptomatic uterine fibroids in October 2004 for patients who have completed child bearing or do not intend to become pregnant. It should be noted that the FDA expedited the review of ExAblate 2000 because it offers significant advantages over existing treatments for uterine fibroids. The agency also published an "FDA Talk Paper" on the approval to raise awareness of this important new treatment option.

Our practice has adopted MRgFUS because it provides time, cost and comfort advantages compared with other treatment approaches for uterine fibroids while yielding excellent therapeutic results. Patients in our practice typically lead active lives, and are reluctant to undergo invasive treatments for uterine fibroids that necessitate time off from work, family and other responsibilities. As a non-invasive procedure, MRgFUS allows patients to avoid both the risks associated with surgery as well as lengthy

recovery times and hospitalization days associated with more traditional uterine fibroids treatments, such as hysterectomy.

MRgFUS is performed as an outpatient procedure and, in our experience, patients typically return to a normal routine within 24 hours after treatment. Additionally, MRgFUS leads to rapid resolution of multiple uterine fibroids symptoms and is associated with a very low rate of adverse events and complications.



**ExAblate treatment.** The physician plans and performs the MRgFUS procedure, while the patient lies in the MRI, continuously communicating with the physician.

## Benefits of Fibroid Treatment with MRgFUS

We offer our patients ExAblate for treatment of uterine fibroids because the procedure has multiple benefits compared with watchful waiting, drug therapy, uterine artery embolization (UAE), myomectomy and hysterectomy. Advantages of MRgFUS include: rapid

resolution of uterine fibroids symptoms, short recovery times, fewer post-operative complications compared with UAE or hysterectomy, and a low incidence of complications.

### • Minimal Recovery Time

In our practice, the non-invasive nature of ExAblate is a key driver for patients choosing to undergo the procedure. We have a number of patients who have previously opted not to have interventional therapy for their uterine fibroids because they perceive that the potential benefits of these treatments are outweighed by extended recovery periods that necessitate time off from work and limit their activities. For these patients, MRgFUS is a breakthrough treatment option that provides relief of uterine fibroids symptoms in a manner that is consistent with their active lifestyles.

Because MRgFUS is a non-invasive procedure that allows a rapid return to normal activities, there are documented fewer disability days (decreased days of missed work or days in bed). This may translate into an economic benefit to patients by reducing their time off from work. The procedure also is associated with a lower use of medical resources: 83% fewer physician visits, 66% fewer additional diagnostic tests, and 66% fewer additional procedures.

### • Rapid and Durable Resolution of Fibroid Symptoms

Another benefit of MRgFUS that we have observed is the rapid resolution of pressure-related uterine fibroids symptoms (abdominal pain, back pain, urinary incontinence, etc.) and pain associated with intercourse. Some patients with these symptoms report

improvements within days of treatment. Patients also report that symptoms of heavy and painful periods resolve within two to three menstrual cycles. These results are durable and appear to increase over time.

### • Favorable Safety Profile in Clinical Trials and Commercial Practice

MRgFUS has been shown to have a very favorable safety profile in clinical trials as well as in our own practice. In over 3000 procedures performed worldwide, serious complications have been rare. These have included a few cases of skin burns, of transient nerve damage, and one serious bowel injury related to the procedure. In clinical studies, adverse events have been minimal and generally resolve on the day of treatment or within a few days.

These results compare very favorably with adverse events associated with other, more invasive procedures.

In our own practice, we have observed only one single adverse event. A patient who had a large fibroid and received an intense dose of FUS reported post-treatment abdominal pain. The pain was managed with non-steroidal analgesics and she returned to work the day after treatment. To date, most of our patients treated with MRgFUS have returned to a normal routine within 24 hours of treatment, including several who have engaged in social activities the night of the procedure.

