Clinical Management of Leiomyoma

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KEYWORDS

• Fibroids • Leiomyoma • Pathophysiology • Clinical management • Research

KEY POINTS

- Uterine leiomyoma, benign monoclonal tumors, afflict an estimated 60% of reproductive-aged women, with higher rates among African American women.
- Leiomyomas are associated with significant medical costs, impaired fertility potential, obstetric complications, and gynecologic morbidity.
- Currently, the effective clinical management of leiomyoma is limited by the fact that hysterectomy is the only cure.
- New methods of diagnosis, medical and surgical treatments, as well as interventional radiology and treatment methods are being examined.

INTRODUCTION

In this section, the demographic characteristics and costs of leiomyoma are examined to provide the reader with a brief review of the scope of the problem.

Uterine leiomyomas are exceedingly common, with 60% of reproductive-aged women being affected, and 80% of women developing disease during their lifetime.[1] More than 600,000 hysterectomies are performed annually, and fibroids are the leading indication for hysterectomy in the United States.[2] The annual costs associated with fibroids are estimated at 4 to 10 billion dollars. Estimated lost work-hour costs ranged from $1.55 to 17.2 billion annually. Obstetric outcomes that were attributed to fibroid tumors resulted in a cost of $238 million to $7.76 billion each year.[3]

In addition to the gynecologic complications associated with leiomyoma, fibroids are associated with 10% of cases of infertility. In a little less than 5% of patients, leiomyomas are the only cause of infertility.[4] Among women undergoing assisted

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reproductive technologies, there is clinical evidence to support an association of cavity distortion by submucosal and intramural leiomyoma and of decreased implantation rates after embryo transfer. The clinical data have been considered compelling enough to support a recommendation of myomectomy before IVF.[5] Recent leiomyoma investigations have elucidated previously unknown demographic factors. The age of onset of disease, for example, has been demonstrated to occur at a younger age based on ultrasound evaluations in asymptomatic women. In a recent study of African American and Caucasian women less than 30 years of age, the overall prevalence of leiomyoma based on transvaginal ultrasound was 14.9%. Leiomyomas were more common among African American women than Caucasian women (25.6% vs 6.9%).[6] These findings challenge the traditional dogma that fibroids are uncommon in women under the age of 30.

Age at menarche has also been shown to be an important demographic characteristic that can help identify women at risk for the development of leiomyoma. In a large epidemiologic study of 5023 women screened by ultrasound, early age at first menses had a positive association with fibroid size, type, and location, with a stronger association noted for multiple fibroids.[7] These findings are consistent with earlier studies that identified early age at menarche as a risk factor for the development of leiomyomas.[8]

Obesity has been shown to be a risk factor for fibroid development and may partially explain the increased incidence of leiomyoma among groups that have a high rate of obesity. In a retrospective cohort study, 50% of women with fibroids were found to be obese and 16% were morbidly obese compared with a 25% rate of obesity and a 7.2% rate of morbid obesity in the general population.[9] In a more recent publication, the risk of uterine fibroid development was reported to be 3 times greater for women who weigh more than 70 kg, compared with women who weigh less than 50 kg.[10] Given the increasing incidence of obesity in the United States, an associated increase in the incidence of leiomyoma can be anticipated.

Like pregnancy, family history has been a subject of debate. A recent study suggested that self-reported family history may not be a reliable marker for a high risk of leiomyoma development. In a study of 1072 women (660 African American, 412 Caucasian), self-reported family history of fibroids was not found to be a useful tool for identifying high-risk women.[11]

In summary, some of the most common demographic risk factors include African American race, obesity, and age at menarche. Other factors, such as parity and family history, remain a subject of debate. Additional epidemiologic factors, such as diet, particularly vitamin D deficiency, and environmental toxins, are the subject of ongoing investigations. Further research is needed to identify additional demographic characteristics that are associated with fibroid development. This information will be helpful in counseling patients about their risk of disease. As effective prophylactic treatments are developed, prospective intervention may be possible.

PATHOPHYSIOLOGY

In this section, the pathophysiology of leiomyoma, including molecular mechanisms and genetics, is discussed. In examining the gross appearance of leiomyoma as well as the molecular structure, it has become clear that these benign tumors are composed of altered collagen fibrils, resulting in an altered extracellular matrix (ECM) compared with adjacent myometrium. The distorted ECM is thought to contribute to the increased rigidity of leiomyoma compared with normal myometrium. This understanding of the ECM in the context of a dynamic uterine muscle has led to

the theory that molecular forces likely play a role in the development and growth of leiomyoma.[12]

It is well known that sex steroids, estrogen and progesterone, promote the growth of uterine fibroids.[13] However, Peddada and colleagues[14] have reported that leiomyomas grow and shrink at different rates within the same woman despite the similar exposure to hormonal milieu. Actually, twice as much variation was noted within women as between women highlighting the multifactorial mechanisms involved in leiomyoma progression.

The observation that leiomyomas resemble scar tissue in conjunction with the discovery that numerous cytokines and integrins are altered in leiomyoma compared with adjacent myometrium has highlighted the likely importance of tissue remodeling, fibrosis, and the inflammatory response in the development and progression of these tumors. It may be that the disordered ECM of leiomyoma arises in the uterus as an altered response to noxious stimuli. In recent years, investigators have also elucidated that leiomyomas exist in a state of severe hypoxia compared with normal myometrium. The hypoxia is thought to result in part from abnormal angiogenesis and resulting vasculature, which also could be part of an overarching altered inflammatory response.[15,16] Still another theory put forward by Cramer and colleagues is that a precursor lesion in the myometrium may lead to the development of uterine leiomyoma. Cramer and colleagues[17] found an association between seedling leiomyoma (<1 cm) and myometrial hyperplasia.

Cytogenetic studies have advanced the understanding of the possible causes of leiomyoma. It is known that leiomyomas are monoclonal in origin and that approximately 40% to 50% harbor a cytogenetic abnormality. Most abnormalities have been found in chromosomes 6, 7, 12, and 14.[18]

The initial cytogenetic studies used analysis of the X-linked glucose-6-phosphate dehydrogenase isoenzyme to demonstrate that multiple leiomyomas within a single uterus harbor random patterns of X-inactivation, suggesting that each tumor develops independently.[19] In approximately 20% of karyotypically abnormal leiomyomas, a t(12;14) chromosomal translocation is seen.[20] Other mesenchymal solid tumors (eg, breast fibroadenomas and lipomas) exhibit translocations involving the same region of Chromosome 12, supporting the hypothesis that the gene mapped to this area is important for tumor development.[21] HMGA2, a member of the high mobility gene group linked to self-renewal ability, has been mapped to this area and is found to be overexpressed in uterine leiomyoma.[22] Similarly, rearrangements in chromosome 6p21, occurring in less than 5% of leiomyoma, have been found to lead to upregulation of another member of the high mobility gene group, HGMA1.[23]

