Innovations in uterine fibroid therapy

Uterine fibroids are benign tumors that are highly prevalent among reproductive-aged women. Hysterectomy remains the only definitive treatment for symptomatic uterine fibroids; however, uterine-sparing treatment options are needed for women desiring future fertility or uterine preservation. Several alternative treatments exist, but these therapies are limited by significant fibroid recurrence within a few years of treatment or significant side effects. Interventional radiology procedures now extend to the management of fibroids and many medical therapies for treatment of symptomatic fibroids are available or are under investigation in clinical trials. Long-term outcome data for newer medical therapies are needed to determine which therapies offer a definitive advantage over traditional therapies. Future investigations into the molecular biology of fibroids will pave the way for the development of innovative therapies in the treatment and prevention of these highly prevalent gynecologic tumors.

KEYWORDS: aromatase inhibitor ■ fibroid ■ hysterectomy ■ magnetic resonance-guided focused ultrasound surgery ■ myomectomy ■ uterine artery embolization

Desireé M McCarthy-Keith[1] & Alicia Y Armstrong[†1]

[1]Program in Reproductive & Adult Endocrinology, Building 10, CRC, Room 1E-1-3140, 10 Center Drive MSC 1109, Bethesda, MD 20892-1109, USA
[†]Author for correspondence:
Tel.: +1 301 496 5800
Fax: +1 301 402 0884
armstroa@mail.nih.gov

Epidemiology of fibroids

Uterine fibroids are the most common benign gynecologic tumor in reproductive-aged women. In the USA, by the time a woman reaches the age of 50 years, her lifetime risk of having fibroids is 70% [1]. Ultrasound screening of asymptomatic women demonstrates that black women develop fibroids at a younger age, 10–15 years earlier than white women [2,3], and have higher cumulative incidence at every age compared with white women [2]. By the end of the reproductive years, the incidence of fibroids in black women is over 80%, compared with 70% in whites [1]. Many uterine fibroids go undiagnosed and although the majority of women with fibroids are asymptomatic, approximately 20–50% of women have symptoms significant enough to warrant clinical intervention [4]. The most common symptoms of uterine fibroids are pelvic pain, pelvic pressure and menorrhagia. Women with fibroids may also experience infertility, miscarriage, preterm deliveries and complications in late pregnancy [4–9]. Treatment of symptomatic fibroids is the leading indication for hysterectomy in the USA and the cost to the US healthcare system for all fibroid-related care is estimated at US$2.1 billion per year [10]. Treatments for symptomatic fibroids include surgical, medical and minimally invasive options, and there are numerous investigations of new therapies on the horizon. At present, only surgical management with hysterectomy offers definitive treatment; however, the ideal alternative to surgery that offers long-term resolution of symptoms has not yet been identified. Since most women present for evaluation of symptomatic fibroids during their reproductive years, therapies must also be developed with preservation of reproductive potential in mind. In this article we review traditional therapies and recent advances in the management of symptomatic uterine fibroids.

Surgical treatment of fibroids

Surgery remains the mainstay of treatment for symptomatic fibroids. Hysterectomy is the only definitive procedure for permanent removal of fibroids, but myomectomy is an alternative for women who desire uterine preservation. As mentioned, treatment of symptomatic fibroids is the most common indication for hysterectomy [11], which accounts for 30% of hysterectomies in white women and more than 50% in black women [201]. Hysterectomy may be preferred over myomectomy because it eliminates current symptoms as well as the possibility of recurrent symptoms in the future. There is significantly greater morbidity associated with hysterectomy than less invasive procedures and this must be considered when electing for surgical management.