### Comparison of treatment options for uterine fibroids by degree of invasiveness

	Procedure Time	Hospital Days	Return to Normal Activity	Adverse Events
Watchful Waiting	0	0	-	Fibroids can continue to grow, leading to worsening symptoms and the need for surgery
Drug Therapy	0	0	-	Effective for only 6-12 months; causes menopausal symptoms; may result in rapid return of symptoms when treatment is stopped
MRgFUS	3 hours	0	1 day	Skin burns, muscle pain
UAE	0.75-2 hours	1 night	2 weeks	Post embolization syndrome, injury to a vessel or ovaries, blood clots, uterine infection
Myomectomy	1-3 hours	1-3 nights	2-6 weeks	Post op. infection, wound infection, internal organ injury, possible c-section in future pregnancy
Hysterectomy	1.5-3 hours	2-5 nights	4-6 weeks	Post op. infection, bleeding, injury to intestines, bladder, loss of reproductive potential

## Robust Data Support Safety and Efficacy

ExAblate has been evaluated in multiple clinical studies, including the trials that provided the basis for FDA approval. These trials were conducted at world-renowned academic medical centers, including: the Mayo Clinic, Brigham and Women's Hospital, the Lahey Clinic, Johns Hopkins University and the Weill Medical Center.

These clinical trials demonstrated that ExAblate is a safe and effective treatment for uterine fibroids. Additional studies confirm the safety and efficacy and demonstrate that treating a larger volume of the fibroid improves results compared with what was observed in the initial studies (in which a limited portion of the fibroid was treated).

### Summary of MRgFUS Clinical Study Results

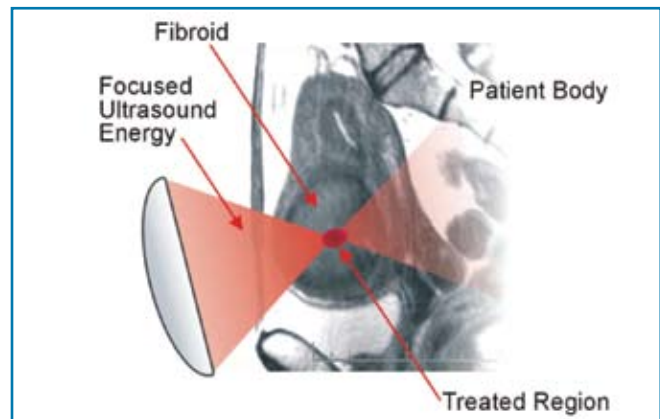
Study	Endpoint	Findings
Pivotal FDA study	Multi-center trial in 109 patients and side by side with 83 patients undergoing total abdominal hysterectomy	Six months post treatment, 79.3% of treated women reported significant improvement in symptoms. FDA approved.
Continued access study	Multi-center study in 160 patients comparing the pivotal protocol with expanded treatment volume and optional second treatment.	At least 87% of patients had improvement in severity of symptoms; the percent of patients with improvements was 5-10% higher using expanded treatment protocols.
African American study	Multi-center study in 73 African American patients	95% of patients showed symptom improvement at 6 and 12 months
Extra large fibroids	Single center study evaluating ablative effect of MRgFUS on fibroids > 10 cm following 3 month GnRH regimen	89% had significant reduction in symptom severity at 12 months

## MR guided Focused Ultrasound: A Breakthrough Technology

Ultrasound is a form of energy that passes through skin, muscle, fat and other soft tissue. When used for diagnostic imaging, low intensity waves produce power densities in the tissue of 0.1 watts per square centimeter and have little to no biologic effect on cells or tissue. However, focused ultrasound (FUS) differs from the type of ultrasound that obstetricians, gynecologists and other physicians use for diagnostic purposes. Focused ultrasound concentrates energy on a specific target and increases the temperature within the targeted tissue, similar to how the sun's rays ignite a flame when focused under a magnifying glass. The transducer used for MRgFUS is able to generate power densities of 1000 watts or more per centimeter, creating heat where the energy is focused that is sufficient to cause tissue death and destruction of the fibroid.