Aside from the known chromosomal abnormalities listed above, a variety of other less frequent cytogenetic abnormalities have been identified in leiomyoma.[18] A recent investigation of the genetics of leiomyoma as it relates to leiomyoma as a health disparity issue found that many genes were differentially expressed in the leiomyoma of older black compared with older white women.[24] One interesting finding of the study was that CAIII, a gene encoding an enzyme that serves to buffer cellular acid-base, was the most highly expressed gene in the leiomyoma of black women compared with leiomyoma from white women. These results could explain how the aberrant smooth muscle cells of leiomyoma survive in such a hypoxic and acidic environment and develop such a severe phenotype in black women.[24]

The existence of a disparity of leiomyoma phenotypes between black and white women underlines a likely genetic liability of the disease in certain groups that cannot be explained by variations in demographics alone. In addition, an inherited factor for

certain types of leiomyoma is certain with the germline mutation having been identified such as patients with hereditary leiomyomatosis and renal cell carcinoma. However, the marked prevalence of leiomyoma overall suggests that genetics is only one component of the overall cause of leiomyoma and further investigation is still needed in this area.

DIAGNOSIS AND ASSESSMENT

In this section, the diagnosis and assessment of leiomyoma, including clinical symptoms and the role of imaging, are discussed.

Most women with uterine fibroids are asymptomatic[25,26]; however, women can experience abnormal uterine bleeding (AUB), pelvic pain, bulk symptoms, reproductive dysfunction, sexual dysfunction, and urologic complications. It has been estimated that approximately 20% to 50% of patients with uterine leiomyoma experience symptoms credited to the presence of myomas.[27,28] It is well known that the symptoms caused by uterine fibroids significantly impact women's quality of life and well-being.[29] With so many women affected by leiomyoma, this condition accounts for a significant burden of disease. Most women are diagnosed with leiomyoma after they present for the evaluation of symptoms, during infertility work-up, or incidentally at the time of other diagnostic imaging.[30,31] It has been estimated in one study that each year approximately 1% of reproductive-aged women affected by uterine leiomyoma will present for consultation with a provider because of their bothersome symptoms.[32]

The most common symptom of leiomyoma, occurring in 30% of women with the disease, is AUB. Excessive bleeding can have a significant impact on quality of life because it may interfere with one's personal and work life and be the precipitating factor in the development of other medical issues, such as iron deficiency anemia.[33] In some cases, AUB from uterine leiomyoma can lead to acute, life-threatening hemorrhage requiring emergent blood transfusion and hospitalization. The cause of AUB in the presence of leiomyoma is poorly understood, but many groups have proposed various theories including obstruction from fibroids leading to venule ectasia in the endometrium,[34] increased surface area of the endometrium,[35] and the dysregulation of local growth factors and aberrant angiogenesis within the uterus and endometrium.[36]

In addition, women with uterine leiomyoma may present with symptoms of pelvic pain, dysmenorrhea, and dyspareunia. One population-based cross-sectional study looking at women who were not seeking care found that women with ultrasound-confirmed fibroids were more likely to report moderate to severe dyspareunia and noncyclic pelvic pain. Interestingly, women without fibroids were just as likely as women with fibroids to report moderate or severe dysmenorrhea. This study also showed that there was no association between the number and total volume of fibroids and pelvic pain.[37]

The suspected diagnosis of leiomyoma may be based in some cases on the palpation of an enlarged irregular uterine contour on pelvic examination in the office.[38] Women may experience urinary frequency, difficulty emptying the bladder, or, in rare cases, hydronephrosis and chronic kidney disease.[39] With posterior pressure from bulky leiomyoma, the patient may suffer from low back pain or constipation.[40] It is important to take a careful history during the assessment of uterine fibroids, because the severity of symptoms will often inform the management of leiomyoma.

Uterine leiomyomas in some women who were previously undiagnosed are discovered during infertility evaluation. Uterine fibroids may be found in approximately 5% to

10% of infertile women. However, when all other factors are excluded, it is estimated that only 2% to 3% of infertility is attributed to uterine fibroids.[25,41] Systematic reviews have shown that submucosal and intracavitary fibroids are associated with decreased clinical pregnancy and implantation rates and that removal appears to improve fertility.[42,43] Consensus is that the proximity of uterine fibroids to the uterine cavity determines detrimental effects on infertility, but there is still much work to be done to elucidate the impact of intramural fibroids on fertility.

Once leiomyoma is suspected by history, physical examination, or incidental discovery, imaging should be undertaken to confirm the presence, location, characterization, and size of uterine leiomyoma. This process is often called uterine mapping or leiomyoma mapping. Although uterine fibroids may be detected on computed tomographic scans or at the time of hysterosalpingogram, there is little to no role for either of these studies in the evaluation of leiomyoma. Ultrasound, both transvaginal and transabdominal, is most frequently used in the assessment of leiomyoma because of its low cost and accessibility.[44] Transvaginal ultrasonography alone has been shown to have sensitivity for detecting uterine fibroids in the range of 65% to 99%.[45–47] There is improved sensitivity of detecting submucosal myomas with the addition of sonohysterography.[48] However, one the major limitations of ultrasonography, as demonstrated above in the wide range of sensitivity, is its operator-dependence, resulting in poor reproducibility as compared with MRI.[49–52] In addition, subserosal fibroids as well as small fibroids may not be identified by transvaginal ultrasound.[53]

MRI is a more costly modality, but is thought to be more exact in its capacity for leiomyoma mapping, especially in large uteri (>375 mL) and in uteri with greater than 4 myomas.[47] MRI is also better able to distinguish uterine leiomyoma from leiomyosarcoma and adenomyosis.[54–56] In addition, because of the precise resolution and anatomic detail afforded by MRI, 69% of benign histologic subtypes of leiomyoma can be identified, including cellular, degenerated, and necrotizing leiomyoma as well as lipoleiomyoma and acutely infarcting leiomyoma.[57]

Proper diagnosis and assessment of uterine fibroids play an important role in deciding the management plans for patients.

FIBROIDS MEDICAL THERAPY

Currently, hysterectomy is the only cure for fibroids, which underscores the need for identification of effective nonsurgical medical treatments, with high efficacy, and a desirable side-effect profile. This section reviews the use of medical treatments, both as adjuvant therapy and as primary therapy. The discussion focuses on gonadotrophin-releasing hormone (GnRH) analogues, selective progesterone receptor (SPRM) modulators, and aromatase inhibitors (AI). The use of levonorgestrel-containing IUDs (LNG-IUS) is also reviewed.

