Emerging Treatment Options for Fibroids

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KEYWORDS

• Fibroids • Abnormal uterine bleeding • Uterine-sparing • Fertility enabling

KEY POINTS

- Uterine fibroids are common benign tumors that can significantly alter the quality of life of patients.
- The options for minimally invasive and nonsurgical treatments have significantly increased in the last decade.
- Clinicians must become familiar with these new technologies to adequately counsel their patients.

BACKGROUND

Leiomyomas or fibroids are extremely common in reproductive aged patients. They are monoclonal tumors that develop from the uterine myometrium and are almost always benign. Fibroids are dependent on estrogen and progesterone, and as such, most fibroids shrink after menopause.[1] Fibroids are commonly classified by their topographic location in the uterus. Generally, fibroids are termed subserosal (located within the serosal layer of the uterus), intramural (located within the contractile smooth muscle of the uterus), or submucosal (located within the endometrial lining). However, many fibroids have a hybrid presentation with both a subserosal and intramural component, an intramural and submucosal component, or a transmural presentation with subserosal, intramural, and submucosal components. Therefore, to establish a universal and more detailed classification system, the International Federation of Gynecology and Obstetrics (FIGO) (**Fig. 1**) created the now widely used eight-type FIGO Leiomyoma Subclassification System (2011).[2] Submucosal fibroids are classified as Type 0 (pedunculated intracavitary), Type 1 (less than 50% intramural), and Type 2 (more than 50% intramural). Intramural fibroids are classified as Type 3 to Type 6. Type 3 fibroids contact the endometrium, and Types 5 to 6 are either less than 50%

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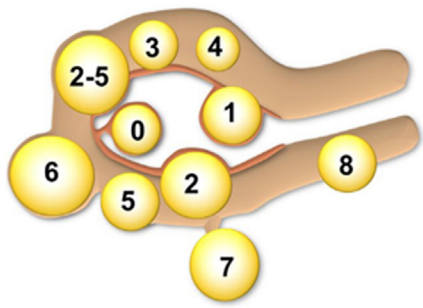

SM - Submucous	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
	3	Contacts endometrium; 100% intramural
O - Other	4	Intramural
	5	Subserous ≥50% intramural
	6	Subserous <50% intramural
	7	Subserous pedunculated
	8	Other (specify e.g. cervical, parasitic)

Hybrid	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
(contact both the endometrium and the serosal layer)	2—5	Submucous and subserous, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

Fig. 1. Leiomyoma Subclassification System. (*Adapted from* Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3-13. https://doi.org/10.1016/j.ijgo.2010.11.011; with permission.)

or more than 50% subserosal. Pedunculated subserosal fibroids are classified as Type 7, and fibroids that are cervical, parasitic, etc., are classified as Type 8. The system also allows for classification of "hybrid leiomyomas" or fibroids that impact multiple layers as a range of stages. For example, a fibroid with a less than 50% submucosal component and less than 50% subserosal components is termed Type 2 to 5.[2,3]

Clinically, management of fibroids can be challenging, especially if childbearing is not complete. Patients may present with abnormal uterine bleeding, pressure or bulk symptoms, infertility, and/or pain, whereas some may have no symptoms at all. Additionally, beyond physical symptoms, fibroids are associated with a significant burden on a patient's emotional and psychosocial health.[4] Fibroids are a public health concern, with annual fibroid-related treatment costs estimated to be as high as $34.4 billion in the United States.[5] Treatment options can be classified as medical, procedural, or surgical. Despite advances in both medical and procedural treatments, symptomatic fibroids remain the most common indication for hysterectomy.[6] However, many patients desire uterine preservation for a variety of reasons, including fertility preservation, maintenance of body integrity, cultural factors, and/or personal preferences. Notably, hysterectomy, even when performed with ovarian conservation, can shorten the time to menopause by 2 to 4 years, which may lead to an increased risk of cardiovascular disease.[7] Thus, when considering fibroid treatment options, important considerations include severity of symptoms, health status, age, surgical risks, family planning goals, and the patient's desire for uterine preservation.

The emerging treatments we present here are nonresective and thus do not allow for definitive tissue diagnosis. Leiomyosarcoma (LMS) is a rare, aggressive, malignant tumor identified in 0.36 per 100,000 women-years. It is difficult to distinguish LMS from a benign leiomyoma preoperatively, and unfortunately there is no standard preoperative assessment.[8] Dynamic MRI and lactate dehydrogenase isoenzyme testing have been suggested to identify LMS preoperatively; however, the evidence is based on limited clinical studies.[9] There are no data supporting biopsy of leiomyomas. Additionally, owing to the low prevalence of this disease, positive predictive values are low. Clearly additional research and techniques are required to better risk-stratify individuals for their risk of this rare diagnosis. However, the prevalence of LMS in presumed leiomyomas is low; in a systematic review by the Agency for Healthcare Research and Quality

(AHRQ) in 2017, the estimated risk of an unexpected LMS is between 1 and 13 per 10,000 surgeries performed for symptomatic fibroids.[9]

Available fibroid treatments include medical (hormonal & nonhormonal), procedural (uterine artery embolization [UAE]), MRI-guided ultrasound ablation (high-intensity focused ultrasound [HIFU]), and surgical options (myomectomy, hysterectomy, and ablative techniques).[10,11] This article will focus on emerging therapies that allow for uterine-sparing, fertility-enabling treatment (**Table 1**).

