Uterine leiomyomas, commonly known as fibroids, are the most common neoplasm of the female reproductive tract, affecting 20% to 40% of premenopausal women. Leiomyomas are benign, monoclonal tumors composed of smooth muscle cells and an abundant extracellular matrix of collagens, proteoglycans, and fibronectin. Many leiomyomas are small and asymptomatic, but larger leiomyomas and those in specific locations can cause debilitating health problems. Common symptoms include heavy or prolonged menstrual bleeding, pelvic discomfort, dyspareunia, and bladder dysfunction. Leiomyomas also have been implicated in reproductive difficulties such as infertility, multiple miscarriages, and preterm labor.

Leiomyomas are the primary indication for hysterectomy, leading to at least 140 000 hysterectomies and 37 000 myomectomies each year in the United States. Based on hospital discharge information, more than $2 billion was spent on inpatient charges for procedures in 1997 alone.

Although their exact etiology is uncertain, leiomyomas are likely the end result of a confluence of genetic, hormonal, and environmental factors. Estrogen, progesterone, and local growth factors stimulate the proliferation of uterine smooth muscle cells and may alter the normal course of programmed cell death. Approximately 40% of leiomyomas have non-random chromosomal rearrangements, translocations, or deletions. Malignant transformation
of leiomyomas is extremely rare. Epidemiologic studies have shown that African American women are about 3 times more likely than white women to be diagnosed with leiomyomas.\textsuperscript{6,7} Other risk factors include early menarche, nulliparity, late age at first birth, high body mass index, and familial predisposition.\textsuperscript{7,8}

The list of treatment options for women with symptomatic leiomyomas is expanding at a rapid rate. Gone are the days when a woman was restricted to hysterectomy or myomectomy. Laparoscopic myolysis, introduced in Europe in the late 1980s, has been slow to gain popularity in the United States.\textsuperscript{9} New procedures such as uterine artery embolization (UAE) and high-intensity focused ultrasound (HIFU) are in demand by women who want to preserve their uteri and minimize recovery time.

Although hormonal manipulation using birth control pills or gonadotropin-releasing analogues can ameliorate abnormal uterine bleeding temporarily, there are no effective pharmacologic therapies on the market at this time. On the horizon are medical therapies targeting sex steroid receptors,\textsuperscript{10} enzymes of estrogen metabolism,\textsuperscript{11} and peptide growth factors.\textsuperscript{12} Also in development are a variety of gene therapies in which genetic material, delivered into target cells, can alter replication or hasten cell death.\textsuperscript{12} Although some of these therapies are years away from clinical implementation, others are in use today. It is important for healthcare providers to review the efficacy and quality-of-life outcomes for traditional therapies as well as to learn how to counsel patients about new and emerging approaches to management of uterine leiomyomas.

**Traditional Therapies**

From the 1950s to the 1980s, treatment options for women with symptomatic leiomyomas were limited to hysterectomy and myomectomy.

**Hysterectomy**

Hysterectomy remains the most common treatment for leiomyomas because it provides guaranteed resolution of bleeding and eliminates the possibility of new leiomyoma growth. A number of factors, including uterine size, prior pelvic surgery, and a surgeon’s expertise, dictate whether a hysterectomy can be performed via a laparotomy, laparoscopy, or transvaginally. Data have shown that the majority of women who undergo hysterectomy report improvement in health-related quality-of-life scores and rarely experience detrimental effects on their sexual function.\textsuperscript{13,14} Nonetheless, hysterectomy is associated with a 4- to 8-week recovery and risk for major complications. Injury to pelvic structures and hemorrhage, possibly requiring blood transfusions, are relatively common events.

**Myomectomy**

Myomectomy, a procedure in which leiomyomas are excised and the uterus preserved, can be performed by laparotomy, laparoscopy, or hysteroscopy. Although rates of symptom improvement exceed 80%, the risk of new leiomyoma growth is as high as 50% after 5 years using this procedure.\textsuperscript{15} Traditionally, myomectomy was reserved for women who desired future childbearing; however, recently women of all ages are choosing to conserve their uteri despite the chance for persistent symptoms and future leiomyoma development.