Adjuvant Therapy

For women with anemia, or fibroids that are extremely large, or located in positions that will make surgical removal challenging, adjuvant preoperative medical therapy may be clinically helpful. GnRH analogues (eg, leuprolide) have been most extensively studied for this indication, and the discussion focuses on these agents. Studies of GnRH analogue effect have shown that fibroid tumor shrinkage is proportional to the number of estrogen receptor-positive cells, suggesting that GnRH analogues mediate their effect via reduction in estrogen levels.[58]

The most comprehensive review of the clinical utility of GnRH analogues is the *Cochrane Systematic Review* of the role of GnRH analogues before hysterectomy or

myomectomy. This review showed a significant improvement in both preoperative and postoperative hemoglobin when GnRH analogues were used before surgery. Operative time for hysterectomy was reduced, and a greater number of patients undergoing hysterectomy were able to have a vaginal hysterectomy. Blood loss, the use of vertical skin incisions, and hospital stay duration were reduced for both myomectomy and hysterectomy.[59]

GnRH analogues are the only drugs that are Food and Drug Administration (FDA)-approved as medical fibroid therapeutics for the indication of preoperative adjunctive therapy to control bleeding, decrease fibroid size, and improve preoperative anemia. Despite FDA approval, the cost, the hypoestrogenic effects, rapid regrowth after cessation of medication, and bone demineralization after long-term use limit GnRH analogues to short-term adjuvant therapy in most patients.[60]

Multiple basic science and clinical investigations have provided evidence that progesterone and the progesterone receptor may play a role in enhancing proliferative activity in leiomyoma. This growing body of literature supports a potential therapeutic role for antiprogestins and drugs that modulate progesterone receptor activity, such as SPRMs.[61]

Much of the early clinical research with selective progesterone modulators involved the use of mifepristone and asoprisnil. Both drugs have been shown to be efficacious in reducing fibroid size and improving fibroid associated symptoms.[62] More recently, ulipristal acetate (UPA), approved for emergency contraception, has been the focus of clinical investigations. UPA has been shown to improve quality of life, reduce fibroid volume, and induce amenorrhea in most of the women treated and is now approved for clinical use in both Europe and Canada.[63,64] In a double-blind study comparing UPA to leuprolide acetate, UPA controlled bleeding in nearly 100% of women, and they became amenorrheic 2 weeks earlier than women treated with leuprolide. UPA was associated with reduction in fibroid volume of approximately 25% when compared with placebo. A major advantage of UPA over leuprolide is the lack of hypoestrogenic side effects and bone loss. These differences between UPA and leuprolide may make UPA a preferred choice for preoperative adjuvant therapy.[65]

The endometrial effects of SPRMs have been a major concern with the use of these agents. Theoretically, SPRM modulators may cause blockade of progesterone action on the endometrium, and inhibition of ovulation could result in unopposed estrogen. Although initial histologic findings associated with the drug were concerning for hyperplasia, more recent histologic assessments have demonstrated histologic changes that are unique to SPRMs, termed progesterone-associated endometrial changes, which appear to be benign in nature.[66] More recent studies have not shown atypical hyperplasia in patients receiving SPRMs, and progesterone-associated changes regress after cessation of therapy, but the long-term effect of these drugs on the endometrium has not been established.

AI represent a class of antiestrogens that block the synthesis of estrogen. AI have become standard adjuvant therapy for postmenopausal women with estrogen receptor–positive breast cancer, as a result of their ability to produce in situ estrogen inhibition as compared with the indirect inhibition induced by GnRH agonists.[67] These properties also made AI very attractive candidates for the medical treatment of leiomyoma.

Basic science studies in the mid-1990s revealed that aromatase mRNA was detected in more than 90% of fibroids, but was undetectable in myometrial tissues from normal uteri.[68] Other investigators found that there were racial differences, with leiomyoma tissue from African American women having the highest levels of

aromatase expression. These differences may explain, in part, the differences in the higher prevalence and earlier incidence in African American women. It also suggests that African American women may be more responsive to aromatase inhibitor therapy.[69]

Multiple clinical studies have shown a reduction in fibroid size and improvement of symptoms with aromatase inhibitor therapy. In a small prospective clinical trial, Gurates and colleagues[70] found that letrozole significantly decreased fibroid size and relieved heavy menstrual bleeding without changing bone mineral density. Several other investigators found that anastrozole was effective in reducing fibroid volume and improving symptoms without changing follicle-stimulating hormone (FSH) or estradiol levels.[71] The unique properties of AI also make it a therapeutic option in postmenopausal women with leiomyoma. In a study of obese postmenopausal women with fibroids and persistent bleeding, Kaunitz[72] demonstrated that anastrozole reduced fibroid size and caused endometrial thinning and cessation of bleeding.

Although AI have great potential as a medical therapy for leiomyoma and have several advantages over GnRH analogues, a recent *Cochrane Review* concluded that evidence was insufficient to support the use of AI drugs in the treatment of women with uterine fibroids.[73] Additional clinical studies, with larger numbers of subjects, will be necessary to determine the long-term safety, optimal treatment regimens, and impact on reproductive function.

No randomized controlled trials of LNG-IUS in women with fibroids have been published; however, multiple clinical studies suggest that bleeding markedly decreases in women with leiomyoma that have heavy menstrual bleeding. In a systematic review by Zapata and colleagues,[74] they reported that menstrual blood loss decreased in the 11 studies included in their analysis. These investigations also demonstrated an increase in hemoglobin, hematocrit, and ferritin. Some, but not all, studies showed an increase in expulsion rates. In the 6 prospective noncomparative studies, expulsion rates varied from 0% to 20%. Unlike uterine bleeding, fibroid volumes measured by MRI were not decreased in women using LNG-IUS.[75] In women with a need for contraception who do not desire surgery, or who need to correct their anemia before surgery, the LNG-IUS is an option that should be offered to these patients.

UTERINE ARTERY EMBOLIZATION

Uterine artery embolization (UAE) is a widely accepted, nonsurgical technique used to treat symptomatic uterine fibroids. This technique has been endorsed by the American College of Obstetricians and Gynecologists as safe and effective for women with uterine fibroids who are appropriately selected.[76] UAE is ideal for women with symptomatic uterine fibroids who have medical management, are poor surgical candidates, wish to avoid surgery, or wish to retain their uterus.

Women seeking UAE most often complain of AUB, especially heavy menstrual bleeding, and bulk symptoms. In a randomized controlled trial that compared UAE to hysterectomy (EMMY trial), UAE was associated with a significantly shorter hospital stay and had a similar improvement in health-related quality of life compared with hysterectomy. However, women who underwent hysterectomy were significantly more satisfied with their received treatment.[77] Similar improvements in quality of life were seen in the REST trial, another multicenter randomized controlled trial performed in the United Kingdom comparing UAE with surgery (myomectomy or hysterectomy). The EMMY trial reported reintervention in the UAE group in 28% of

patients and the REST trial reported a cumulative intervention rate of 32% with both trials following the patients for up to 5 years.[78] One analysis of trials examining UAE versus surgical intervention demonstrated that UAE is associated with a shorter hospital stay, a quicker return to activities, and a higher minor complication rate after discharge.[79]

Contraindications to UAE include on-going pregnancy and active uterine or adnexal infections. Allergy to intravenous contrast and renal insufficiency are relative contraindications and special considerations should be made for patients on anticoagulation medications. As with all therapies dealing with fibroids, physicians should consider size and location of myomas when counseling patients for UAE. Women with very large uteri (greater than 22-weeks size) may not have significant improvement in their symptoms after UAE, and cervical or broad ligament fibroids are less likely to respond to UAE because these fibroids are more likely to have collateral blood supplies.