MEDICAL THERAPIES

Medical therapies for fibroids are usually directed at managing heavy menstrual bleeding (HMB) or bulk symptoms. Comparative data between medical treatments are limited; thus, fibroid management is often guided by patient factors such as medical comorbidities and safety, desire for fertility, tolerability, ancillary benefits (ie, contraceptive), and cost.

Heavy Menstrual Bleeding

Medical therapies for HMB include hormonal and nonhormonal options. Nonhormonal medical options include nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid, both of which are usually taken during menses. In contrast, hormonal options are typically taken throughout the cycle. Hormonal options include combined estrogen–progesterone contraceptives, progestin-only contraceptives, (Gonadotropin releasing hormone (GnRH) analogs, and selective progesterone receptor modulators (**Table 2**).

NSAIDs have been studied for treatment of HMB due to fibroids owing to the presumed impact they may play on elevated prostaglandin levels seen in patients with fibroids. However, a Cochrane review published in 2019 found that although NSAIDs reduced HMB compared with placebo, they were significantly less effective than tranexamic acid or the levonorgestrel intrauterine device (LNG-IUD).[12] Tranexamic acid is a synthetic antifibrinolytic drug that is available in both oral and intravenous formulations and can reduce bleeding up to 40%.[13] It is typically administered orally, initiated with onset of menses, and used for up to 5 days during the menstrual cycle.[6]

Table 1
Treatment options for fibroids

Medical	Procedural (Nonresective Treatments)	Surgical (Fibroid Resection)
Nonhormonal medications (nonsteroidal anti-inflammatory drugs, tranexamic acid)	Uterine artery embolization (UAE)	Myomectomy (hysteroscopic, laparoscopic/robotic, open)
Combined oral contraceptives (COCs)	High-intensity focused ultrasound (HIFU)	Hysterectomy (vaginal, laparoscopic/robotic, open)
Progestin-only options (pills, injection, implants, IUD)		Radiofrequency ablation (RFA)[a]
GnRH analogs (Lupron, Oriahnn, Myfembree)		
Selective progesterone receptor modulators (SPRMs)		

[a] Radiofrequency ablation techniques are *nonresective surgical* procedure.

Table 2
Medical management options for fibroids

Heavy Menstrual Bleeding	Bulk Symptoms
Nonhormonal medications (NSAIDS, tranexamic acid)	GnRH analogs (Lupron, Oriahnn, Myfembree)
Combined oral contraceptives (COCs)	Selective progesterone receptor modulators (SPRMs)
Progestin-only contraceptives (pills, injection, implants, IUD)	
GnRH analogs (Lupron, Oriahnn, Myfembree)	
Selective progesterone receptor modulators (SPRMs)	

Although there is little evidence supporting the use of combined estrogen–progesterone contraceptives for treatment of HMB due to fibroids, it is typically used as a first-line medical treatment for fibroid-related bleeding. Combined estrogen–progesterone contraceptives are available in many forms including pills, patch, and ring. The choice of formulation can be left to the patient's preference and compliance patterns. In addition to medical treatment of HMB, combined oral contraceptives offer other health benefits including contraception, reduction of uterine and ovarian cancer, ovarian cyst suppression, and potential treatment of acne.[11,13–15] Clinicians who prescribe combined contraceptive therapy for the treatment of menorrhagia due to fibroids should be aware of the various contraindications to their use.[16]

For patients with contraindications to estrogen therapy or for those who choose to avoid estrogen-containing methods, progesterone-only therapies are available. Progesterone-only treatments are available in many formulations including the pill, implant, injection, and IUD, with varying degrees of efficacy in the reduction of HMB. Among the progesterone-only options, the LNG-IUD is associated with the greatest reduction in blood loss compared with placebo or alternative hormonal medical treatments.[10,17] Currently, the American College of Obstetricians and Gynecologists (ACOG) supports the use of the 52-mg LNG-IUD for the treatment of abnormal uterine bleeding due to fibroids. It is important to note that rates of IUD expulsion are higher in patients with fibroids (11%) than in patients without fibroids (0%–3%). Additionally, the risk for expulsion seems to be higher for patients with fibroids distorting the cavity.[11,14]

