

CLINICAL PRACTICE

Patrick G. O'Malley, M.D., M.P.H., *Editor*

Uterine Fibroids

Elizabeth A. Stewart, M.D., and Shannon K. Laughlin-Tommaso, M.D., M.P.H.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 33-year-old gravida 0 Black woman presents to her primary care clinician with heavy menstrual bleeding and abdominal bloating. She is noted to have iron-deficiency anemia. Evaluation for thalassemia and sickle cell anemia is negative. She has no hematochezia and no family history of colon cancer or inflammatory bowel disease. She describes her menses as regular and monthly, lasting for 8 days, and unchanged over time. She uses eight or nine tampons per day for the three heaviest days of her cycle and occasionally has menstrual accidents. She is in a Ph.D. program and anticipates pursuing pregnancy in 2 years. Ultrasonography reveals an enlarged uterus with multiple fibroids and normal ovaries. How would you treat this patient?

THE CLINICAL PROBLEM

UTERINE FIBROIDS (LEIOMYOMAS) ARE MYOMETRIAL MASSES (FIG. 1) AND are the leading indication for hysterectomy. Fibroids affect 70 to 80% of persons with a uterus during their lifetime.¹ Up to 50% of persons with fibroids have symptoms, including heavy and prolonged menstrual bleeding, anemia-associated fatigue, pelvic pressure, and both menstrual and nonmenstrual pain. Fibroids can cause compression of surrounding structures with resultant bulk-related symptoms, including in the bowel (constipation), bladder (urinary frequency, urgency, or retention), and vagina (painful intercourse). Slow growth of uterine fibroids is typical, although both shrinkage and growth spurts do occur.²

Fibroid-related morbidity is compounded by underdetection and its symptoms being attributed to other conditions, such as gastrointestinal or hematologic disease. Owing to the stigma associated with discussing menstruation, many persons with long or heavy menses are unaware that their experience is abnormal. Symptomatic persons often receive a delayed diagnosis. In one third of patients, diagnosis can take 5 years, with some patients waiting more than 8 years.³ Delays in diagnosis adversely affect fertility, quality of life, and financial welfare,^{4,5} and in a qualitative study, 95% of persons with symptomatic fibroids reported psychological sequelae, including depression, worry, anger, and body-image distress.⁶ Menstruation-related stigma and shame inhibit discussion, study, advocacy, and innovation in this field. A total of 50 to 72% of persons who receive a diagnosis of uterine fibroids on the basis of ultrasonography were not previously aware that they had fibroids, which suggests a potential role for wider ultrasonographic assessment for this common condition.⁴

From the Divisions of Reproductive Endocrinology (E.A.S.) and Gynecology (S.K.L.-T.), Department of Obstetrics and Gynecology, the Department of Physiology and Biomedical Engineering (E.A.S.), the Division of Endocrinology, Department of Medicine (E.A.S.), the Department of Surgery (E.A.S., S.K.L.-T.), and the Women's Health Research Center (E.A.S., S.K.L.-T.), Mayo Clinic, and the Mayo Clinic College of Medicine and Science (E.A.S., S.K.L.-T.) — both in Rochester, MN. Dr. Laughlin-Tommaso can be contacted at laughlintommaso.shannon@mayo.edu or at the Department of Obstetrics and Gynecology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905.

N Engl J Med 2024;391:1721-33.

DOI: 10.1056/NEJMc2309623

Copyright © 2024 Massachusetts Medical Society.

CME



KEY POINTS

UTERINE FIBROIDS

- Uterine fibroids are a common disease of the uterus and are more common and more severe in Black persons than in White persons.
- Fibroids are a frequent cause of heavy menstrual bleeding and are associated with iron-deficiency anemia.
- Although hysterectomy remains the most common procedure to treat fibroids, long-term sequelae of hysterectomy suggest that alternative therapies, such as medical therapies, uterine-artery embolization, focused ultrasound ablation, and radiofrequency ablation, should be used more widely.
- Oral combination therapy with gonadotropin-releasing hormone antagonists results in substantial reductions in heavy menstrual bleeding and bulk-related symptoms, with low risks of hypogonadal and thromboembolic side effects.

The incidence of fibroids increases with age until menopause and is higher among Black persons than among White persons.^{1,7} Black persons have earlier onset of fibroids, a higher cumulative risk of symptoms, and a greater disease burden overall than non-Black persons. Black persons also present with more severe disease and have a higher likelihood of surgical hysterectomy and myomectomy than White persons.⁸ In addition, Black persons are more likely than White persons to prefer noninvasive therapy and avoidance of surgery referral in order to avoid the potential for hysterectomy.^{3,9,10}

Diagnosis of fibroids is straightforward with pelvic ultrasonography, but determining whom to screen is not and usually occurs after the fibroids are large or the patients are symptomatic. The symptoms associated with fibroids may overlap with those of ovulatory disorders, adenomyosis, and secondary dysmenorrhea, as well as with those of gastrointestinal conditions.

Because sarcomas and fibroids both manifest as myometrial masses, often with abnormal uterine bleeding, concern arises about a diagnosis of uterine sarcoma being potentially missed, even though this cancer is relatively rare (1 case per 770 to 10,000 persons who present with abnormal uterine bleeding).¹¹ Because of the poor prognosis when this cancer spreads outside the uterus, concern regarding undiagnosed leiomyosarcoma has led to increased rates of hysterectomy and reduced use of minimally invasive approaches, which has resulted in exposing patients to higher risks of complications than is necessary.^{12,13}

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Pelvic ultrasonography is the most cost-effective imaging method for the diagnosis of fibroids, given that it provides information on the size, location, and number of fibroids and can rule out adnexal masses. Ambulatory pelvic ultrasonography is also indicated in the evaluation of abnormal uterine bleeding, pelvic masses that are palpated on examination, and bulk-related symptoms, including pelvic pressure and bloating. Ultrasonography is limited by less-accurate resolution if the uterine volume is greater than 375 ml or there are more than four fibroids — a common situation.¹⁴ Magnetic resonance imaging is useful when there is suspicion of uterine sarcoma and when planning alternatives to hysterectomy, in which case accurate information about size, imaging characteristics, and location is important for outcomes (Fig. 1).¹³ If submucosal fibroids or other endometrial lesions are suspected, saline-infusion sonography or hysteroscopy can be useful. Computed tomography is not useful for fibroids owing to low definition and imprecise visualization of tissue planes.