According to the fibroid registry, the most common complication of UAE is severe pain requiring hospitalization. Postembolization syndrome, consisting of mild-to-moderate pain, low-grade fever, and malaise, is also very common following the procedure and is usually managed with analgesics and antipyrectics. Sloughing of an embolized fibroid into the uterine cavity resulting in foul-smelling vaginal discharge will be experienced by 2.2% to 7% of patients.[80] Mortality resulting from UAE is exceedingly rare, with only a few cases ever reported. The most common potentially fatal complication is pulmonary embolism (1 in 400 patients). The potential detrimental effect of UAE on the ovaries is also an area of controversy. There is a 3% chance of amenorrhea in young women attributed to impairment of ovarian function from embolization of collateral blood supply.[81] This risk seems to be age-related and, in some women not desiring future childbearing, amenorrhea could be the therapeutic goal. The EMMY randomized clinical trial of UAE versus hysterectomy reported similar ovarian impairment as measured by preprocedure and postprocedure antimullerian hormone and FSH levels.[82]

The effects of UAE on fertility and pregnancy are still areas of controversy. At present, if fibroids are determined to be the cause of infertility, then myomectomy is the preferred treatment. One of the best studies to investigate the effects of UAE on fertility was a randomized trial in 121 women with fibroids desiring fertility undergoing myomectomy versus UAE and followed for up to 2 years. This study found that women were significantly more able to achieve pregnancy after myomectomy (78%) versus UAE (50%). They also found that UAE was associated with a greater risk of spontaneous abortion.[83] In addition, some authors have suggested a concern that UAE increases the complication rate during future pregnancies. One retrospective study examining pregnancies after UAE (n = 53) compared with myomectomy (n = 139) demonstrated that in the UAE group there was a higher rate of preterm birth, malpresentation, and cesarean section.[84] The Ontario multicenter trial included a cohort of 24 pregnancies occurring in women after UAE. They found a 12% risk of placentation complications (2 placenta previa and 1 placenta accreta) all occurring in nulliparous women with no other identified risk factors. Given the biologic plausibility of UAE leading to compromised endometrial perfusion and thus abnormal placentation, UAE should be recommended with caution for women desiring future fertility.[85]

In general, UAE is an excellent treatment option for women who have failed medical management, completed childbearing, have contraindications to surgery, or wish to avoid surgical intervention. More studies are needed to investigate the risks and benefits of UAE in women with infertility and those desiring future pregnancies. Based on

the current evidence, UAE should be offered with caution and only after careful counseling to women desiring future fertility.

MAGNETIC RESONANCE–GUIDED FOCUSED ULTRASOUND SURGERY

In 2004, the FDA approved the first magnetic resonance–guided focused ultrasound surgery (MRgFUS) device as a noninvasive thermal ablation therapy for uterine fibroids. The technology uses MRI guidance to map and monitor high-intensity ultrasound-focused ablation of fibroid tumors. The goal of therapy is to achieve an increase in temperature within the fibroid leading to coagulation necrosis while avoiding patient discomfort and damage to surrounding structures (eg, bowel, bladder, neurovascular bundles).[86]

The ideal candidate for this therapy has symptomatic fibroids, which are usually limited to a few moderately sized fibroids (4–6 cm) or a single fibroid no more than 10 cm, has low signal intensity on T2-weighted MRI, and can be safely accessed by the ultrasound beam (no more than 12 cm from abdominal wall and no closer than 4 cm to sacrum). The patient must be able to lie prone for the therapy, which typically takes up to 3 hours, and receive intravenous conscious sedation, which is used to limit patient movement. Patients are typically excluded if they have serious health complications, have contraindications to MRI such as claustrophobia or implants, have significant abdominal scarring, have very large uteri (greater than 24-weeks size), or have pedunculated, nonenhancing, or heavily calcified fibroids.[87] In one study of women with large fibroids (>10 cm), treatment with GnRH agonist before MRgFUS improved treatment success by shrinking the fibroid to a more manageable size. GnRH agonists also decrease vascularity, which has been shown to increase the destructive effect of the thermal ablation.[88]

MRgFUS is usually well-tolerated with the recent studies showing no serious side effects and few minor complications, including abdominal pain, skin burns, and sciatic nerve paresthesia.[89] MRgFUS has been shown to improve quality of life and symptom severity scores, which most authors associate with the increased nonperfusion volume of the treated fibroids seen on MRI.[86] Initial FDA labeling of the MRgFUS device stated that it was for women who had completed child-bearing.[90] However, there have been 35 reported successful pregnancies without increased complications in women post-MRgFUS, which have raised the question of whether this technology, given its noninvasive approach, may actually be the treatment of choice for women who desire future fertility.[86] More studies are needed to address this question and determine the role for MRgFUS in the treatment of uterine fibroids.

SURGICAL THERAPIES

For women who desire surgery, the most important considerations are size and location (**Fig. 1**) of the fibroids and fertility potential. Although hysterectomy is the only cure, myomectomy is the only viable surgical option for women who want to maintain an option for future pregnancies. This section reviews surgical options, with a focus on patient selection and outcomes.

Patients who elect conservative surgery should be apprised of their risk of recurrence and likelihood of eventual hysterectomy. Although a precise individual risk cannot be identified, the literature suggests a recurrence rate of fibroids of nearly 60%, with most of the fibroids recurring between 3 and 5 years after surgery.[91] Women who are at risk for diminished ovarian reserve, or who have other infertility factors, should be offered assessment to help them in the decision to proceed with conservative surgery.

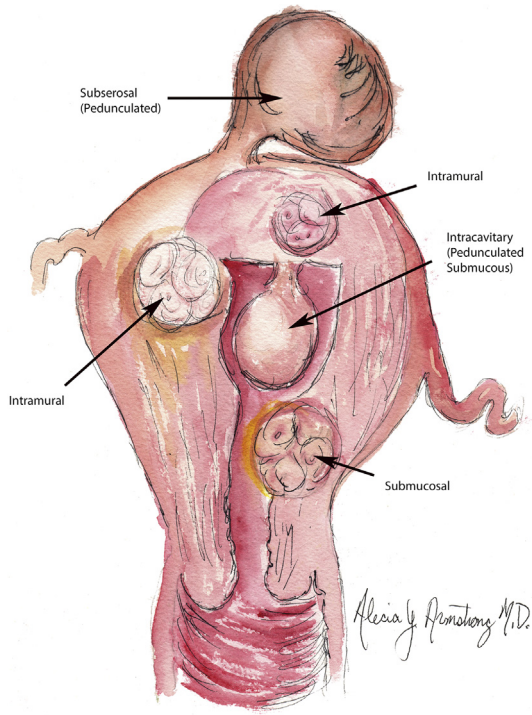

Fig. 1. Locations of fibroid tumors.

