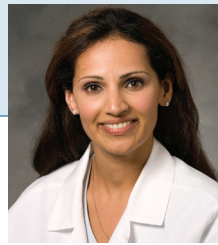


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UTERINE FIBROIDS, also known as leiomyomas or myomas, are the most common gynecologic tumor in women of reproductive age, affecting approximately 30 to 40 percent of premenopausal females. The prevalence increases with age, with an estimated 70 to 80 percent of women developing fibroids by age 50.¹

While typically classified as benign, uterine fibroids can cause troublesome symptoms to approximately 30 percent of affected women, including heavy vaginal bleeding, pelvic pressure, pain, obstructive urinary and bowel symptoms, as well as reproductive difficulties.^{1,2} Fibroids are one of the most common indications for hysterectomy in the U.S., accounting for approximately 200,000 cases per year. Fibroid-related morbidity has a significant economic impact on health care: the cost of health care for women with fibroids is more than double that of women without this condition, and annual costs related to the diagnosis of fibroids are over \$2 billion.³

Fortunately, new approaches to managing uterine fibroids are improving the outlook. Minimally invasive and non-invasive treatments such as MRgFUS (MRI-guided focused ultrasound)—a novel therapy recently introduced at Duke—are providing effective treatment for fibroids while offering faster recovery and fewer complications than hysterectomy.⁴ At the same time, new studies have increased our understanding of the biology of uterine fibroids and created inroads for developing more effective medical therapies.

WHAT CAUSES UTERINE FIBROIDS, AND WHO IS AT RISK?

While the exact etiology of fibroids is still unclear, physician-scientists at the Duke

Center for Uterine Fibroid Biology and Therapy have co-authored several of the most recent studies examining the underlying disease process that leads to the formation of uterine fibroids.^{5,6,7} These studies indicate that fibroids grow by accumulation of collagen and components of the extracellular matrix. This fibrosis is similar to that observed in the formation of keloid scars. The Center, which includes physician investigators, basic scientists, and epidemiologists, is currently involved in several studies to elucidate the molecular biology of uterine fibroid growth and etiology for associated bleeding and subfertility.

Factors implicated in the development of fibroids include genetic, hormonal, and growth factors, especially transforming growth factor beta (TGFβ)-related cellular changes.^{8,9} Clinical risk factors associated with fibroids include obesity, hypertension, nulliparity (having no biological children), family history, and race. Up to 70 percent of African American women have uterine fibroids, and these generally tend to be larger, more numerous, and produce more severe symptoms.¹

HOW ARE UTERINE FIBROIDS BEST DIAGNOSED?

Given the fact that uterine fibroids are highly prevalent in childbearing women and are associated with decreased fertility, prompt and accurate diagnosis is important. Uterine fibroids are most often diagnosed by ultrasound as part of the evaluation for associated symptoms or when an enlarged uterus is found on physical examination. However, other imaging modalities such as saline infusion sonography (3-D) and MRI may provide more accurate diagnosis and better delineation of fibroid size and location.

Fibroids are classified based on location within the uterine wall: subserosal, intramural, and submucosal. These definitions are often used to determine appropriate interventions and/or surgical approach.

WHAT ARE CURRENT TREATMENT APPROACHES—AND WHAT THERAPIES ARE ON THE HORIZON?

Current treatment options for uterine fibroids run the gamut from medical intervention to non-invasive and minimally invasive therapies to hysterectomy. Several factors must be addressed in determining the appropriate treatment for each individual, including size and location of fibroids, severity of symptoms, and desire to retain fertility or uterine preservation.

Medical options. Current medical options for fibroid management are limited. Of the established interventions, GnRh agonists are the most effective. GnRHa have been used to control bleeding and pressure-related symptoms by reducing fibroid size and decreasing bleeding. Within three to six months, fibroid size is reduced by approximately 30 to 50 percent. However, these effects are short-lived; fibroids grow and symptoms recur soon after treatment is discontinued. Furthermore, due to hypoestrogenic effects, treatment time is limited to six months, after which bone density can be affected. Add-back hormone therapy can be used to combat this effect, but some studies have found that this regimen may decrease the treatment efficacy. Hence GnRh agonists have been found to be most useful as an adjunct to surgical treatment of fibroids, since preoperative use results in improvement in hematocrit levels and less blood loss during surgery.¹⁰