Using MRI to guide the localization of FUS allows these powerful energy waves to be concentrated specifically on fibroid tissue, sparing healthy tissue in the vicinity of the fibroid. The use of magnetic resonance technologies

in MRgFUS not only enables targeted treatment of uterine fibroids, it also allows for real time monitoring and adjustment of the temperature in targeted tissues. This enables the physician to optimize the treatment while it is in progress. MR images with gadolinium

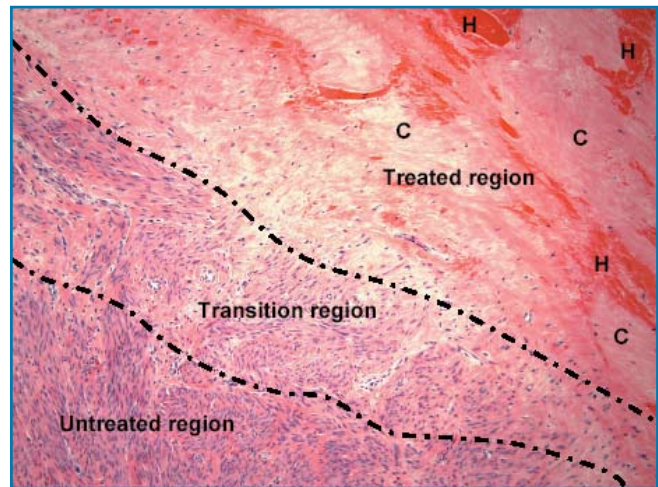


**How focused ultrasound works.** Beam of focused ultrasound energy passes through the skin and uterus to treat a specific spot in the uterine fibroid.

contrast taken at the end of the procedure enable the physician to identify which regions of the fibroid have been ablated and allow an immediate assessment of how successful the treatment was. Subsequent MRI's can be used to assess the effect of treatment on fibroid volume.

The breakthrough technology behind MRgFUS has been recognized with numerous awards, including:

- 2007 Red Herring 100 Prize for Europe, Middle East and Africa
- 2005 Frost & Sullivan Technical Innovation Award
- 2004 Grand Prize of the Information Society Technologies of the European Union
- Wall St. Journal's 2004 Bronze Prize for Technology Innovation.



**Histology analysis of UF treated with ExAblate.** Note sharp demarcation between treated and non-treated regions.

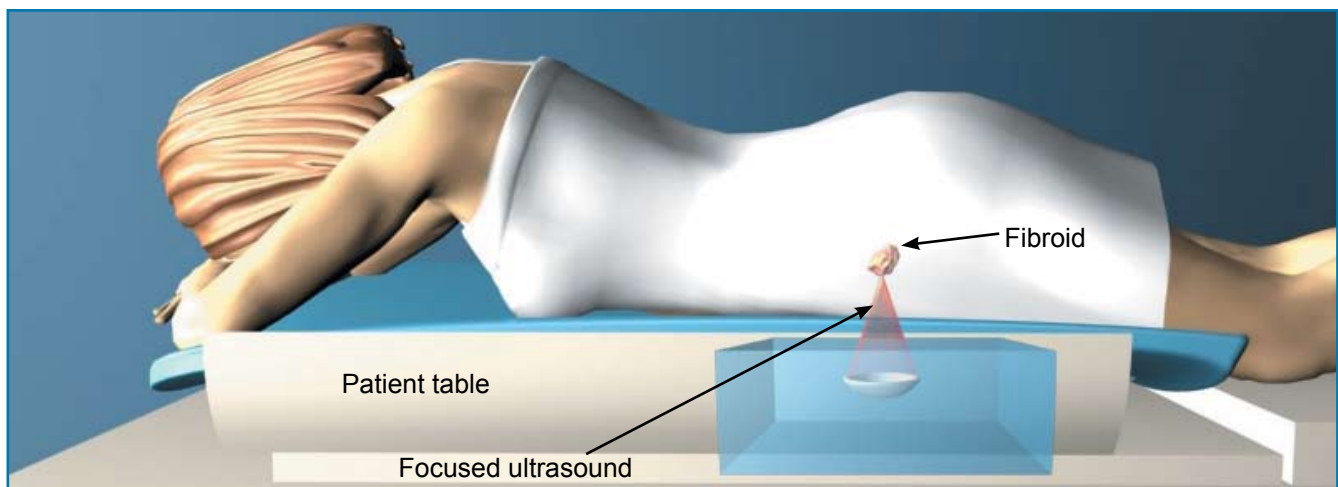
## ExAblate Uterine Fibroid Treatment in Our Practice

