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Foreword

Myomas

William F. Rayburn, MD
Consulting Editor

This issue of the *Obstetrics and Gynecology Clinics of North America*, guest edited by Dr. Aydin Arici, is a comprehensive overview about uterine myomas. Myomas, also known as fibroids or leiomyomas, are the most common solid tumors in the pelvis. Myomas are clinically apparent in 25%–50% of women (especially African American women) and in up to 80% of select populations after careful examination of the uterus.

This issue begins with presentations about the epidemiology, genetic heterogeneity, and cell biology of myomas. These tumors contain varying amounts of fibrous tissue that comprises proliferating and degenerated smooth-muscle cells. Myomas are usually multiple and grow by pushing borders with a pseudocapsule. Degeneration occurs from ischemia when the blood supply can no longer reach the myoma's center. Sarcomatous or malignant degeneration is rare, regardless of the rapidity of tumor growth.

Although very common, myomas are often asymptomatic. Symptoms can include pelvic pressure and urinary frequency or ureteral obstruction from a mass effect. Abnormal bleeding results from either submucous myomas having a thin endometrium over the surface that may not respond normally to hormonal influences or from ulceration or necrosis with direct bleeding. Interstitial fibroids can cause an increase in the surface area of the endometrium as the uterus increases in size, leading to menorrhagia and anemia. Infertility can result from impaired implantation or from occlusion of the cornual portion of the uterine

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tube. Pregnancy complications can include preterm abortion, labor, abruptio, placentae, and dystocia. Fibroids may grow rapidly (especially during pregnancy) and may infarct, leading to severe pain.

The diagnosis of fibroids can be established based on physical examination and diagnostic imaging. Refinement in ultrasonography described here may also be useful to diagnose small submucous fibroids. Laparoscopy may be needed to differentiate a myoma in the broad ligament from a solid adnexal mass.

This issue provides an excellent overview of current options for medical, radiologic, and conservative surgical therapies. Until recently, simple, inexpensive, and safe medical treatment was not possible for most women with symptomatic leiomyomas. Hysterectomy still remains the most common treatment, because it is curative and eliminates the possibility of recurrence. Conservative surgery is now available as alternatives to hysterectomy.

Efficacies of these conservative treatments and the risk of potential problems are delineated in this issue. Although these options may prove to be as effective as a hysterectomy, the number of patients treated at any center is often small, follow-up periods are relatively short, and the overall safety of the procedures has not yet been demonstrated. The authors attempt to describe both safety and efficacy criteria when selecting a surgical alternative to hysterectomy. These alternatives do not remove the myoma entirely, however, and pre-existing leiomyomas may be too small to be detected or may eventually exhibit significant growth, necessitating another procedure.

The outstanding group of international experts in this issue addresses many questions of current clinical interest. For example, in women with leiomyomas who are candidates for surgery, does the use of adjunctive medical treatment or uterine artery embolization result in improved outcomes? For women who are infertile, does removal of myomas increase the pregnancy rate? When are assisted reproductive technologies to be chosen in the presence of myomas? For women who have undergone a myomectomy before pregnancy, does a planned cesarean delivery reduce the added risk of uterine rupture? What is the effect in menopausal women of hormone replacement therapy on leiomyoma growth, bleeding, and pain? And is malignant transformation of myomas a myth or reality?

William F. Rayburn, MD
Department of Obstetrics and Gynecology
University of New Mexico Health Science Center
MSC 10 5580
1 University of New Mexico
Albuquerque, NM 87131-0001, USA
E-mail address: wrayburn@salud.unm.edu

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33 (2006) xvii–xviii

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Preface

Myomas

Aydin Arici, MD
Guest Editor

Uterine myomas are the most common benign tumors in women, affecting 20%–50% of reproductive age population. Myomas cause significant morbidity and are the single most common indication for hysterectomy in the United States, representing a major personal and public health concern worldwide. Recent research on the cellular and molecular biology of myomas has enabled us to understand better the pathogenesis and pathophysiology of this tumor, but more remains to be done. In the clinical arena, novel methods of conservative treatments for myomas have been developed to allow many women to keep their reproductive capacity, and more novel treatments are available on the horizon.

This issue of the *Obstetrics and Gynecology Clinics of North America* is devoted to myomas, covering both recent advances in our understanding of their biology, and an overview of the current options for their medical, radiologic, and surgical conservative treatments. As we learn more about the molecular and cellular biology of myomas, we will be able to develop more innovative treatments. For this issue, an outstanding group of international experts have come together to provide a detailed discussion of basic research and clinical aspects of myomas. I would like to express my gratitude to all authors, who despite their other responsibilities have contributed their time, effort, and expertise to this issue.