**New Therapies**

**Uterine Artery Embolization**

UAE for leiomyomas, first described by Ravina et al in 1995,\textsuperscript{16} has gained tremendous popularity in the United States and Europe, with an estimated 14,000 procedures performed annually in the United States alone. The goal of UAE is to significantly reduce perfusion of leiomyomas by occluding the uterine arteries. It is performed by an interventional radiologist who introduces a catheter into a patient’s femoral artery and uses real-time fluoroscopic imaging to guide it through the pelvic vasculature and into the uterine arteries. Small particles of polyvinyl alcohol or tris-acryl gelatin microspheres, injected into each uterine artery, adhere together to form an obstruction to blood flow. Without sufficient perfusion, the leiomyomas become ischemic, leading to degeneration and involution. Collateral blood flow through ovarian and cervical arteries prevents uterine necrosis. Patients undergoing UAE receive conscious sedation and usually remain 1 night in the hospital for pain control. Many women resume light activities within a few days and the majority of women are able to return to normal activities within 7 to 10 days.\textsuperscript{17}

Figure 1 illustrates the abundant vascularity associated with leiomyomas before UAE and the absence of blood flow after UAE. Figure 2 shows the sequence of contrast-enhanced magnetic resonance (MR) images before and after UAE in a 53-year-old woman with menorrhagia and a large fundal leiomyoma. In panel 1, the hypervascular leiomyoma and enlarged uterus significantly compress the bladder. Subsequent images demonstrate the loss of perfusion into the leiomyoma, reduction in leiomyoma size, and restoration of full bladder capacity.

Observational studies have described the outcomes of more than 3000 patients who have undergone UAE. Overall, the mean reduction in leiomyoma size ranged from 31% to 52%.\textsuperscript{18-23} Based on patient self-reports, 85% to 90% experience significant improvement in both bulk-related symptoms and menorrhagia following UAE.\textsuperscript{18-23}

The Fibroid Registry for Outcomes Data
(FIBROID), the largest multicenter prospective registry, recently published the outcomes of 1700 women who have completed 1 year of follow-up.24 The mean symptom score and mean health-related quality-of-life score improved significantly, with only 5% of the subjects reporting no improvement. After 1 year, 82% of the women would recommend UAE to family members or friends. Predictors for symptom improvement included small leiomyoma size, submucosal location, and preprocedure menorrhagia. In the first 12 months after UAE, slightly fewer than 10% of the patients underwent an additional surgical procedure, such as hysterectomy, myomectomy, or dilatation and curettage.

Long-term, prospective outcome data are limited to one study of 200 women who were followed for 5 years.25 Of the 91% who completed follow-up, 73% had durable symptom improvement and 20% had undergone a major surgical intervention. Among the 76% reporting satisfaction, predictors for a positive experience were diminished bleeding and pain as well as a greater reduction in leiomyoma volume than experienced by their less satisfied counterparts.

PATIENT SELECTION

Patient selection for UAE must take several factors into consideration, including uterine size, leiomyoma size and location, and desire for future childbearing. Published data are inconsistent regarding the effect of uterine and leiomyoma size on UAE success. One small case series evaluating uterine size found that efficacy was not decreased in women with uterine size ≥24 week gravid uterus.26 Similarly, a study of 47 women with leiomyomas ≥10 cm experienced no increased risks and had comparable clinical outcomes with those of 105 women who had smaller leiomyomas.27 Conversely, data from another study showed that women with leiomyomas larger than the median baseline volume were 3 times more likely to fail than were those with smaller leiomyoma volumes.25

The association between leiomyoma location and UAE outcomes has not been formally studied, however anecdotal evidence suggests that leiomyomas within the uterine cavity are associated with higher rates of persistent abnormal bleeding, transcervical leiomyoma expulsion, and endomyometritis. Similarly, embolization of exophytic subserosal leiomyomas may result in higher rates of pelvic pain, hysterectomy, and systemic infectious morbidity.