In our practice, we offer ExAblate to patients with subserosal, intramural and submucosal uterine fibroids. We do not treat pedunculated fibroids (those that are attached to the uterus by a “stalk”). We do not treat patients when scars or other impediments may absorb energy by being in the beam path. We also do not treat more than 6 fibroids or fibroids which reside deeper than 12 cm from the skin line.

The MRgFUS uterine fibroid procedure is straightforward:

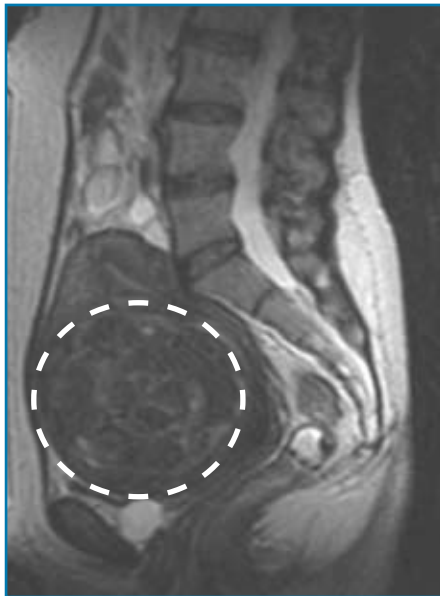
- Prior to the procedure, patients provide informed consent for the treatment and undergo a screening MRI to determine if they are candidates for MRgFUS.

- On the day of the procedure, patients arrive approximately 30 minutes before treatment for placement of an intravenous (IV) line and a Foley catheter. The IV is used to administer anesthesia that allows for conscious sedation, while the catheter collects any urine that accumulates in the patient's bladder while she is undergoing treatment.
- The patient is positioned on the ExAblate 2000 table and moved into the MRI. During the procedure the patient lies on her stomach. In our experience, patients appear comfortable throughout the procedure and the conscious sedation helps them to remain relaxed.



**Patient being treated with ExAblate.** Patient lies prone on a patient table. Sound waves are focused inside the body, similar to how a magnifying glass focuses the sun's rays.

- Once inside the MRI, the patient's abdomen is re-scanned in order to localize the fibroids targeted for treatment, and the treatment plan is created.



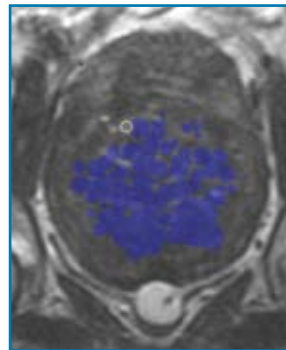
MR image of fibroid. Sagittal view of uterus with target fibroid highlighted.

- Focused ultrasound energy is then applied to targeted tissues, which may include multiple fibroids. The procedure typically takes from 1.5 to 3 hours. Because the patient is conscious during treatment, she can provide feedback about any discomfort and has a button she can use to stop treatment if discomfort becomes too great. In our experience, few patients have had discomfort significant to stop treatment. Additionally, although there have been questions as to patients' willingness to undergo several hours of treatment, we have observed that women who chose

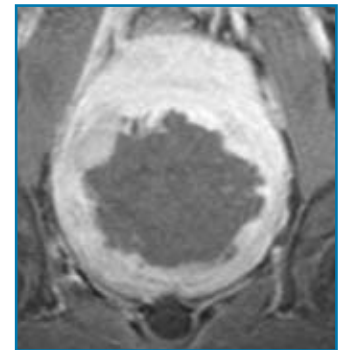
MRgFUS are so glad to have a non-invasive option that they find the minimal discomfort a worthwhile trade-off for finally resolving their uterine fibroids symptoms.

