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A 41-Year-Old Woman With Menorrhagia, Anemia, and Fibroids

Review of Treatment of Uterine Fibroids

Bradley Van Voorhis, MD, Discussant

DR SHIP: Ms P is a 41-year-old woman, gravida 2, para 1, with recurrent uterine fibroids. In her 30s, she experienced increasingly uncomfortable, prolonged menses and reported persistent fatigue.

Blood work revealed iron-deficiency anemia, with a hematocrit of 22%. A pelvic examination revealed an enlarged, midline, but mobile firm pelvic mass. An ultrasound revealed a uterus measuring 14 × 9.7 × 9.9 cm with multiple fibroids, with the largest at the fundus measuring 6.7 × 6.1 × 6.9 cm (FIGURE 1 and interactive eFigure). The fibroids distorted the endometrial stripe. She underwent a myomectomy via laparotomy of multiple fibroids and, initially, her symptoms resolved. About 1 year later, however, they returned, manifested as heavy periods and constant fatigue. Her hematocrit became dependent on adherence to iron supplementation, which she found challenging because it caused constipation. When she did not take iron consistently, her hematocrit declined to as low as 28%. Six months ago, a pelvic ultrasound assessed the size of her uterus as 11.9 × 13.2 × 5.5 cm with multiple fibroids, including a fundal fibroid of 5.2 × 4.5 × 4.3 cm.

Ms P's medical history is notable for a therapeutic abortion in her 20s, birth of her son by cesarean delivery, chronic migraine headaches, depression, and obstructive sleep apnea. She is sexually active with men only and has never had a sexually transmitted infection or abnormal Papanicolaou test result. She is not currently in a sexual relationship. Her medications include paroxetine, 37.5 mg sustained-release daily; lorazepam, 1 mg/d as needed for anxiety; ferrous sulfate, 325 mg/d; zolpidem, 10 mg at night as needed for insomnia; and ibuprofen, 800 mg 3 times per day as needed for pain. She has no known drug allergies.

See also Patient Page.



CME available online at www.jamaarchivescme.com and questions on p 112.

Uterine fibroids are common tumors that can cause heavy menstrual bleeding, pelvic pressure symptoms, and reproductive disorders. The incidence of fibroids peaks in the fifth decade of age and they are more common in African American women. Often, fibroids are asymptomatic and require no treatment. However, the case of Ms P, a 41-year-old woman with recurrent uterine fibroids, menorrhagia, anemia, and fatigue who wishes to retain fertility, illustrates the symptoms that require treatment. Evaluation usually begins with a pelvic examination and an ultrasound to determine both the size and location of the fibroids within the uterus. Standard treatment of symptomatic fibroids is surgical removal by myomectomy or hysterectomy, depending in part on the desire for future fertility; new treatment options include uterine artery embolization via interventional radiologic techniques as well as various medical interventions. Several new therapies show promise but are still experimental at this time. The evidence for treatment options for Ms P and symptomatic patients with fibroids in general is discussed.

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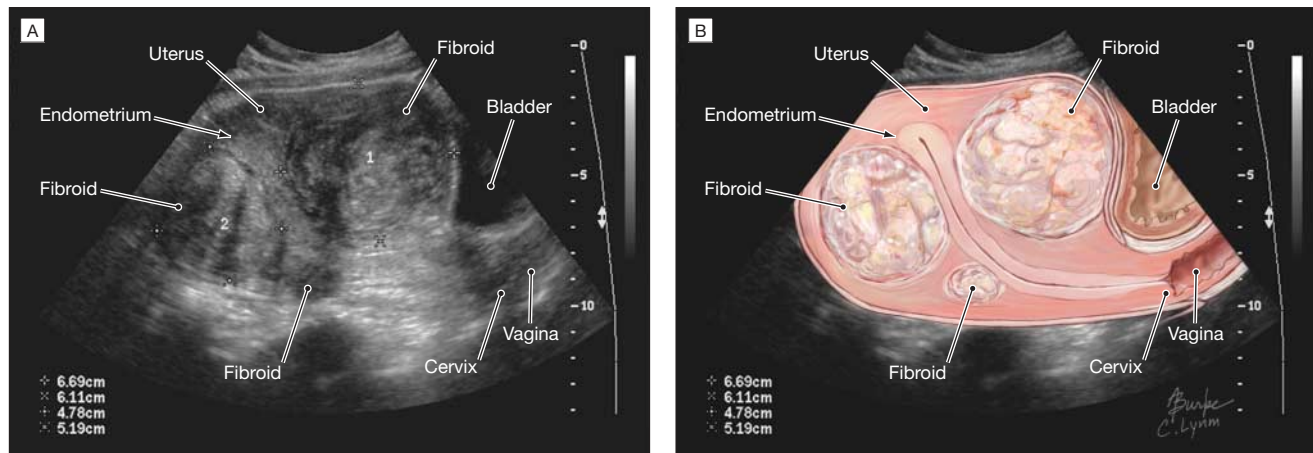
Ms P is attending school and lives with her young adult son. She smokes about a half-pack of cigarettes per day and has done so for 23 years. She drinks 1 to 2 drinks a week socially.

This conference took place at the Obstetrics and Gynecology Grand Rounds at Beth Israel Deaconess Medical Center, Boston, Massachusetts, on May 7, 2008. **Author Affiliation:** Dr Van Voorhis is F. K. "Ted" Chapler Professor of Obstetrics and Gynecology and Director of the Reproductive Endocrinology Division at University of Iowa Carver College of Medicine, Iowa City.

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Figure 1. Ms P's Uterine Ultrasound

A, Abdominal ultrasound shows large fibroids distorting the shape of the uterus. B, Illustration of anatomical structures in view. (See also interactive eFigure.)

Ms P is bothered by her persistent symptoms and seeks treatment for her fibroids but does not want to undergo another “big” surgery. She also very much wants to retain her capacity to bear children. She wonders how to proceed.

MS P: HER VIEW

I believe my symptoms started around the age of 30. I just remember feeling very tired all the time. I felt so tired that I really didn't want to go out. I also had very heavy periods. As I got older, it just got worse. I progressively started to have more pain and more of the heavy bleeding. My quality of life was not there just because I was so tired all the time. So I started with the iron. But over the years, it's just gotten progressively worse instead of better.