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Finally, I greatly appreciate the support of the staff at Elsevier for their outstanding editorial competence. I hope that this issue will serve women and their physicians well.

Aydin Arici, MD
Section of Reproductive Endocrinology and Infertility
Department of Obstetrics, Gynecology, and Reproductive Sciences
Yale University School of Medicine
P.O. Box 208063
New Haven, CT 06520, USA
E-mail address: aydin.arici@yale.edu

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Epidemiology of Myomas

Mark Payson, MD[a,b], Phyllis Leppert, MD, PhD[a,b], James Segars, MD[a,b,*]

[a]*Reproductive Biology and Medicine Branch, NICHD, National Institutes of Health, Building 10, CRC, 1E-3140, 9000 Rockville Pike, Bethesda, MD 20892, USA*
[b]*Department of Obstetrics and Gynecology, Uniformed Services University of the Health Sciences, 8900 Wisconsin Avenue, Bethesda, MD 20814, USA*

Uterine leiomyomas (or fibroids) are a prevalent and morbid disease. Leiomyomas place an enormous health care burden on American women, and disproportionately affect African American women. Despite their prevalence, the disease has remained enigmatic, with the incidence, natural history, and progression incompletely understood [1]. A scholarly examination of the epidemiology of fibroid disease faces five sizeable challenges.

First, is fibroid disease a single entity or more than one disease? It is now appreciated that leiomyoma development is a phenotype featured in several genetic diseases; leiomyoma encountered clinically may not represent a single disease entity. Most obviously, disease progression and outcome might vary between the different types of disease, perhaps in different ethnic groups. The appreciation that there may be different phenotypes of fibroid disease is suggested by recent molecular profiling studies, described later in this article.

Second, there is not a widely accepted, standardized classification system for leiomyomas; fibroids are different sizes and occur in different areas of the uterus. The absence of a scoring system to classify disease makes comparative assessment of disease problematic. The inability accurately to classify disease stage compromises studies of disease epidemiology.

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* Corresponding author. Reproductive Biology and Medicine Branch, NICHD, National Institutes of Health, Building 10, CRC, 1E-3140, 9000 Rockville Pike, Bethesda, MD 20892.

E-mail address: segarsj@mail.nih.gov (J. Segars).

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Third, the incidence of disease (fibroids) varies as women age and with race. If these variables are not taken into consideration or carefully controlled, it is easy to draw false conclusions, or to be misled by the confounding variables that are age- or race-dependent and not an element of the fibroid evolution per se.

Fourth, diagnostic methods used to detect disease vary in sensitivity and specificity, and some are notably operator-dependent. This fact further obfuscates assessment of disease progression and comparison across studies.

Fifth, the incidence of fibroids that are sonographically detectable, but asymptomatic, is remarkably high, and in fact encompasses most American women by the age of menopause. Studies that simply use self-reporting underestimate prevalence of disease in a considerable number of patients with leiomyomas, and tend to draw incorrect conclusions. This form of bias may cause the detrimental nature of fibroids to be overemphasized or symptoms to be assigned incorrectly to leiomyomas. Stated differently, the medical literature is naturally biased toward assignment of clinical conditions to fibroid disease, a problem compounded by the fact that few studies have included appropriate age-matched control groups.

Bearing in mind these formidable obstacles, this article reviews the epidemiology of uterine fibroids. Clues to the etiology of fibroids may be gleaned by identification of individuals at risk and elucidation of risk factors. Furthermore, identification of modifiable risk factors may lead to strategies for prevention.

Prevalence in different populations

An oft cited study from the United States assessed the prevalence of fibroids in a population of patients undergoing tubal sterilization [2]. The prevalence in white women was 9%, and in African American women 16%. Interestingly, only one third of the women who had fibroids diagnosed during their tubal procedure had previously been given a diagnosis of fibroids, indicating that fibroids had either not been detected on previous examinations or that the patients had not reported sufficient symptoms to have been diagnosed. This fact emphasizes that the prevalence of fibroid symptoms reflects a fraction of the overall prevalence of disease.