Location of leiomyoma is a significant determinant of surgical route, and appropriate diagnostic imaging should be performed before selecting surgical approach (see **Fig. 1**). The best candidates for hysteroscopic myomectomy are patients with submucosal fibroids less than 3 cm, with greater than 50% of the fibroid being intracavitary. Type 0 (entirely intracavitary) and type 1 (greater than 50% intracavitary) may be candidates for this surgical approach. Patients with type 2, less than 50% intracavitary, are better candidates for abdominal surgery.[92] Although surgical experience and expertise are important factors, there are little published objective data related to this variable.

The selection of distension media is an important factor, particularly when prolonged surgical times are anticipated. Because myometrial integrity is breached in the performance of myomectomy, these procedures are at greater risk of systemic absorption. Carbon dioxide should only be used for diagnostic and not operative hysteroscopy. The maximum volumes for various types of distention media are shown in **Table 1**. Injection of dilute vasopressin solution preoperatively can decrease distending media absorption. Saline has the lowest risk of hyponatremia and hypo-osmolarity, but it requires the use of bipolar instruments (see **Table 1**).

LAPAROSCOPIC AND ROBOTIC MYOMECTOMY

For appropriate candidates, laparoscopic myomectomy offers the advantage of lower blood loss, more rapid return to normal activities, shorter hospital stays, and a more cosmetically acceptable scar. A large multicenter trial and other clinical investigations have reported uterine rupture after laparoscopic myomectomy, and it has been

Table 1
Maximum volumes for hysteroscopic distension media

Media Type	Maximum Volume	Comment
Saline	2500 mL	Isotonic media should be used whenever possible to reduce risk of hyponatremia. Requires use of bipolar instruments
Glycine (low viscosity)	1000 mL	Fluid overload with low viscosity media can result in hypotonic hyponatremia
Dextran (high viscosity)	500 mL	Volumes as low as 300 mL associated with adverse outcomes. Dextran 70 associated with anaphylaxis. Can caramelize on instruments
Sorbitol (low viscosity)	1000 mL	
Mannitol (low viscosity)	1000 mL	

Data from AAGL Practice Report: Practice Guidelines for the Management of Hysteroscopic Distending Media. J Minimally Invasive Gynecology 2013. Available at: http://www.aagl.org/wp-content/uploads/2013/03/aagl-Practice-Guidelines-for-the-Management-of-Hysteroscopic-Distending-Media.pdf. Accessed September 25, 2014.

recommended that women with fibroids greater than 5 cm multiple myomas and deep intramural myomas consider abdominal myomectomy.[93] Although there are many advantages to laparoscopic myomectomy, mastery of this procedure often requires considerable training.

The introduction of robotic assistance has helped to facilitate the surgeon's ability to perform myomectomy laparoscopically. There is also the additional advantage of expanding the number of patients who are candidates for laparoscopic myomectomy. Unfortunately, long-term outcomes data for alleviation of symptoms, residual fibroid burden, subsequent fertility, and patient satisfaction are lacking for robotic-assisted myomectomy.

ABDOMINAL MYOMECTOMY

Abdominal myomectomy is the preferred surgical option when hysteroscopy or laparoscopy is not an option, or the patient has another indication for laparotomy (**Fig. 2**). Other recommendations based on earlier studies suggested that women with more than 3 to 4 fibroids or total uterine size greater than 9 cm consider abdominal myomectomy. The increasing experience of surgeons and the advent of robotic technology have made it possible for women with larger uteri to avoid laparotomy. In a recent comparison of robotic surgery versus abdominal myomectomy, the uterine size limit was 20 weeks. Robotic surgery and abdominal myomectomy were equally efficacious in alleviating symptoms, but operative times were significantly longer with robotic surgery, and the residual fibroid burden was greater. Compared with abdominal myomectomy, patients undergoing robotic surgery had shorter hospital stays and a faster return to work.[93]

HYSTERECTOMY

For women who desire definitive therapy, there are several options, which include vaginal hysterectomy, total laparoscopic hysterectomy (TLH), laparoscopic-assisted vaginal hysterectomy (LAVH), and laparotomy. Like myomectomy, the surgical route is determined by size and location of the fibroids, surgeon experience, and patient

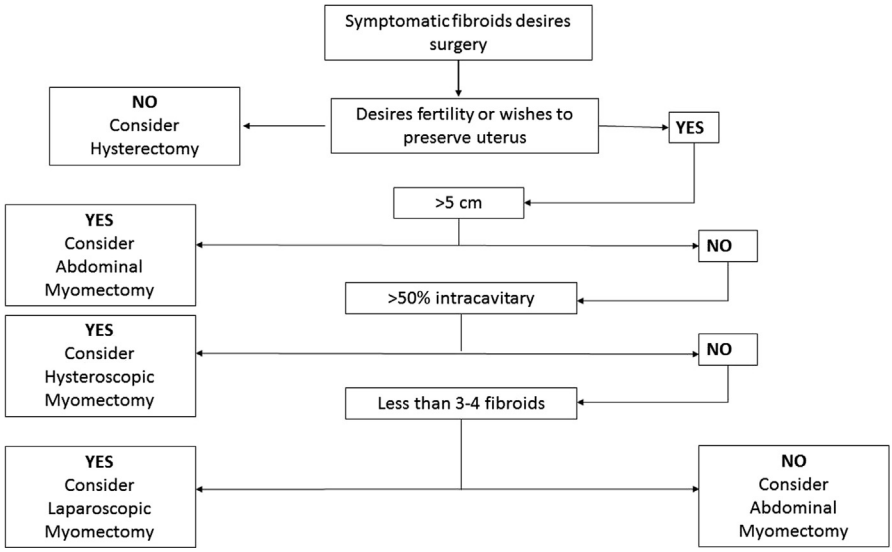

Fig. 2. Algorithm for surgical management of symptomatic fibroids. (*From* Heitmann RJ, Duke CM, Catherino WH, et al. Surgical treatments and outcomes. In: Segars JH, editor. Gynecology in practice: fibroids. Hoboken (NJ): Wiley-Blackwell, and imprint of John Wiley & Sons; 2013. p. 110; with permission.)

preference. In a recent randomized comparison of vaginal hysterectomy in Europe, TLH and LAVH for leiomyoma, the study found vaginal hysterectomy was the faster operative technique with lower blood loss and shorter time to discharge. The authors recommended that vaginal hysterectomy be considered the preferred approach. When vaginal hysterectomy is not feasible or salpingo-oophrectomy is required, LAVH or TLH should be considered.[94]

Morcellation allows appropriately selected patients to undergo minimally invasive surgery instead of laparotomy. Recent reports of dissemination of malignant tissue with this procedure, however, caused safety concerns. On April 17, 2014, the FDA issued a Safety Communication that discouraged the use of laparoscopic power morcellation in hysterectomy and myomectomy for fibroids. In May of 2014, American College of Obstetricians and Gynecologists released a Special Report stating that power morcellation remains an option for some women, but informed consent is critical.[95] The Special Report included the following:

- Minimally invasive surgery, including gynecologic power morcellation, continues to be an option for some patients undergoing hysterectomy or myomectomy;
- In women with strongly suspected or known uterine cancer, power morcellation should not be used;
- Preoperative evaluation and diagnosis play an important role when power morcellation is being considered; and
- Patient counseling and the informed consent process also play an important role. Physicians and patients considering power morcellation as an option during gynecologic surgery should discuss the risks, benefits, and alternatives.