- Following treatment, the patient recovers for about 30 minutes and is then able to resume her normal activities. Most women require nothing more than non-steroidal analgesics.
- In the absence of post-treatment complications (excessive or persistent pain, bleeding), post-treatment follow-up is minimal. In our practice, we may not see patients again for six to 12 months, when they return for their annual check-up.

#### Evaluating treatment outcome



The system tracks the treated area that has reached the temperature threshold for necrosis.



Post-treatment MR image with contrast enhancement. Note similarity between treated area and non-perfused area.

MRgFUS is an important addition to the treatment armamentarium for uterine fibroids that is becoming more widely available in the United States. It should be considered as first line of treatment for your patients.

### Patients Share Their Experiences

*I didn't even realize the extent to which my symptoms had been bothering me until a day after I had the ExAblate procedure, when I'd already noticed improvement (I even noticed a surprising improvement in energy level). I would recommend ExAblate to anyone who is significantly affected by fibroids."*

*D. Shair, CA*

*"The results have been incredible! My period, which for three or more years had lasted for 9 to 12 days at extremely heavy flow, causing me chronic anemia, now lasts 4 days and is normal. Also, I had grown accustomed to an intense feeling of pressure and difficult digestion, so much so that I never even reported them to my physician as issues. These problems are entirely gone. Also, and perhaps this is unrelated, for about a year I was having pain in the backs of my legs when I would sit for long periods, such as on airplane flights. This too has entirely subsided. I began to feel amazing within a couple of weeks of the procedure."*