At this author’s institution, UAE is not offered to women who hope to have children in the future, except in special cases in which myomectomy is not feasible. In a recent study, 7.3% of the 1701 women followed for 1 year after UAE developed ovarian failure.24 Although this was more likely to occur in women in their 40s, 3 of the 125 women in their 30s were affected.24 Because ovarian failure is irreversible and can occur at any age, UAE should be reserved for women who have completed childbearing.

Nonetheless, several small case series have been published describing pregnancy outcomes among women who have undergone UAE. One review of 34 pregnancies reported high rates of miscarriage (32%), malpresentation (22%), cesarean delivery (65%), preterm delivery (22%), and postpartum hemorrhage (9%).28 A separate
study comparing UAE and laparoscopic myomectomy found comparable pregnancy outcomes in both groups for most of these complications. However, UAE was associated with a greater risk for preterm delivery and malpresentation than was laparoscopic myomectomy.

**Uterine Artery Embolization Versus Hysterectomy and Myomectomy**

Women choosing between UAE and hysterectomy should take into consideration data comparing the 2 treatments. A multicenter, prospective study of 102 patients treated with UAE and 50 patients having hysterectomy reported shorter hospital stays, fewer complications, and a faster return to work following UAE. Both procedures demonstrated marked improvement in patient assessment of overall health. After 12 months of follow-up, women who had undergone hysterectomy had improvement in pelvic pain compared with the UAE group (98% vs 84%, \( P = .021 \)). Overall morbidity was significantly higher in the hysterectomy group (34% vs 15%; \( P = .01 \)), specifically in regards to hemorrhage during the procedure (8% vs 0%; \( P = .01 \)).

A randomized controlled trial of 177 premenopausal women previously scheduled for hysterectomy was performed to evaluate the peri- and postprocedure complication rates in women undergoing hysterectomy and UAE. Although major and minor complication rates in both groups were comparable, minor complications were statistically higher in the UAE group during the first 6 weeks after discharge from the hospital.

A recent, multicenter, prospective cohort study compared the outcomes of 149 women who underwent UAE with 60 women who underwent myomectomy. Both groups experienced statistically significant improvements in the uterine leiomyoma quality-of-life score, menstrual bleeding patterns, and uterine volume reduction. Women undergoing UAE required fewer days in the hospital (1 vs 2.5 days), fewer days off from work (10 vs 37 days), and had fewer adverse events (20.1% vs 40.1%) compared with the myomectomy group.

**Conclusions and Recommendations**

UAE is an effective procedure for women who have completed childbearing. Advantages over myomectomy and hysterectomy include avoidance of general anesthesia, shorter hospital stays, and faster return to daily activities. Nonetheless, women should be aware that complications such as uterine infections necessitating a hysterectomy (<0.5%), partial leiomyoma expulsion requiring hysteroscopic removal (<2%), and ovarian failure leading to an early menopause can occur in as many as 5% of women in their 40s. Relative contraindications to UAE are submucosal leiomyomas that extend to ≥50% of the uterine cavity, which should be removed hysteroscopically, and exo-phytic, pedunculated leiomyomas, which should be excised laparoscopically or by minilaparotomy.

**High-Intensity Focused Ultrasound**

HIFU is a promising technology that has been used in a variety of medical settings, including the treatment of benign prostatic hyperplasia, prostate cancer, and soft-tissue tumors of the liver and kidney. Unlike diagnostic ultrasound in which sound waves generated by the transducer are parallel to one another, HIFU uses converging sound beams to create a focus of intense heat within a well-defined area. This principle allows for harmless transmission of energy through the skin and internal structures, but the creation of temperatures in excess of 60°C within targeted tissues. This results in protein denaturation, coagulative necrosis, and irreversible cell damage.