GnRH analogs are either agonists (leuprolide) or antagonists (elagolix and relugolix) that inhibit the hypothalamic–pituitary–ovarian axis, resulting in a decrease in estrogen levels.[10,11] GnRH agonists have been used for the treatment of fibroids for many years and are associated with a reduction in fibroid size, total uterine volume, and menstrual bleeding. Leuprolide is typically dosed at one- or 3-month intervals and is administered as a depot injection. GnRH suppression typically occurs after 7 to 14 days and is preceded by an initial "flare" where a transient increase in Luteinizing hormone (LH) and Follice Stimulating Hormone (FSH) can cause a temporary worsening of HMB.[6,14] Because GnRH agonists work by inducing hypogonadism, use is often limited by hypoestrogenic adverse effects such as menopausal symptoms, unfavorable changes in lipid profile, and/or decrease in bone density. GnRH agonists are often used preoperatively as a surgical adjunct to improve anemia and decrease total uterine size or as a bridge to natural menopause for perimenopausal patients. The Food and Drug Administration (FDA)–approved labeling for fibroids states that leuprolide

is approved for concomitant use with iron therapy for preoperative hematologic improvement of patients with anemia caused by fibroids for whom 3 months of hormonal suppression is deemed necessary. It is not approved with norethindrone acetate add-back specifically for the preoperative hematologic improvement prior to surgery. Treatment is typically limited to 6 months but can be used for up to 1 year if used with add-back therapy or concomitant use with low-dose estrogen and/or progestin.[6,11]

GnRH antagonists also decrease estrogen levels by inhibiting LH and FSH and similarly significantly improve fibroid-related HMB. However, GnRH antagonists are available in oral preparations and are conveniently formulated with low-dose add-back to limit hypoestrogenic side effects.[18] Oral GnRH antagonists, elagolix and relugolix, in combination with estradiol and norethindrone acetate have recently been FDA-approved for the treatment of fibroid-related HMB for up to 24 months of use. Elagolix is formulated with add-back therapy in the twice daily administered Oriahnn and is associated with significant reduction in HMB from baseline.[19] Alternatively, relugolix combination therapy (Myfembree) is administered once daily and is also associated with significant reduction in HMB from baseline. In addition, relugolix has been shown to have a possible reduction in pain and bulk symptoms compared with elagolix.[20]

Both GnRH agonists and antagonists are not reliable contraceptives and are contraindicated in pregnancy. Patients may use leuprolide with either hormonal or nonhormonal contraceptives (condom, spermicide). The use of hormonal contraception is not recommended with hormonal add-back combinations of elagolix or relugolix. Patients are advised to use nonhormonal contraceptives. Additionally, patients with contraindications to estrogen therapy are not candidates for GnRH antagonist add-back combination methods (Oriahnn or Myfembree).

Progesterone Receptor Modulators

After the discovery that progesterone and progesterone receptors are essential for fibroid growth, selective progesterone receptor modulators (SPRMs) were studied for the treatment of fibroids.[21] The original SPRM, mifepristone, a progesterone antagonist, was initially commercialized for pregnancy termination and has recently been studied for treatment of fibroids. Ulipristal acetate (UPA), another SPRM commercialized for use as an emergency contraceptive, has also been studied for the treatment of fibroids. As a class, SPRMs have been shown to decrease menstrual blood loss and achieve amenorrhea. A Cochrane review of 14 randomized controlled trials (RCTs) concluded that short-term use of SPRMs results in improved quality of life, reduced menstrual bleeding, and higher rates of amenorrhea than placebo.[22] Despite their clear benefit on fibroid symptoms, the use of SPRMs has been limited by initial concerns owing to their unique effect on the endometrium, termed “progesterone receptor modulator–associated endometrial changes” or PAECs. These changes include thickening of the endometrium, cyst formation, and changes in gland cells and vascular cells. However, these changes have been found to be benign, not precancerous, and reversible.[21,23,24] Additionally, UPA has been associated with rare cases of serious liver toxicity, with some cases requiring liver transplantation.[11] Currently, UPA is only approved for use in Europe, for intermittent treatment of moderate to severe symptoms of fibroids before menopause and when surgical procedures (including UAE) are not possible or have failed. Underlying hepatic disorders are a contraindication to treatment, and liver function tests must be monitored before, during, and after treatment. An additional limitation to the use of mifepristone for treatment of fibroids is that a compounded formulation is required for doses suitable for

treatment of this indication. Neither UPA nor mifepristone is presently FDA-approved for the treatment of fibroids.