In 2011, the International Federation of Gynecology and Obstetrics published a fibroid classification system to better describe the location of fibroids in relationship to the uterine cavity and the serosal surface, beyond the historical terms of submucosal, intramural, and subserosal, thus enabling clearer communication and treatment planning (Table S3 in the Supplementary Appendix, available with the full text of this article

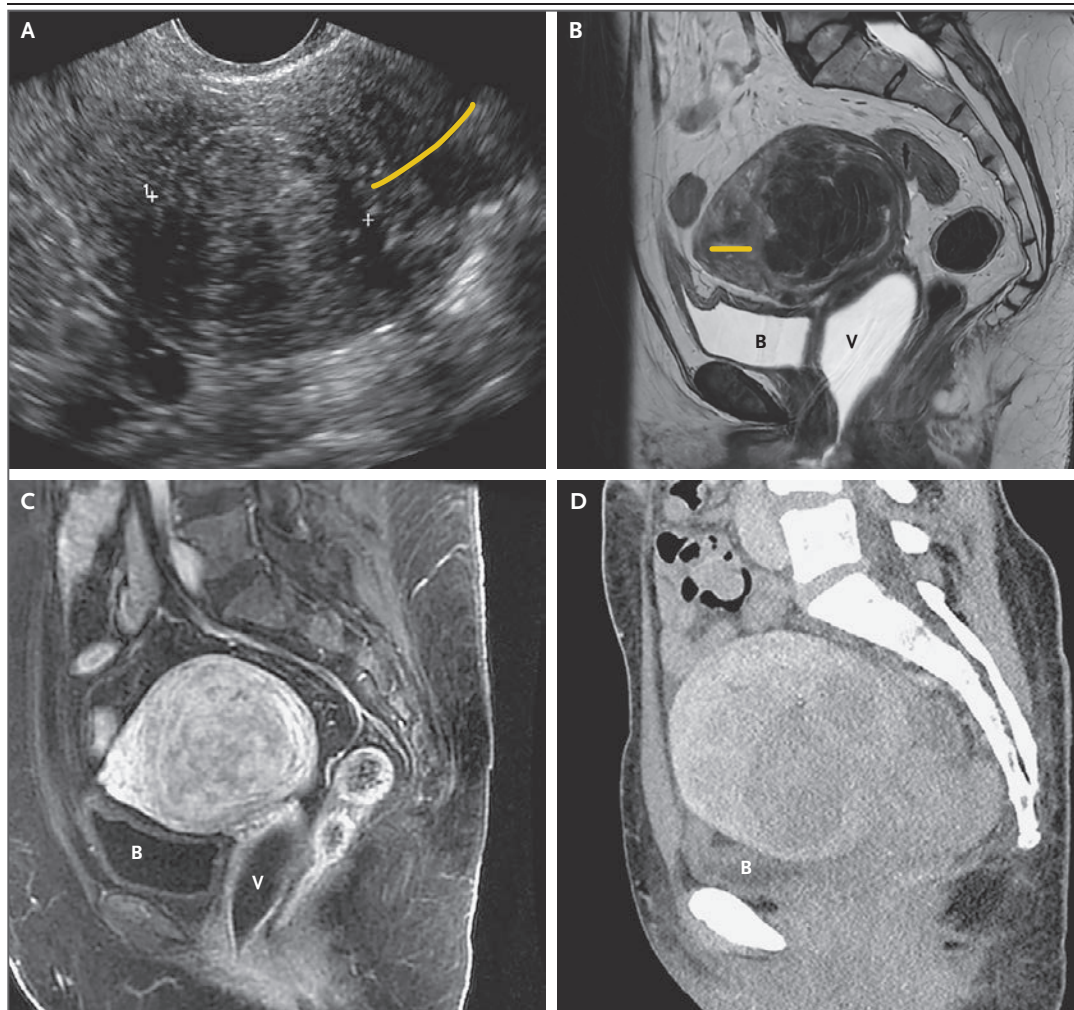


Figure 1 (facing page). Imaging for Diagnosis of Uterine Fibroids.

Although the presence of fibroids can be confirmed on transvaginal ultrasound (Panel A, the plus signs and numeral 1 define the length of the fibroid), magnetic resonance imaging (MRI) can provide more information on the location of fibroids and their proximity to other pelvic structures (Panel B, sagittal view), such as the bladder (B) and the vagina filled with gel (V). The International Federation of Gynecology and Obstetrics created a fibroid classification system, on a scale from type 0 to 8, with lower numbers indicating fibroids closer to the endometrium (yellow line in Panels A and B). Hybrid leiomyomas are indicated by two numbers that are separated by a hyphen; the first number indicates the relationship of the fibroid to the endometrium, and the second indicates the relationship of the fibroid to the serosa. The T2-weighted sagittal MRI scan in Panel B shows a fibroid of type 2–5, with deviation of the uterine cavity and contact with the serosal surface. A T1-weighted sagittal MRI scan such as the one shown in Panel C (sagittal view), which was obtained with the use of intravenous gadolinium as contrast material, is helpful in determining blood flow or enhancement, which indicates better fibroid response to nonexcisional therapy. Computed tomographic scans are not used for fibroid diagnosis owing to low definition and visualization (Panel D, sagittal view).

at NEJM.org).¹⁵ Types range from 0 to 8, with lower numbers indicating fibroids closer to the endometrium. Hybrid leiomyomas are indicated by two numbers that are separated by a hyphen; the first number indicates the relationship of the

fibroid to the endometrium, and the second indicates the relationship of the fibroid to the serosa. This system of categorization of fibroids allows the clinician to tailor further diagnosis and management and to improve communication.

Table 1. Medical Therapies for Fibroids and Fibroid-Related Symptoms.*

Class of Agent	Reduction in Heavy Menstrual Bleeding	Reduction in Uterine Size	Pain Reduction	FDA-Approved for Fibroid Treatment	Data Primarily from Studies of Idiopathic Heavy Menstrual Bleeding [‡]			Side Effects in >5% of Patients	Contraindications	“Black Box” Warning
NSAID (e.g., mefenamic acid, naproxen, and ibuprofen)	Modest reduction [†]	NR	Moderate reduction [†]	No	Yes	Yes	Headache, dyspepsia, and influenza syndrome	Asthma or urticaria after aspirin or NSAID use	Increased risk of CVD thrombotic events and GI bleeding	None
Antifibrinolytic agent (tranexamic acid)	Moderate reduction [†]	NR	NR	No	Yes	Yes	Headache, sinus and nasal symptoms, and abdominal, back, and musculoskeletal pain	Active thromboembolic disease or intrinsic risk of thrombosis		None
Contraceptive steroids (oral, patch, and implants)	Levonorgestrel IUD most effective; amenorrhea in 40% of patients at 12 mo	NR	NR	No	Yes [‡]	Yes [‡]	Headache, vaginitis, abdominal pain, and IUD expulsion	VTE, hormone-sensitive cancers, migraine with focal neurologic symptoms (for estrogen-containing contraceptives), hepatic adenomas, and acute pelvic infection (due to IUD use)	Increased risk of serious CVD events with cigarette smoking (for estrogen-containing contraceptives)	
GnRH antagonist combinations (elagolix, relugolix, or linzagolix, each with estradiol and norethindrone acetate)	80–200 ml and amenorrhea in 48–52% of patients	14%	10–40% reduction reported with relugolix	Yes for 24 mo for elagolix and relugolix, but not linzagolix	No	No	Headache, fatigue, and hot flashes	Current or history of VTE, increased risk of VTE, and hormone-sensitive cancer	Increased risk of VTE	
GnRH agonist (depot leuprolide)	Amenorrhea in 80% of patients; normal bleeding in 89% of patients [§]	47%	Improvement in pain scores and health-related quality of life	Yes, for 3 mo preoperatively for reduction of bleeding	No	No	Headache, nausea, hot flashes, emotional lability, and decreased libido	Pregnancy, lactation, and undiagnosed abnormal bleeding	None	
Selective progesterone-receptor modulators (ulipristal acetate)	Amenorrhea in 62–100% of patients	12–73%	Improvement in pain scores and health-related quality of life	No	No	No	Hot flashes, endometrial hyperplasia, and rarely, liver failure leading to transplantation	Liver disease	NA	