The best designed studies examining overall prevalence have applied ultrasound diagnosis to a randomly sampled population. In another study from the United States [3] 1364 women 35 to 49 years old were screened by ultrasound. A third of the women had already been given a diagnosis of fibroids, and half of those who had not had a previous diagnosis had ultrasound evidence of fibroids. The cumulative incidence of fibroids by age 50 included most American women, almost 70% for whites and 80% for African Americans. Included in this number is 19% of women who did not have a ‘‘focal’’ fibroid identified, but simply had diffusely heterogeneous echo patterns indicative of fibroids. It is possible that not all of these patients had fibroids, that some had adenomyosis or simply myometrial contractions; however, even if this subset is excluded, uterine fibroids

were still found in most cases. By the age of menopause in America, the presence of uterine fibroids seems to be the norm, not the exception.

The striking increased prevalence of disease in African American women brings into question the incidence of fibroids in populations in Africa, and whether the high prevalence of disease might reflect a genetic predisposition, or conversely diet or other environmental influences. Few studies have specifically addressed this point. In a Nigerian study the number of hospital admissions that could be attributed to fibroids was examined. Although not controlled for the population, 13.4% of new gynecologic admissions in Nigeria were admitted as a direct result of fibroids [4].

Fibroid disease seems to be less prevalent in European populations. In a German study began in 1998 [5], the German Cohort Study, a questionnaire-based survey of women's health among 10,241 women, the incidence of fibroid disease was only 12.7 per 100,000 years. If prevalence is calculated from their numbers, it seems to be surprisingly low at 5%. This does not include, however, an equal number of patients who responded that they were given a diagnosis of "benign tumors of the uterus," which presumably were also fibroids. Including these patients, the prevalence doubles to 10.7%. This reflects the number of women of mean age 39.6 who reported having been given those diagnoses, which certainly underestimates asymptomatic or undiagnosed fibroid burden. Despite these methodologic limitations, the results suggest that fibroid disease may be less common in central Europe.

The Seveso Women's Health Study [6] followed a cohort of women in Italy. In this study of 341 women aged 30 to 60 with a uterus, the incidence of ultrasonographically detectable fibroids was 21.4%. This provides one of the best prevalence estimates for fibroids in a European population because the presence or absence of fibroids was determined independent of symptomatology.

A Swedish study also using ultrasound for detection of disease reported a relatively low prevalence of fibroids [7]. Five hundred fifty-four women aged 25 to 50, all Swedish citizens, were randomly selected from the national population register and asked to join the study; three quarters accepted. Fibroids were diagnosed in 3.3% of 25 to 32 year olds and in 7.8% of the 33 to 40 year olds.

Although not specifically addressing the population prevalence of disease, a Japanese study [8] examined the prevalence of fibroid disease in first-degree relatives of women undergoing surgery for fibroids. Thirty-one percent of women undergoing fibroid surgery reported a first degree relative with fibroids, as opposed to 15% of controls. Despite the limitations of a questionnaire-based survey about relatives' health status, it does provide information about the prevalence of fibroid disease in the Japanese population, and hints at a familial link.

Prevalence in different race and ethnic groups

Studies that have examined prevalence in different racial groups principally have been conducted in the United States. Because of the homogeneous nature

of some of the populations in the samples referenced in the preceding section, it can be inferred that there may be significant differences in disease prevalence between women of different racial and ethnic background. Unfortunately, many reports do not specifically assess the incidence of fibroids between races within their population. In a study comparing prevalence of fibroids as diagnosed by ultrasound or hysterectomy across races only African Americans had an increased risk. Both Hispanics and Asians in the United States had risks similar to whites [9].

Several studies have shown an increased prevalence of fibroids in African Americans [2,3,10,11]. This disproportionate disease burden is manifest in the number of hysterectomies performed on African American women, 75% of which were performed for the indication of fibroids [12]. Studies in the United States revealed an incidence twofold to threefold greater in African American than white women. The likelihood of being diagnosed with fibroids was approximately 3% per year for reproductive-age African American women [10]. In one ultrasound study that confirmed the high prevalence of fibroids in American women [3], there was an increased prevalence in African Americans. Fibroids were diagnosed at a younger age, were more often multiple, and tended to be larger in African Americans, with the cumulative incidence in excess of 80% by age 50.

A carefully conducted case-control study [11] found self-reported African American heritage to be associated with a relative risk (RR) of fibroids of 9.4 compared with white women. The subjects in this study were women being seen for symptoms of fibroid disease and had fibroids confirmed either sonographically or surgically.

Are there different types of fibroid disease?