Myomectomy is an alternative option for women desiring surgical removal of fibroids, but who plan to have children in the future or who wish to retain their uterus. Abdominal myomectomy is usually reserved for cases where the uterus is significantly enlarged, there are multiple fibroids present or the fibroids are

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deep within the uterine wall. The operative time, blood loss and length of postoperative hospitalization for abdominal myomectomy are similar to those for abdominal hysterectomy [12–14]. A disadvantage of this procedure is the risk of recurrence or development of new fibroids following surgery, thus leading to repeat operation. Studies of ultrasound surveillance following myomectomy show that 50–60% of patients will have new fibroids detected 5 years after surgery [15,16]. Furthermore, up to 25% of patients will require a repeat major surgery following their first myomectomy [4,15,17–19]. In one study, smaller uterine size (at less than 12 weeks) and weight gain in excess of 30 lbs after the age of 18 years were associated with increased risk for reoperation [20]. There are limited data that the risk of fibroid recurrence is lower in women who have the presence and removal of a solitary fibroid and who give birth subsequent to myomectomy [17,21].

Abdominal adhesions, which can impair fertility, can also be a complication of myomectomy. The role of uterine-sparing surgery in women who desire fertility remains controversial, particularly in those patients who are not undergoing IVF. The development of adhesive disease after myomectomy is common and can involve the fallopian tubes, causing tubal factor infertility [22].

While the general techniques for surgical management of fibroids via hysterectomy or myomectomy have remained the same, the surgical approach has evolved with the increasing use of laparoscopy and now robot-assisted laparoscopic surgery. Large fibroids that were once routinely removed through a laparotomy incision may now be removed laparoscopically, with tissue morcellation to facilitate their removal from the abdominal cavity. Morcellation can be performed manually; however, automatic morcellators significantly reduce operating time and can be used to remove fibroids weighing up to 500 g [23]. Laparoscopic myomectomy has the advantages of shorter hospital stay, less postoperative pain and faster recovery compared with the abdominal approach [24,25]. In a recent multicenter study of 512 women who underwent laparoscopic myomectomy, the cumulative probability of fibroid recurrence increased from 12% after 1 year to 53% after 5 years. A total of 8 years following myomectomy, the cumulative fibroid incidence reached 84%; however, the probability of reoperation for recurrent fibroids was low (7% at 5 years and 16% at 8 years) [26]. As with abdominal myomectomy, laparoscopic myomectomy is associated with adhesion formation and measures to prevent adhesions are recommended [27].

Laparoscopic myomectomy is best performed by a skilled laparoscopic surgeon and its success is dependent upon optimal closure of the uterine wall defect following fibroid removal [28,29]. The complex skill of laparoscopic suturing may be enhanced by the assistance of a robotic device. The da Vinci Surgical System was approved by the US FDA in 2005 and is the first robotic device endorsed for gynecologic surgery [30]. The surgeon is seated away from the patient, at a console that operates the camera, energy source and the robotically controlled instruments. An endoscopic imaging system provides a 3D view of the operative field. A variety of laparoscopic instruments may be attached to robotic arms positioned beside the patient, allowing the surgeon to perform the full range of motion laparoscopic maneuvers [31]. These combined elements greatly enhance the dexterity and precision of critical laparoscopic skills, such as suturing and knot tying. Recent trials comparing robot-assisted laparoscopic myomectomy to standard laparoscopic myomectomy demonstrate that the procedures are similar with regard to blood loss, length of hospital stay and postoperative complications [32,33]. At present, the greatest drawbacks of the procedure are extended operative time and increased cost compared with laparoscopy. In a retrospective study of 15 robot-assisted myomectomies compared with 35 standard laparoscopic myomectomies, the mean operative time was 29 min longer in the robotic group (234 vs 203 min) [32]. The prolonged operative time was attributed in part to assembly/disassembly of the robot and changing of the instruments for the robotic arms during the procedure. In a retrospective review of 40 robot-assisted and 41 laparoscopic myomectomies, operative times were no different when adjusted for uterine size, fibroid size and number [33]. In 2009, the average hospital charge for robot-assisted myomectomy at one center was US$56,000 compared with US$34,500 for standard laparoscopic myomectomy. These charges included the US$2 million cost of the robot, plus a US$150,000 annual maintenance fee [32]. Until prospective trials demonstrate a definitive advantage of robotic laparoscopic myomectomy over laparoscopic myomectomy, this procedure may be most useful for training novice endoscopic surgeons to master laparoscopic techniques in a 3D environment.