I knew that there were surgeries available to me. There was also some procedure to shrink the fibroid. I discussed this with my physician, and she referred me to the gynecology doctor, who in turn suggested I have surgery. So about 3 years ago, I had 11 fibroids removed. And I felt much better. But, unfortunately, they returned. Probably a year after the surgery, I started to feel once again that I was tired all the time.

I have my menstrual cycle for 5 days. I have 4 days of heavy, constant bleeding where I'm changing pads basically every hour. Then I have 1 day of very light bleeding. I have 1 week off with no symptoms. Then I start to “premenstruate” for 2 weeks. So I have a total of 3 weeks of this; I'm not feeling well, there's fatigue and all the premenstrual symptoms: the bloating, the pain in the legs, the tenderness in the breasts.

I don't have the energy to do those things that I like to do, especially in the summertime, when I like to do outdoor activities. If I have really heavy bleeding or if I'm just in my cycle, I don't want to do anything. I'd just rather stay home.

I am very concerned about having future procedures done because I know that there are risks with every procedure. I want to make sure that my uterus and my reproductive organs are kept intact for as long as possible because I do want to be able to, in the future, grow my family.

How can I get rid of the fibroids? What would be the healthiest approach to having them eradicated, just totally gone? Is that possible?

AT THE CROSSROADS: QUESTIONS FOR DR VAN VOORHIS

What is the epidemiology of uterine fibroids? What are the indications for treatment? What is the evidence for treatment modes and what are their risks and long-term outcomes? What are the consequences of untreated uterine fibroids? What does the future hold? What do you recommend for Ms P?

DR VAN VOORHIS: Ms P is a 41-year-old woman with menorrhagia, anemia, and fatigue due to uterine fibroids. She previously had a myomectomy, which was temporarily helpful, but new fibroids have developed and she now desires treatment that will allow her to preserve her fertility while effectively improving her symptoms. She would like to avoid a major surgical procedure if possible.

Fibroids are very common, benign, smooth muscle tumors of the uterus that are also referred to as leiomyomata or myomas. In addition to smooth muscle proliferation, these tumors are characterized by high extracellular matrix content including collagen, causing a generally hard, fibrous texture; hence the name fibroids. Fibroids are clinically categorized as intracavitary, submucosal, intramural, and subserosal, depending on where they are located within the uterus (FIGURE 2). Although the precise cause of fibroid development and growth is unknown, molecular studies have revealed that each tumor is unicellular in origin and about 40% have non-

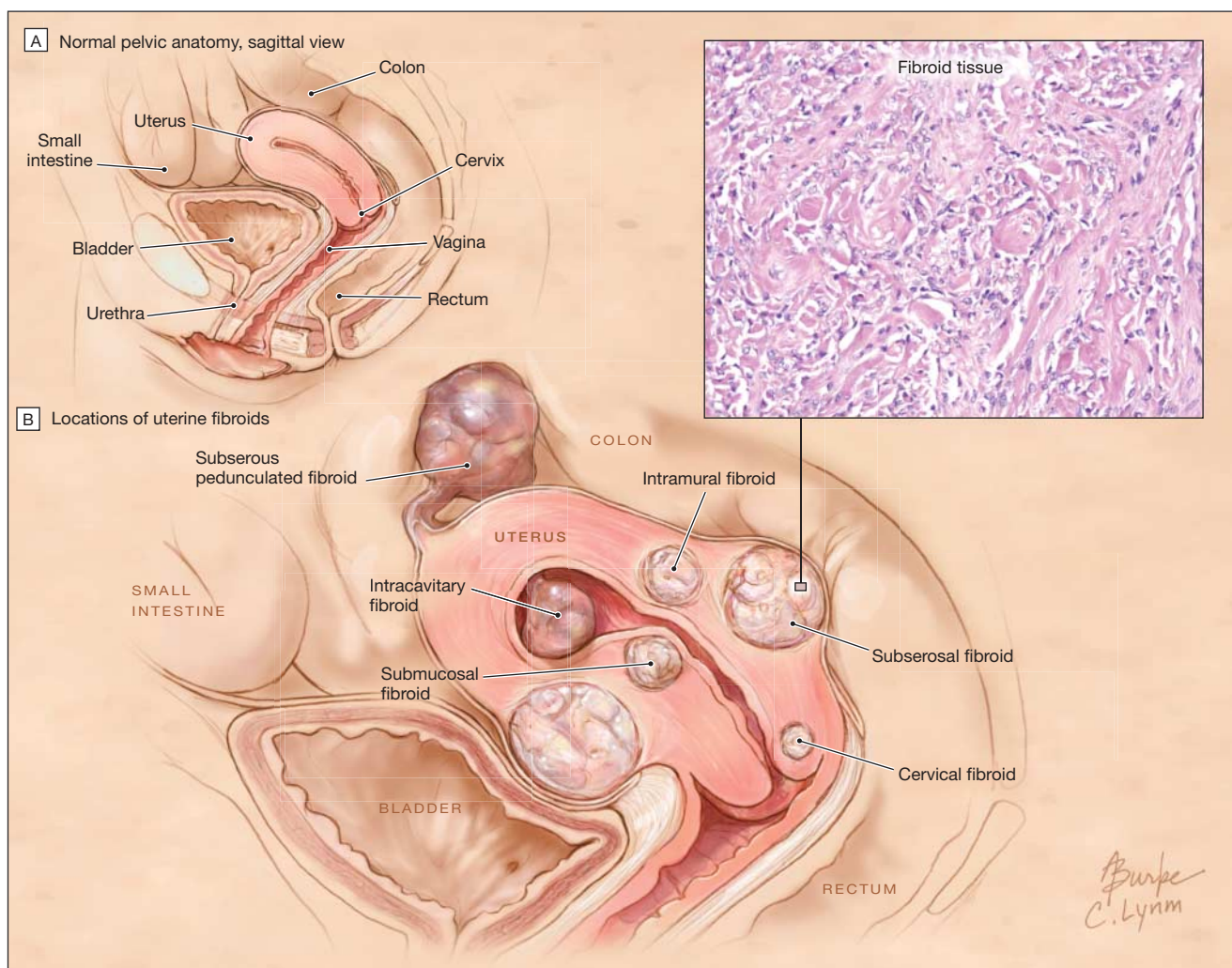
random and tumor-specific chromosomal abnormalities that may affect growth rates.¹

Epidemiology of Fibroids

Estimates of the prevalence of fibroids vary widely depending on the age and racial mix of the study population as well as the method used for detection. A large, population-based study in the United States found a cumulative incidence of greater than 66% by ultrasound examination of women approaching age 50 years.² However, ultrasound is very sensitive for detecting fibroids, and not all of these tumors are clinically significant. The prevalence of clinically significant fibroids was estimated to be 50% among African American women and 35% among white women.²