* Data are from Donnez et al.,¹⁶ Schlaff et al.,¹⁷ Al-Hendy et al.,¹⁸ Donnez et al.,¹⁹ and a 2021 American College of Obstetricians and Gynecologists practice bulletin.²⁰ CVD denotes cardiovascular disease, FDA Food and Drug Administration, GI gastrointestinal, GnRH gonadotropin-releasing hormone, IUD intrauterine device, NA not applicable, NR not reported, NSAID nonsteroidal antiinflammatory drug, and VTE venous thromboembolism.

[†] Results do not include data for fibroid-related abnormal uterine bleeding and clinically relevant fibroids that are often excluded from trials.

[‡] The unblinded trial of the levonorgestrel-releasing intrauterine system included 67 patients with fibroids.²¹

[§] Normal bleeding was defined as blood loss of less than 75 ml according to a pictorial assessment chart.

TREATMENT

MEDICAL ALTERNATIVES TO HYSTERECTOMY

Contraceptive hormones to control heavy menstrual bleeding constitute the first step in most algorithms for the treatment of fibroid-related heavy menstrual bleeding, despite low-quality evidence (Table 1). Nonsteroidal antiinflammatory agents and tranexamic acid taken during menses are also used to limit heavy menses, but these drugs have more evidence of efficacy for idiopathic heavy menses, a situation in which persons with large or submucosal fibroids have typically been excluded from clinical trials. Depot forms of gonadotropin-releasing hormone (GnRH) agonists are approved for short-term

preoperative therapy for fibroids, cause amenorrhea in nearly 90% of patients, and reduce uterine volume by 30 to 60%; however, they are accompanied by a high incidence of hypogonadal symptoms, including bone loss and hot flushes.¹⁶ They also cause a “steroidal flare” in most patients, which occurs when stored gonadotropins are released and cause subsequent heavy menstrual bleeding when estrogen levels decrease rapidly.

The introduction of oral GnRH antagonist combinations to fibroid care has been a major treatment advance (Table S1). The agents that have been approved in the United States combine in one tablet or capsule an oral GnRH antagonist (elagolix or relugolix), which rapidly

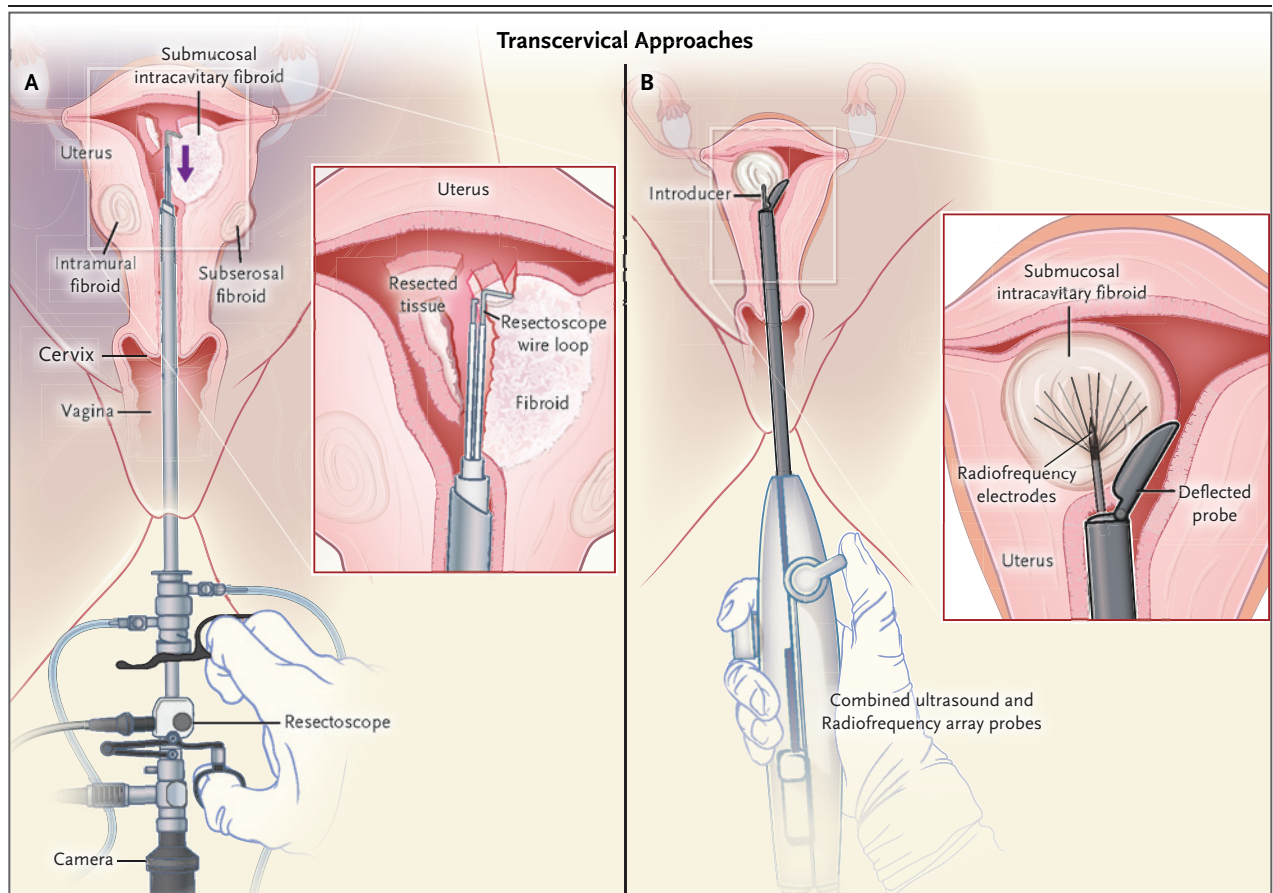


Figure 2. Transcervical Approaches to Uterine-Preserving Fibroid Therapies.