Minimally invasive treatment of fibroids

Minimally invasive alternatives to surgical management of fibroids are emerging. A reliable measure of the clinical outcomes of patients undergoing novel therapies is essential to the evaluation of these treatments. The Uterine Fibroid Symptom Quality Of Life (UFS-QOL) questionnaire developed by Spies *et al.* is the only validated survey for the assessment of fibroid-related symptoms. The questionnaire consists of eight fibroid symptom questions and 29 QOL questions, which effectively discriminated degrees of symptom severity among women with fibroids [34]. The UFS-QOL has demonstrated responsiveness to uterine-sparing fibroid treatments and is a valuable measure of improvements in symptom severity and QOL outcomes following alternative fibroid therapies [35].

Uterine artery embolization

In 1987, uterine artery embolization (UAE) was described as an effective treatment for obstetric and gynecologic hemorrhage, which avoided major surgery and allowed uterine preservation [36]. The procedure was first described in the successful treatment of symptomatic uterine fibroids in France in 1994 [37] and in the USA 3 years later [38]. Increasing interest in uterine preservation among many women with symptomatic fibroids has pushed UAE to the forefront of minimally invasive fibroid treatments. UAE is indicated for most women with symptomatic fibroids, including women who may not be candidates for surgical management or who have failed other therapy. A systematic review of reproductive outcomes following UAE reported increased rates of miscarriage, cesarean section and postpartum hemorrhage in women who underwent UAE compared with controls [39]. Published trials of pregnancy outcomes following UAE also described higher incidence of preterm labor [40,41], and cases of abnormal placentation following UAE have been reported [42,43].

Uterine artery embolization is performed in an outpatient setting under conscious sedation. The procedure is performed through a right or left femoral arterial puncture and the uterine artery is catheterized via catheterization of the hypogastric artery. A uterine arteriogram is performed, followed by injection of an embolic agent into the uterine arteries. The embolic particles preferentially flow into the large fibroid vessels, primarily occluding these, while maintaining some uterine artery blood flow [44]. Several embolic agents are currently in use, including polyvinyl alcohol (PVA) particles, PVA microspheres and tris-acryl gelatin microspheres. In a recent trial comparing embolic agents, PVA microspheres were associated with higher post-treatment fibroid enhancement on MRI than PVA or gelatin microspheres [45]. A separate trial found greater tumor infarction following embolization with tris-acryl gelatin microspheres than with PVA microspheres [46].

In studies of long-term follow-up after UAE, over 70% of patients reported symptom improvement 5 years postprocedure, while 16–23% of patients required repeat intervention for symptomatic fibroids [47–49]. Two randomized trials have compared UAE with surgical management of fibroids. In the EMbolization versus hysterectoMY (EMMY) trial, women with symptomatic fibroids were randomly assigned to UAE (n = 88) or hysterectomy (n = 89). QOL measures improved significantly, remained stable and were similar in both treatment groups until the 5-year follow-up period. A total of 5 years following treatment with UAE, 28% of patients had undergone hysterectomy due to persistent symptoms [50]. UAE was also associated with lower mean total treatment cost (US$11,626 vs $18,563) and lower cost related to absence from work (mean difference -US$5453) compared with hysterectomy in this trial [51]. The Randomized trial of Embolization versus Surgical Treatment for fibroids (REST) was a multicenter study that compared 106 patients undergoing UAE with 51 patients undergoing surgical intervention (43 hysterectomies and eight myomectomies) for symptomatic fibroids. Women in both treatment groups reported comparable improvement in QOL 1 year postprocedure. Patients in the UAE group required a shorter hospital stay (1 vs 5 days) and returned to work earlier than women in the surgical group. After 1 year, ten patients in the UAE group underwent another intervention (hysterectomy or repeat UAE) for persistent or recurrent symptoms. After the 1-year follow-up, 11 additional patients required subsequent procedures for symptoms. In total, 13% of women (n = 14) in the UAE group were hospitalized following the first year of follow-up for major adverse events or treatment failure requiring a repeat procedure [52]. These randomized studies demonstrate the efficacy of UAE, which improves QOL comparable to surgical management and offers the benefit of uterine preservation. Recurrence rates are similar to those reported following myomectomy and a small proportion of patients will require repeat intervention for treatment failure or return of symptoms.