Fibroids are known to grow in response to both estrogen and progesterone stimulation. Compared with normal myometrium, fibroids have higher concentrations of estrogen receptors, progesterone receptors, and aromatase, an enzyme important for local estrogen production.³⁻⁵ The importance of steroid hormones in the pathogenesis of fibroids is supported by the observations that fibroids are never present in preadolescent girls, that their prevalence increases throughout the reproductive years, peaking in the fifth decade, and that their prevalence is markedly reduced after menopause. Other factors associated with the presence of fibroids are early age at menarche and obesity (relative risk [RR] ≤2), conditions that are associated with a greater exposure to endogenous steroid hormones.⁶ Protective fac-

Figure 2. Normal Pelvic Anatomy, Locations of Uterine Fibroids, and Fibroid Tissue Histology



Abnormal uterine bleeding is influenced by the size and location of fibroids. Larger fibroids and fibroids located in or near the endometrial cavity tend to cause more bleeding symptoms and reproductive disorders. In a representative tissue sample, a fascicular pattern of smooth muscle bundles can be seen, separated by vascularized connective tissue. Individual smooth muscle cells are elongated with eosinophilic cytoplasm, distinct cell membranes, and uniform "boxcar-shaped" nuclei. Mitoses, in this case and in most fibroids, are extremely rare and, if present, raise the possibility of leiomyosarcoma, a malignant tumor of smooth muscle origin.

tors include increasing parity (50%-80% reduced risk compared with nulliparous women) as well as cigarette smoking (20%-50% reduced risk compared with nonsmokers), which may act by decreasing endogenous estrogen levels.⁶ Two studies indicate that use of progestins such as depot medroxyprogesterone acetate may reduce the risk of developing fibroids.^{7,8} Use of birth control pills has no clear effect on the prevalence of fibroids⁶ and low-dose pills do not stimulate growth of existing fibroids in most women.⁹ There may be a familial predisposition to the development of fibroids because having a first-degree relative with fibroids increases a woman's risk 2- to 3-fold.^{10,11} Ms P has some of the risk factors for fibroids, including having just 1 child and having a family history (sister and maternal aunt) of fibroids.

A striking and, as yet, unexplained finding is that African American women have a 3-fold higher incidence of clinically recognized fibroids than white, Hispanic, or Asian women.¹² Furthermore, there is some evidence that African American women develop fibroids at a younger age and that they have larger tumors associated with more symptoms.²

Indications for Treatment

Fibroids are often asymptomatic and require no therapy. However, depending in part on location and size, fibroids can be a cause of abnormal uterine bleeding as well as pelvic pressure and, less commonly, pain. A large study found that significantly more US women with fibroids detected by ultrasound reported at least 1 recent episode of heavy, "gushing" menses compared with women without fibroids (46% vs 28%).¹³ A similarly conducted Italian study found that 35% of women with fibroids reported heavy menses vs 28% of women without fibroids, a difference that did not reach statistical significance.¹⁴ In both studies, women with fibroids tended to use more sanitary products during menses than women without fibroids. Ms P has many of the classic symptoms of uterine fibroids including periods with 4 to 5 days of heavy bleeding, fatigue that is likely secondary to iron-deficiency anemia, and pelvic "tension" or pressure. She also describes episodes of "flooding" or "gushing," with accidents occurring when sanitary products cannot contain the heavy bleeding, leading to embarrassment, social isolation, and a poor quality of life. Although menorrhagia can sometimes be difficult to accurately define clinically,^{15,16} a woman's subjective assessment as to the "heaviness" of her period has been shown to correlate with measured blood loss, and women are able to compare their own experiences over time and to determine the degree that menses disrupt their daily activities.¹⁷ Treatment decisions are often based on these factors from the woman's history.

Fibroids are found more often in women presenting with abnormal menstrual bleeding,^{13,18} and the amount of bleeding is related to the size of the fibroids. However, the high prevalence of intracavitary or submucosal fibroids in women with abnormal bleeding suggests that the location of the fi-

broids is an important factor in severity of bleeding.¹⁸ Among perimenopausal women in their mid to late 40s, the presence of fibroids is associated with about a 2-fold higher risk of having prolonged duration of menses (>7 days) and of having 3 or more very heavy bleeding days in a period after controlling for other factors.¹⁹ The exact cause of menorrhagia with fibroids is not known, but fibroid-associated changes in uterine vasculature, contractility, and endometrial surface area may contribute to the problem.

Because fibroids can grow very large (weights as high as 100 lb [45 kg] have been reported), they can cause a sense of pelvic pressure.²⁰ Urinary frequency caused by bladder compression is common in women with large fibroids. Pelvic pain is much less common and most fibroids are painless. However, 1 study found a slightly higher rate of dyspareunia and noncyclic pelvic pain in women with fibroids compared with those with no fibroids (7% vs 4%).²¹ Occasionally, fibroids can cause acute pelvic pain if they undergo torsion and necrosis because of loss of blood supply. Fibroids have also been associated with infertility but are rarely the sole cause, so in an infertility evaluation other possible factors must be investigated. In pregnancy, fibroids have been associated with an increased risk of miscarriage along with complications including bleeding, pain, and placental abruption. Reproductive disorders appear to be more common with fibroids that are located within or distort the endometrial cavity, and treatment is often warranted.^{20,22}

Evaluation of Fibroids

The initial step in evaluating a woman with menorrhagia is a pelvic examination, including a bimanual and speculum examination. However, if fibroids are suspected, transvaginal ultrasound is often necessary to confirm the source of a pelvic mass and define the anatomy or to detect small, nonpalpable fibroids that can be the cause of menorrhagia.²³ Intracavitary endometrial polyps or fibroids are found in 25% to 50% of women with severe menorrhagia¹⁶ and, if there is uncertainty on the initial ultrasound, their presence and location is best confirmed with either saline-infusion sonography or hysteroscopy. If a solitary intracavitary fibroid, submucosal fibroid, or endometrial polyp is found, strong consideration should be given to hysteroscopic resection of the lesion, since this is relatively easily accomplished on an outpatient basis and is highly effective, based on satisfaction rates (65%-100%) and absence of reported menorrhagia (70%-100%) 1 to 5 years after surgery.²⁴⁻²⁶ Intraoperative complication rates of 0.3% to 28% have been reported, with uterine perforation and fluid overload with the uterine distending media being the most common problems.²⁶ Intrauterine adhesions are the major long-term complication, occurring in 1% to 13% of patients.²⁶

In addition to fibroids, other causes of abnormal uterine bleeding include endometrial polyps, adenomyosis, anovulation, endometrial hyperplasia and cancer, cervicitis, cervical cancer, complications of pregnancy, hypothyroidism,

and inherited or acquired clotting disorders due to systemic disease.²⁷ Each must be considered as a potential cause before attributing a woman's menorrhagia to the presence of fibroids, particularly since fibroids can often be asymptomatic.