The Special Report also called for further research, adequate training, development of safer methods, and a national prospective gynecologic power morcellation surgery registry to help acquire consistent and reliable data.

OUTCOMES

Rates of mortality for fibroid surgery are low, and the risk of serious complications is small. Surgical site infection rates vary from 1% to 11%, but most of these are superficial infections. Although rates of deep vein thromboses are high among surgical patients who do not receive prophylaxis, the risk of fatal pulmonary embolism is less than 1%. The risk of postoperative bleeding that requires transfusion is 2% after abdominal hysterectomy, but transfusion rates vary from 2% to 28% with myomectomy. Ninety-nine percent of women undergoing hysterectomy indicated that surgery improved or resolved their symptoms.

In conclusion, the specific indications for each surgical approach are subjective. Surgical route depends on the surgeon's experience, coexisting medical conditions, uterine size and location of the fibroids, and patient preference.

SUMMARY

Although hysterectomy remains the only cure for fibroids, there are several exciting candidates for medical therapies in the treatment of fibroids. Vitamin D, epigallocatechin gallate (EGCG), or green tea extract, compounds that increase retinoic acid and dietary supplements such as curcumin, all appear to have potential as nonsurgical therapies.

There is evidence to suggest that vitamin D inhibits growth, induces apoptosis in human leiomyoma cell cultures, and may act as an antifibrotic factor. Human studies examining vitamin D levels in healthy controls, and women with fibroids, indicate that there is a correlation with disease severity and vitamin D levels in women with symptomatic leiomyomas. There was a strong dose-response correlation, with women with more severe disease having lower levels of vitamin D.[96] These agents may have promise as a novel treatment option, or preventative therapy.

EGCG, or green tea extract, has been shown to inhibit proliferation of leiomyoma cells in vitro and in nude mice. EGCG has also been found to induce apoptosis as well as to inhibit cell proliferation through multiple signal transduction pathways, making it a potential medical therapy with a low side-effect profile.[97]

Another nutrition supplement that may have therapeutic benefit is curcumin, a dietary spice with antineoplastic activity. Curcumin inhibited leiomyoma cellular proliferation and decreased ECM proteoglycan expression in fibroids.[98] Distortions in the ECM are thought to contribute to the increased rigidity of leiomyoma compared with normal myometrium. This understanding of the ECM has led to the theory that molecular forces likely play a role in the development and growth of leiomyoma.[12] Given the ability of curcumin to decrease ECM proteoglycan expression, curcumin may be a potential medical therapy with very few safety issues.

Retinoids appear to modulate proliferative and apoptotic pathways in leiomyoma.[99] Abnormal ECM production appears to be linked to decreased endogenous retinoic acid, suggesting a possible role for compounds that increase endogenous retinoic acid. One such compound, liarozole, a retinoic acid metabolism blocking agent, may inhibit ECM formation through the retinoic pathway.

As the understanding of cellular differentiation pathways increases, new potential preventative and treatment modalities will be identified. For women who desire a surgical option, minimally invasive surgery technologies will offer options such as robotic and laparoscopic techniques, which have shorter hospital stays, lower complication rates, and shorter recovery times. Additional review and evaluation will be necessary to determine if some procedures, such as morcellation, offer more risk than benefit. Clinical research trial networks will facilitate the conduct of large clinical trials, which

help to answer important questions about the potential benefit of new and existing clinical therapies.

REFERENCES

1. Baird DD, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
2. Moorman PG, Leppert P, Myers ER, et al. Comparison of characteristics of fibroids in African American and white women undergoing premenopausal hysterectomy. Fertil Steril 2013;99:768–76.e1.
3. Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol 2012;206:211.e1–9.
4. Kolankaya A, Arici A. Myomas and assisted reproductive technologies: when and how to act? Obstet Gynecol Clin North Am 2006;33:145–52.
5. Sunkara SK, Khairy M, El-Toukhy T, et al. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod 2010;25:418–29.
6. Marsh EE, Ekpo GE, Cardozo ER, et al. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18-30 years old): a pilot study. Fertil Steril 2013;99:1951–7.
7. Velez Edwards DR, Baird DD, Hartmann KE. Association of age at menarche with increasing number of fibroids in a cohort of women who underwent standardized ultrasound assessment. Am J Epidemiol 2013;178:426–33.
8. Dragomir AD, Schroeder JC, Connolly A, et al. Potential risk factors associated with subtypes of uterine leiomyomata. Reprod Sci 2010;17:1029–35.
9. Shikora SA, Niloff JM, Bistrian BR, et al. Relationship between obesity and uterine leiomyomata. Nutrition 1991;7:251–5.
10. Eltoukhi HM, Modi MN, Weston M, et al. The health disparities of uterine fibroid tumors for African American women: a public health issue. Am J Obstet Gynecol 2014;210:194–9.
11. Saldana TM, Moshesh M, Baird DD. Self-reported family history of leiomyoma: not a reliable marker of high risk. Ann Epidemiol 2013;23:286–90.
12. Norian JM, Owen CM, Taboas J, et al. Characterization of tissue biomechanics and mechanical signaling in uterine leiomyoma. Matrix Biol 2012;31:57–65.
13. Fields KR, Neinstein LS. Uterine myomas in adolescents: case reports and a review of the literature. J Pediatr Adolesc Gynecol 1996;9:195–8.
14. Peddada SD, Laughlin SK, Miner K, et al. Growth of uterine leiomyomata among premenopausal black and white women. Proc Natl Acad Sci U S A 2008;105:19887–92.
15. Tal R, Segars JH. The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy. Hum Reprod Update 2014;20:194–216.
16. Mayer A, Hockel M, Wree A, et al. Lack of hypoxic response in uterine leiomyomas despite severe tissue hypoxia. Cancer Res 2008;68:4719–26.
17. Cramer SF, Mann L, Calianese E, et al. Association of seedling myomas with myometrial hyperplasia. Hum Pathol 2009;40:218–25.
18. Ligon AH, Morton CC. Leiomyomata: heritability and cytogenetic studies. Hum Reprod Update 2001;7:8–14.
19. Hashimoto K, Azuma C, Kamiura S, et al. Clonal determination of uterine leiomyomas by analyzing differential inactivation of the X-chromosome-linked phosphoglycerokinase gene. Gynecol Obstet Invest 1995;40:204–8.