Fertility-compromising complications following UAE should be considered when recommending this treatment to reproductive-aged women. Both intra-abdominal [53] and intrauterine adhesions [54] have been observed after UAE. Reports of ovarian failure following UAE have also raised concerns; however, two recent randomized trials failed to demonstrate a significant decerase in ovarian reserve after UAE compared with other uterine fibroid therapies [55,56]. Due to the potential negative impact on ovarian reserve and the possibility of both intra- and extra-uterine adhesion formation following UAE, this procedure should be reserved for patients who have completed childbearing.

Magnetic resonance-guided ultrasound surgery

The success of UAE for the treatment of uterine fibroids fostered development of the latest noninvasive fibroid treatment, magnetic resonance-guided focused ultrasound surgery (MRgFUS). This thermoablative treatment was approved by the FDA for the treatment of symptomatic uterine fibroids in 2004. Similar to UAE, MRgFUS offers uterine preservation and eliminates the need for general anesthesia. MRgFUS is unique in that it utilizes real-time MRI to localize fibroids and to monitor ultrasound-directed thermal ablation of the fibroid targets. This allows optimal fibroid characterization and precise target definition throughout the procedure, and response to treatment can be assessed immediately by post-treatment MRI.

The contraindications to MRgFUS are unique compared with other fibroid therapies. Women who are unsuitable to undergo MRI (e.g., those with cardiac pacemakers or large body habitus) are not candidates for MRgFUS. Furthermore, women with extensive scarring in the lower abdominal wall or scarring within the path of the ultrasound beam should not undergo MRgFUS due to risk of thermal damage of the skin [57]. Minor skin burns following MRgFUS are described [58,59] and one case of a full thickness burn of the abdominal wall following MRgFUS has been reported [60]. Recently published trials have described MRgFUS treatment of fibroids up to 10 cm in size. It is key that target fibroids are in a location and position that can be adequately targeted by the ultrasound beam while the patient is in the prone position [57,61].

Magnetic resonance-guided focused ultrasound surgery utilizes high-intensity focused ultrasound to raise target tissue temperatures above 55°C, which results in tissue destruction and coagulative necrosis in the targeted area [57,62]. The onset of coagulative necrosis is immediate, differing from the gradual ischemic necrosis that develops following UAE. MRgFUS is performed under conscious sedation, which allows the patient to provide continuous feedback during the procedure. The patient is placed in the prone position with the ultrasound transducer directed at the anterior abdominal wall [62,63]. MRI is performed throughout the procedure to monitor tissue temperature and a postprocedure MRI is used to determine the nonperfused volume (NPV) of the target area. Pathologic examination of hysterectomy specimens collected following preoperative MRgFUS confirmed that NPV was a good indicator of tissue necrosis and is a reliable surrogate for treatment success [64]. Since all fibroids within the uterus may not be targeted for treatment, the NPV ratio is often described as a more precise measure of treatment effect. The NPV ratio is determined by adding the NPV of all treated fibroids and dividing the sum by the volume of all fibroids (treated and untreated) [65].