In hysteroscopic myomectomy, the clinician uses a small endoscope inserted through the cervix to excise fibroids of International Federation of Gynecology and Obstetrics types 0, 1, and 2 under direct visualization, with removal of the pieces through the cervix. A bipolar resectoscope or an intrauterine morcellator creates the tissue fragments (Panel A). Transcervical radiofrequency ablation is performed through the cervix and uses targeted radiofrequency energy guided by intrauterine ultrasonography to cause coagulative necrosis (Panel B). The fibroid is not excised and will shrink over time.

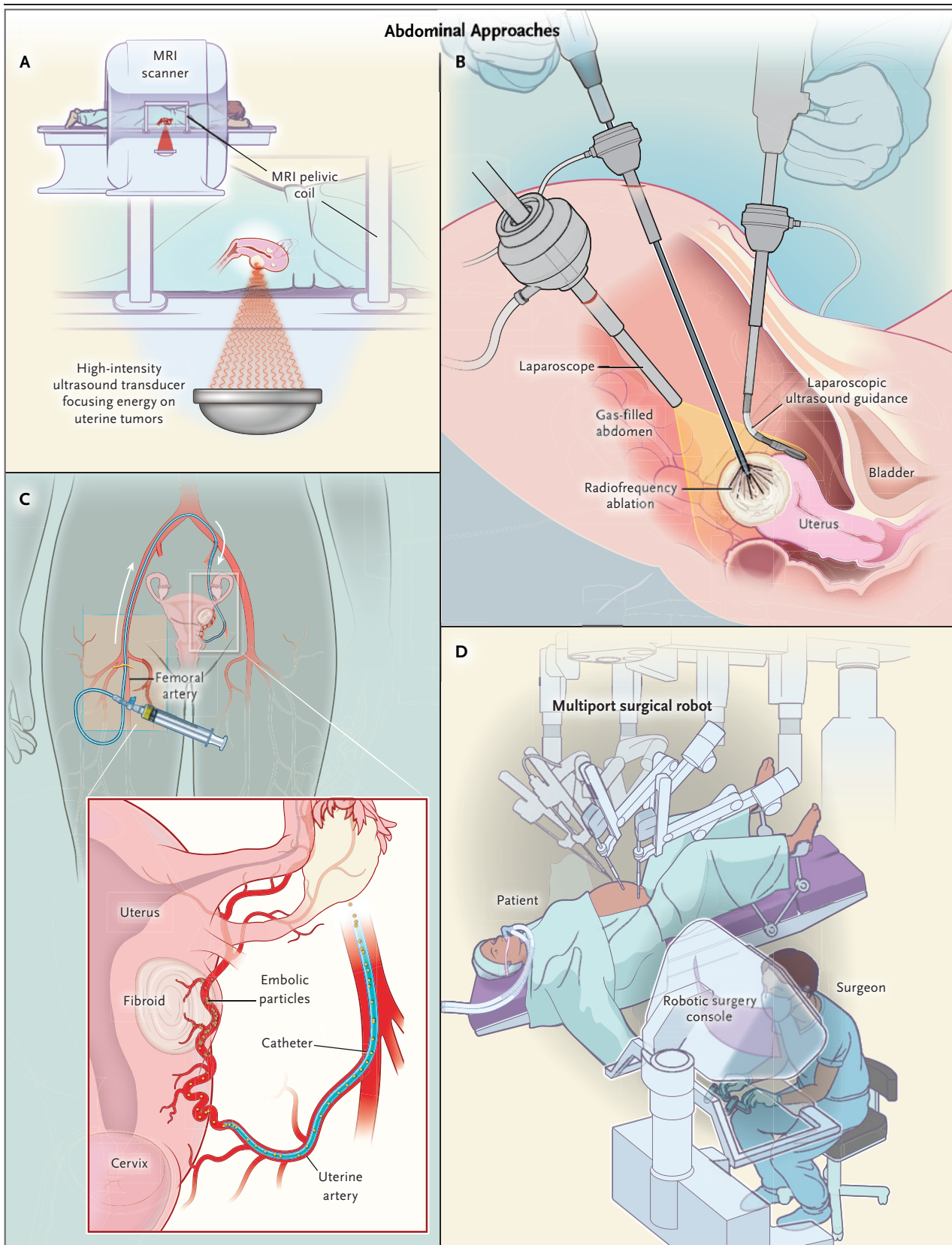


Figure 3 (facing page). Abdominal Approaches to Uterine-Preserving Fibroid Therapies.

Magnetic resonance imaging (MRI)–guided focused ultrasound ablation is performed with no incisions through the abdominal wall (Panel A). Ultrasonic energy is targeted to fibroids with the use of MRI guidance and thermal feedback. Fibroids are not excised and will shrink over time. Laparoscopic radiofrequency ablation is performed through two or three laparoscopic incisions in the abdominal wall (Panel B). With the use of intraoperative ultrasound guidance, targeted radiofrequency energy ablates the fibroid with coagulative necrosis to shrink the fibroid. Uterine-artery embolization is performed percutaneously through a catheter introduced into the femoral or radial artery that delivers embolic particles to the uterine arteries under fluoroscopic guidance (Panel C). Fibroids will shrink over time owing to ischemic necrosis and reabsorption. Myomectomy, an excisional technique that removes the fibroids through incisions through the uterine serosa, can be performed laparoscopically (Panel D) or abdominally (not shown).

inhibits ovarian steroidogenesis (without causing a flare), with estradiol and progestin at doses resulting in systemic levels that are equivalent to those in the early follicular phase. One agent that has been approved in the European Union (linzagolix) is available in two doses: one dose that partially suppresses hypothalamic function and another that provides complete suppression of hypothalamic function, similar to that seen with the approved doses of elagolix and relugolix. Each of these formulations is available with or without estrogen and progestin. The low-dose formulation of linzagolix without added gonadal steroids (estrogen and progestin) provides the same effect as the high-dose combination with exogenous hormone in persons who prefer not to take exogenous gonadal steroids.¹⁷⁻¹⁹ The approach of combination therapy or partial suppression of hypothalamic function provides symptomatic relief that is equivalent to monotherapy with a full-dose GnRH antagonist, with a better side-effect profile. The one advantage of high-dose monotherapy is that it leads to a greater reduction in uterine volume, similar to that seen with GnRH agonist treatment, albeit with more hypogonadal symptoms.¹⁹

Data from clinical trials show that oral GnRH antagonist combinations effectively decrease heavy menstrual bleeding (by 50 to 75%), pain (by 40 to 50%), and bulk-related symptoms with modest volume reduction (decrease in uter-

ine volume, approximately 10%), with low levels of side effects (with hot flushes, headaches, and nausea occurring in <20% of participants). The efficacy of oral GnRH antagonist combination therapy is independent of the extent of fibroid disease (size, number, or location of fibroids), the presence of concomitant adenomyosis, or other factors that limit surgical therapies.¹⁸ Oral GnRH antagonist combinations are currently approved in the United States for 24 months of use and in the European Union for an unlimited duration of treatment. However, these drugs have not been shown to provide contraception, which is a limitation for long-term use in many persons. One clinical trial is under way to test the contraceptive efficacy of relugolix combination therapy (ClinicalTrials.gov number, NCT04756037).