20. Meloni AM, Surti U, Contento AM, et al. Uterine leiomyomas: cytogenetic and histologic profile. Obstet Gynecol 1992;80:209–17.
21. Calabrese G, Di Virgilio C, Cianchetti E, et al. Chromosome abnormalities in breast fibroadenomas. Genes Chromosomes Cancer 1991;3:202–4.
22. Schoenmakers EF, Wanschura S, Mols R, et al. Recurrent rearrangements in the high mobility group protein gene, HMGI-C, in benign mesenchymal tumours. Nat Genet 1995;10:436–44.
23. Tallini G, Vanni R, Manfioletti G, et al. HMGI-C and HMGI(Y) immunoreactivity correlates with cytogenetic abnormalities in lipomas, pulmonary chondroid hamartomas, endometrial polyps, and uterine leiomyomas and is compatible with rearrangement of the HMGI-C and HMGI(Y) genes. Lab Invest 2000;80:359–69.
24. Davis BJ, Risinger JI, Chandramouli GV, et al. Gene expression in uterine leiomyoma from tumors likely to be growing (from black women over 35) and tumors likely to be non-growing (from white women over 35). PLoS One 2013;8:e63909.
25. Buttram VC Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril 1981;36:433–45.
26. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435–8.
27. Gupta S, Jose J, Manyonda I. Clinical presentation of fibroids. Best Pract Res Clin Obstet Gynaecol 2008;22:615–26.
28. Marino JL, Eskenazi B, Warner M, et al. Uterine leiomyoma and menstrual cycle characteristics in a population-based cohort study. Hum Reprod 2004;19:2350–5.
29. Spies JB, Coyne K, Guaou NG, et al. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 2002;99:290–300.
30. Levy G, Hill MJ, Beall S, et al. Leiomyoma: genetics, assisted reproduction, pregnancy and therapeutic advances. J Assist Reprod Genet 2012;29:703–12.
31. Levy G, Hill MJ, Plowden TC, et al. Biomarkers in uterine leiomyoma. Fertil Steril 2013;99:1146–52.
32. Marshall LM, Spiegelman D, Manson JE, et al. Risk of uterine leiomyomata among premenopausal women in relation to body size and cigarette smoking. Epidemiology 1998;9:511–7.
33. Wegienka G, Baird DD, Hertz-Picciotto I, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003;101:431–7.
34. Farrer-Brown G, Beilby JO, Tarbit MH. Venous changes in the endometrium of myomatous uteri. Obstet Gynecol 1971;38:743–51.
35. Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. Obstet Gynecol 2004;104:393–406.
36. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update 1996;2:295–306.
37. Lippman SA, Warner M, Samuels S, et al. Uterine fibroids and gynecologic pain symptoms in a population-based study. Fertil Steril 2003;80:1488–94.
38. Grover SR, Quinn MA. Is there any value in bimanual pelvic examination as a screening test. Med J Aust 1995;162:408–10.
39. Bansal T, Mehrotra P, Jayasena D, et al. Obstructive nephropathy and chronic kidney disease secondary to uterine leiomyomas. Arch Gynecol Obstet 2009;279:785–8.
40. Bukulmez O, Doody KJ. Clinical features of myomas. Obstet Gynecol Clin North Am 2006;33:69–84.

41. Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons. Myomas and reproductive function. Fertil Steril 2008;90:S125–30.
42. Pritts EA. Fibroids and infertility: a systematic review of the evidence. Obstet Gynecol Surv 2001;56:483–91.
43. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009;91:1215–23.
44. Levens ED, Wesley R, Premkumar A, et al. Magnetic resonance imaging and transvaginal ultrasound for determining fibroid burden: implications for research and clinical care. Am J Obstet Gynecol 2009;200:537.e1–7.
45. Cicinelli E, Romano F, Anastasio PS, et al. Transabdominal sonohysterography, transvaginal sonography, and hysteroscopy in the evaluation of submucous myomas. Obstet Gynecol 1995;85:42–7.
46. Griffin KW, Ellis MR, Wilder L, et al. Clinical inquiries. What is the appropriate diagnostic evaluation of fibroids? J Fam Pract 2005;54:458, 460, 462.
47. Dueholm M, Lundorf E, Hansen ES, et al. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. Am J Obstet Gynecol 2002;186:409–15.
48. Becker E Jr, Lev-Toaff AS, Kaufman EP, et al. The added value of transvaginal sonohysterography over transvaginal sonography alone in women with known or suspected leiomyoma. J Ultrasound Med 2002;21:237–47.
49. Volkers NA, Hehenkamp WJ, Spijkerboer AM, et al. MR reproducibility in the assessment of uterine fibroids for patients scheduled for uterine artery embolization. Cardiovasc Intervent Radiol 2008;31:260–8.
50. Dueholm M, Lundorf E, Hansen ES, et al. Evaluation of the uterine cavity with magnetic resonance imaging, transvaginal sonography, hysterosonographic examination, and diagnostic hysteroscopy. Fertil Steril 2001;76:350–7.
51. Dueholm M, Lundorf E, Sorensen JS, et al. Reproducibility of evaluation of the uterus by transvaginal sonography, hysterosonographic examination, hysteroscopy and magnetic resonance imaging. Hum Reprod 2002;17:195–200.
52. Dudiak CM, Turner DA, Patel SK, et al. Uterine leiomyomas in the infertile patient: preoperative localization with MR imaging versus US and hysterosalpingography. Radiology 1988;167:627–30.
53. Vitiello D, McCarthy S. Diagnostic imaging of myomas. Obstet Gynecol Clin North Am 2006;33:85–95.
54. Mayer DP, Shipilov V. Ultrasonography and magnetic resonance imaging of uterine fibroids. Obstet Gynecol Clin North Am 1995;22:667–725.
55. Ascher SM, Arnold LL, Patt RH, et al. Adenomyosis: prospective comparison of MR imaging and transvaginal sonography. Radiology 1994;190:803–6.
56. Togashi K, Ozasa H, Konishi I, et al. Enlarged uterus: differentiation between adenomyosis and leiomyoma with MR imaging. Radiology 1989;171:531–4.
57. Schwartz LB, Zawin M, Carcangiu ML, et al. Does pelvic magnetic resonance imaging differentiate among the histologic subtypes of uterine leiomyomata? Fertil Steril 1998;70:580–7.
58. Deligdisch L, Hirschmann S, Altchek A. Pathologic changes in gonadotropin releasing hormone agonist analogue treated uterine leiomyomata. Fertil Steril 1997;67:837–41.
59. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev 2000;(2):CD000547.