Several studies of MRgFUS for symptomatic fibroids demonstrate a consistent decrease in symptoms observed at 6 months following treatment [64,66–68]. In one study, 71% of women achieved their target symptom severity reduction at 6 months and 51% reached their goal at 12 months following treatment. Most women also reported improvement in QOL measures, including return to normal activities and fewer lost workdays [64]. In a study of 48 women undergoing MRgFUS, the mean NPV ratio immediately after the procedure was 60% and for 39 patients evaluated at the 6-month follow-up, the average reduction in fibroid volume was 33%. Fibroid volume reduction at 6 months was greatest in women with a NPV ratio greater than 60% compared with women with lower post-treatment NPV ratio (39 vs 27%) [67], indicating that larger treatment NPV ratio correlates directly with fibroid volume reduction. Funaki and colleagues described fibroid volume change ratios in relation to signal intensity (low, intermediate and high) of T_2-weighted MR images. Of the 35 patients treated with MRgFUS, they observed a fibroid volume reduction of between 30 and 40% at 6 months and 20 and 40% at 12 months. Fibroids with low or intermediate signal intensity demonstrated the greatest volume reduction [68]. In a series of 359 women completing 24 months of follow-up after MRgFUS, Stewart *et al.* demonstrated sustained symptom relief following treatment. A

significant reduction in symptom severity score was observed at 3 months of follow-up and improvement continued until 24 months in all patients. The group of women with the greatest improvement in symptoms over time had higher treatment NPV ratios [69].

In a US study, an economic model was created to evaluate the cost–effectiveness of MRgFUS. In 2005, the estimated cost of MRgFUS was US$27,300 compared with $28,900 for UAE, $35,100 for myomectomy, $19,800 for hysterectomy and US$9200 for pharmacotherapy [70]. A cost–effectiveness study of MRgFUS conducted in the UK also estimated lower costs for MRgFUS compared with UAE and traditional surgical management [71]. Although costs for MRgFUS are comparable to UAE, current insurance coverage limitations in the USA may hinder the accessibility of this treatment to some women [72].

Accumulating data on clinical outcomes following MRgFUS for the treatment of fibroids demonstrate its rapid therapeutic effect and continued symptom relief in long-term follow-up. Following reports of successful pregnancy in women following MRgFUS [73–75], the FDA changed the labeling of the high-intensity focused ultrasound device to include treatment of women desiring future pregnancies. Applicability to women desiring pregnancy makes this unique therapy potentially suitable for a wide range of patients.

Medical treatment of fibroids

Gonadotropin-releasing hormone analogs

Fibroids are hormone-sensitive tumors that grow in response to ovarian steroid hormone (estrogen and progesterone) stimulation. Gonadotropin-releasing hormone (GnRH) analogs reduce the hormonal stimulation of fibroids through downregulation and desensitization of pituitary GnRH receptors. The pituitary hormones follicle-stimulating hormone and luteinizing hormone direct ovarian steroid hormone production, and downregulation of the GnRH receptors produces a decrease in follicle-stimulating hormone and luteinizing hormone and a subsequent reduction in ovarian estrogen and progesterone production. This reduction in ovarian hormones results in reduction in fibroid volume. Treatment of fibroids with GnRH agonist is a well-established therapy to reduce the volume of fibroids and thus reduce their associated symptoms [76,77]. The use of GnRH agonist treatment is associated with an initial flare effect, as gonadotropins initially increase and cause an exacerbation of symptoms in response to GnRH agonist stimulation of the GnRH receptor. GnRH antagonists have also been shown to be an effective treatment and may provide an advantage over GnRH agonists as they do not produce a flare effect and may produce results following a shorter treatment period [78,79]. GnRH agonists are available in depot form and can be administered on a monthly basis; however, current GnRH antagonist preparations are limited by short half-lives, requiring daily subcutaneous administration.

Gonadotropin-releasing hormone analogs induce a hypoestrogenic state and patients often experience hot flashes and vaginal dryness due to this effect. These symptoms may reduce the tolerability of GnRH analog treatment and adverse effects, such as a decrease in bone mineral density, limit the duration of which these treatments can be used. A study of long-term GnRH agonist therapy for endometriosis demonstrated that over a 12-month treatment course, women experienced a 5.4% bone loss and then regained 3% of bone density 1 year after therapy was discontinued [80]. A treatment course no longer than 6–12 months is usually recommended due to the effect on bone loss. Add-back therapy with low-dose estrogen–progestin or progestin alone can be administered with a GnRH agonist to minimize the effects of long-term GnRH agonist treatment. In a randomized study of 51 premenopausal women treated with leuprolide for symptomatic fibroids, an estrogen–progestin add-back regimen effectively prevented the hypoestrogenic effects of treatment, while maintaining uterine volume reduction. Uterine volume increased in women receiving progestin-only add-back therapy [81].

