

TECHNOLOGY

A look at the latest fibroid treatments, including uterine artery embolization, focused ultrasound, and drug therapy.

Not long ago, women with uterine fibroids had to choose between hysterectomy and abdominal myomectomy to alleviate their symptoms. Then came minimally invasive surgeries such as laparoscopic myomectomy and hysteroscopic myoma resection, although even now these surgeries are offered by a limited number of skilled gynecologic surgeons. And despite their substantially shorter recovery times, these procedures are still surgeries, with inherent complications.

On top of that, long-term outcomes data are limited.

Enter the next generation of fibroid treatments: uterine artery embolization (UAE), focused ultrasound with magnetic resonance imaging (MRI) guidance, and selective progesterone receptor modulators—though the last option is still in the pipeline. Gynecologists will be seeing advertisements and promotional materials for these interventions in the near and not-so-distant future.

Uterine artery embolization: In the right hands, a worthwhile strategy

Myers ER, Goodwin S, Landow W, et al. Prospective data collection of a new procedure by a specialty society: the FIBROID Registry. Obstet Gynecol. 2005;106:44–51.

Worthington-Kirsch R, Spies JB, Myers ER, et al. The Fibroid Registry for outcomes data (FIBROID) for uterine embolization: short-term outcomes. Obstet Gynecol. 2005;106:52–59.

Congratulations are in order. When the Society of Interventional Radiology created the Fibroid Registry in 2000, it was looking for early data on UAE to share with patients. In its short but impressive life, the registry has collected more data about UAE than we have about “tried-and-true” surgeries.

In the United States, UAE was first used to treat fibroids in 1997. Although numerous studies since then have reported on its safety and effectiveness, many gynecologists continue to question the suitability of UAE for symptomatic women.

The Web-based registry was established with Duke Clinical Research Institute to track short- and long-term outcomes after UAE in various settings.

What we know from the registry
The Fibroid Registry enrolled its first patient in December 2000, and collected data from 72 sites on 3,319 UAE procedures through December 2002. The



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reports by Myers et al and Worthington-Kirsch and colleagues contain patient demographics, procedural details, and 30-day outcomes.

The registry defined adverse events as any unexpected event that necessitated an unscheduled office or emergency room visit or unanticipated therapy (medical or surgical). Major complications required increased care or additional hospitalization or had permanent adverse sequelae. Minor complications required medical management or no therapy.

Thirty-day outcomes were available for approximately 91% of patients.

A low complication rate

Complications were uncommon during the first 30 days after UAE, with a 1.1% incidence of additional surgery. In fact, complication rates and recovery times compared favorably with myomectomy and abdominal hysterectomy for large fibroids.

The UAE procedure averaged 56 minutes, with 96.2% technical success and a return to normal activities in about 2 weeks.

Other findings:

- 26% of patients had an adverse event, but only 4% had a major event, most commonly emergency care or hospital readmission for pain management (2.1%) or possible infection (<1%).
- 31 women required another procedure within 30 days, including 3 myomectomies, 9 dilatation and curettage procedures for sloughing leiomyomata, 5 hysteroscopic resections, and 3 hysterectomies for unrecorded indications.
- 1 patient was hospitalized for pain 10 days after UAE and underwent exploratory laparotomy with bilateral oophorectomy.
- The most common minor adverse events were hot flushes (5.7%) and pain requiring additional therapy (9.6%).

Predictors of adverse outcomes:

- current or recent smoking (odds ratio [OR] 1.14, 95% confidence interval [CI] 1.007–1.293),

- African-American race (OR 1.129, 95% CI 1.019–1.251),
- prior procedures (OR 1.23, 95% CI 1.02–1.38), and
- duration of procedure (OR 1.004, 95% CI 1.001–1.006).

Interestingly, short-term outcomes did not differ among centers, nor did procedure times, length of stay, and incidence of adverse events during the first 30 days.

What to tell patients

I inform patients with symptomatic fibroids about all available treatments—including the option of doing nothing at all. Most have no interest in UAE, and are distressed by the thought of their bodies reabsorbing dead tissue.

However, I have had several patients whose operative risks were very high. For example, 1 woman was morbidly obese (>250 lb, which required her UAE treatment at a special facility equipped to perform fluoroscopy in morbidly obese patients), hypertensive, diabetic, and hemiparetic after a stroke. She was also a Jehovah's Witness. Obviously, nonsurgical intervention was to her benefit. Her bleeding stopped almost immediately.

A reasonable alternative

The lay press recently focused on our obligation, as ObGyns, to inform patients about alternative therapies for fibroids. These first reports from the Fibroid Registry are clear: UAE is a reproducible, low-risk procedure—certainly lower in risk than complex surgeries (though situations may arise when myomectomy is preferred, such as a desire for future fertility¹).

The registry will continue to provide data we can share with our patients regarding risks, complications, and long-term outcomes. More importantly, our radiology colleagues have taken the lead in developing a voluntary patient registry to track the outcomes of new technology as it disseminates into the general medical community. Our patients would be well served if we developed similar registries to track our surgical outcomes.

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Counsel women about *all* fibroid treatments—including the option of doing nothing

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Focused ultrasound shrinks fibroids, but has strict eligibility requirements

Hindley J, Gedroyc WM, Regan L, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. *AJR Am J Roentgenol.* 2004;183:1713-1719.

Using MRI guidance, a completely noninvasive treatment is now possible: focused ultrasound ablation of uterine fibroids. This procedure, the newest high-tech treatment for symptomatic fibroids, was successfully tested in an earlier pilot study.² Although it eased symptoms to a remarkable degree during this phase III trial, how many women will ultimately be suitable for the treatment remains unclear.