The literature of fibroid epidemiology treats fibroids as a single disease. Clinically, however, leiomyoma seem to exhibit at least three somewhat distinct phenotypes that although they have not been clearly defined, seem to carry different prognoses. Specifically, leiomyoma (1) may be single; (2) may be multiple and the uterus virtually peppered with multiple leiomyoma of varying size; and (3) may be found in association with adenomyosis, or alone. For example, in an interesting study [3] the diagnosis of fibroids was subcategorized as to whether fibroids were multiple or not. Seventy-three percent of black women had multiple fibroid tumors versus 45% of white women. Analysis at myomectomy suggests that fibroids from African Americans are larger than those from whites [1]. At myomectomy the affected uterus may feature a single tumor, or many tumors that are practically impossible to extirpate.

In some women the tumors are singular, and if removed rarely recur. In contrast in other women a uterus normalized by removal of several tumors may rapidly develop several more tumors within a few months. It is certainly possible that the myometrium of some women is more prone to develop fibroids and once

fibroids develop they may grow more rapidly. Few studies [13] have reported the number of fibroids rather than simply their presence or absence. These markedly different clinical phenotypes of one pathologic condition beg the question: is there more than one type of fibroid disease?

The answer to this question seems to be, yes. Some leiomyoma clearly reflect underlying genetic predisposition to tumor development. For example, several reported genetic syndromes feature leiomyoma development, such as hereditary leiomyomatosis and renal cell cancer, Reed's syndrome, and Alport's syndrome [14–16]. The leiomyoma in such conditions are associated with known mutations, or abnormalities, such as fumarate hydratase in hereditary leiomyomatosis and renal cell cancer [17]. Leiomyoma associated with these rare genetic syndromes are grossly indistinguishable from common leiomyomata, but clearly these leiomyoma do not portend the same risk and disease, because in such a condition as hereditary leiomyomatosis and renal cell cancer, leiomyosarcoma may be a concern. Interestingly, preliminary reports of gene profiling studies suggest that fibroids from at least one syndrome, hereditary leiomyomatosis and renal cell cancer, may not resemble those of common leiomyoma (Mayers C and coworkers, unpublished data).

Recent molecular profiling studies of fibroids lend support to the notion that fibroids may exist as different clinical phenotypes. That these two presentations may represent different types of fibroid disease is supported by gene profiling studies comparing fibroids from African Americans with whites [18]. This observation, coupled with the genetic syndromes mentioned, suggests that fibroids may represent a common smooth muscle response to several different disorders rather than a discrete disease. If this is indeed the case, it is important to elucidate the prevalence of different types of fibroids and the clinical course of the subtypes.

Incidence at different ages and progression

The incidence of pathologically diagnosed fibroids increases steadily with age [19]. At 25 to 30 years the incidence of fibroids is only 0.31 per 1000 women years, but by ages 45 to 50 the incidence has increased 20-fold to 6.20 per 1000 women years. Advancing age increases the risk for fibroids many fold, and mirrors the understanding of the biologic development of fibroids: most grow in time and are expected to be diagnosed in greater numbers in older cohorts. A small sample of patients who had their fibroids followed-up ultrasonographically [20] saw an average growth of 1.2 cm in 2.5 years. The chance of being diagnosed with fibroids increases with age until about 50 years and then declines sharply [8,11].

How quickly fibroids grow or recur was examined in a study of 145 women followed after abdominal myomectomy [21]. The recurrence of fibroids was diagnosed by ultrasound demonstrating fibroids at least 2 cm in diameter. The 5-year risk of recurrence was 62%, with a 9% risk of an additional major surgery,

an important number to be aware of when counseling patients for myomectomy. The recurrence risk was lower in patients with a solitary fibroid, a smaller total uterine size, and those who subsequently had a successful pregnancy.

Preliminary results from the ongoing NIEHS study [22] suggested that any fibroid documented on MRI does grow over time but at variable rates. Notably, no fibroids were seen that regressed during their observations [22]. The disappearance or shrinking seen in other studies [20] may be caused by the imprecise nature of ultrasound examinations, where a fibroid could be incorrectly mapped or other features of the myometrium, such as a myometrial contraction, may be incorrectly scored as a fibroid, which might then later be seen to disappear.

Hormones and fibroids

A case control study of 535 women who developed fibroids from a cohort selected from a family planning clinic found risk factors associated with events that could change estrogen levels [19]. In this study the diagnosis of fibroids was confined to those patients who had surgery to remove them. Oral contraceptive use decreased association with fibroids, with the RR decreasing in a dose-dependent fashion to the duration of oral contraceptive use. In the group with the longest use (>145 months), the risk of fibroids was half that of controls. What can be seen as a dramatic protective effect in these patients, however, can be attributed to the population studied. The patients with fibroids had a more difficult time achieving pregnancy, and would have less time during which they were using contraception. If the analysis had included any type of contraception, rather than just hormonal contraception, it might have shown a similar effect. Other studies [11] also reported a protective effect of oral contraceptives with a RR of 0.2, but the confounders mentioned need to be kept in mind.