PROCEDURAL MANAGEMENT

Uterine Artery Embolization

UAE is a minimally invasive, percutaneous, image-guided procedure that is performed by an interventional radiologist. The procedure is usually performed under intravenous conscious sedation and involves the catheterization and occlusion of the bilateral uterine arteries using particulate embolic agents, resulting in ischemic necrosis of the fibroids. Since its introduction in 1995, UAE has been associated with significant decrease in fibroid and uterine volume (by 50%–60%) that based on long-term follow-up data is maintained for up to 5 years.[25] Additionally, it is associated with improvement in HMB, bulk symptoms, and quality of life (80%–90%).[26] In fact, patient satisfaction and quality of life rating at 2 and 5 years after treatment are similar among patients undergoing UAE, myomectomy, or hysterectomy.[27] Advantages of UAE include that it is uterine sparing, short procedure and recovery time, decreased risk of transfusion when compared with myomectomy or hysterectomy, and is not limited by the number of fibroids or the patient's surgical history (intra-abdominal adhesions). Contraindications to UAE are pelvic inflammatory disease, gynecologic malignancy, and pregnancy. Relative contraindications include desire for future fertility, postmenopausal patients (due to risk of malignancy), severe renal insufficiency (contraindication to radiologic contrast agents), coagulopathy, and fibroid location (submucosal and pedunculated subserosal fibroids due to risk of intracavitary/intraperitoneal sloughing).[26]

The most common complication after UAE is postprocedure pain due to nonspecific ischemia of the uterus which often requires postoperative narcotics for pain management. Up to 40% of patients experience postembolization syndrome with diffuse abdominal pain, malaise, anorexia, nausea and vomiting, low-grade fever, and leukocytosis. This syndrome usually resolves within 48 hours, is self-limited, and usually only requires supportive therapy.[25] Overall complication rates after UAE as reported by the Society of Interventional Radiology are prolonged vaginal discharge 20%, transcervical expulsion of fibroids 15%, permanent amenorrhea 3% in patients younger than 45 years and 15% in those older than 45 years, 3% septicemia, and less than 1% for thromboembolism and nontarget embolization.[26] The most feared complication after UAE is intrauterine infection and, if untreated or refractory to antibiotics, can lead to sepsis and the need for hysterectomy. Despite significant initial success, rates of reintervention after UAE with hysterectomy, myomectomy, repeat embolization, medical management, or endometrial ablation are high. A Cochrane review found a five-fold increase in the likelihood of further intervention after UAE when compared with myomectomy or hysterectomy.[27] The EMMY trial, the largest randomized trial comparing UAE with hysterectomy, has published 10-year follow-up data demonstrating that 35% of patients who underwent a UAE ultimately required a hysterectomy. Despite this rate of intervention, 78% of subjects who underwent a UAE were very satisfied when compared with 87% who initially underwent a hysterectomy.[28]

The effect UAE may have on fertility and pregnancy is a topic of debate owing to the concern for potential adverse effects to ovarian reserve and endometrium. Compared with the general population, patients that have undergone a UAE seem to demonstrate higher rates of spontaneous abortion, preterm delivery, cesarean section, abnormal placentation, and postpartum hemorrhage. The degree to which confounding factors (advanced maternal age, prior infertility, and fibroid burden) contribute to these findings is unclear.[10,11]

In summary, UAE is a treatment option for patients with symptomatic fibroids who wish to avoid surgery or are poor surgical candidates. Patients that are considering further childbearing can undergo a UAE but require appropriate consultation regarding the pros and cons of the procedure and alternative therapies.

High-Intensity Focused Ultrasound

HIFU is a uterine-sparing, percutaneous procedure that utilizes high-intensity ultrasound waves to ablate fibroids, thereby inducing coagulative necrosis. It is usually performed with conscious sedation as an outpatient procedure. Although this technique can be performed with either magnetic resonance–guided focused ultrasound (MRgFUS) or ultrasound guided focused ultrasound (USgFUS), only MRgFUS is currently FDA-approved.[10,29,30] MRI allows for real-time anatomic guidance and thermal monitoring for safe ablation.[31] Despite encouraging fertility and pregnancy reports, MRgFUS is best offered to premenopausal patients that do not desire future fertility. A recent systematic review of reproductive outcomes after MRgFUS reported a live birth rate of 73%. However, the outcomes data were heterogeneous and largely derived from retrospective analyses.[29]

Contraindications for HIFU treatment include pelvic inflammatory disease, gynecologic malignancy, and any contraindication to undergoing MRI (defibrillators, metal implants).[10] HIFU treatment works well with fibroids measuring 2 to 3 cm and has been successful with fibroids measuring less than 10 cm and uteri 20 to 24 weeks or smaller.[30] Additionally, factors such as tissue characteristics (T1 & T2 signal intensity, FIGO type) and technical limitations (scar tissue, abdominal subcutaneous fat, distance between fibroid and sacrum, bowel interposition between beam and fibroid) also dictate a patient's candidacy for this procedure.[32]

A recent single-center study of 252 patients undergoing MRgFUS reported significant symptom improvement in 74% of patients and a 12.7% reintervention rate.[31] Symptom relief and fibroid volume reduction rates are dependent on the volume of tissue that is not perfused (NPV) after treatment, and an NPV ratio of more than 80% has been suggested as a threshold for treatment success.[31] MRgFUS is a promising nonresective treatment approach for fibroids in patients that wish to avoid surgery; however, its effectiveness depends on careful patient selection.