In many countries, selective progesterone-receptor modulators are an option for medical therapy.²² However, concerns about rare but severe hepatic toxic effects have limited their acceptance and availability. No selective progesterone-receptor modulator has been approved in the United States for the treatment of fibroids.²²

SURGICAL AND INTERVENTIONAL ALTERNATIVES TO HYSTERECTOMY

Numerous procedures have been developed to reduce bleeding and fibroid size and improve quality of life without hysterectomy. Information about the size and location of the fibroids is important for determining whether a transcervical or abdominal approach is needed. Generally, smaller fibroids that are categorized as types 1 to 4 (which are in the submucosal to intramural spaces) can be treated transcervically (Fig. 2). Larger fibroids of any type, or smaller fibroids that are subserosal (types 5, 6, and 7), are treated abdominally (Fig. 3).

The procedure with the most evidence of efficacy is uterine-artery embolization, which uses a minimally invasive interventional catheterization, guided radiologically, to release embolic particles directly into both uterine arteries; this process causes ischemic infarction of the fibroids and subsequent decreases in bleeding, pain, and bulk-related symptoms.^{23,24} Uterine-artery embolization is widely available. Although a randomized trial showed that myomectomy was superior to uterine-artery embolization with regard to improvement in quality of life, both approaches provided substantial symptom relief, although

Table 2. Outcomes of Randomized, Controlled Trials of Fibroid Therapies.

Therapy	Reduction in Heavy Menstrual Bleeding	Percent Reduction in Fibroids	Improvement from Baseline in Health-Related Quality of Life ^{*,†}	Abatement of Symptom Severity [‡]	Percentage of Patients with Reintervention	Adverse Events in >10% of Patients	Length of Hospital Stay
Uterine-artery embolization [‡]	67–89% had substantial reduction in heavy menstrual bleeding at 2 yr ^{33,34}	39–60% reduction in size of the dominant fibroid at 5 yr ^{26,31,34} 50% reduction in total fibroid load at 2 yr ²⁸	38 points at 2 yr ²⁴	37 points at 2 yr ²⁴	29–33% at 5 yr and 35% at 10 yr ^{5,27,31,32}	Pain, transient fevers (postembolization syndrome), nausea, and infection ²⁴ and readmission ³⁵	1–2.5 days ^{26,30,33}
Focused ultrasound ablation [§]	NR	50% of total fibroid load at 24 mo ²⁸	20 points at 2 yr ²⁹	22 points at 2 yr ²⁹	≤30% at 2 yr ²⁹	Skin reaction, leiomyoma sloughing, and peripheral nerve injury	Same-day discharge
Laparoscopic radiofrequency ablation [¶]	45–51% decrease at 2 yr in patients who had reported heavy menstrual bleeding ^{36,37} 55% at 2 yr ²⁸	40% at 2 yr ³⁶	32 points at 12 mo ³⁷ ; 23 points at 2 yr ³⁸	40 points at 12 mo ³⁷ ; 12 points at 2 yr ³⁸	3% at 12 mo ³⁷	Pelvic infection and fever	Mean (±SD) of 6.7±3.0 hr ³⁹

* Health-related quality of life was determined on the basis of the Uterine Fibroid Symptoms–Quality of Life questionnaire. Scores range from 0 to 100, with higher scores indicating better quality of life.

† The symptom severity score was determined on the basis of the Uterine Fibroid Symptoms–Quality of Life questionnaire. Scores range from 0 to 100, with lower scores indicating less severe symptoms.

‡ Randomized, controlled trials of uterine-artery embolization include the FEMME (Fibroids with Embolization or Myomectomy to Measure the Effect) trial^{24,25} (uterine-artery embolization vs. myomectomy), the trial by Mara et al.³⁶ (uterine-artery embolization vs. myomectomy), the EMMY (Embolization vs. Hysterectomy) trial²⁷ (uterine-artery embolization vs. hysterectomy), the FIRSTT (Fibroid Interventions: Reducing Symptoms Today and Tomorrow) trial^{28,30} (uterine-artery embolization vs. focused ultrasound ablation), the REST (Randomized Trial of Embolization vs. Surgical Treatment for Fibroid) trial^{31,32} (uterine-artery embolization vs. surgical therapy), and the trial by Ruuskanen et al.³³ (uterine-artery embolization vs. hysterectomy).

§ Focused ultrasound ablation was compared with uterine-artery embolization in a randomized, controlled trial by Laughlin-Tommaso et al.^{28,29}

¶ Randomized, controlled trials of laparoscopic radiofrequency ablation include the trials by Hahn et al.,³⁶ Yu et al.,³⁷ Kramer et al.,³⁸ and Rattray et al.³⁹ (radiofrequency ablation vs. laparoscopic myomectomy) and the trial by Meng et al.⁴⁰ (radiofrequency ablation vs. high-intensity focused ultrasound ablation). Data from randomized, controlled trials of transcervical radiofrequency ablation are lacking.

no sham treatment comparator was used in the trial (Table 2).²⁴

Procedures that shrink individual fibroids with the use of energy to create coagulative necrosis include focused ultrasound ablation (with the use of MRI or ultrasound guidance) and radiofrequency ablation (with the use of laparoscopic or transcervical ultrasound guidance). These interventions reduce heavy menstrual bleeding and bulk-related symptoms. However, unlike uterine-artery embolization, in which all fibroids can be treated concurrently, these therapies require the individual targeting of each fibroid, and they are not as readily available. Radiofrequency ablation of fibroids can be done concurrently with other surgical therapies, such as laparoscopic excision of endometriosis or hysteroscopic myomectomy of a type 0 fibroid. Data from randomized, controlled trials comparing all minimally invasive procedures are limited (Table 2).