Maheux and colleagues were the first to describe the effective treatment of fibroids with daily administration of a GnRH agonist [76] and the efficacy of GnRH agonist therapy has been substantiated in numerous subsequent trials [77,82,83]. With treatment, most patients develop amenorrhea and have considerable improvement in fibroid-related anemia. Uterine volume reduction between 25 and 50% within 3 months of beginning treatment is consistently reported in the literature. Despite considerable uterine volume reduction during treatment, uterine volume returns to pretreatment size within 3–6 months of cessation of therapy [77]. Owing to the rapid regrowth of fibroids following treatment and the limitations regarding duration of treatment, GnRH agonists are best

suited for short-term, preoperative therapy. A 3–6-month preoperative treatment course effectively reduces uterine volume and corrects anemia, which may facilitate planned surgical management by decreasing operating time and blood loss [84,85]. Although other medical therapies are applied in the management of symptomatic fibroids, the GnRH agonist, leuprolide, is the only medical therapy approved by the FDA for treatment of fibroids. Recent investigations demonstrate that GnRH agonists improve the thermoablative effect of MRgFUS, when used as an adjunct to this radiologic treatment [86]. This effect is explained by a reduction in fibroid vascularity following GnRH agonist treatment, which results in poor heat conduction and greater temperature increase in target tissues [87].

Gonadotropin-releasing hormone antagonist treatment produces comparable effects on uterine volume and fibroid-related symptoms. GnRH antagonists also produce their effects through downregulation of pituitary GnRH receptors; however, they directly inhibit GnRH release without the initial stimulation of GnRH receptors, which occurs with GnRH agonist treatment. Thus, GnRH anatagonist treatment produces a more rapid reduction in fibroid volume without the initial flare effect. Clinical results with GnRH antagonist treatment are observed within 2–3 weeks of treatment [78,79,88]. Although clinical results are promising, long-term preparations of GnRH antagonist are unavailable and daily subcutaneous dosing is inconvenient for long-term treatment of fibroids. Oral GnRH antagonist preparations are available, but they are currently investigational and have not been evaluated in the treatment of fibroids [89,90].

Selective progesterone receptor modulators

Traditional theories of fibroid growth support a critical role for the stimulatory effect of estrogen; however, emerging evaluations of medical therapies targeted at the progesterone receptor stress an important role for progesterone in fibroid growth. The progesterone receptor modulators (PRMs) are a family of progesterone receptor ligands that demonstrate agonistic or antagonistic properties [91]. The antiprogestin mifepristone (RU-486) is well known for its application in early pregnancy termination, but it is also effective in the treatment of fibroids [92]. In a recent investigation of mifepristone treatment for fibroids, 30 women were treated for 3 months with either 50 mg of mifepristone every other day or placebo. Fibroid volume decreased 28% in the mifepristone treatment group and bleeding was significantly reduced [93]. A small trial evaluating low-dose mifepristone treatment (2.5 mg daily) for fibroids demonstrated an 11% decrease in uterine volume following 6 months of treatment. Anemia and fibroid-related symptoms improved during the 6-month course of the trial [94].

The selective progesterone receptor modulator, asoprisnil, and the compound CDB-2914 effectively decrease fibroid and uterine volume, decrease bleeding and relieve fibroid-related symptoms. In a placebo-controlled investigation of 129 women with symptomatic fibroids, asoprisnil (5, 10 and 25 mg) administered daily for 12 weeks produced amenorrhea in 83% of patients at the highest dose. Pelvic pressure symptoms were significantly reduced and fibroid volume was decreased by 36% in women receiving the 25-mg dose [95]. In a subsequent study, investigators observed a reduction in uterine artery blood flow with asoprisnil administration, suggesting regulation of fibroid perfusion as the mechanism for the clinical effects of the treatment [96]. The novel PRM, CDB-2914 (Proellex®), was administered to 22 women with fibroids (10 or 20 mg). Compared with placebo, fibroid volume decreased by 36% in the 10-mg group and 21% in the 20-mg group. Women receiving CDB-2914 became amenorrheic and fibroid-related symptoms were reduced [97].