Table 1. Medical therapy for fibroids¹⁰⁻¹⁶

DRUG CLASS	MECHANISM	EFFECTS	CONSIDERATIONS
GnRH agonists	Suppression of ovarian steroidogenesis production—delayed pituitary downregulation	Fibroid size and symptom reduction up to 50% within 3-6 months	Hypoestrogenic side effects: hot flashes, vaginal dryness, headaches. Prolonged use associated with reduced bone mineral density
GnRh antagonists	Suppression of ovarian steroidogenesis production—immediate pituitary downregulation	Reduction in fibroid size 25-40% and symptom improvement within 3 weeks	Hypoestrogenic side effects: hot flashes, vaginal dryness, headaches. Prolonged use associated with reduced bone mineral density
Oral contraceptives	Endometrial stabilization, variable effects on leiomyomas	May improve uterine bleeding, but no significant decrease in fibroid size	Use judiciously—both estrogen and progesterone may promote fibroid growth (increased mitotic activity)
Progestin only	Endometrial stabilization/atrophy, variable effects on leiomyomas	Mixed results—both fibroid shrinkage and enlargement have been shown; may induce amenorrhea	Use judiciously—progesterone may promote fibroid growth (increased mitotic activity)
Androgens	Combination hormonal and vascular effects (androgenic, progestogenic, antiprogestogenic, and antiestrogenic actions)	24% fibroid size reduction in 4 months, may improve bleeding symptoms	Side effects: weight gain, edema, acne, oily skin, hirsutism, voice changes, headaches, hot flashes, altered libido, decreased breast size, and muscle cramps
Aromatase inhibitors*	Reduces estrogen synthesis and effects	Fibroid size reduced 60-70% within 1-2 months in case report	Hypoestrogenic side effects; further studies needed
Antiprogestins*	Anti-progesterone effect—reduces action and number of progesterone receptors in fibroids and myometrium	Improved symptoms in 60-75%, may induce amenorrhea, reduction in fibroid volume 25-50% within 3 months	Side effects include hot flashes, elevated hepatic enzymes, and endometrial hyperplasia
Mixed progesterone receptor antagonist/agonists*	Local progesterone-mediated effects on leiomyomas and endometrium	Decreased menstrual bleeding (up to 80%) and fibroid size reduction up to 36% within 12 wks, may induce amenorrhea	Maintains follicular phase estrogen levels, no adverse endometrial effects—causes nonphysiologic secretory changes (clinical relevance unknown)
Mixed estrogen receptor antagonist/agonists*	Estrogen antagonist effects on fibroid and endometrium	Inconsistent results—trend to decreased fibroid size in small heterogeneous studies	Side effects: leg cramps, hot flashes. Increased risk of thromboembolic events
Antifibrotics*	Interfere with growth factors, leiomyoma cell proliferation and extracellular matrix/collagen production	Interfere with fibroid growth	Long-term effects not known, further studies needed

*Investigational medical therapies

Several other hormone-related medical treatments have been used to treat uterine fibroids; however, most of these medications are still being evaluated in clinical trials and are considered investigational.¹¹ Some of these proposed interventions are aimed at controlling fibroid growth and related symptoms by targeting ovarian steroid production. These include combined birth control pills, progestin-only preparations, androgens, both estrogen and progesterone receptor antagonists, and mixed receptor antagonist/agonists. Other medications, such as antifibrotic agents, target growth factors and affect extracellular matrix production and angiogenesis within the fibroid. These medical treatments are

summarized in Table 1. The Duke Center for Uterine Fibroid Biology and Therapy is actively investigating new drug therapies to treat uterine fibroids, and we expect this to be an area of significant advancement and progress over the next several years.

Non-medical options. Since most medical options are investigational and not recommended as first-line, long-term treatment for symptomatic fibroids at this time, the most common treatments remain either conservative surgical intervention or definitive surgery. Until now, the most prevalent treatments have been hysterectomy (surgical removal of the uterus) and myomectomy (surgical removal of individual fibroids). However, more women

are looking for options that provide minimal intervention and shorter recovery time.

Minimally invasive surgical treatments can provide excellent results when patient and fibroid characteristics are appropriate. In general, such treatments are best suited for women with a few, discrete symptomatic fibroids, while extensive fibroids are best treated with more definitive approaches. Minimally invasive approaches include laparoscopic and hysteroscopic myomectomy, as well as uterine artery embolization, a radiologic procedure that has also become more popular over the last several years.

continued

Table 2. Non-medical treatment interventions—conservative and definitive ^{4, 17–19}

TREATMENT	MECHANISM	EFFECTS	CONSIDERATIONS
Uterine artery embolization	Ischemic necrosis	Fibroid size reduction 40-60% within 4 months, menorrhagia improvement up to 85%	Post-procedure pain, risk of major adverse events (such as serious infectious complications) 1-2%, may be associated with adverse pregnancy outcomes, ovarian failure in 1-2%
MRI-guided focused ultrasound	Localized thermal necrosis	Symptomatic improvement up to 71% within 3 months, fibroid size reduction up to 30%—increased in proportion to treated fibroid volume, treatment effects sustained up to 24 months with low rates of secondary or repeat procedures	Patient selection criteria and fibroid characteristics important—post-treatment volume determines efficiency/duration of clinical results; minimal risk of adverse events (skin burn, nerve injury)
Myolysis (Laparoscopic)	Thermal necrosis	Fibroid shrinkage up to 70% by 12 months	Surgical risks, significant postoperative adhesions
Laparoscopic myomectomy	Excision	Removal of large fibroids, high patient satisfaction with symptomatic improvement	Surgical risks; often requires cesarean delivery with future pregnancy—labor is not advised, due to small risk of uterine rupture
Abdominal myomectomy	Excision	Removal of all palpable fibroids, high patient satisfaction with symptomatic improvement	Surgical risks; often requires cesarean delivery with future pregnancy—labor is not advised, due to small risk of uterine rupture
Hysterectomy	Excision	Definitive treatment—high patient satisfaction rate with symptomatic improvement	Surgical risks

A recent addition to the treatment toolkit is MRI-guided focused ultrasound (MRgFUS), in which precisely pinpointed, high-intensity ultrasound waves are used to “burn away” fibroids without harming normal surrounding tissues. This cutting-edge technology, which offers women the option of same-day, non-surgical treatment, is available at Duke through the Duke MRI-Guided Focused Ultrasound Treatment Program. With increasing availability of conservative treatment

choices, both patients and their physicians have the opportunity to individualize therapy based on the goals of each patient. More details on the pros and cons of various non-medical therapies are in Table 2.

For more information about uterine fibroid treatment at Duke or to refer a patient, call 919-572-8851, e-mail fibroidcenter@mc.duke.edu, or visit dukehealth.org/uterinefibroids.

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