Myomectomy, or the surgical removal of fibroids, remains an option for many persons, although it is most often used in persons who are actively seeking pregnancy or in those with very large fibroids in whom shrinkage would be inadequate. Most guidelines suggest the surgical removal of fibroids, rather than procedures that shrink fibroids, in order to optimize fertility, owing to long experience with myomectomy. However, myomectomy often commits patients to future cesarean section, which itself increases pregnancy-related morbidity.

FIBROID RECURRENCE

A major limitation of all surgical and interventional therapies is that the incidence of fibroid recurrence is high, with new fibroid development occurring in approximately 50% of persons within 5 years after myomectomy. However, not all new fibroids will become symptomatic, which is especially true in persons who are closer to menopause. The percentages of patients who undergo reintervention vary according to the procedure, patient age, the extent of fibroids, and symptoms and generally range up to 33% over a period of up to 5 years after treatment, with lower percentages seen among persons older than 45 years of age than among those 45 years of age or younger.^{23,41} Longer-term follow-up studies have not been conducted.

Although patients can undergo multiple sequential uterine-sparing interventions, hysterectomy is the most common mode of therapy. A recent study in a commercially insured population showed that nearly 60% of patients undergoing hysterectomy for fibroids had not received a conservative treatment previously.⁴²

HYSTERECTOMY

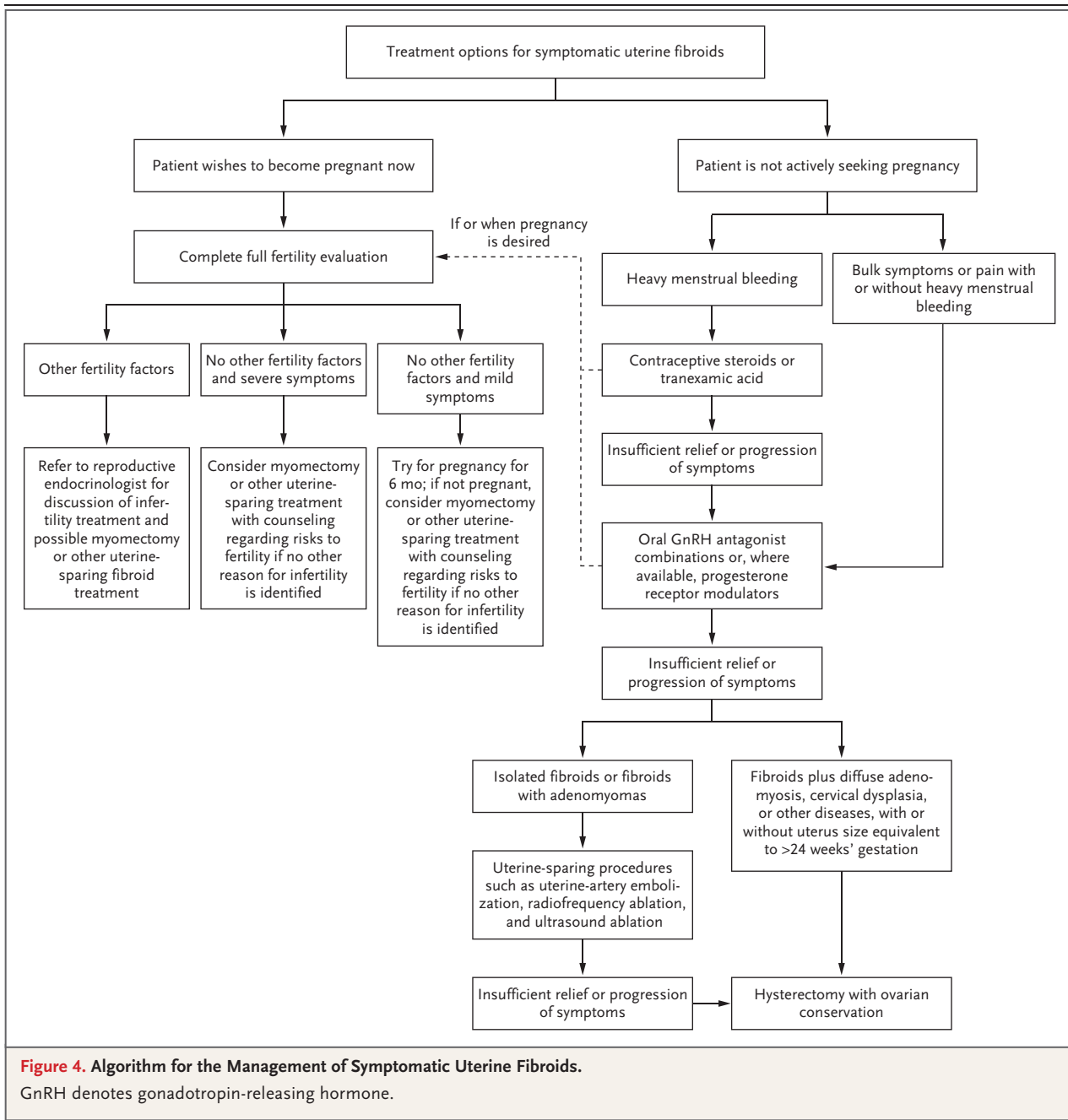
Although hysterectomy has traditionally been viewed as the cure for fibroids, new data on outcomes after the use of appropriate alternatives show that these alternatives may have effectiveness similar to hysterectomy with regard to controlling heavy bleeding. Drawbacks to hysterectomy, as compared with alternatives, include perioperative risk and oophorectomy (if it is included as part of the procedure). The removal of both ovaries at the time of hysterectomy was a common procedure until the early 2000s, when large cohort studies showed elevated risks of death, cardiovascular disease, dementia, and other illnesses as compared with hysterectomy plus ovarian conservation.^{43,44} Since then, oophorectomy rates have decreased, whereas the rates of hysterectomy have not.⁴⁵

Several studies have shown substantially increased risks of cardiovascular disease, anxiety, depression, and death after hysterectomy, even with the conservation of both ovaries (Table S2).⁴⁶⁻⁴⁸ The risks are greatest among patients who are 35 years of age or younger at the time of hysterectomy. Among these patients, the risks of coronary artery disease (with adjustment for confounders) were 2.5 times as high and the risks of congestive heart failure were 4.6 times as high, over a median follow-up of 22 years, among those who had undergone hysterectomy as among women without hysterectomy. Mortality was 8 to 29% higher among patients who had undergone hysterectomy with ovarian conservation before 40 years of age than among women without hysterectomy.^{49,50} However, patients who undergo hysterectomy have more coexisting conditions, such as obesity, hyperlipidemia, or a history of surgery, than women without hysterectomy, and owing to the observational nature of these studies, causality cannot be confirmed.⁴⁶ Although studies control for these inherent risks, unmeasured confounding may still be present. Persons who are contemplating hysterectomy deserve counseling

about these risks since many persons with fibroids can take advantage of less-invasive alternatives to hysterectomy.