The major safety concern with PRMs is their associated endometrial effects [98], particularly thickening of the endometrium and an association with endometrial hyperplasia [99,100]. Unique morphological changes in the endometrium were observed in patients treated with asoprisnil [101]. One case of endometrial cystic hyperplasia without atypia in a patient treated with CDB-2914 has been reported [97].

The promising results of mifepristone treatment of fibroids are limited by political concern over its off-label use for this indication. Current evaluations of other PRMs for the treatment of fibroids are investigational and future studies are needed to determine the efficacy and safety of PRMs for long-term treatment of fibroids.

Selective estrogen receptor modulators

The selective estrogen receptor modulator (SERM) raloxifene is indicated for the prevention and treatment of postmenopausal osteoporosis. Although preclinical animal studies of SERMs [102,103] and evaluations of SERMs in postmenopausal women with fibroids were promising [104], investigations

of SERMs in reproductive-aged women have produced conflicting results. A pilot study of 90 premenopausal women with asymptomatic fibroids treated with raloxifene demonstrated no significant reduction in uterine and fibroid volume and no effect on bleeding following a 6-month treatment cycle [105]. In a subsequent combination study, 100 women were randomized to treatment with raloxifene plus the GnRH agonist leuprolide or leuprolide alone. Following a 6-month treatment cycle, women in both groups experienced a reduction in uterine and fibroid volume, but the reductions were greater in the raloxifene plus leuprolide group [106]. The reduction in fibroid volume was maintained in women who continued the combination treatment for 18 months [107]. In a small trial by another investigator, raloxifene treatment alone produced a reduction in fibroid volume compared with no treatment; however, fibroid-related symptoms were unchanged between groups [108]. Larger randomized trials are needed to determine the efficacy of this treatment for the management of symptomatic fibroids in premenopausal women.

Aromatase inhibitors

Aromatase inhibitors (AIs) are used for the treatment of ovarian and breast cancer in postmenopausal women. They inhibit the activity of the estrogen-synthesizing enzyme, aromatase, which results in decreased estrogen levels and decreased stimulation of estrogen-responsive tissues. Varelas and colleagues conducted a prospective trial of 35 premenopausal women with symptomatic fibroids treated with the AI anastrozole. Following 3 months of treatment, fibroid volume was reduced by 55%, uterine volume was reduced by 30% and hematocrit levels increased by 11%. Fibroid-related symptoms were also improved [109]. Hilario *et al.* also reported a 32% reduction in uterine volume following 3 months of treatment with anastrozole [110]. Evaluation of the AI letrozole for the treatment of symptomatic fibroids has produced encouraging results as well [111]. In a recent randomized trial, 70 premenopausal women were treated with letrozole or the GnRH agonist triptorelin for 3 months. Fibroid volume was decreased by 45% in the letrozole group compared with 33% in the triptorelin group. Serum hormone levels were not significantly altered in the letrozole group and the avoidance of the initial gonadotropin flare seen with triptorelin made this treatment advantageous [112]. Black women have the highest incidence of fibroids and fibroids in black women express higher aromatase levels compared with other ethnic groups [113]. Larger prospective trials are needed to identify gene targets such as these for the development of novel therapies and to establish the efficacy of AIs for the treatment of symptomatic fibroids.