*J. Prince, CO*

## Bibliography

1. Fennessy FM, Tempany CM, McDannold NJ, So MJ, Hesley G, Gostout B, Kim HS, Holland GA, Sarti DA, Hynynen K, Jolesz FA, Stewart EA. Uterine Leiomyomas: MR Imaging-guided Focused Ultrasound Surgery – Results of Different Treatment Protocols, *Radiology*, 2007.
2. Funaki K, Fukunishi H, Funaki T, Sawada K, Kaji Y, Maruo T. Magnetic Resonance-Guided Focused Ultrasound Surgery for Uterine Fibroids: Relationship between the Therapeutic Effects and Signal Intensity of Pre-existing T2-Weighted MR Images, *Am J Obstet. Gynecol.*, 2007, 196(2):184.e1-6.
3. Hanstede MF, Tempany MC, Stewart EA. Focused Ultrasound Surgery of Intramural Leiomyomas May Facilitate Fertility: A Case Report, *Fertility & Sterility*, 2007.
4. Fukunishi H, Funaki K, Ikuma K, Kaji Y, Sugimura K, Kitazawa R, Kitazawa S. Unsuspected Uterine Leiomyosarcoma: Magnetic Resonance Imaging Findings Before and After Focused Ultrasound Surgery. *Int J Gynecol Cancer*. 2007, Feb.
5. Gavrilova-Jordan LP, Rose CH, Traynor KD, Brost BC, Gostout BS. Successful Term Pregnancy Following MR-guided Focused Ultrasound Treatment of Uterine Leiomyoma, *Journal of Perinatology*, 2007, 27:59-61.
6. Smart OC, Hindley JT, Regan L, Gedroyc W. Gonadotrophin-Releasing Hormone and Magnetic-Resonance-Guided Ultrasound Surgery for Uterine Leiomyomata, *Obstetrics & Gynecology*, 2006, 108(1):49-54.
7. Hesley G, Felmlee JP, Gebhart JB, Dunagan KT, Gorny KR, Kesler JB, Brandt KR, Glantz JN, Gostout BS. Noninvasive Treatment of Uterine Fibroids: Early Mayo Clinic Experience with Magnetic Resonance Imaging-Guided Focused Ultrasound, *Mayo Clinic Proceedings*, 2006, 81(7):936-942.
8. So MJ, Fennessy FM, Zou KH, McDannold N, Hynynen K, Jolesz FA, Stewart EA, Rybicki FJ, Tempany CM. Does the Phase of Menstrual Cycle Affect MR-guided Focused Ultrasound Surgery of Uterine Leiomyomas?, *Eur J of Radiology*, 2006, 59(2):203-207.
9. Smart OC, Hindley JT, Regan L, Gedroyc WMW. Magnetic Resonance guided Focused Ultrasound Surgery of Uterine Fibroids – The Tissue Effects of GnRH Agonist Pre-treatment, *European J of Radiology*, 2006, 59(2):163-167.
10. Stewart EA, Rabinovici J, Tempany C, Inbar Y, Regan L, Gostout B, Hesley G, Kim HS, Hengst S, Gedroyc W. Clinical Outcomes of Focused Ultrasound Surgery for the Treatment of Uterine Fibroids, *Fertility and Sterility*, 2006, 85(1):22-29.
11. Rabinovici J, Inbar Y, Eylon-Cohen S, Schiff E, Hananel A, Freundlich D. Pregnancy and live Birth after Focused Ultrasound Surgery for Symptomatic Focal Adenomyosis: A Case Report, *Human Reproduction*, 2006, pp. 1-5.
12. Fennessy FM, Tempany CM. MRI-guided Focused Ultrasound Surgery of Uterine Leiomyomas, *Acad Radiol.*, 2005, 12:1158-1166.
13. Jolesz F, Hynynen K, McDannold N, Tempany CM. MR Imaging-Controlled Focused Ultrasound Ablation: A Noninvasive Image-Guided Surgery, in Lewin Jonathan S, *Magnetic Resonance Imaging Clinics of North America, MR-Guided Interventions*, 2005, 13(3):545-560.
14. Jacobs MA et al. Uterine Fibroids: Diffusion-Weighted MRI Imaging for Monitoring Therapy with Focused Ultrasound Surgery-Preliminary Study, *Radiology*, 2005, 236:196-203.
15. Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynynen K, McDannold N, Inbar Y, Itzhak Y, Rabinovici J, Kim K, Geschwind JF, Hesley G, Gostout B, Ehrenstein T, Hengst S, Sklair-Levy M, Shushan A, Jolesz F. MRI Guidance of Focused Ultrasound Therapy of Uterine Fibroids: Early Results, *AJR*, 2004, 183:1713-1719.
16. Stewart EA, Gedroyc W, Tempany CM, Quade B, Inbar Y, Ehrenstein T, Shushan A, Hindley J, Goldin R, David M, Sklair M, Rabinovici J. Focused Ultrasound Treatment of Uterine Fibroids: Safety and Feasibility of a Noninvasive Thermoablative Technique, *Am J Obstet Gynecol*, 2003, pp. 48-54.
17. Tempany CM, Stewart EA, McDannold N, Quade B, Jolesz F, Hynynen K. MRI Guided Focused Ultrasound Surgery (FUS) of Uterine Leiomyomas: A Feasibility Study, *Radiology*, 2003, 227:897-905.

## About the Author



Dr. Eric Fassler has been practicing OB/GYN in Washington for 17 years. He is a member of Women's and Family Health Specialists, a practice in suburban Seattle that combines Obstetrics and Gynecology with family medicine. Dr. Fassler has always had an interest in gynecology, with a

special interest in minimally invasive surgery and other alternatives to major abdominal procedures, and his group is one of the leading practices in the Seattle area

in laparoscopic procedures for the treatment of ovarian and other pelvic disorders. He and his partners began performing endometrial ablations for the treatment of abnormal bleeding as an alternative to hysterectomy in 1992, and have performed more ablations than any other group in Washington. He has completed his obstetric and gynecology training at the University of Arizona.

Dr. Fassler was one of the first gynecologists in the United States trained in the use of the focused ultrasound for the treatment of uterine fibroids using the ExAblate 2000 system. He also is a member of Focused Ultrasound Northwest, a designated training site where Dr. Fassler and his colleagues are training other physicians wanting to learn about this breakthrough procedure.