No strategies for the primary or secondary prevention of fibroids are currently available. Epidemiologic studies have identified various factors associated with a reduced risk of fibroids, including the following: diets rich in fruits and vegetables with limited red meat,

regular exercise, weight control, normal levels of vitamin D,⁵¹ successful live birth (parity), use of oral contraceptives, and depot formulations of progesterone. Randomized, controlled trials are needed to determine whether modification of these factors will reduce risks. Finally, studies suggest that stress and racism may play a role in the health disparities with regard to the development of fibroids.⁵²



AREAS OF UNCERTAINTY

Many unmet needs exist in the field of fibroid medicine, including a risk-prediction model; a staging system; large, randomized, comparative-effectiveness clinical trials; and methods for primary and secondary prevention. Moreover, given that fibroid care has traditionally been viewed as being confined to the gynecology department, earlier screening and medical treatment in primary care settings could potentially minimize morbidity and the incidence of unnecessary hysterectomies, and primary care-based screening trials are warranted.

Future areas of study should include screening of young persons (particularly of young Black persons) who have symptoms of fibroids or a strong family history of fibroids to determine whether early therapy would reduce long-term risks (Fig. 4). An ultrasound screening study involving 1600 Black participants 23 to 35 years of age showed a baseline prevalence of fibroids of 23%.⁵³ Early initiation of contraceptive steroids or oral GnRH antagonist combinations in affected persons with symptomatic fibroids may reduce the risk of surgery or the extent of surgery.

A recent study showing the undertreatment of Black persons with fibroids with uterine-sparing options early in their fibroid journey emphasizes the deficits in addressing health disparities.⁵⁴ Understanding and removing barriers by means of behavioral and social science research would be an important step in reducing health disparities in fibroid care.

GUIDELINES

Practice guidelines and committee opinions for the treatment of uterine fibroids have been published by the American College of Obstetricians and Gynecologists and the Society for

Obstetricians and Gynecologists of Canada.^{20,22} Both organizations endorse the individualization of care for the patient and account for desire to preserve fertility or the uterus, increase quality of life, and reduce symptoms. Both organizations also recommend medical management as the first-line treatment for symptomatic fibroids.^{20,22} When interventional approaches are indicated, these organizations also recommend minimally invasive approaches to treat symptomatic fibroids, including minimally invasive approaches to hysterectomy. Our recommendations are concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

With regard to the patient presented in the case vignette, we would recommend that the patient begin oral GnRH antagonist combination therapy, with iron and multivitamin supplementation, and would also recommend annual reassessment or earlier follow-up if pregnancy is desired or if symptoms escalate. Surgical or procedural intervention would also bring symptom relief, but these options have an increased risk of complications. Given that the patient prioritized fertility, hysterectomy would be appropriate only if she had biopsy-proven cancer. For a patient who has completed childbearing, although hysterectomy provides definitive removal of fibroids and cessation of menstrual bleeding, the long-term risks associated with hysterectomy (even with ovarian conservation) should be discussed during counseling and shared decision making. Identification and medical treatment of fibroids at earlier stages of the disease, and in primary care settings, are preferred.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003;188:100-7.
2. 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.
3. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. *Am J Obstet Gynecol* 2013;209(4):319.e1-319.e20.
4. Ghant MS, Sengoba KS, Vogelzang R, Lawson AK, Marsh EE. An altered perception of normal: understanding causes for treatment delay in women with symptomatic uterine fibroids. *J Womens Health (Larchmt)* 2016;25:846-52.
5. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol* 2012;206(3):211.e1-211.e9.
6. Ghant MS, Sengoba KS, Recht H, Cameron KA, Lawson AK, Marsh EE. Beyond