Ms P has multiple intramural fibroids on ultrasound examination, with the largest being 5 × 4 cm in diameter. She also has a thickened endometrium of 1.9 cm, and the endometrium is distorted by her fibroids. Her treatment decisions must consider her desire to retain fertility at age 41 years, her desire to avoid further invasive procedures that might "injure her uterus," and her desire to "get rid of [the fibroids]."

Surgical Treatments for Fibroids

Myomectomy. Myomectomy is a common procedure performed in women with symptomatic fibroids who desire to retain fertility. The objective of this surgery is to remove all fibroids while preserving the normal uterine myometrium. Myomectomy can be performed by laparotomy, laparoscopy, or hysteroscopic resection depending on the number, size, and location of the fibroids. Most myomectomies are performed by laparotomy, but minimally invasive procedures (laparoscopic and hysteroscopic approaches) can be performed in some cases and allow for a more rapid recovery (2-4 weeks vs 4-6 weeks for return to regular activities).²⁸ The hysteroscopic approach requires that the fibroid be at least partially within the endometrial cavity and that it not be too large. Each surgeon has his or her own limits for attempting a laparoscopic myomectomy, but in general, this approach is attempted only for 1 or 2 fibroids not larger than 5 to 8 cm.²⁹

Compared with hysterectomy, myomectomy is associated with more intraoperative blood loss but less risk of injury to other pelvic organs including the bladder and ureter.³⁰ In the postoperative period following myomectomy, febrile morbidity as high as 36%,³¹ wound infections in 5%,³² and blood transfusion rates of up to 20% have been reported.³³ Adhesion formation is found in up to 59% of patients after myomectomy, and this may affect future fertility if the scarring involves the fallopian tubes and ovaries.³⁴

There are no prospective randomized trials of myomectomy compared with alternative treatments for menorrhagia.³⁵ Evidence about expected outcomes of myomectomy is limited to several small patient series with follow-up from 6 months to 3 years after surgery. Although methods for measuring outcomes vary, more than 70% of patients report improvement in menorrhagia and pelvic pain or being "satisfied" with the results.³⁵ Pregnancy rates after myomectomy have been reported to be approximately 55% and do not differ when comparing the laparoscopic approach vs laparotomy.^{28,36}

One long-term risk of myomectomy is the development of new fibroids after surgery, as Ms P experienced. Five years after myomectomy, as many as 50% of women have new fi-

broids and 11% to 26% require additional surgery.^{37,38} Risk factors for the development of new fibroids include increased uterine size and increased numbers of fibroids (RR, 2.4 for recurrence in women with multiple fibroids compared with women with 1 fibroid) at the time of the myomectomy.³⁵ In some cases, fibroids were likely present at the time of the myomectomy but were not removed because they were not detected. This may be more likely when fibroids are "shrunk" by preoperative use of medications like gonadotropin-releasing hormone agonists³⁹ or when myomectomy is performed by laparoscopy⁴⁰ because the ability to palpate small tumors is lost with this technique.

Ms P had 11 fibroids removed at her initial myomectomy 2 years ago, putting her at high risk of developing new fibroids. One option for her would be to proceed with a second myomectomy, but she would once again be at risk of recurrence in the future. The surgical approach for Ms P would be laparotomy due to the likely presence of adhesions from her first surgery and the presence of multiple large fibroids.

Hysterectomy. Hysterectomy is often performed for women with symptomatic fibroids who do not desire to retain fertility. Among all hysterectomies, fibroids are the leading cause (32%), followed by abnormal menstrual bleeding (17%).⁴¹ The most common type of hysterectomy is a total abdominal hysterectomy (60%), performed by removing the entire uterus through an abdominal incision.^{41,42} Other means of performing hysterectomies are through a vaginal approach or by minimally invasive laparoscopic approaches, providing that the uterus is not too large. A prospective randomized trial in women with benign indications for surgery and a relatively small uterus (uterine size less than the size of a uterus at 12 weeks' gestation) has confirmed that, compared with the abdominal approach, the short-term advantages of both the laparoscopic and vaginal approaches to hysterectomy are less postoperative pain, shorter hospital stay (3 vs 4 days), and quicker recovery as measured by improved quality-of-life scores 6 weeks after surgery.⁴³ Despite these advantages as well as a smaller scar, many hysterectomies for fibroids are still performed by laparotomy because the large size of the fibroid uterus limits the ability to perform the surgery vaginally or by laparoscopy. Laparoscopic hysterectomies have longer surgical times, and some difficult laparoscopic and vaginal cases need to be converted to an abdominal approach (conversion rate of 3%-4% even when the uterus is small) to successfully complete the surgery.⁴³ If this complication is excluded, all approaches have similar complication rates, including major hemorrhage requiring transfusion (2%-5%) and injury to bowel (1%) and the urinary tract (1%-3%).⁴³

Hysterectomies are nearly 100% effective in relieving symptoms of bleeding, pressure, or pain caused by fibroids. Three large prospective studies have evaluated outcomes of hysterectomy at 1 to 2 years of follow-up.⁴⁴⁻⁴⁶ The hysterectomies were done for a variety of indications, but fibroids were