SURGICAL (NONRESECTIVE TREATMENT)

Radiofrequency Fibroid Ablation

In recent years, radiofrequency ablation (RFA) of fibroids has been presented as a less invasive alternative to treating symptomatic fibroids. RFA was developed by adopting techniques used to treat solid tumors of the liver and adapting them to management of fibroids. RFA uses real-time ultrasound to identify the fibroids and apply radiofrequency energy from a handpiece using a laparoscopic or transcervical approach.[33] Ultrasound guidance allows placement of radiofrequency needles directly into the fibroid to target local treatment to only the fibroid tissue only. Radiofrequency fibroid ablation produces hyperthermic energy that induces coagulative necrosis of the fibroid. Once the fibroid undergoes coagulative necrosis, the process of fibroid resorption and volume reduction occurs over weeks to months depending on the fibroid size. A recent systematic review and meta-analysis of laparoscopic, vaginal, and transcervical RFA fibroid treatments by Bradley and colleagues reports health-related quality of life (HRQoL) scores increased by 39 points and Symptom Severity Score (SSS) decreased by 42 points. They also found a low annual cumulative reintervention rate of 4.2%, 8.2%, and 11.5% at 1, 2, and 3 years after ablation.[34] In addition to

improved fibroid-related symptoms, RFA fibroid treatment also reduces fibroid volume. In a systematic review comparing RFA, UAE, and focused US treatments, RFA had the greatest reduction in mean fibroid volume compared with both UAE and MRgFUS. The pooled fibroid volume reductions at 6 month after treatment were as follows: RFA 70%, UAE 54%, FUS 32%.[35] Currently, there are two RFA modalities available for use in the U.S.: laparoscopic RFA (Lap-RFA) and transcervical RFA (TC-RFA).

Individuals who are considering RFA should be fully counseled about the risks of the procedure and the anticipated reduction in symptoms (further discussed in the later part of the article). It is important to have a good understanding of the anatomy of the uterus and associated fibroids before performing the procedure. In addition to standard of care preoperative evaluation for endometrial abnormalities with endometrial sampling, preoperative high-quality ultrasound or MRI is also recommended to map the location of the fibroids.

Laparoscopic radiofrequency fibroid ablation

The first reported case of Lap-RFA was described by Lee in 2002.[33] The first device to be FDA-approved for the treatment of fibroids was the Acessa device (Hologic). The present system is called the Acessa ProVu system (**Fig. 2**). Lap-RFA requires an intra-abdominal ultrasound transducer (10 mm) that is placed directly on the uterine serosal surface to localize the fibroids. Next, the Acessa handpiece is introduced intra-abdominally and inserted directly into the fibroid where it delivers RF energy via a series of electrodes that can create ablation zones ranging from 1 cm to 6 cm (**Fig. 3**). The entire procedure is controlled with a single console and uses a tabletop field generator that produces a magnetic field detected by the guidance sensors in the handpiece. This system assists the surgeon in localizing the handpiece as it is introduced into the fibroid to maximize the ablation of the fibroid. Two return electrodes are placed on the legs of the patient. The FDA approval for the device is for patients with fibroids and a uterus less than 14-week size. Lap-RFA is capable of ablating fibroids in most anatomic positions, but is not recommended for FIGO types 0, 1, and

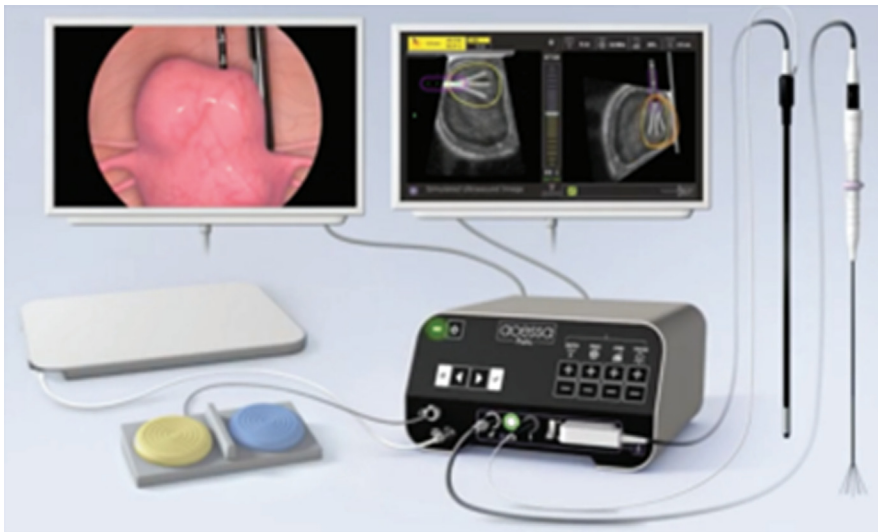

Fig. 2. Acessa ProVu system Equipment. (*Courtesy of* Hologic, Marlborough, MA; with permission.)