Of note, a large study that examined similar factors in 95,000 premenopausal nurses [23] found the only change in risk associated with oral contraceptives was age at first use; women who had first used oral contraceptives between 13 and 16 years of age had a significantly increased risk of uterine fibroids (RR 1.9). This could be attributed to either the known increased incidence of sexually transmitted disease among early initiators of sexual activity, or as a marker for metrorrhagia, which in and of itself could be a uterine irritant. Starting oral contraceptives at a young age could be a marker for other risk factors for fibroids, rather than a cause itself.

Obesity increased risk roughly 18% for each 10 kg increase, whereas two packs of cigarettes a day decreased the risk the same amount. Another study [11] showed an increased risk of 2.3 for fibroids for women in the upper quartile of body mass index. Although higher estrogen levels are present in obesity, one study that examined this variable [24] reported a reduced RR of fibroids in these patients (RR 0.6). This may be attributable to the difficulty of diagnosing fibroids in the obese population rather than a true protective effect, but it does not seem that obesity causes a marked increase in fibroid risk.

Pregnancy and fibroids

Several studies have shown a protective effect of pregnancy on the development of fibroids [2], with parity decreasing the risk of fibroids up to fivefold. These numbers may be deceptively high, however, given the known decrement in fertility attributable to fibroids. If a woman does not have fibroids she is more likely to have been pregnant and delivered a child, and because many of the studies look at parity rather than simply a history of being pregnant, the effect may be inflated even more, because fibroids not only interfere with implantation, but with successful delivery. There is biologic plausibility to the protective effect of progestins on fibroid growth, however, because in the Eker rat the incidence of fibroid disease was reduced with progestins [25].

The confounding effects that subfertility caused by fibroids has on analysis of effect of pregnancy on fibroids is well illustrated in a study examining the risk of fibroids and age at delivery [19]. A diagnosis of fibroids did not change the age of delivery of first children, but did change the age of last term delivery. Having a child later in life was conveyed as being protective, when in fact it may merely illustrate the fact that there was a greater disease burden of fibroids later in life and these women did not have their fertility affected at age19, but fertility was affected at age 38.

Menstrual cycle characteristics

Fibroids are generally associated with an increased risk of heavy menstrual flow or a longer duration of menses [2]. The biologic plausibility was attributed to submucosal fibroids interrupting the normal endometrial development, or the burden of fibroids influencing normal myometrial contractility. Not all studies, however, have shown this relationship. In a cohort of women being followed independent of fibroid risk [6], 73 of who had ultrasonographically detectable fibroids, there was no significant difference in their menstrual cycle characteristics compared with controls. Because by definition these women were not selected for symptoms of fibroids, however, the sample size was not large enough to demonstrate the effect. This illustrates the point that disruption of the menstrual cycle is far from an inevitable outcome in women with fibroids. There is a bias to attribute symptoms to the tumors in women with fibroids.

Hypertension

A recent study demonstrated an intriguing link between diastolic blood pressure and fibroids [26]. In line with theories that show a graded response of diastolic blood pressures to atherogenesis, it was suggested that elevated blood pressure could cause injury or cytokine release in the uterine smooth muscle that

promotes fibroid growth. In a 10-year analysis of more than 100,000 nurses there were 7466 diagnoses of fibroids by ultrasound or hysterectomy. After adjusting for age, race, body mass index, and other factors, an independent risk of diastolic blood pressure was found. Hypertensive women were 24% more likely to report fibroids, and the risk increased with duration of hypertension. The risk for fibroids also increased with the degree of hypertension. For every 10 mm HG increase in diastolic blood pressure, the risk for fibroids increased 8% to 10%. The increased pressure may be affecting uterine smooth muscle, causing damage with a similar mechanism as in vascular smooth muscle and hypertension.

Infection and fibroids

If fibroids may be triggered by myometrial injury as suggested [27], either through ischemia, pressure, or irritation from atherogenic-type mechanisms, such as hypertension, it is logical to inquire about the affect of infection on fibroid development. A case-control study of 318 women [28] that adjusted for hypertension, diabetes, age, ethnicity, body mass index, smoking, and oral contraceptive use, found a positive association with pelvic infection. A history of pelvic inflammatory disease increased the risk of fibroids, with the risk increasing with the number of infectious episodes. A history of three episodes of pelvic inflammatory disease conferred a RR of 3.7. Likewise, a history of *Chlamydia* conferred a RR of 3.2. Sexually transmitted diseases that mainly affected the external genitalia (genital warts and herpes) showed no association. It seems that the intrauterine irritation may contribute to the appearance or growth of fibroids.

