

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Uterine Fibroids

Elizabeth A. Stewart, M.D.

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 author's clinical recommendations.

A 47-year-old black woman has heavy menstrual bleeding and iron-deficiency anemia. She reports nocturia and urinary frequency. A colonoscopy is negative. Ultrasonography shows a modestly enlarged uterus with three uterine fibroids. She is not planning to become pregnant. How should this case be evaluated and managed?

THE CLINICAL PROBLEM

From the Division of Reproductive Endocrinology and Infertility, Departments of Obstetrics and Gynecology and Surgery, Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Stewart at the Division of Reproductive Endocrinology and Infertility, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at stewart.elizabeth@mayo.edu.

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Uterine fibroids (leiomyomas or myomas) are extremely common benign neoplasms of the uterus.¹ The lifetime prevalence of fibroids exceeds 80% among black women and approaches 70% among white women.² In a study using ultrasonographic screening, 51% of premenopausal women received a new diagnosis of fibroids.²

Fibroids can cause heavy or prolonged menstrual bleeding and resultant anemia in women of reproductive age. Fibroid-related bleeding can also occur in postmenopausal women, but bleeding in this population should prompt evaluation for more worrisome causes of this symptom, including endometrial hyperplasia and carcinoma. Large fibroids and an enlarged uterus can also result in “bulk” symptoms, including bowel and bladder dysfunction and abdominal protrusion. Painful menses, noncyclic pelvic pain, infertility, and recurrent miscarriage can also be symptoms of fibroids, but many fibroids remain asymptomatic. In women with symptomatic fibroids, heavy menstrual bleeding resolves at menopause, and most women with symptoms related to leiomyoma bulk will have some fibroid shrinkage and symptom relief after this time.



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Increasing age up to menopause and black race are the major risk factors for fibroids.³ The rate of hospitalization in which fibroid is a discharge diagnosis is approximately three times as high and the rate of uterine-sparing myomectomy (surgical removal of fibroids) is nearly seven times as high among black women as among white women.⁴ Black women also report significantly more severe fibroid symptoms and more impairment of daily activities.⁵

Both reproductive and environmental factors influence the risk of fibroids. Increasing parity is associated with a decreased risk,^{6,7} possibly through elimination of incipient fibroids as the uterus involutes post partum.⁸ Early menarche and the use of oral contraceptives before 16 years of age are associated with an increased risk, whereas the use of progestin-only injectable contraceptives is associated with a reduced risk.^{6,7,9} Observational data suggest that dietary factors, including increased consumption of fruit, vegetables, and low-fat dairy products, are associated with a reduced risk.¹⁰ Some studies have shown that a high body-mass index is a risk factor.¹¹ Specific genetic mutations have also been linked to fibroid formation.^{12,13}

KEY CLINICAL POINTS

UTERINE FIBROIDS

- Uterine fibroids are common in women of reproductive age; they are particularly prevalent among black women and are more often associated with severe symptoms in black women than in white women.
- Hysterectomy provides the most effective treatment for fibroids and eliminates the risk of new fibroid formation, but it is not acceptable to many women and is often more invasive than alternative treatments.
- The choice among uterine-sparing options is guided by the size, number, and location of fibroids, the woman's symptoms, and where she is in her reproductive life span.
- In most women in whom submucosal fibroids are found to be the cause of bleeding, hysteroscopic myomectomy is first-line therapy and results in rapid recovery with a beneficial effect on future pregnancy.
- In women with heavy menstrual bleeding who do not have submucosal fibroids, effective medical therapies include hormonal contraceptives (including the levonorgestrel-releasing intrauterine device), tranexamic acid, and nonsteroidal antiinflammatory drugs.
- In women with symptoms related to leiomyoma bulk, interventional treatments that are alternatives to hysterectomy include myomectomy, uterine-artery embolization, focused ultrasound surgery, and radiofrequency ablation.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Uterine fibroids are often suspected in a premenopausal woman when an enlarged uterus or a mass is palpated during a pelvic examination or when she reports heavy menstrual bleeding. Ultrasonography is the standard confirmatory test because it can easily and inexpensively differentiate a fibroid from a pregnant uterus or an adnexal mass.