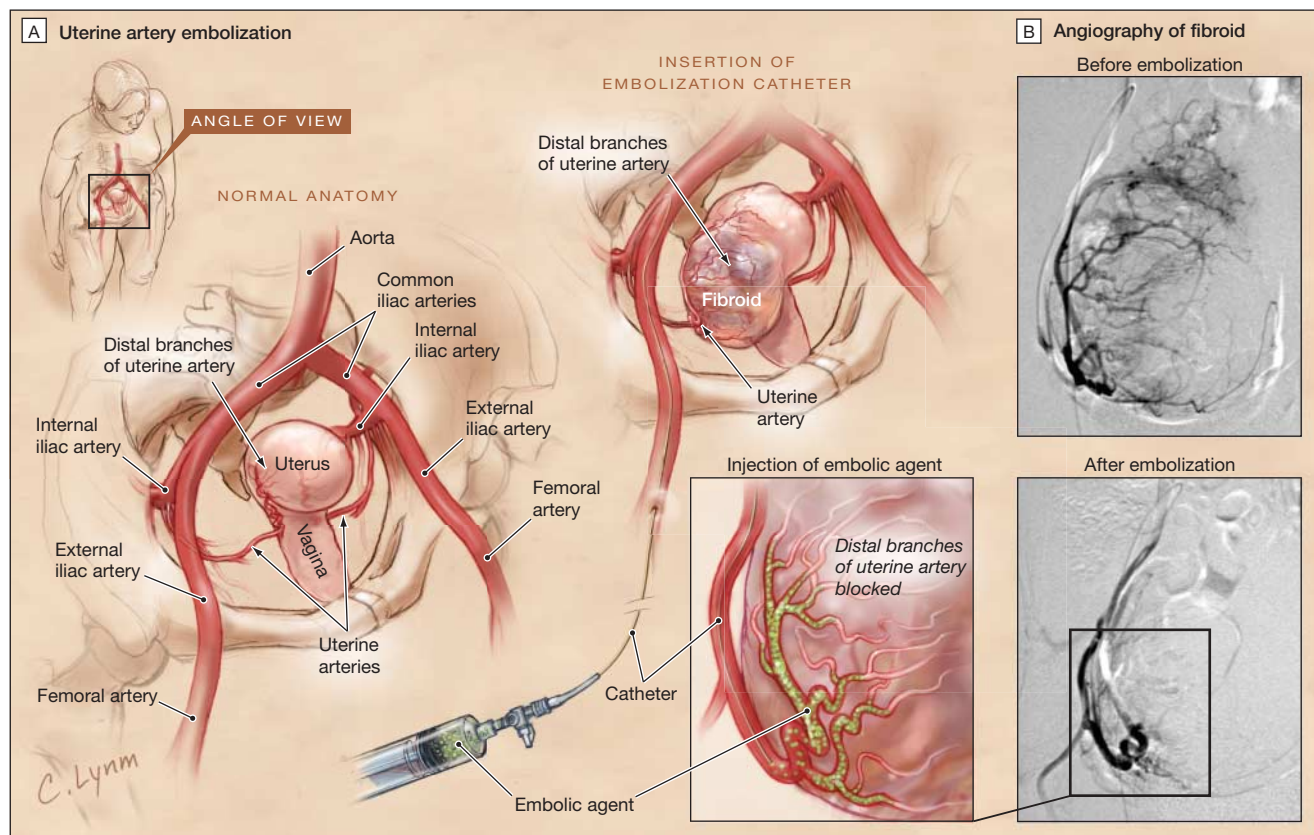
the underlying diagnosis in 35% to 71% of patients. All 3 studies reported significant improvements in symptoms and quality of life as well as very high satisfaction rates. New symptoms developed in 5% to 12% of patients, with menopausal symptoms being the most common.³⁵ In the short term, most women report either unchanged or improved sexual functioning after hysterectomy, with little impact on frequency of intercourse, libido, or sexual interest.^{44,47} In addition, hysterectomy is a reasonably safe procedure. Minor complications, including postoperative infection, fever, wound hematoma, or separation, occur in about 25% of patients, and major complications, including blood transfusion and injury to bowel, bladder, or ureter, occur in 5% to 14% of patients.^{35,48}

In a survey of 397 women (survey response rate, 60%), an average of 9 years following hysterectomy,⁴⁸ 99% of respondents reported continued relief of fibroid symptoms, 94% reported that hysterectomy met their expectations, 86% stated that they would recommend the procedure to a friend, and 75% reported improved health status.⁴⁸ Potential long-

term adverse outcomes from hysterectomy include an earlier menopause by 3 to 4 years on average, even when the ovaries are retained.⁴⁹ In addition, psychological ramifications from loss of fertility can occur. The effect of hysterectomy on subsequent risk of urinary incontinence is controversial,⁵⁰ but a recent Swedish national cohort study found that hysterectomy, regardless of surgical technique, increased the risk of subsequent stress urinary incontinence surgery (0.18% per year vs 0.08% per year; hazard ratio, 2.4; 95% confidence interval [CI], 2.3-2.5).⁵¹ The highest risk of incontinence surgery was in the first 5 years after hysterectomy, and the risk increased with increasing parity of the woman. Finally, there may be an increased risk of vaginal prolapse (cumulative incidence, 0.5%-2%) following hysterectomy.⁵²

Ms P is not a candidate for hysterectomy because of her desire to retain fertility, although this would be a consideration if this desire changed and she wanted "definitive" therapy for her bleeding symptoms. Hysterectomy is virtually 100% effective in relieving symptoms of abnormal bleed-

Figure 3. Uterine Artery Embolization (UAE)



A, During UAE, a catheter is introduced along a guide wire into the femoral artery and advanced through the external iliac artery into the common iliac artery. The catheter is then guided into the internal iliac artery and then into the uterine artery. Microspheres injected through the catheter embolize the distal branches of the uterine artery that supply the fibroid and block perfusion, causing necrosis and shrinkage of the fibroid. B, Angiogram prior to UAE shows the blood supply of a large fibroid. After embolization of the uterine artery, absence of contrast in the distal branches confirms occlusion.

ing; however, it is a major surgery associated with some complications, requiring a recovery period of 4 to 6 weeks after abdominal hysterectomy and 2 to 4 weeks after vaginal hysterectomy or minimally invasive laparoscopic approaches before patients can expect to return to regular activities.