Chagas' disease, the result of a parasitic infection endemic to portions of South America, has been reported to lead to an increased risk of various cancers. In an intriguing study [29] it was shown that the incidence of a positive history of Chagas' disease, diagnosed by serology, was significantly higher in women presenting for leiomyoma surgery. Twenty-seven percent of women undergoing fibroid surgery had a serologically documented Chagas' infection versus 16% of controls. When the groups were further analyzed by race, white women with fibroids had a 40% prevalence of Chagas' versus 10% for nonwhite controls. It is known that Chagas' can parasitize the uterine smooth muscle, and this irritation may explain the association observed.

Smoking, alcohol, and caffeine

It has been suggested that cigarette smoking could lower the risk of fibroids because it is associated with lower estrogen levels in some studies. The data are conflicting, with a RR of 1.6 for greater than one pack per day [2] to a decrease in risk (RR 0.7) [19,24]. In the well done Black Women's Health Study follow-

ing almost 22,000 women there was no change in risk associated with tobacco smoking [30].

The Black Women's Health Study was able to demonstrate no change in risk related to caffeine consumption, but did see a small (RR 1.57) increase in risk for more than seven drinks of beer per week. Lesser amounts of beer and other alcohols showed smaller risks but did not reach statistical significance.

Diet and fibroids

One study [31] has specifically addressed the question of dietary influences on the prevalence of fibroids. In an Italian population, 843 women with fibroids were compared with 1557 women without. A diet weighted toward green vegetables was protective (RR 0.5), whereas a higher intake of meats was associated with a greater incidence of fibroids (RR 1.7). Given that diet is an essential component of lifestyle there are multiple confounding factors. This study does suggest, however, that lifestyle and environmental exposures seem to affect the incidence of fibroid disease.

Summary

Fibroids are a prevalent disorder occurring in at least half of American reproductive-age women. In general, the incidence and size increases with age. Most women never attribute or report any symptoms from their fibroids, and because of this the actual contribution of disease to symptoms of pelvic pain, menstrual symptoms, and infertility is poorly understood. The presence of fibroids can lead to multiple and disabling difficulties. Fibroids may cause pain and menstrual bleeding to the point of anemia. Fibroids clearly reduce fertility, increase preterm labor and delivery, and markedly increase the risk for cesarean delivery. Because the incidence varies according to population of interest, fibroids may explain some health disparities in different populations. For example, African Americans have a relatively poor outcome with assisted reproductive techniques compared with whites [32]. Controlling for fibroid disease may explain this disparity, at least in part [33].

Fibroids represent a tremendous public health burden on women and economic cost on society. Strategies to prevent, limit growth, and treat nonsurgically are needed. Fundamental and significant questions remain about fibroid disease, such as whether different clinical disease phenotypes (multiple versus single leiomyomas) contribute equally to symptoms and possess an equal likelihood of disease progression. For epidemiologic assessment of disease, a scoring system is urgently needed. Well-designed, controlled, prospective studies are still needed to define the natural history and correlate the presence of disease with symptomatology in women [34].

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The Genetic Heterogeneity of Uterine Leiomyomata

Melissa K. Lobel, BS, Priya Somasundaram, MD,
Cynthia C. Morton, PhD*

Departments of Obstetrics, Gynecology, and Reproductive Biology and Pathology, Brigham and Women's Hospital and Harvard Medical School, 77 Avenue Louis Pasteur, NRB, Room 160, Boston, MA 02115, USA

Got fibroids? For most women in the third or fourth decade of life, the answer to this question is probably "yes." Pathologic examination of the uterus shows that approximately 77% of women of reproductive age have uterine leiomyomata (UL); however, only 20% to 25% of these women are symptomatic. UL show considerable morbidity, causing medically and socially significant symptoms, such as severe menorrhagia and pelvic discomfort. While a typical menstrual period lasts 4 to 5 days, women with UL often endure periods of 7 or more days. Such severe bleeding can be debilitating in restricting women from engaging in their daily activities, and has been reported to lead to anemia and even blood transfusions in some cases. Women with symptomatic UL can also suffer from urinary incontinence, or rectal tenesmus and constipation, if tumors impinge on the urinary bladder or rectum, respectively [1,2]. Further, UL are associated with reproductive dysfunction, often contributing to infertility and complications in pregnancy. UL are responsible for approximately 2% to 3% of all infertility cases [2], and are present in 1.4% to 2% of all pregnancies [3,4]. Of these pregnancies, 10% develop complications [4], such as spontaneous abortion, premature labor, premature rupture of the membranes, antepartum and postpartum

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* Corresponding author.
E-mail address: cmorton@partners.org (C.C. Morton).