The need for further imaging depends on the clinical findings in the patient. In women with heavy menstrual bleeding, ultrasonographic examination after the infusion of saline into the endometrial cavity can identify the extent of intracavitary fibroids (as defined according to the International Federation of Gynecology and Obstetrics [FIGO] fibroid classification system, in which types of fibroids range from 0 to 8, with lower numbers indicating greater proximity to the endometrium) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).¹⁴

Magnetic resonance imaging (MRI) with gadolinium contrast can provide information on devascularized (degenerated) fibroids and the relationship of fibroids to the endometrial and serosal surfaces. This relationship influences the choice among uterine-sparing treatment options.

Although pelvic ultrasonographic imaging at yearly intervals is often recommended for disease surveillance, no high-quality evidence supports this practice.¹⁵ Limited evidence on the natural

course of disease suggests that both substantial growth and substantial regression are normal; in one study in which there was a 6-month interval between MRI examinations, changes in fibroid size ranged from 89% shrinkage to 138% growth, with a median of 9% growth.¹⁶ Moreover, fibroids can have growth spurts,¹⁷ and most,^{18,19} but not all,²⁰ guidelines suggest that rapid growth of fibroids is not an indication for treatment.

In women with heavy menstrual bleeding, the severity of bleeding, its potential consequences, and causes other than fibroids should be assessed.²¹ Testing in these patients should include a complete blood count and screening for thyroid dysfunction. Selected screening may include evaluation for coagulation disorders (especially von Willebrand's disease if heavy bleeding dates to menarche or if the patient has a pertinent personal or family history^{14,18,21}) and an endometrial biopsy if irregular bleeding occurs or the patient has risk factors for endometrial hyperplasia (obesity, chronic anovulation, or the use of estrogen without progestin therapy).²¹

Recently, there has been considerable debate regarding the prevalence of undiagnosed uterine cancers among women with "presumed benign leiomyoma." A recent study showed that although the risk of any uterine cancer among women with presumed fibroids who were undergoing minimally invasive hysterectomy with morcellation was approximately 1 case per 300 women, among women younger than 40 years of age, the risk was approximately 1 case per 1500 women and among

women 40 through 44 years of age, about 1 case per 1100 women.²² Risk factors for leiomyosarcoma, the cancer that most resembles fibroids, include a history of pelvic irradiation, use of tamoxifen, and rare genetic syndromes.¹⁸ In some cases, endometrial biopsy or MRI findings suggest the diagnosis,^{18,23} but no form of preoperative testing can definitively rule out sarcoma; all women who undergo treatment for presumed fibroids require counseling about the risk, albeit low, that uterine tissue may contain cancer.²⁴

TREATMENT

Despite the high prevalence of fibroids and related annual U.S. health care costs exceeding \$34 billion, there are few randomized trials to guide treatment.^{25,26} In addition, because the size, number, location, and clinical presentation of fibroids vary markedly among women, therapies must be directed to a range of clinical manifestations (Fig. 1).

The nature of symptoms informs the choice of therapy. There is no evidence to support routine treatment of asymptomatic fibroids.^{15,18,20}

Hysterectomy

Hysterectomy remains a treatment option for women who have completed childbearing. It is the only treatment that prevents the common problem of new fibroid formation (which is typically termed recurrence)¹⁵ and also treats concomitant diseases, including adenomyosis and cervical neoplasia. Observational data suggest that women who have undergone hysterectomy have improvements in quality of life over the next 1 to 10 years.^{15,27}

Routes of hysterectomy include the abdominal, vaginal, and laparoscopic (including robotic) approaches. Vaginal hysterectomy is associated with fewer complications, but the size of the myomatous uterus may prohibit this approach in some women.^{15,28} Studies suggest that an endoscopic approach is associated with decreased morbidity. However, this benefit has to be weighed against the risk of dissemination of undiagnosed cancer when power morcellation is used for specimen removal, given concern regarding peritoneal dissemination and its effect on survival.^{22,28} Although the magnitude of this risk is debated, recent guidance from the Food and Drug Administration (FDA) recommends limiting the use of power morcellation to hysterectomy in premeno-

pausal women who are not candidates for en bloc resection and counseling all women about the risks of power morcellation.²⁴

Adverse events are common in patients who undergo hysterectomy. In particular, one study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was up to a 28% risk of medical or surgical complications (such as major blood loss, wound complications, and febrile episodes) and a 10% risk of transfusion.²⁶

Although rates of hysterectomy are decreasing, the lifetime prevalence of hysterectomy is 45% among U.S. women.²⁷ Hysterectomies account for almost three quarters of all fibroid procedures, and the rate varies significantly according to geographic region. Concern has been raised regarding overuse of this procedure.²⁷

Uterine-Sparing Interventions

Professional guidelines support tailoring therapy to a woman's preference; uterine-conserving therapy should be an available option for women even if there is no plan for childbearing.¹⁸ In the United States, black women in particular have been reported to value uterine-sparing and fertility-sparing therapies.⁵ Although myomectomy is the traditional option, there are other options for medical and interventional treatment. The severity of symptoms caused by fibroids must first be assessed before appropriate alternatives to hysterectomy can be determined (Fig. 2).