Basic science investigations into novel therapies

Fibroids are estrogen- and progesterone-responsive tumors and current medical therapies regulate fibroid growth through manipulation of these hormones. To develop novel therapeutic interventions and strategies for the prevention of fibroid development, researchers are expanding their investigations of fibroid biology beyond steroid hormone regulation. Research efforts to identify gene polymorphisms in fibroids [114–116] and potential targets for gene therapy are ongoing [117,118]. Regulation of the retinoic acid pathway [119,120], growth factors and receptor tyrosine kinase signaling [121] in fibroids are also areas of innovative investigation. The role of vitamin and herbal treatments in the regulation of fibroids is another exciting area of research. In laboratory studies, vitamin D and green tea extract each inhibited fibroid cell proliferation, highlighting their potential role in the regulation of fibroids [122–124]. These novel investigations into the etiology, genetics and molecular mechanisms of fibroid regulation will undoubtedly increase our understanding of fibroid biology and ultimately expand treatment options for women affected by fibroids.

Conclusion

Uterine fibroids affect millions of women worldwide and fibroid-related care consumes billions of healthcare dollars in the USA annually. Surgical removal of fibroids via hysterectomy or myomectomy is the mainstay of traditional fibroid therapy, and laparoscopic and robot-assisted approaches have brought innovation to these conventional treatments. Noninvasive alternative therapies are also on the rise. Procedures such as UAE and MRgFUS offer symptomatic women long-term improvement in fibroid-related symptoms while allowing uterine and, in some instances, fertility preservation. GnRH analogs are highly effective for short-term medical treatment of fibroids. Treatment results with newer medical therapies, such as estrogen and progesterone receptor modulators and AIs are encouraging, although data on long-term outcomes are needed. Ongoing basic science investigations into the biology of

fibroids hold great promise for the future development of novel therapies for the treatment and prevention of fibroids.

Future perspective

Current fibroid therapies offer a glimpse of the future, which will undoubtedly focus on the minimally invasive approach to the management of this disease that affects so many women. Future investigations will most likely attempt to elucidate the molecular mechanisms of fibroid growth and regulation and then translate this understanding into the development of novel therapies. Medical therapies directed at specific gene targets or signaling pathways in fibroids will most likely surpass traditional therapies based on steroid hormone regulation. Surgical management of fibroids will continue to be a practical option for women desiring definitive treatment and for the proportion of women who experience fibroid recurrence or treatment failures with other therapies.

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Executive summary

Epidemiology of fibroids

- By the end of their reproductive years, a woman's lifetime risk of developing fibroids is over 70%.
- Black women are disproportionately affected by fibroids at every age until menopause.
- Between 20 and 50% of women with fibroids experience symptoms significant enough to warrant clinical intervention.
- Treatment of fibroids is the leading indication for hysterectomy in the USA and fibroid-related healthcare costs are high.
- Development of novel fibroid therapies must consider the increased interest in uterine/fertility preservation of women affected by fibroids.

Surgical treatment of fibroids

- Hysterectomy is the mainstay of traditional fibroid therapy, but myomectomy is a surgical alternative for women desiring uterine preservation.
- Risk of fibroid recurrence following uterine-sparing surgery is high.
- Laparoscopic and robot-assisted techniques have brought innovation to standard surgical management.

Minimally invasive treatment of fibroids

- Uterine artery embolization effectively reduces fibroid volume, improves quality of life and offers uterine preservation; although the effect of this treatment on future fertility is unclear.
- Magnetic resonance-guided focused ultrasound surgery utilizes MRI to characterize fibroids and monitor treatment effects during and after thermal ultrasound treatment of fibroids.
- Magnetic resonance-guided focused ultrasound surgery reduces fibroid volume and is indicated for the treatment of symptomatic fibroids in women desiring future fertility.

Medical treatment of fibroids

- Gonadotropin-releasing hormone analogs are useful for short-term treatment of fibroids, but their effects on bone mineral density limit the duration that these treatments can be administered.
- Selective progesterone receptor modulators are effective fibroid therapies, but potential negative endometrial effects warrant further investigation before these treatments can be adopted.
- Clinical outcomes following aromatase inhibitor treatment of fibroids are encouraging, but large prospective investigations are needed to determine the efficacy of these therapies.

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