Uterine Artery Embolization. Ms P expresses interest in uterine artery embolization (UAE), which is a new, minimally invasive approach generally performed by interventional radiologists. Uterine artery embolization is performed by placing a catheter into the femoral artery and accessing both uterine arteries in a retrograde fashion. The ascending branches of the uterine artery supplying the fibroids are then embolized with microspheres to achieve complete loss of fibroid perfusion (FIGURE 3). This causes necrosis and shrinkage of the fibroid (volume decrease of 30%-50%), leading to a reduction in symptoms. Expected short-term adverse effects of UAE include ischemic pain in virtually all patients and fever secondary to postembolization syndrome and tissue necrosis in about 25% of patients.⁵³ Nevertheless, most patients can be discharged from the hospital within 24 to 48 hours and have a rapid return to daily activities. Complications include groin hematomas (15%), prolonged vaginal discharge (25%), and expulsion of a fibroid after the procedure (8%).⁵⁴

Two large multicenter cohort studies have confirmed that a majority of patients have significant symptom reduction and a return to a normal quality of life within 6 months of UAE, and the results are durable through 3 to 5 years.^{48,55} In aggregate, 86% to 91% of women surveyed after UAE (1934 [63%] responded of 3094 surveyed) reported that they would recommend the procedure to others. However, by 3

to 7 years, 14% to 23% of respondents required an additional procedure for symptoms of fibroids and most chose hysterectomy.^{48,55} Risk factors for poor outcomes after UAE include increased size of the fibroid(s), younger age, higher body mass index, worse symptom scores at presentation, and fibroid location in or near the cervix.⁵⁶ Technical difficulties leading to only unilateral embolization also increase the risk of failure of UAE.⁵⁶ Favorable prognostic factors include submucous fibroid location and presenting symptoms of menorrhagia, as opposed to other symptoms, including pressure sensations.⁵⁵

Three prospective randomized trials have compared UAE with hysterectomy for symptomatic fibroids (TABLE).^{53,57,58} These studies have confirmed that UAE is associated with a shorter hospital stay and faster return to regular activities. There are similar procedural complication rates, although the type of complication differs, with hysterectomy being associated with more transfusions (0%-10%), wound infections (4%-15%), and injury to other pelvic organs (4%-5%), while UAE was associated with groin hematomas (14%-20%), postembolization syndrome with fever and pain (25%), and vaginal discharge (8%-23%). From 6 to 24 months after the procedure, quality-of-life scores show similar improvement, although bleeding symptoms are noted more often after UAE. Approximately 20% to 25% of patients after UAE will require additional surgery or embolization within 1 to 2 years of the procedure.^{53,57,58}

Based on current evidence, UAE is a good option for Ms P to consider for the relief of her symptoms. However, whether UAE should be used in women like Ms P who de-

Table. Randomized Trials Comparing Uterine Artery Embolization vs Surgery for Symptomatic Fibroids

Source	Inclusion Criteria	Procedure	No. of Patients	Age, Mean, y	Short-term Outcomes	Long-term Outcomes
Hehenkamp et al, ⁵⁷ 2008	Uterine fibroids	UAE	88	44.6	Greater improvement in physical component summary of Short Form-36 at 6 wk	At 24-mo follow-up, no difference in health-related quality of life, patients in hysterectomy group were more satisfied with treatment, 23.5% in UAE group had hysterectomy
	Menorrhagia (100%) or pressure (26%)	Hysterectomy	89	45.4	Similar improvement in all health-related quality-of-life outcomes by 6-mo follow-up	
Edwards et al, ⁵³ 2007	Uterine fibroids	UAE	106	43.6	At 1 mo, similar procedural complication rates, greater improvement in physical function in the Short Form-36 general health survey associated with UAE, hospital stay shorter after UAE (1 d vs 5 d), faster return to work after UAE (20 d vs 62 d)	At 12 mo, no difference in SF-36 scores, symptom scores better after surgery, no difference in major adverse events, 10 patients (9%) after UAE required an additional procedure (20% required an additional procedure with longer follow-up), UAE more cost-effective
	Menorrhagia (56%) or pressure (23%)	Surgery (hysterectomy, 84%; myomectomy, 16%)	51	43.3		
Pinto et al, ⁵⁸ 2003	Uterine fibroids <10 cm in diameter	UAE	38	46.4	Similar procedural complication rates (more transfusions [n=2] with hysterectomy), hospital stay shorter after UAE (1.7 d vs 5.8 d), faster return to regular activities with UAE (9.5 d vs 36.2 d)	
	Menorrhagia (95%)	Hysterectomy	19	44.6		

Abbreviation: UAE, uterine artery embolization.

sire future fertility is uncertain. There is concern that microspheres used for the procedure might migrate and cause collateral embolization of the ovaries, leading to diminished ovarian function.⁵⁵ Transient ovarian failure can occur after UAE, but permanent cessation of function (menopause) has been thought to be relatively uncommon and seen more often in women older than 45 years. In a large study, 3 years after UAE, 29% of women had amenorrhea but nearly 80% of these women were older than 45 years.⁵⁵ Of concern is that 1.6% of women who had a UAE and were younger than 40 years reported amenorrhea. Another study found that levels of anti-Müllerian hormone, a serum marker that correlates with the number of ovarian follicles, were diminished following UAE, suggesting a damaging effect of UAE on ovarian follicles.⁵⁹ Further studies will be needed to determine if a clinical consequence of this observation occurs, such as reduced fertility or an earlier age of menopause.

In addition to the potential for compromised ovarian function, embolization of the uterine arteries may impair embryo implantation or inhibit blood supply to a developing fetus. Uterine artery embolization is generally performed in relatively older reproductive-age women.⁵⁵ Since both age and fibroids are associated with increased complications of pregnancy, the additional risk associated with UAE can be difficult to determine. However, a recent randomized trial comparing UAE and myomectomy in women desiring continued fertility found an increased infertility rate (RR, 2.2; 95% CI, 1.1-4.4) and an increased miscarriage rate (RR, 2.8; 95% CI, 1.2-6.2) following UAE.⁶⁰ Of pregnancies that went on to delivery, neonatal outcomes did not differ, although the numbers were small. Several large patient series have raised concerns about possible increases in miscarriages, preterm deliveries, and abnormal placentation and postpartum hemorrhage following UAE⁶¹⁻⁶⁴ compared with the general population. At this time, the evidence favors myomectomy over UAE in women desiring future fertility.

Endometrial Ablation. Endometrial ablation is commonly performed for the treatment of menorrhagia in women who are finished with childbearing. The endometrial lining of the uterus can be ablated by a number of techniques and energy sources, including endometrial resection, electrocautery, thermal balloon, circulated hot fluid, cryotherapy, and microwave energy.⁶⁵ In women with a normal endometrial cavity, amenorrhea rates of 13% to 55% have been reported depending on the device used.⁶⁵ Long-term satisfaction rates are approximately 75%, although some have continued menorrhagia and increasing pelvic pain, and 10% to 20% will eventually require additional procedures, including hysterectomy, for these symptoms.⁶⁶ Many of the techniques require a normal-sized uterine cavity, and women with large fibroids have often been excluded from efficacy trials. No long-term studies of endometrial ablation in women with menorrhagia due to fibroids have been conducted. Ms P would not be a candidate for this procedure because of her desire to maintain fertility and her enlarged uterus secondary to fibroids.