Therapies for Isolated Heavy Menstrual Bleeding

For women in whom heavy menstrual bleeding is the only symptom, limited data from randomized trials support the effectiveness of medical therapies, including tranexamic acid and the levonorgestrel-releasing intrauterine device (IUD).^{15,20,29} Tranexamic acid, an oral antifibrinolytic agent that is taken only during heavy menstrual bleeding, results in decreased bleeding and improved quality of life with minimal side effects.^{20,30} Although its mechanism of action raises concern about thrombotic risk, this association has not been seen in clinical studies.³⁰ It should not be used concomitantly with oral contraceptives. The levonorgestrel-releasing IUD effectively decreases menstrual bleeding and provides contraception; however, the rate of expulsion of the IUD among women with submucosal fibroids may be high (12% in one case series).^{15,31}

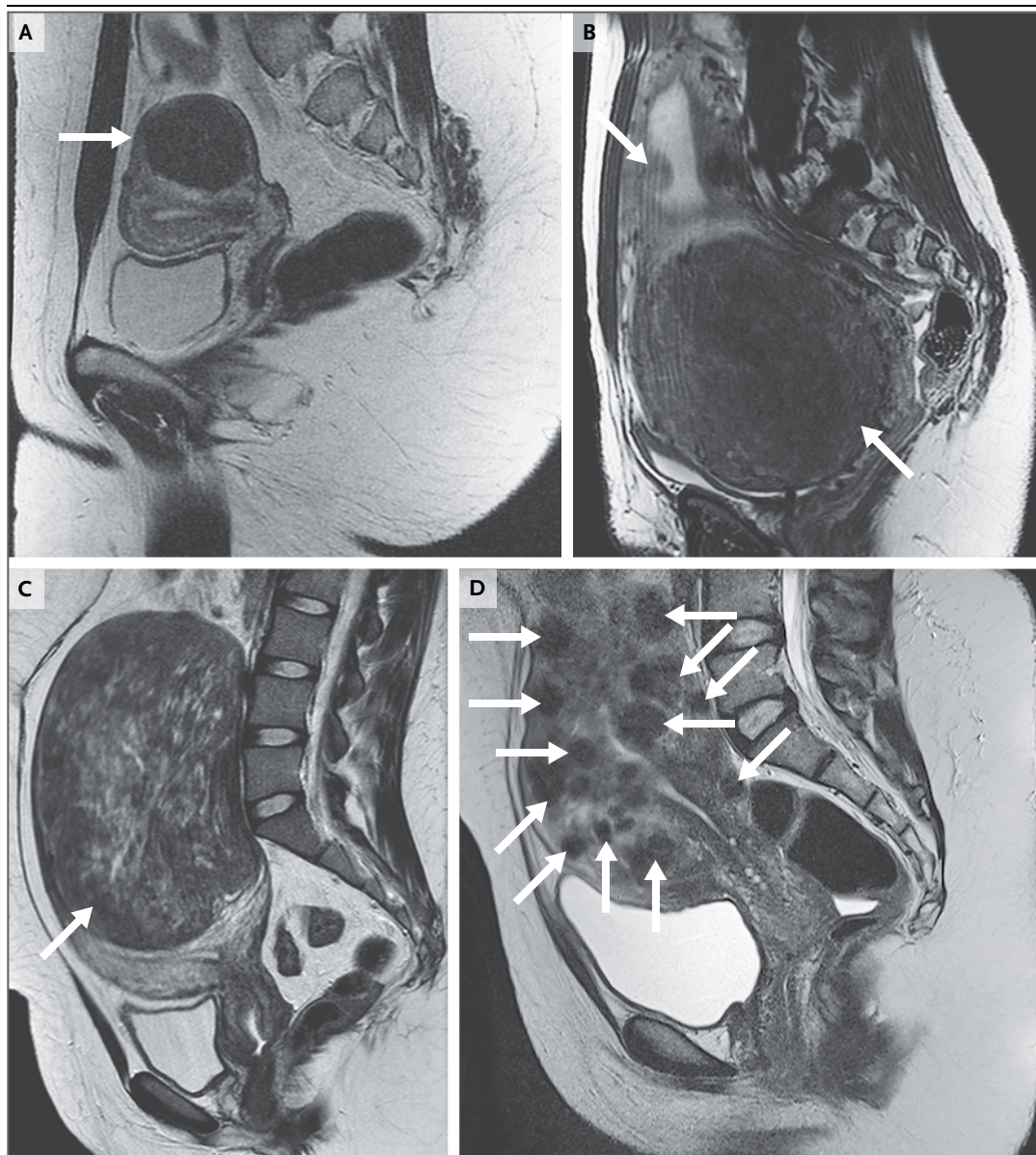
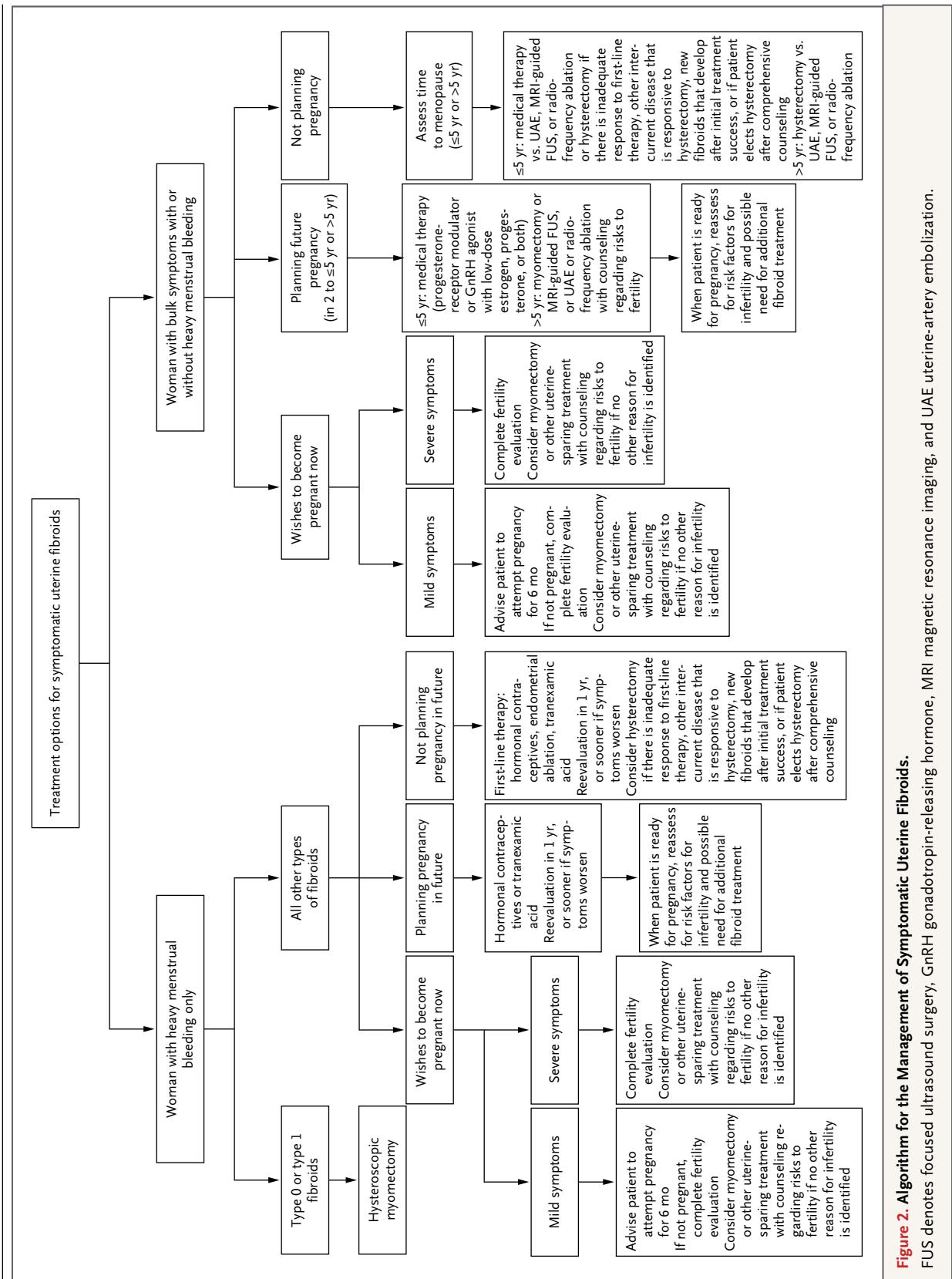


Figure 1. Magnetic Resonance Images of Fibroids.