- the physical: a qualitative assessment of the burden of symptomatic uterine fibroids on women's emotional and psychosocial health. *J Psychosom Res* 2015; 78:499-503.
7. Marsh EE, Ekpo GE, Cardozo ER, Brocks M, Dune T, Cohen LS. 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.
 8. Wechter ME, Stewart EA, Myers ER, Kho RM, Wu JM. Leiomyoma-related hospitalization and surgery: prevalence and predicted growth based on population trends. *Am J Obstet Gynecol* 2011;205(5): 492.e1-5.
 9. Wegienka G, Stewart EA, Nicholson WK, et al. Black women are more likely than white women to schedule a uterine-sparing treatment for leiomyomas. *J Womens Health (Larchmt)* 2021;30:355-66.
 10. Orellana M, Riggan KA, DSouza K, et al. Perceptions of ethnoracial factors in the management and treatment of uterine fibroids. *J Racial Ethn Health Disparities* 2022;9:1184-91.
 11. Hartmann KE, Fonnesebeck C, Surawicz T, et al. Management of uterine fibroids. Rockville, MD: Agency for Healthcare Research and Quality, December 2017 (<https://effectivehealthcare.ahrq.gov/products/uterine-fibroids/research-2017>).
 12. Siedhoff MT, Wheeler SB, Rutstein SE, et al. Laparoscopic hysterectomy with morcellation vs abdominal hysterectomy for presumed fibroid tumors in premenopausal women: a decision analysis. *Am J Obstet Gynecol* 2015;212(5):591.e1-591.e8.
 13. Hindman N, Kang S, Fournier L, et al. MRI evaluation of uterine masses for risk of leiomyosarcoma: a consensus statement. *Radiology* 2023;306(2):e211658.
 14. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. 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.
 15. Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynaecol Obstet* 2011;113:3-13.
 16. Donnez J, Tomaszewski J, Vázquez F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med* 2012;366:421-32.
 17. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med* 2020;382:328-40.
 18. Al-Hendy A, Lukes AS, Poindexter AN III, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. *N Engl J Med* 2021;384:630-42.
 19. Donnez J, Taylor HS, Stewart EA, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. *Lancet* 2022;400:896-907.
 20. Management of symptomatic uterine leiomyomas: ACOG practice bulletin, number 228. *Obstet Gynecol* 2021;137(6): e100-e115.
 21. Grigorieva V, Chen-Mok M, Tarasova M, Mikhailov A. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. *Fertil Steril* 2003;79:1194-8.
 22. Laberge P-Y, Murji A, Vilos GA, Allaire C, Leyland N, Singh SS. Guideline no. 389 — medical management of symptomatic uterine leiomyomas: an addendum. *J Obstet Gynaecol Can* 2019;41: 1521-4.
 23. Spies JB, Bruno J, Czeyda-Pommersheim F, Magee ST, Ascher SA, Jha RC. Long-term outcome of uterine artery embolization of leiomyomata. *Obstet Gynecol* 2005;106:933-9.
 24. Manyonda I, Belli A-M, Lumsden M-A, et al. Uterine-artery embolization or myomectomy for uterine fibroids. *N Engl J Med* 2020;383:440-51.
 25. Daniels J, Middleton LJ, Cheed V, et al. Uterine artery embolization or myomectomy for women with uterine fibroids: four-year follow-up of a randomised controlled trial. *Eur J Obstet Gynecol Reprod Biol X* 2021;13:100139.
 26. Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. *Cardiovasc Intervent Radiol* 2008;31: 73-85.
 27. de Bruijn AM, Ankum WM, Reekers JA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial. *Am J Obstet Gynecol* 2016;215(6):745.e1-745.e12.
 28. Laughlin-Tommaso SK, Gorny KR, Hesley GK, et al. Uterine and fibroid imaging analysis from the FIRSST study. *J Womens Health (Larchmt)* 2022;31: 546-54.
 29. Laughlin-Tommaso S, Barnard EP, Abdelmagied AM, et al. FIRSST study: randomized controlled trial of uterine artery embolization vs focused ultrasound surgery. *Am J Obstet Gynecol* 2019; 220(2):174.e1-174.e13.
 30. Barnard EP, Abdelmagied AM, Vaughan LE, et al. Periprocedural outcomes comparing fibroid embolization and focused ultrasound: a randomized controlled trial and comprehensive cohort analysis. *Am J Obstet Gynecol* 2017;216(5):500.e1-500.e11.
 31. Ananthakrishnan G, Murray L, Ritchie M, et al. Randomized comparison of uterine artery embolization (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): subanalysis of 5-year MRI findings. *Cardiovasc Intervent Radiol* 2013;36:676-81.
 32. 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.
 33. Ruuskanen A, Hippeläinen M, Sipola P, Manninen H. Uterine artery embolisation versus hysterectomy for leiomyomas: primary and 2-year follow-up results of a randomised prospective clinical trial. *Eur Radiol* 2010;20:2524-32.
 34. Volkers NA, Hehenkamp WJ, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial. *Am J Obstet Gynecol* 2007;196(6):519.e1-519.e11.
 35. Hehenkamp WJ, Volkers NA, Donderwinkel PF, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. *Am J Obstet Gynecol* 2005;193:1618-29.
 36. Hahn M, Brucker S, Kraemer D, et al. Radiofrequency volumetric thermal ablation of fibroids and laparoscopic myomectomy: long-term follow-up from a randomized trial. *Geburtshilfe Frauenheilkd* 2015;75:442-9.
 37. Yu S, Bhagavath B, Shobeiri SA, Eisenstein D, Levy B. Clinical and patient reported outcomes of pre- and postsurgical treatment of symptomatic uterine leiomyomas: a 12-month follow-up review of TRUST, a surgical randomized clinical trial comparing laparoscopic radiofrequency ablation and myomectomy. *J Minim Invasive Gynecol* 2022;29:726-37.
 38. Krämer B, Hahn M, Taran F-A, Kraemer D, Isaacson KB, Brucker SY. Interim analysis of a randomized controlled trial comparing laparoscopic radiofrequency volumetric thermal ablation of uterine fibroids with laparoscopic myomectomy. *Int J Gynaecol Obstet* 2016;133:206-11.
 39. Rattray DD, Weins L, Regush LC, Bowen JM, O'Reilly D, Thiel JA. Clinical outcomes and health care utilization pre- and post-laparoscopic radiofrequency ablation of symptomatic fibroids and laparoscopic myomectomy: a randomized trial of uterine-sparing techniques (TRUST) in Canada. *Clinicoecon Outcomes Res* 2018; 10:201-12.
 40. Meng X, He G, Zhang J, et al. A comparative study of fibroid ablation rates using radio frequency or high-intensity focused ultrasound. *Cardiovasc Intervent Radiol* 2010;33:794-9.
 41. Baird DD, Saldana TM, Shore DL, Hill

- MC, Schectman JM. A single baseline ultrasound assessment of fibroid presence and size is strongly predictive of future uterine procedure: 8-year follow-up of randomly sampled premenopausal women aged 35-49 years. *Hum Reprod* 2015;30: 2936-44.
42. Liao L, Chen L, Melamed A, Hershtman DL, Wright JD. Use of conservative therapies before hysterectomy for uterine leiomyomas. *Obstet Gynecol* 2023;141: 371-4.
43. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009;113:1027-37.
44. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol* 2005;106: 219-26.
45. Perera HK, Ananth CV, Richards CA, et al. Variation in ovarian conservation in women undergoing hysterectomy for benign indications. *Obstet Gynecol* 2013; 121:717-26.
46. Laughlin-Tommaso SK, Khan Z, Weaver AL, Smith CY, Rocca WA, Stewart EA. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. *Menopause* 2018;25:483-92.
47. Laughlin-Tommaso SK, Satish A, Khan Z, Smith CY, Rocca WA, Stewart EA. Long-term risk of de novo mental health conditions after hysterectomy with ovarian conservation: a cohort study. *Menopause* 2020;27:33-42.
48. Ding D-C, Tsai I-J, Hsu CY, Wang J-H, Lin S-Z, Sung F-C. Risk of hypertension after hysterectomy: a population-based study. *BJOG* 2018;125:1717-24.
49. Gierach GL, Pfeiffer RM, Patel DA, et al. Long-term overall and disease-specific mortality associated with benign gynecologic surgery performed at different ages. *Menopause* 2014;21:592-601.
50. Tuesley KM, Protani MM, Webb PM, et al. Hysterectomy with and without oophorectomy and all-cause and cause-specific mortality. *Am J Obstet Gynecol* 2020;223(5):723.e1-723.e16.
51. Davari Tanha F, Feizabad E, Vasheghani Farahani M, Amuzegar H, Moradi B, Samimi Sadeh S. The effect of vitamin D deficiency on overgrowth of uterine fibroids: a blinded randomized clinical trial. *Int J Fertil Steril* 2021;15: 95-100.
52. Wise LA, Palmer JR, Cozier YC, Hunt MO, Stewart EA, Rosenberg L. Perceived racial discrimination and risk of uterine leiomyomata. *Epidemiology* 2007;18:747-57.
53. Wegienka G, Havstad S, Coleman C, et al. Ultrasound-confirmed, age-specific uterine leiomyoma incidence in a cohort of Black individuals. *Obstet Gynecol* 2022;140:1042-8.
54. Robinson WR, Mathias JG, Wood ME, et al. Ethnoracial differences in premenopausal hysterectomy: the role of symptom severity. *Obstet Gynecol* 2023;142:350-9.

Copyright © 2024 Massachusetts Medical Society.