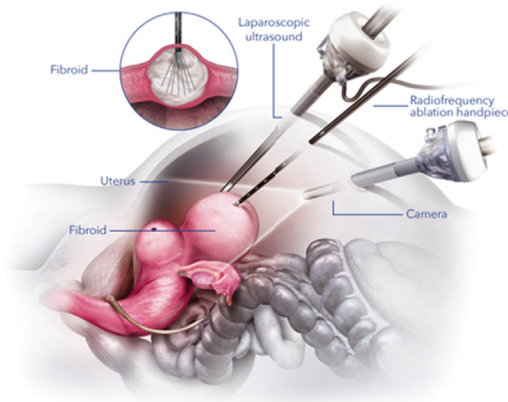

Fig. 3. Acessa ProVu system for laparoscopic RFA of fibroids demonstrated. (*Courtesy of* Hologic, Marlborough, MA; with permission.)

7. With clinical experience, larger fibroids and uteri can be treated in an off-label manner.

There have been several clinical trials that address the feasibility, safety, and ultimate long-term outcome of Lap-RFA. Thirty-one subjects involved in a single-site study with 1-year follow-up demonstrated that the procedure was safe and showed significant improvement in symptoms, with a 41% reduction in the mean uterine volume.[36] There was only one major complication from the procedure, an early postoperative vascular injury and hematoma of the abdominal wall that required a laparotomy that was believed to be a trocar injury, but an injury by the Lap-RFA needle could not be ruled out.

The Acessa device was ultimately approved by the FDA following a pivotal trial involving 135 subjects in a prospective trial with a 3-year follow-up period. The overall reintervention rate at 36 months was 11%.[37] The subjects were followed up using the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) scoring system. There were statistically significant improvements in both symptom severity, decreasing from 60.2 at baseline to 27.6 at 3 years, and an increase in the quality of life score from 39.2 at baseline to 77.8 at 3 years. There are two RCTs that evaluate Lap-RFA with laparoscopic myomectomy.[38] In the first by Hahn and colleagues, fifty subjects were randomized 1:1 to laparoscopic myomectomy versus Lap-RFA with 12 months of follow-up. The study had intraoperative ultrasound to map the location of the fibroids before randomization as a strength. There was no statistical difference between the two procedures regarding improvement in the mean symptom scores and quality of life (UFS-QOL), demonstrating an overall equivalent outcome with Lap-RFA compared with the gold standard of therapy. However, subjects who underwent a myomectomy reported being very satisfied at a higher rate (86.5%) than (42.9%) those undergoing a Lap-RFA ($P = .004$), but in general, both therapies were well received. Additionally, two subjects who underwent a Lap-RFA subsequently conceived and subsequently delivered via healthy infants vaginal delivery.

The second trial was a randomized, postmarket, prospective multicenter, longitudinal study analyzing clinical outcomes and health care utilization.[39] The trial followed forty-five subjects, 23 in the Lap-RFA group and 22 in the laparoscopic myomectomy group for a period of 3 months. The Lap-RFA had a shorter hospital stay (6.7 hours vs 9.9 hours), had a shorter operative time (70 vs 86.5 minutes), and required fewer units of surgical equipment. At 3 months, the two treatments had similar reduction in

symptoms scores and the combined per-patient direct and indirect costs were comparable. One myomectomy subject required overnight admission, and one Lap-RFA patient underwent a reintervention. The Lap-RFA subjects demonstrated a quicker return to work than the myomectomy subjects.

Transcervical Radiofrequency Fibroid Ablation

TC-RFA offers a unique conservative fibroid treatment option because it allows for a vaginal procedure that is entirely "incision-free." Avoiding an incision on both the abdomen and the uterus offers the least invasive approach, faster recovery, and less intraperitoneal risk, while minimizing uterine risks such as the risk of uterine rupture, intrauterine adhesions (Asherman syndrome), abnormal placentation, and the potential need for cesarean delivery.[40] (**Fig. 4**)

Currently, there is only one transcervical RFA device available in the U.S., the Sonata® System (Gynesonics Inc.), which was FDA-approved in 2018 (**Fig. 5**). Unlike the Lap-RFA, which requires 3 incisions (1 for the laparoscope, 1 for the ultrasound probe, and 1 for the RF device), the TC-RFA procedure allows for an incisionless vaginal approach because the ultrasound probe and the RF device are both in the same handheld TC-RFA instrument.[41,42] The device provides the operator with visual feedback as to the size of the ablation zone as well as the safety borders, which helps prevent unwanted thermal injury (**Fig. 6**). The TC-RFA device has a minimum and maximum ablation ring size (minimum: 2.0 $\times$ 1.3 cm and maximum: 5.0 $\times$ 4.0 cm). For fibroids larger than 5 cm, one may consider ablating multiple different areas within the same fibroid or decreasing the fibroid size preoperatively with Lupron before treatment.