To enable accurate tissue targeting, both MR-guided and ultrasound (US)-guided imaging systems have been coupled to HIFU. An advantage of the MR-guided focused ultrasound (MRgFUS) is the ability to measure the temperature within the targeted tissue in real time, allowing the physician to adjust treatment parameters as needed. Following therapy, contrast-enhanced MR imaging is used to map the regions of ablated tissue (Figure 3).

The first commercially available MRgFUS system

**Figure 3. Magnetic Resonance-Guided Focused Ultrasound**

A: Sagittal T2-weighted MR image of the uterus used to locate the leiomyoma and ensure proper patient positioning.
B: The designated region intended for treatment of the leiomyoma (orange). The system marks the area targeted for sonifications (green circles).
C: Accumulated dose during treatment. Thermal imaging displays areas that have exceeded the threshold sufficient for 100% cell necrosis (blue).
D: Post-treatment T1-weighted contrast enhanced MR image shows the nonperfusing treatment area.

Images courtesy of InSightec and Sheba Medical Center, Israel.
was approved by the US Food and Drug Administration (FDA) for the treatment of leiomyomas in October 2004. For the duration of the 2- to 4-hour outpatient procedure, a woman lays prone with her abdomen positioned over the HIFU apparatus and within the MR magnet. Pain control consists of narcotics, nonsteroidal anti-inflammatory drugs, and benzodiazepines. The recovery time is minimal with most women returning to full activities in 1 to 2 days.

The first published study of MRgFUS confirmed the safety and feasibility of the procedure in 55 subjects. A second study evaluated symptom improvement in 109 patients undergoing MRgFUS. Study inclusion criteria were a leiomyoma size ≤10 cm and uterine size ≤24 weeks. The FDA-approved study had stringent safety guidelines requiring a minimum margin of 1.5 cm from the edge of the ablated tissue to the serosa of the uterus. As a result, on average, only 10% of the leiomyoma volume was sonicated. In spite of the strict treatment guidelines, 71% of the patients reported significant symptom improvement after 6 months and 51% reported persistent improvement after 12 months. Reduction in leiomyoma volume at 6 and 12 months correlated with the treatment area. Complications were rare and most women reported high satisfaction.

**Conclusions and Recommendations**

HIFU is a powerful technology with the potential for treating leiomyomas as well as a variety of other tumors. Given the limited data, it is too early to verify the efficacy and safety of MRgFUS at this time. US-guided HIFU may diminish the cost associated with MR, however, technical barriers remain before human trials can begin.

**Myolysis**

Laparoscopic myolysis is another method for the thermal destruction and devascularization of leiomyoma tissue. Different energy sources, including the Nd:YAG laser, carbon dioxide laser, bipolar needles, and radiofrequency needle electrodes, have been used to make multiple perforations into the leiomyoma over the entire surface. Similarly, laparoscopic cryomyolysis employs a probe that causes cell necrosis by reducing the tissue temperature to -20°C. The literature contains a number of small case series claiming successful reduction in leiomyoma volume and symptoms, but all of these studies have short follow-up and lack comparison groups. Another limitation of this approach is the finding of dense adhesions between the uterus and surrounding structures in 10% to 50% of the women treated with the Nd:YAG laser and bipolar needles. The safety of myolysis in women who want to conceive has not been established.

**Future Directions for Therapy**

**Selective Progesterone Receptor Modulators and Progesterone Antagonists**

For many years, it has been known that the female hormones estrogen and progesterone play an important role in promoting growth of leiomyomas. Recently a new class of medications that selectively blocks progesterone receptors has been investigated for its beneficial effects on leiomyomas. This class of drugs known as selective progesterone receptor modulators (SPRMs) has many favorable characteristics. For example, these agents are highly selective for the endometrium and myometrium and are highly specific to the progesterone receptor. By competitively binding to progesterone receptors, they prevent the biologic effects of the endogenous hormone. As a class, these drugs have a range of activity, with some acting as complete progesterone antagonists and others exhibiting partial agonist and antagonist effects. Because they are progesterone selective, they do not suppress estrogen production.