As shown in these midline sagittal T₂-weighted magnetic resonance images, fibroids (arrows) vary extensively in size, number, and position within the uterus and abdomen. This diversity influences both symptoms and treatment options. According to the International Federation of Gynecology and Obstetrics fibroid classification system, types of fibroids range from 0 through 8, with lower numbers indicating greater proximity to the endometrium. Panel A shows a type 6 subserosal fibroid that caused bladder symptoms in the patient. Panel B shows a large type 4 intramural fibroid that caused clinically significant symptoms related to leiomyoma bulk, including urinary and bowel symptoms. In this patient, the endometrial cavity moved out of the pelvis, and a small type 1 submucosal fibroid contributed to her heavy menstrual bleeding. Panel C shows a single transmural fibroid of type 3 through 6 that was associated with heavy menstrual bleeding, abdominal distention, and bulk symptoms. Panel D shows an endometrial cavity that is considerably elongated and distorted by submucosal fibroids. Some uteri have dozens of fibroids.

Observational data support the use of oral contraceptives to reduce menstrual bleeding in women with fibroids.^{15,18} A meta-analysis of randomized trials concluded that nonsteroidal anti-inflammatory drugs, as compared with placebo, decreased menstrual pain and heavy menstrual



bleeding, but they were less effective in reducing bleeding than tranexamic acid or the levonorgestrel-releasing IUD.³²

For most women in whom submucosal fibroids with a large intracavitary component (FIGO types 0 and 1) are found to be the cause of bleeding, hysteroscopic myomectomy is the best therapeutic option^{15,18,20,33,34} (Fig. 3). This outpatient procedure allows a return to work within a few days and increases the potential for clinical pregnancy (a pregnancy in which the fetal heartbeat can be visualized by means of ultrasonography), although data are lacking to show that it is associated with an increase in the rate of live births.³³

For women who have completed childbearing, endometrial ablation, which uses heat, cold, or mechanical means to destroy the endometrium, is another option to reduce menstrual bleeding. In women with a submucosal fibroid that is classified as FIGO type 0 through 2, ablation can be combined with hysteroscopic myomectomy,^{15,20} with a recovery time that is similar to that of hysteroscopic myomectomy alone but with increased efficacy. Contraception is required after ablation, since subsequent pregnancies among women who have undergone ablation may involve an increased risk of complications (e.g., ectopic pregnancy, abnormal placentation, and prematurity).¹⁵

Therapies for Bulk Symptoms

In women with either isolated symptoms related to leiomyoma bulk or bulk symptoms associated with heavy menstrual bleeding, a reduction in the size of the myomatous uterus is an important outcome. Both medical and interventional options are available.

Gonadotropin-releasing hormone (GnRH) agonists induce amenorrhea and cause a significant reduction in uterine volume. GnRH agonists are primarily used preoperatively with concomitant iron therapy to decrease anemia, facilitate less invasive surgery, or both.^{15,18,20} Long-term use of GnRH agonists with concomitant use of gonadal steroid compounds to attenuate menopausal symptoms and bone loss has been studied. However, GnRH agonists are chiefly indicated for short-term use (2 to 6 months) when there is a clear therapeutic goal such as scheduled surgery or when menopause is incipient.^{15,18,20}

Drugs that modulate progesterone action are an alternative treatment. Randomized trials have