TC-RFA has shown to be an effective minimally invasive treatment of symptomatic fibroids, reducing HMB in up to 95% of patients.[43] In this prospective, multicenter, single-arm transcervical ablation trial of 147 subjects, there was a very low 0.7% reintervention rate at 1 year, with 65% of patients reporting more than 50% reduction in bleeding and 62.4% fibroid volume reduction. Long-term improvements for fibroid-related symptoms have also been reported. Three-year follow-up results from the prospective SONATA Pivotal Trial also demonstrated a very high patient satisfaction rate (94%), decreased SSS (pre-RFA SSS 55 $\pm$ 19–22 $\pm$ 21 at 3 years), increased HRQoL scores (pre-RFA HRQoL mean score 40 compared with 83 at 3 years), decreased work impairment from fibroids (51% pre-RFA to 12% at 3 years), and low reintervention rates (8.2%).[44] The longest longitudinal data available for TC-RFA were published in the VITALITY study, a retrospective study that reported an 11.8% surgical

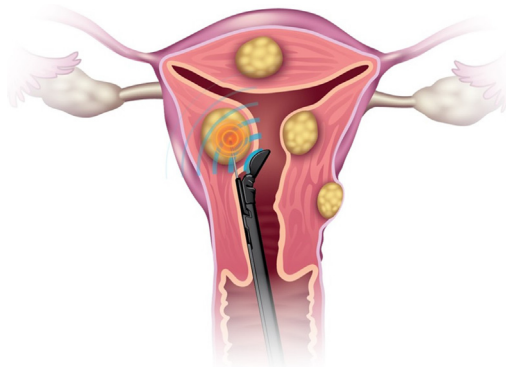

Fig. 4. Sonata system transcervical ablation demonstrated. (*Courtesy of* Gynesonics Inc., Redwood City, CA; with permission.)

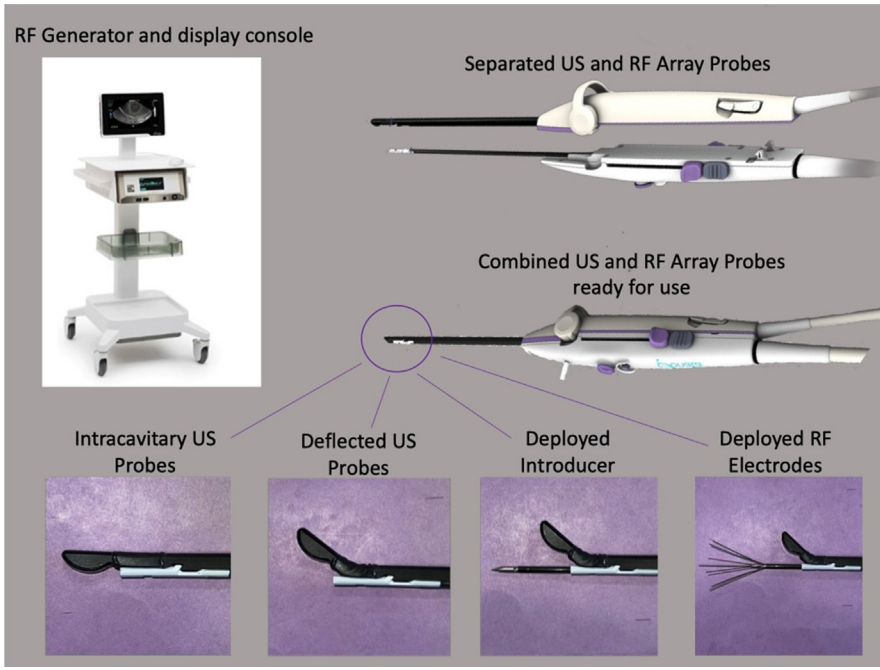

Fig. 5. Sonata system detailed images of the components. (*Courtesy of* Gynesonics Inc., Redwood City, CA; with permission.)

reintervention rate over 64.4 months of follow up.[45] However, this study was limited by its small sample size (n = 17). Overall, TC-RFA seems to be an effective treatment with low reintervention rates of 0% to 4% at 1 year, 5% to 8% at 2 years, 8% to 11% at 3 years, and 11.8% at 5.4 years after treatment.[34,43–46] Additionally, the Fibroid Ablation Study-EU (FAST-EU) study reported a 67% fibroid volume reduction at 12 months.[41] These findings were maintained even among larger fibroids. In a subanalysis of the FAST-EU study, patients with fibroids larger than 5 cm demonstrated a 68% fibroid volume reduction 12 months after RFA treatment.[47] Additional studies support similar conclusions regarding reduction in fibroid volume after TC-RFA treatment.[43]