Selection criteria

This trial of the ExAblate 2000 (*InSightec, Tirat Carmel, Israel*) recruited symptomatic women who were otherwise suitable candidates for conventional surgeries. Excluded were postmenopausal patients, women weighing more than 250 lb, and women who had a uterus larger than 24 weeks' size or any single myoma larger than 10 cm. Women with extensive abdominal scars were carefully examined and excluded if the scars lay in the path of the ultrasound beam. The reason: During the earlier study, these scars tended to absorb ultrasound energy, increasing the risk of thermal injury at the skin surface.

Before proceeding, patients underwent MRI or ultrasound to confirm a clear pathway from the anterior abdominal wall to the fibroids without traversing the bladder or bowel.

Hindley et al did not reveal how many women were initially screened, but 109 were finally enrolled at 7 international sites and completed a Uterine Fibroid Symptoms and Quality of Life Questionnaire before and 3 and 6 months after treatment. As for the location of the fibroids: 22% were submucosal, 57% were intramural, and 21% were subserosal.

Up to 4 fibroids were treated per patient—with MRI mapping and thermographic monitoring—with a margin of 1.5

cm from the edge of the ablated area to the edge of the uterus. Conscious sedation was provided as needed, and tolerance of the procedure was measured using a 4-point pain scale. Mean time in the MRI scanner was 202 minutes (range, 90-370 minutes).

Pain stopped when treatment ended

Most women reported mild to moderate pain during the procedure (66%), and 16% complained of severe pain. This discomfort ended immediately when treatment stopped in virtually all patients—only 1% reported severe pain afterwards.

Adverse events

Serious adverse events included: 5 women with heavy menses requiring blood transfusions, 1 patient with pain and bleeding consistent with preprocedure symptoms, 1 woman needing overnight hospitalization for nausea related to opioid analgesia during the procedure, and 1 patient with leg and buttock pain immediately after treatment (it was later discovered that the sciatic nerve was in the far field of the sonication pathway). These symptoms resolved by the follow-up visit.

Two other patients had adverse events unrelated to the procedure.

6-month outcomes

The mean fibroid volume reduction was 13.5% ± 32%. Although this improvement seems modest, women reported significant relief from fibroid-related symptoms, and the mean severity score on the quality-of-life questionnaire decreased.

Substantial improvement was seen for both mass effect and bleeding symptoms (32.8 points out of 100 for each).

Pros and cons for symptomatic women
Advantages over UAE include the absence

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Pain during focused ultrasound eased as soon as the procedure ended

of postprocedural pain in almost all patients, which eliminates the need for an overnight stay and likely speeds the return to normal activities.

Disadvantages are that women with major abdominal scarring, anterior myomas underneath the bladder flap, or adhesive disease that causes small or large bowel to lie in the path of the sound waves cannot take

advantage of this new technology, nor can women who have myomas close to neurovascular bundles. Add to that the extremely long procedure time (over 3 hours) and the modest reduction in uterine volume.

Six-month outcomes are promising, but this approach is probably best reserved for an academic setting, so careful screening and long-term tracking can continue.

A drug of great promise

Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev. 2005;26:423-438.

In this comprehensive review, the authors draw from their extensive expertise in endocrinology to describe the rationale behind asoprisnil, a mixed progesterone receptor agonist/antagonist—the most promising pharmaceutical development in gynecology in several decades.

How the drug works

Mifepristone (RU-486) was the first progesterone receptor antagonist. Despite its ability to reduce myoma volume and suppress endometriosis symptoms in small pilot studies, it induces endometrial hyperplasia at doses higher than 5 to 10 mg, probably by acting similarly to unopposed estrogen. In contrast, asoprisnil has antiproliferative effects and no labor-inducing activity. It directly affects blood vessels in the endometrium, creating a local antiproliferative effect that induces amenorrhea despite normal estrogen levels.

What phase II studies reveal

A multicenter, double-blind, placebo-controlled trial involved 5-, 10-, and 25-mg daily doses of oral asoprisnil over 12 weeks. In a dose-dependent manner, asoprisnil induced amenorrhea or significantly suppressed bleeding without causing breakthrough or intermenstrual flow. It also decreased the volume of both the largest fibroid and the uterus as a whole. At 10- and 25-mg doses, pressure symp-

toms eased substantially over placebo. Adverse effects were minimal and affected the placebo and asoprisnil groups equally.

Phase III trials are now under way to assess the safety and efficacy of asoprisnil in the treatment of menorrhagia and uterine fibroids. Early results in the treatment of endometriosis are also promising.

What this means for fibroid patients

Though asoprisnil is not yet available for use, the phase III trial is winding down and the drug's impressive potential seems clear.

A useful strategy may be to counsel marginally symptomatic women with fibroids that treatments are in the pipeline that would permit pharmaceutical management of their symptoms. Because this drug induces amenorrhea in the presence of normal circulating estrogen levels, it eliminates hot flashes and, more importantly, the bone loss associated with gonadotropin-releasing hormone agonists.

REFERENCES

1. Pron G, Mocarski E, Bennett J, et al. Pregnancy after uterine artery embolization for leiomyomata: the Ontario multicenter trial. *Obstet Gynecol.* 2005;105:67-76.
2. Stewart EA, Gedroyc WM, Tempany CM, et al. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. *Am J Obstet Gynecol.* 2003;189:48-54.

DISCLOSURE

The author reports no financial relationships relevant to this article.

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Asoprisnil has antiproliferative effects that induce amenorrhea despite normal estrogen levels