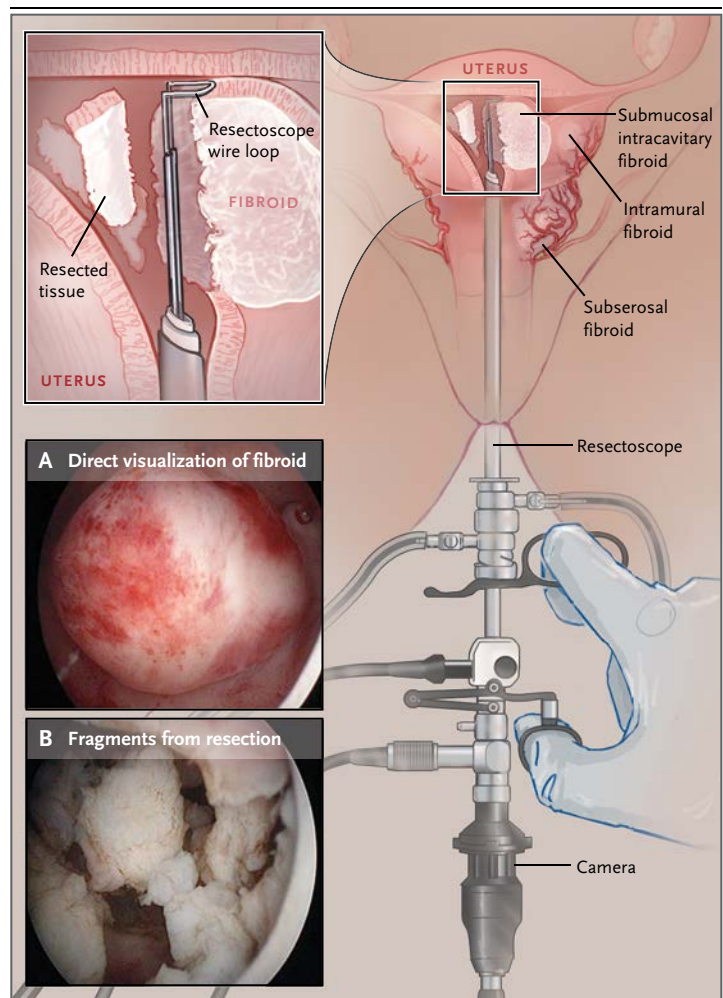


Figure 3. Hysteroscopic Myomectomy.

Hysteroscopic myomectomy involves the use of an endoscope placed through the cervix to remove fibroids intruding into the endometrial cavity. The procedure is conducted by means of direct visualization (Inset A), typically with the use of a camera. The wire loop of the resectoscope uses bipolar energy and physical extension of the loop to resect the tissue, and the resected fragments can then be removed for pathological analysis (Inset B).

shown that the progesterone-receptor modulators mifepristone and ulipristal acetate decrease fibroid symptoms and reduce fibroid volume.³⁵⁻³⁸

Outside the United States, ulipristal acetate is approved for 3 months of preoperative therapy; in the United States, this drug is not approved for treatment of fibroids and is not available in an adequate dose for this indication. Long-term safety data are lacking to show that progesterone modulators do not increase the risk of endometrial abnormalities. Finally, aromatase inhibi-

tors and androgenic steroids have been shown to be efficacious in the treatment of fibroids, but the limited available evidence does not support their clinical use.³⁹

With respect to interventional options, myomectomy by means of laparotomy or laparoscopy can be performed to treat one or more fibroids and can reduce bulk and bleeding symptoms and preserve fertility. Complications associated with myomectomy and recovery after this procedure are similar to those associated with hysterectomy.^{18,20} Power morcellation can be used with laparoscopic myomectomy; the recent safety guidelines regarding power morcellation with hysterectomy also apply to power morcellation with myomectomy,²⁴ although women who undergo myomectomy tend to be younger and at lower risk for leiomyosarcoma.

Most guidelines support surgical myomectomy as the preferred option for treatment of symptomatic intramural and subserosal fibroids in women who wish to have a subsequent pregnancy.^{15,18,20,34,40} Nonetheless, abdominal myomectomy confers substantial risks with respect to fertility, including a 3 to 4% risk of intraoperative conversion to hysterectomy and frequent development of postoperative adhesions.^{19,26} Data are lacking from comparative-effectiveness research regarding fertility in women who have received therapies for fibroids. Since intramural fibroids are themselves associated with an increased risk of infertility and pregnancy complications, and myomectomy does not reduce that risk, treatment of asymptomatic intramural fibroids is not recommended.^{15,33} Recurrence of fibroids is also common; at least 25% of women who have undergone myomectomy require additional treatment.^{15,18}

Uterine-artery embolization is a minimally invasive interventional radiologic technique that has been shown in randomized trials to result in quality of life that is similar to that after surgery, with shorter hospital stays and less time to resumption of usual activities (Fig. 4).⁴¹ Like hysterectomy, embolization is a global uterine therapy; because most fibroids are supplied by the uterine arteries, there is no decision making regarding which fibroids to treat. The rates of major complications after embolization are similar to those after surgery, but embolization is associated with a higher risk of minor complications and of the need for additional surgical intervention (typically hysterectomy).^{15,41} In large case

series and multisite registries, common complications include mild fever and pain (a constellation of symptoms called the postembolization syndrome) and vaginal expulsion of fibroids.⁴² Absolute contraindications to embolization include pregnancy, suspected cancer, and active infection.⁴² Women with degenerated fibroids do not benefit from embolization.