Mifepristone, also known as RU-486, was the first progesterone antagonist investigated for leiomyoma treatment. Although mifepristone is an FDA-approved therapy for medical abortions, it is not approved for the treatment of leiomyomas. In the setting of pregnancy terminations, mifepristone is administered in a 200-mg dose. Conversely, in clinical trials of women with leiomyomas, mifepristone doses ranged from 5 mg to 25 mg daily for 3 to 6 months. A systematic review of 6 investigative studies of mifepristone for leiomyomas reported uterine and leiomyoma size reduction ranging from 26% to 74%. In addition, overall symptoms improved in 70% to 75% of the treated subjects.

Although apparently effective, mifepristone does have several side effects. Nearly all treated women experienced amenorrhea, which reversed following discontinuation of mifepristone. Interestingly, hot flushes were reported by 38% of the subjects even though estradiol levels were within the early follicular range. The most significant adverse effect was endometrial hyperplasia resulting from unopposed estrogen effects on the endometrium. Simple endometrial hyperplasia, detected in approximately 10% of the subjects, could prohibit further clinical development of this agent. No cases of cellular atypia or complex hyperplasia were reported, but long-term data are needed in this area.

Asoprisnil, which has yet to be FDA-approved for any indication, is the first SPRM to reach advanced clinical development in multiple, large, placebo-controlled trials. In theory, because asoprisnil is a partial progesterone agonist, it may cause less endometrial hyperplasia than mifepristone, but that has not been proven. Phase II trials showed a progressive reduction in
uterginal and leiomyoma size over time, with a correlation between dose and effect.44 In addition, more than two thirds of subjects receiving asoprisnil reported symptom improvement compared with one third of the subjects receiving placebo. Although the incidence of side effects is not yet known, rates of amenorrhea in subjects taking 10 mg/day and 25 mg/day were 64% and 83%, respectively. In animal models, exposure to asoprisnil during pregnancy caused craniofacial abnormalities.

CONCLUSION AND RECOMMENDATIONS

The prospect of a medical treatment for leiomyomas is exciting and promising, but many questions remain. Although mifepristone is efficacious for reducing leiomyoma size and symptoms, the manufacturer has not pursued FDA approval for this indication thus far. Clinical trials of asoprisnil are ongoing but several hurdles remain. Because asoprisnil is teratogenic at low doses in animals, effective, nonhormonal birth control methods will be imperative for users.

GENE THERAPY

Leiomyomas have several inherent biologic features that make them favorable targets for gene therapy. In1998, Niu et al were the first to describe the successful transfer of a gene lethal to human and rat cultured uterine leiomyoma cells.42 Importantly, the genetic material was cytotoxic not only to the 5% of transfected cells but it also mediated a “bystander effect” in which cell death occurred in 48% of the nontransfected cells. Another potential target for gene therapy is the signaling pathway for estrogen and progesterone. Al-Hendy et al were able to transfect a human leiomyoma cell line with a gene coding for an abnormal estrogen receptor (ER).43 The mutant ER adhered to the wild-type ER, making it unable to bind the estrogen-responsive element and unable to activate transcription. Although this work is still far from clinical application, leiomyoma-specific gene therapy may provide women with a nonsurgical alternative in the future.

CONCLUSION

The last 10 years have seen a virtual explosion in less-invasive treatment options for leiomyomas, including uterine artery embolization, MR-guided focused ultrasound, and myolysis. Although preliminary results are promising, complications can occur, long-term data are lacking, and appropriate patient selection is paramount. Physicians need to be prepared to discuss these options with their patients, many of whom will have researched them online prior to their office visit. Even if a traditional hysterectomy is ultimately the best clinical choice, reviewing the alternatives is essential for informed decision making.

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