Medical Management of Fibroids

Several medical therapies have been shown to reduce menstrual bleeding in women with idiopathic menorrhagia but have not been studied in women with menorrhagia due to fibroids. Birth control pills reduce menstrual blood loss by about 40% in most women, but clinical trials have excluded women with fibroids.^{67,68} Nonsteroidal anti-inflammatory drugs also reduce not only menstrual cramping but also menstrual blood loss by about 40%, but there is evidence from a small trial that nonsteroidal anti-inflammatory drugs are not effective in women with fibroids.^{67,69} Relative to other therapies, short-term or cyclic use of progestins is ineffective in treating menorrhagia.⁷⁰ Prolonged use of progestins (eg, norethindrone or medroxyprogesterone acetate) can significantly reduce blood loss or even result in amenorrhea when given to women with menorrhagia, although again, this therapy has not been studied in women with menorrhagia due to fibroids.⁷¹ Systemic adverse effects of progestins, including weight gain, breakthrough bleeding, and mood changes, can be limiting.⁷¹

Local administration of progesterone through a progestin (levonorgestrel)-releasing intrauterine device (LNG-IUD) can reduce menstrual bleeding in many women while reducing the systemic effects of oral progestins. There is good and consistent evidence that insertion of an LNG-IUD results in significantly reduced menstrual bleeding in women with menorrhagia and no fibroids.⁷¹⁻⁷³ The evidence for use of an LNG-IUD for menorrhagia associated with uterine fibroids is limited to small patient series without control groups. These studies have predominantly included women with small fibroids that did not distort the cavity, since distortion of the cavity can make placement of the IUD more difficult. In most of these series, the uterus was smaller than a uterus would be at 12 weeks of pregnancy (at the level of the symphysis pubis). Results in women with fibroids have varied, as some case series have reported poor symptomatic relief⁷⁴ and higher expulsion rates of the IUD,^{74,75} whereas others have found reduced bleeding and good satisfaction rates at 1 year.^{76,77} Further studies are needed before this therapy can be considered as evidence-based for women with fibroids, although it is likely a reasonable option in women with menorrhagia and small fibroids remote from the endometrium.

A prospective trial enrolled women with menorrhagia⁷⁸ refractory to an initial trial of cyclic progestins, of whom 65% had fibroids (although women with submucous fibroids were excluded), and compared medical therapy with hysterectomy. The medical therapy was individualized, but the most commonly used agents were birth control pills and/or various nonsteroidal anti-inflammatory agents. At 6 months, hysterectomy was associated with significantly greater improvement (based on quality-of-life and symptom scores) in bleeding, pain, and urinary symptoms. Furthermore, 53% of women randomized to medical therapy crossed over and had a hysterectomy by 18 months following randomization.⁷⁸ Women with fibroids had similar findings compared with women without

fibroids. Clearly, more effective medical regimens for bleeding secondary to fibroids are needed.

Consequences of Untreated Fibroids

Fibroids grow at variable rates prior to menopause but are usually slow-growing. In a longitudinal ultrasound-based study, the average fibroid growth was 0.5 cm/y in diameter, but growth of 3 cm/y in diameter or greater was observed.⁷⁹ Since larger fibroids are more symptomatic,^{13,79} symptoms tend to increase over time until menopause, when fibroids shrink and symptoms lessen because of the lack of menstrual periods and sex steroid stimulation of fibroid growth. Unfortunately, it is difficult to predict when menopause—and symptom relief—will occur in an individual.

Most uterine smooth muscle tumors are benign fibroids. In a study of more than 1300 hysterectomy specimens removed for presumed fibroids in mostly premenopausal women, sarcomas were found in 2 to 3 per 1000 specimens; sarcomas were not more common in the subgroup of women with rapid fibroid growth.⁸⁰ Therefore, rapid growth alone should not be used as the sole indication for surgical removal before menopause. After menopause, significant growth of a presumed fibroid raises suspicion of a sarcoma, and further investigation, if not removal, is warranted.

Future Treatment Options

Because of the responsiveness of the uterus and uterine fibroids to estrogen and progesterone, investigators have studied ways to affect estrogen and progesterone action as a means of controlling symptoms. Gonadotropin-releasing hormone agonists act by down-regulating the secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary gland, ultimately resulting in menopausal-range serum estradiol and progesterone levels, leading to shrinkage of fibroids and a high rate of amenorrhea. This can be helpful in the short term before surgery to allow for correction of anemia secondary to menorrhagia or to change the surgical approach from an abdominal to a vaginal hysterectomy.⁸¹ However, long-term use is limited by menopausal symptoms, bone loss secondary to low estrogen levels, and the high cost of the medication.⁸¹

A strategy to prolong use of gonadotropin-releasing hormone agonists is to give low doses of “add-back” steroids in conjunction with the agonist to prevent bone loss and hot flashes while maintaining the beneficial effects of reduced symptoms from the fibroids. The ideal add-back steroid regimen has yet to be developed and widely accepted.⁸¹ Use of estrogens and/or progestins either does not fully protect against adverse effects or causes fibroid growth and resumption of bleeding problems. Tibolone, a synthetic steroid with mixed androgenic, progestogenic, and estrogenic activity, may have potential for this use but is not available in the United States.⁸²

Other candidate drugs for fibroid treatment include selective estrogen receptor modulators (SERMs), selective pro-

gesterone receptor modulators (SPRMs), and blockers of hormone production, including aromatase inhibitors. In early studies, the SERM raloxifene was shown to reduce uterine and fibroid size in menopausal women but it has not been effective in premenopausal women, who have higher endogenous estrogen levels.⁸³ Aromatase inhibitors that block estrogen production reduced fibroid size and symptoms in preliminary, noncontrolled studies.^{84,85} Long-term use of this class of drugs may be limited by osteoporosis, hot flashes, and the tendency of premenopausal women to develop ovarian follicular cysts.⁸⁶

The SPRM mifepristone (RU 486) was shown to reduce uterine volume by approximately 50% and produced amenorrhea rates of about 65% when used at a dose of 5 to 10 mg/d in women with fibroids.⁸⁷ In this study, mifepristone was associated with development of simple hyperplasia of the endometrium in 30% of women, an adverse effect likely secondary to the actions of estrogen on the endometrium that are unopposed by the antiproliferative effects of progesterone.⁸⁷ However, a recent prospective randomized trial evaluating 5 mg/d of mifepristone found no instances of endometrial hyperplasia in 20 women after 6 months of use.⁸⁸ Furthermore, relative to placebo, women had a significantly improved quality of life, reduced bleeding, and a 50% reduction in uterine and fibroid volume.⁸⁸ Longer duration of use has not been studied, and it is not known how quickly symptoms return after cessation of use. Selective progesterone receptor modulators remain a potentially promising medical therapy for women with symptomatic fibroids.