Concerns about the safety of future pregnancies and impaired ovarian function currently limit wider use of embolization. Although successful deliveries after embolization have been reported in case series, a randomized trial comparing myomectomy with embolization showed a significantly higher delivery rate and lower miscarriage rate after myomectomy.^{15,41} However, a randomized trial comparing embolization with hysterectomy showed no significant differences with respect to ovarian reserve 12 to 24 months after the procedures.⁴³ Moreover, a systematic review of 15 randomized trials and prospective cohort studies showed that loss of ovarian function after embolization occurred primarily in women older than 45 years of age.⁴⁴

MRI-guided focused ultrasound surgery is a fibroid-specific therapy that uses ultrasound thermal ablation to treat fibroids.⁴⁵ Case series have shown reductions in symptoms for 5 years after thermal ablation, but trial data are lacking to compare it with alternatives.⁴⁶ Side effects are rare but include skin burns and reversible pelvic neuropathies. A case series involving 51 women who became pregnant after this procedure showed a high rate of successful or ongoing (i.e., beyond 20 weeks' gestation at the time the results were reported) pregnancy,⁴⁷ but data are lacking to inform pregnancy risks and outcomes.

Recently, a radiofrequency ablation device was approved by the FDA for destruction of fibroids during laparoscopy.⁴⁸ In a single-center randomized trial comparing this procedure with laparoscopic myomectomy, ablation resulted in significantly less blood loss and a shorter hospitalization,⁴⁹ but longer-term data, including data regarding subsequent pregnancies, are needed. Neither this approach nor focused ultrasound surgery is currently widely available.

AREAS OF UNCERTAINTY

Few randomized trials have compared various therapies for fibroids, and data are lacking to inform prevention strategies.²⁶ However, enroll-