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hemorrhage, postpartum sepsis, breech presentation, and placental abruption, and may require cesarean section [3–8].

Also known as ‘‘fibroids’’ or ‘‘myomas,’’ UL are the most common pelvic tumor in women. Arising from the myometrium of the uterus, UL are benign neoplasms that are histologically seen as well-differentiated, whorled bundles of smooth muscle cells forming distinct nodules. Very rarely, estimated at a rate of <0.1%, do malignancies arise attributed to UL in the form of uterine leiomyosarcomas [2]. The average affected uterus exhibits six to seven UL, which can range in size from 10 mm to over 20 cm [1]. Anatomically, UL are found in intramural, subserosal, or submucosal locations, and tumors sometimes appear as pedunculated or polyploid. Although UL are most commonly found intramurally, submucosal UL are reported to be the most symptomatic [9].

UL are steroid hormone–dependent tumors, with estrogen and progesterone playing an important role in growth and development [10]. Estrogen in particular is believed to be a major growth stimulus for these tumors [11], demonstrated by the fact that UL are only seen postpuberty, grow rapidly during pregnancy, and regress postmenopausally [12,13]. Risk factors for UL, such as obesity and early age of menarche, further support estrogen’s role in UL development, as these elements increase a woman’s overall lifetime exposure to the hormone. In contrast, it was found that childbearing at a later age is inversely associated with the risk of developing UL; this finding is intuitive given that parity decreases estrogen exposure [14]. Despite the growing evidence for estrogen’s effects on UL, however, the role of oral contraceptive pills and hormone replacement therapy in UL growth and development remains controversial [15].

Several recently developed nonsurgical medical therapies are hormone-based, but the traditional treatment for UL is hysterectomy. UL are the most common indication for hysterectomy in the United States, leading to over 200,000 procedures performed annually [16]. By age 60, 30% of women in the United States have had a hysterectomy, and 60% of these surgeries are due to UL [17]. Because UL most often affect women of reproductive age, and hysterectomy is the only definitive treatment for this condition [16], many women must grapple with the emotional implications of surrendering their fertility prior to childbearing. Hysterectomy is also a major invasive procedure with an established mortality of 11 per 10,000 surgeries [18].

Another surgical option for women is myomectomy, which is a more conservative procedure than hysterectomy. Myomectomy serves to remove UL but retain the uterus, thus preserving fertility, and can even be performed during pregnancy. Up to 25% of women have a recurrence of UL postmyomectomy, however, and 10% need a second major procedure within 1 to 10 years [19–21]. Further, myomectomy is more limited anatomically than hysterectomy in that intramural UL are difficult to access by this procedure [22]. Uterine artery embolization on the other hand is particularly useful in the treatment of intramural UL [23]. Although uterine artery embolization is shown to significantly to improve menorrhagia and pelvic pain by 85% and to reduce tumor size by 50% [24,25], the impact on future fertility and pregnancy is unclear [22].

In October 2004, Food and Drug Administration approval was received for MRI-guided focused ultrasound surgery, a noninvasive thermoablative therapy. This procedure is innovative in its ability to target specific UL, and conserves health care dollars by allowing for outpatient treatment and shorter recovery periods [26]. As of yet, however, the procedure is neither widely available nor covered by health insurance.

Although desirable, currently available nonsurgical medical therapies are often ineffective in eliminating UL and preventing recurrence. Gonadotropin-releasing hormone (GnRH) analogue therapy is a Food and Drug Administration–approved drug for UL treatment, but is severely limited in its use. While GnRH is effective as a short-term preoperative treatment by reducing tumor size and bleeding, it can induce menopausal-like symptoms [22]. In addition, discontinuation of GnRH therapy often results in regrowth of UL to their original volume [27]. Other therapies, such as synthetic progestins and oral contraceptive pills, were expected to decrease uterine size and menorrhagia by promoting endometrial atrophy, but these treatments were instead found to stimulate UL growth [28,29].