A new US Food and Drug Administration–approved treatment of uterine fibroids relies on the ability of focused, converging ultrasound beams to generate heat (65°C–85°C) at the focal point, causing coagulative necrosis of tissue. Magnetic resonance imaging, used in conjunction with the procedure, allows for accurate targeting of the focal point and for monitoring tissue temperatures.⁸⁹ The major advantages of this treatment are that it is noninvasive, requiring no surgical incisions, and allows for a very rapid recovery and return to daily activities. Pain during the procedure can be managed with intravenous sedation. Disadvantages are that the technology is not widely available and treatment times can be lengthy (up to 3 hours to treat a 5-cm sphere of fibroid tissue).⁹⁰ In addition, use of focused ultrasound can be limited by the anatomy. In an early study, approximately 40% of potential candidates were excluded because the ultrasound beam would traverse either bowel or bladder and could potentially injure these structures.⁹⁰ Although early outcomes up to 1 year are encouraging, long-term effectiveness and comparative studies are needed before this new technology can be recommended.⁹¹

RECOMMENDATIONS FOR MS P

Ms P's initial evaluation should include a thyroid-stimulating hormone measurement, since hypothyroidism could cause both her fatigue and her menorrhagia, and care-

ful evaluation of her endometrial cavity by either saline infusion sonography or hysteroscopy. She has a thick endometrium on ultrasound and she may have an intracavitary fibroid or polyp that could be relatively easily removed, improving her symptoms. If these test results are normal, a frank discussion about her desires for fertility and about the effects of aging on fertility needs to occur. At age 41 years, Ms P almost certainly has reduced fertility and time is running out. If fertility is still desired after discussion, I would obtain a hysterosalpingogram to evaluate fallopian tube patency, since her previous myomectomy could have caused scarring that results in tubal blockage. I would then recommend repeat myomectomy, as evidence to date favors this over UAE in patients who desire future fertility.⁶⁰ If she does not desire fertility but wants to avoid major surgery and retain her uterus, UAE would be a good option. If she does not desire fertility and wants definitive therapy, I would recommend a hysterectomy.

QUESTIONS AND DISCUSSION

QUESTION: You said that there are data to suggest that [depot medroxyprogesterone acetate] reduces the incidence or problems with fibroids. We used to think that birth control pills stimulated fibroids. I've seen other data suggesting that perhaps women who have been on oral contraceptives have fewer fibroids. Could you comment?

DR VAN VOORHIS: A study in Thailand found a strong inverse association (RR, 0.4; 95% CI, 0.3-0.5) between a history of depot medroxyprogesterone acetate use and risk of surgically confirmed leiomyomata.⁸ A prospective cohort study of African American women also found an inverse relationship between the current use of depot medroxyprogesterone acetate and risk of fibroids, although no consistent patterns were observed for birth control pill use.⁷ Epidemiologic studies on the effect of birth control pills on the incidence of fibroids are mixed, suggesting that use is not a major factor in the development or growth of fibroids.⁶ Longitudinal studies have found that, in most women, existing fibroids do not grow significantly in response to either standard birth control pills or hormone therapy after menopause.^{9,92} From a clinical standpoint, these agents can be used safely in women with fibroids.

QUESTION: What is the relationship between fibroids and fertility? In other words, do fibroids cause the infertility or do fibroids result from infertility? Or are both the results of the same underlying mechanism? And how useful are myomectomies in patients with otherwise unexplained infertility?

DR VAN VOORHIS: Fibroids are seldom the sole cause of infertility, so I always perform a complete infertility workup looking for anything else that may be causing the infertility. Many women with fibroids are fertile and we have no prospective randomized trials comparing fertility in women after myomectomy vs fertility in women with fibroids that

are not removed. Therefore, it is still very debatable what role fibroids have as a cause of infertility. However, retrospective data from in vitro fertilization procedures suggest that fibroids, particularly large fibroids or fibroids that distort the endometrial cavity, adversely affect embryo implantation rates.⁹³ Therefore, if no other cause for infertility can be found, it is reasonable to assume that either a large (>5 cm in diameter) intramural fibroid or a fibroid that distorts the endometrium is adversely affecting fertility, and myomectomy should be considered. Case series suggest that pregnancy rates are high (50%-60%) following myomectomy.⁹³

QUESTION: Often, asymptomatic fibroids are found incidentally on ultrasound or by other imaging. How do we as a medical community avoid overtreatment of these tumors, especially now that we have less invasive treatments available, such as magnetic resonance imaging-guided ultrasound therapy, that work better in smaller fibroids?

DR VAN VOORHIS: I think the key is to educate both physicians and the public about the high prevalence of fibroids and that treatment should be based on symptoms and not just the presence of a fibroid. There is no role for prophylactic treatment of asymptomatic fibroids at this time.

QUESTION: I don't think fibroids are very frequently responsible for pain, although both in medical literature and, certainly, in the lay literature, fibroids are listed as a cause of pelvic pain. What are your thoughts?

DR VAN VOORHIS: The most common presenting symptoms of fibroids are abnormal bleeding and pressure sensations, which may be associated with frequency of urination and, more rarely, bowel symptoms. Pelvic pain, especially chronic pelvic pain, is a much less common presenting symptom. A large population-based study of Italian women found a trend toward a modest increased risk of dyspareunia (odds ratio, 2.8; 95% CI, 0.9-8.3) and noncyclic pelvic pain (odds ratio, 2.6; 95% CI, 0.9-7.6) among women with fibroids detected by ultrasound, although these differences were not statistically significant.²¹ Fibroids can sometimes cause more acute pain because of torsion of a pedunculated fibroid or with ischemia and necrosis that sometimes accompany degeneration of fibroids, especially during pregnancy. However, these situations are rare, and the majority of fibroids are not painful.

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Additional Information: eFigure 1 is available at <http://www.jama.com>.

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