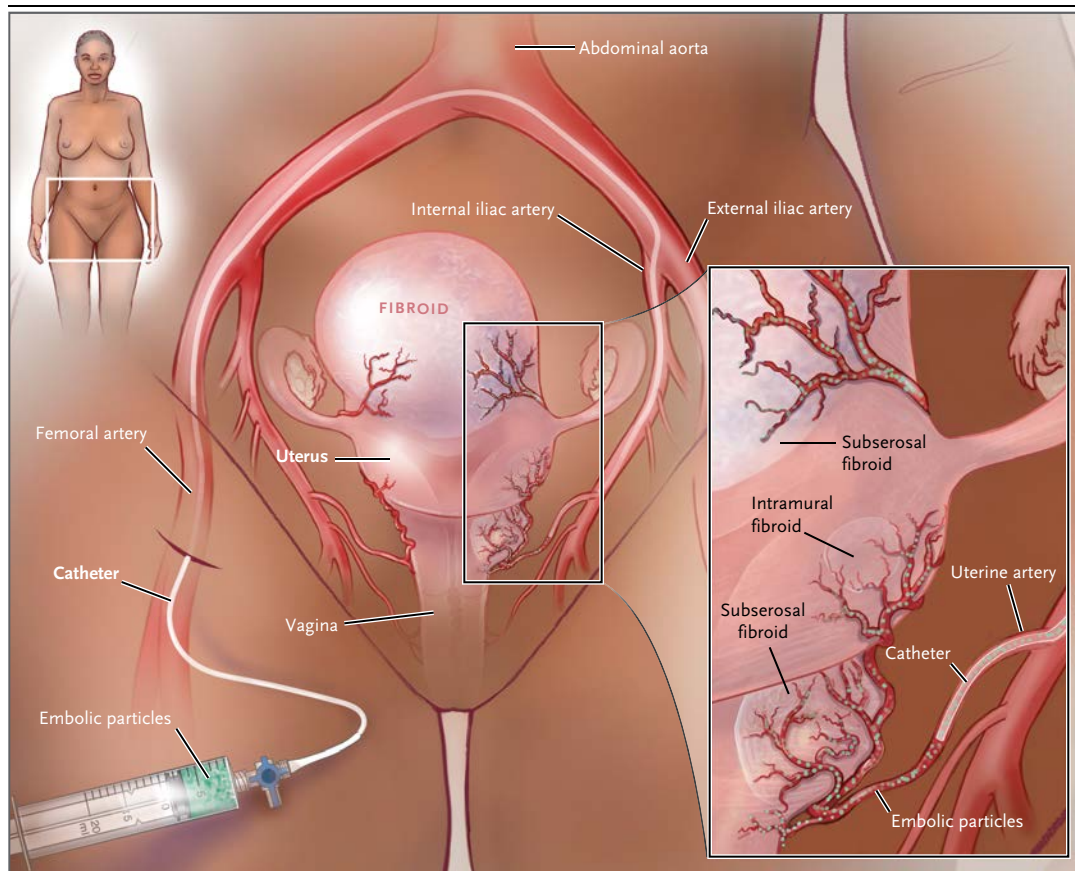


Figure 4. Uterine-Artery Embolization.

In uterine-artery embolization, percutaneous ablation of the fibroid uterus is used to induce ischemic necrosis of the fibroids while the myometrium revascularizes. A catheter that is introduced into the femoral artery is used to deliver embolic particles to both the contralateral and ipsilateral uterine arteries. This procedure has the advantage of targeting most, if not all, fibroids simultaneously and excludes only fibroids that receive their major blood supply from the ovarian or cervical arteries.

ment was recently completed in a randomized trial comparing fibroid embolization with focused ultrasound surgery in a U.S. population (ClinicalTrials.gov number, NCT00995878). In addition, a large multisite registry of patients who plan to receive treatment for fibroids (www.compare-uf.org/) was recently funded by the Patient-Centered Outcomes Research Institute and the Agency for Healthcare Research and Quality. Studies of treatments for fibroids should include attention to subsequent reproductive outcomes and to effect modification according to clinical variables, including race.

Prospective data are needed regarding long-term outcomes of various treatments, including hysterectomy.²⁶ Observational data have shown a higher rate of death from any cause among women who have undergone bilateral oophorectomy with

hysterectomy than among women who have undergone hysterectomy with ovarian conservation.⁵⁰ Data are lacking regarding long-term outcomes in women who have undergone hysterectomy as compared with population-based controls, stratified according to the indication for hysterectomy.

GUIDELINES

The most comprehensive and recent guidelines for the treatment of women with uterine fibroids are the French national guidelines.¹⁵ The European Menopause and Andropause Society recently published guidelines for management that are largely concordant with the French guidelines but less explicit in the grading of evidence.²⁰ This review is largely consistent with these two guidelines. Guidelines from the American College of

Obstetricians and Gynecologists and the American Society for Reproductive Medicine antedate many of the recent key studies.^{18,19} Guidelines from the United Kingdom are also available (www.nice.org.uk/guidance/conditions-and-diseases/gynaecological-conditions/endometriosis-and-fibroids).

CONCLUSIONS AND RECOMMENDATIONS

The woman in the vignette has symptomatic fibroids that warrant intervention. Because she does not wish to become pregnant, hysterectomy with ovarian conservation is an option, but alternatives to hysterectomy should also be discussed. Given her symptoms related to leiomyoma bulk in addition to heavy menstrual bleeding, as well as her multiple fibroids and modest uterine enlargement, I would recommend embolization, focused ultrasound surgery, or radiofrequency ab-

lation if available. Although there are no data from randomized trials to compare options, these procedures, as compared with hysterectomy, would be anticipated to result in rapid recovery and low risks of complications. They also would probably provide effective management until menopause, which would be expected in the next 3 years or so. I would counsel her regarding the risks and benefits associated with each option and respect her autonomy in choosing among these treatments.

Dr. Stewart reports receiving fees for serving on an advisory board from Gynesonics, consulting fees from Abbott, Bayer, GlaxoSmithKline, Astellas Pharma, and Welltigs, and fees from InSightec, paid to her institution, to cover costs of focused ultrasound surgery in a clinical trial, holding a patent (US 6440445) related to methods and compounds for the treatment of abnormal uterine bleeding, and planned consulting with Viteava Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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

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