60. Tropeano G, Amoroso S, Scambia G. Non-surgical management of uterine fibroids. Hum Reprod Update 2008;14:259–74.
61. Spitz IM. Clinical utility of progesterone receptor modulators and their effect on the endometrium. Curr Opin Obstet Gynecol 2009;21:318–24.
62. Chwalisz K, Larsen L, Mattia-Goldberg C, et al. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. Fertil Steril 2007;87:1399–412.
63. Levens ED, Potlog-Nahari C, Armstrong AY, et al. CDB-2914 for uterine leiomyomata treatment: a randomized controlled trial. Obstet Gynecol 2008;111:1129–36.
64. Nieman LK, Blocker W, Nansel T, et al. Efficacy and tolerability of CDB-2914 treatment for symptomatic uterine fibroids: a randomized, double-blind, placebo-controlled, phase IIb study. Fertil Steril 2011;95:767–72.e1-2.
65. Donnez J, Tatarchuk TF, Bouchard P, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409–20.
66. Mutter GL, Bergeron C, Deligdisch L, et al. The spectrum of endometrial pathology induced by progesterone receptor modulators. Mod Pathol 2008;21:591–8.
67. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–2.
68. Bulun SE, Simpson ER, Word RA. Expression of the CYP19 gene and its product aromatase cytochrome P450 in human uterine leiomyoma tissues and cells in culture. J Clin Endocrinol Metab 1994;78:736–43.
69. Ishikawa H, Reierstad S, Demura M, et al. High aromatase expression in uterine leiomyoma tissues of African-American women. J Clin Endocrinol Metab 2009;94:1752–6.
70. Gurates B, Parmaksiz C, Kilic G, et al. Treatment of symptomatic uterine leiomyoma with letrozole. Reprod Biomed Online 2008;17:569–74.
71. Hilario SG, Bozzini N, Borsari R, et al. Action of aromatase inhibitor for treatment of uterine leiomyoma in perimenopausal patients. Fertil Steril 2009;91:240–3.
72. Kaunitz AM. Aromatase inhibitor therapy for uterine bleeding in a postmenopausal woman with leiomyomata. Menopause 2007;14:941–3.
73. Song H, Lu D, Navaratnam K, et al. Aromatase inhibitors for uterine fibroids. Cochrane Database Syst Rev 2013;(10):CD009505.
74. Zapata LB, Whiteman MK, Tepper NK, et al. Intrauterine device use among women with uterine fibroids: a systematic review. Contraception 2010;82:41–55.
75. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. Int J Womens Health 2014;6:95–114.
76. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol 2008;112:387–400.
77. Hehenkamp WJ, Volkers NA, Birnie E, et al. Symptomatic uterine fibroids: treatment with uterine artery embolization or hysterectomy–results from the randomized clinical Embolisation versus Hysterectomy (EMMY) Trial. Radiology 2008;246:823–32.
78. Moss JG, Cooper KG, Khaund A, et al. Randomised comparison of uterine artery embolisation (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-year results. BJOG 2011;118:936–44.
79. Gupta JK, Sinha AS, Lumsden MA, et al. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev 2006;(1):CD005073.

80. Walker WJ, Carpenter TT, Kent AS. Persistent vaginal discharge after uterine artery embolization for fibroid tumors: cause of the condition, magnetic resonance imaging appearance, and surgical treatment. Am J Obstet Gynecol 2004;190:1230–3.
81. Pron G, Bennett J, Common A, et al. The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. Fertil Steril 2003;79:120–7.
82. Hehenkamp WJ, Volkers NA, Broekmans FJ, et al. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. Hum Reprod 2007;22:1996–2005.
83. Mara M, Maskova J, Fucikova Z, et al. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. Cardiovasc Intervent Radiol 2008;31:73–85.
84. Goldberg J, Pereira L, Berghella V, et al. Pregnancy outcomes after treatment for fibromyomata: uterine artery embolization versus laparoscopic myomectomy. Am J Obstet Gynecol 2004;191:18–21.
85. Pron G, Mocarski E, Bennett J, et al. Pregnancy after uterine artery embolization for leiomyomata: the Ontario multicenter trial. Obstet Gynecol 2005;105:67–76.
86. Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. Curr Opin Obstet Gynecol 2014;26:151–61.
87. Behera MA, Leong M, Johnson L, et al. Eligibility and accessibility of magnetic resonance-guided focused ultrasound (MRgFUS) for the treatment of uterine leiomyomas. Fertil Steril 2010;94:1864–8.
88. Smart OC, Hindley JT, Regan L, et al. Gonadotrophin-releasing hormone and magnetic-resonance-guided ultrasound surgery for uterine leiomyomata. Obstet Gynecol 2006;108:49–54.
89. Gizzo S, Saccardi C, Patrelli TS, et al. Magnetic resonance-guided focused ultrasound myomectomy: safety, efficacy, subsequent fertility and quality-of-life improvements, a systematic review. Reprod Sci 2014;21:465–76.
90. Ringold S. FDA approves ultrasound fibroid therapy. JAMA 2004;292:2826.
91. Segars J. Fibroids. Chichester (West Sussex): John Wiley & Sons; 2013.
92. Camanni M, Bonino L, Delpiano EM, et al. Hysteroscopic management of large symptomatic submucous uterine myomas. J Minim Invasive Gynecol 2010;17:59–65.
93. Griffin L, Feinglass J, Garrett A, et al. Postoperative outcomes after robotic versus abdominal myomectomy. JSLS 2013;17:407–13.
94. Sesti F, Cosi V, Calonzi F, et al. Randomized comparison of total laparoscopic, laparoscopically assisted vaginal and vaginal hysterectomies for myomatous uteri. Arch Gynecol Obstet 2014;290:485–91.
95. ACOG Releases Special Report on Power Morcellation and Occult Malignancy in Gynecologic Surgery. 2014. Available at: http://www.acog.org/About-ACOG/News-Room/News-Releases/2014/ACOG-Releases-Special-Report-on-Power-Morcellation-and-Occult-Malignancy-in-Gynecologic-Surgery. Accessed August 28, 2014.
96. Halder SK, Goodwin JS, Al-Hendy A. 1,25-Dihydroxyvitamin D3 reduces TGF-beta3-induced fibrosis-related gene expression in human uterine leiomyoma cells. J Clin Endocrinol Metab 2011;96:E754–62.
97. Zhang D, Al-Hendy M, Richard-Davis G, et al. Antiproliferative and proapoptotic effects of epigallocatechin gallate on human leiomyoma cells. Fertil Steril 2010;94:1887–93.

98. Malik M, Mendoza M, Payson M, et al. Curcumin, a nutritional supplement with antineoplastic activity, enhances leiomyoma cell apoptosis and decreases fibronectin expression. Fertil Steril 2009;91:2177–84.
99. Catherino WH, Malik M. Uterine leiomyomas express a molecular pattern that lowers retinoic acid exposure. Fertil Steril 2007;87:1388–98.