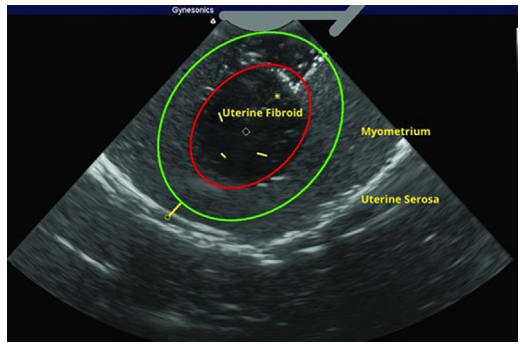

Fig. 6. Sonata system demonstration of ablation zone (*red*) and safety borders (*green*). (*Courtesy of* Gynesonics Inc., Redwood City, CA; with permission.)

Pregnancy Outcomes and Radiofrequency Ablation

Review of the currently available literature on treatment efficacy and pregnancy outcomes for transcervical and laparoscopic radiofrequency ablation of uterine fibroids looks promising as a uterine-sparing, fertility-enabling treatment option. Currently, both Lap-RFA and TC-RFA are not approved by the US FDA as a fertility-enabling treatment. As a result, fertility-seeking patients have been excluded from RFA studies; however, the reproductive-age patient who desires future conception may benefit most from RFA.

Studies have analyzed post-RFA uterine wall thickness and intrauterine adhesion formation given the potential impact on pregnancy outcomes.[48,49] The INTEGRITY Trial, a large secondary analysis of the FAST-EU trial assessing the Sonata transcervical fibroid ablation system, showed there was no significant decrease in uterine wall integrity with little to no change in minimum myometrial wall thickness on follow-up MRI 12 months after TC-RFA compared with baseline measurements.[50] A prospective trial assessing the endometrial cavity after TC-RFA fibroid treatment with the Sonata system found no new intrauterine adhesions on hysteroscopic assessment 6 weeks after ablation compared with baseline hysteroscopy.[51] Six of these patients had opposing myomas, and none had new postablation adhesions. These studies suggest RFA fibroid treatment may potentially offer fertility benefits compared with standard myomectomy with favorable outcomes in terms of uterine wall thickness and adhesion formation. To our best knowledge, there have been no reported uterine ruptures following TC-RFA fibroid treatment.[52,53] However, given the rare incidence of uterine rupture, additional data are required to make any reliable conclusions.[51]

Subsequent pregnancies following TC-RFA trials show promising data for both safety and favorable reproductive outcomes.[53,54] A systematic review of all pregnancies reported after LSC-RFA and TC-RFA found 50 pregnancies among 923 RFA patients (40 among 559 LSC-RFAs and 10 among 364 TC-RFAs). Among the 50 who conceived, there were 6 spontaneous abortions (12%) and 44 full-term pregnancies (88%). Among the 44 deliveries, 24 were vaginal (54.5%) and 20 were cesarean (45.5%). There were no uterine ruptures, placenta accretas, or fetal complications, and the spontaneous abortion rate was comparable with the general obstetric population.[54]

RFA seems to be a safe option for reproductive-aged patients who desire future fertility and may offer potential fertility benefits compared with myomectomy in regards to uterine wall integrity and adhesion formation. Further research is needed to establish long-term outcomes for fibroid symptoms, fibroid volume reduction, and reproductive outcomes.

Lap-RFA and TC -RFA both represent new skills that require adequate training to become familiar with localization of the fibroids using an ultrasound being applied in a nonfamiliar manner. In addition, not all fibroids can be managed successfully with these technologies because both require careful attention to the zone of thermal injury produced by the devices to avoid injury to surrounding tissue. Introduction of these technologies should be done with appropriate training and observation until which time a clinician becomes comfortable with the localization process and the safe operation of the equipment.

SUMMARY

Uterine fibroids are common and can significantly alter the quality of life of patients via abnormal bleeding, pressure sensation, and altered fertility. Previously, patients had a limited number of invasive procedures (myomectomy and hysterectomy) to treat their

fibroids. The options for treatment have significantly increased in the last decade with the expanded use of UAE, HIFU, and the introduction of RFA and GnRH antagonists with combined add-back therapy. Clinicians who manage patients with fibroids now must become familiar with these new technologies to adequately counsel their patient or refer to someone who has expertise with fibroid management.

CLINICS CARE POINTS

- Management and treatment of fibroids remains challenging because of the wide variety of sizes, locations, and symptoms associated with this pathology.
- Medical and nonresective treatment options represent advancements in the treatment of fibroids and should be offered to appropriate patients.
- Fibroid management should be carefully tailored to each individual patient to address fibroid symptoms while considering the patient's medical profile, family planning goals, age and risks.
- Managing fibroids among women who wish to conceive can be challenging because providers must balance optimal fibroid treatment with the patient's reproductive goals.

DISCLOSURE

The authors have nothing to disclose.

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