Because UL have been shown to possess elevated levels of estrogen receptors and progesterone receptors [30], therapies have been developed targeting this characteristic. An antiprogesterone, RU 486, which remains unavailable in the United States, has been found to reduce estrogen receptors and progesterone receptors, suppress UL growth, and produce amenorrhea; the long-term effects of this drug, however, remain unknown [31]. More recent medical therapies have been developed in the form of selective estrogen receptor modulators and selective progesterone receptor modulators. Selective estrogen receptor modulator treatment with raloxifene has been shown to decrease UL size in postmenopausal women, but only is effective in combination with GnRH treatment in premenopausal women [32].

Despite the major public health impact of UL, little is known about the etiology of these tumors. UL currently account for over $1.2 billion health care dollars annually [33], yet research remains grossly underfunded when compared with that of other benign diseases [22]. Nevertheless, epidemiologic, molecular, and cytogenetic research has begun to explore the pathogenesis and pathobiology of UL, uncovering a clinical, pathologic, and cytogenetic heterogeneity in UL tumors. This research suggests a strong genetic component to UL development, and implies the presence of multiple mechanisms of tumor growth.

Epidemiologic aspects of genetic liability

An epidemiologic approach to UL research is essential, as it serves to assess the genetic basis of tumor development. Ethnic predisposition, twin, and familial aggregation studies have all been undertaken to understand the causes of heritability. In addition, other genetic diseases associated with UL have been examined in depth to identify related predisposition genes.

Epidemiologic studies

Ethnic predisposition studies have shown that African American women have a three- to nine-times higher prevalence of UL in comparison with women of other racial and ethnic backgrounds [34]. The Nurses' Health Study confirmed this data, after adjusting for differences between races in such factors as socioeconomic status and access to health care, as well as obesity and parity [35]. African American women have also been shown to have an earlier age of UL diagnosis, higher hysterectomy rate for UL, larger and more abundant tumors, and more severe symptoms. Differences between races in other gynecologic conditions, however, such as menstrual problems and adnexal ailments, are minimal, suggesting a genetic component to UL pathogenesis [35–37].

Familial aggregation studies have examined the clustering of UL within family groups, and further support the heritability of these tumors. A study performed in the United States showed that first-degree relatives of women with UL are 2.5 times more at risk of developing tumors when compared with women without affected relatives. This risk increases to 5.7 for patients with an affected first-degree relative of less than 45 years old [38], thus concluding that UL are more prevalent in families with an early onset of the disease. A similar Russian study echoed this familial aggregation, determining that UL diagnosis is more commonly made when two or more family members have already developed tumors [39].

Twin studies have suggested a genetic predisposition for UL through examination of hysterectomy data, as UL are the most common indication for the procedure. Monozygotic twins have been shown to have two times the correlation for hysterectomy than dizygotic twins, concordant with the degree of their genetic relationship [40]. In addition, a Finnish twin cohort study found that monozygotic twins ($r = 0.31$) had nearly twice the rate of hospitalization because of UL when compared with dizygotic twins ($r = 0.18$) [41], suggesting that severity of the disease is also an inherited factor.

Heritable diseases related to uterine leiomyomata

Examining heritable diseases that include UL as a phenotypic feature of the syndrome is invaluable in determining predisposition genes, especially when evaluating such a nonsyndromic and heterogeneous disorder as UL. In particular, syndromes inherited in a clear Mendelian pattern are useful in gene identification by employing genetic linkage analysis. UL have been associated with Reed's syndrome, Bannayan-Zonana syndrome, Cowden syndrome, and hereditary leiomyomatosis and renal cell cancer (HLRCC) and share a pathogenetic relationship in some instances.

Reed's syndrome, also known as "familial leiomyomatosis cutis and uteri" (MIM150800), is an autosomal dominant trait with reduced penetrance. Females with Reed's syndrome suffer from both UL and cutaneous leiomyomata, the latter of which appear to originate from erector pili muscles [42]. Studies of families

with this disorder suggest that predisposition for UL alone may also be inherited in an autosomal dominant manner, or may possibly be an autosomal-recessive or X-linked dominant trait. None of these patterns of inheritance, however, have yet been clearly demonstrated in UL as a solitary phenotype [43].

Bannayan-Zonana (MIM153480) and Cowden (MIM158350) syndromes are both types of autosomally dominant hamartomatous polyposis disorders that are characterized by lipomas, intestinal hamartomatous polyps, and other nonneoplastic manifestations [44]. Cowden syndrome, however, remains unique in its potentially malignant nature, and carries a high risk of developing breast and thyroid cancers [45]. Since the two diseases involve lipomas and hamartomas, both of which are pathogenetically related to UL, they are important tools in the identification of potential predisposition genes [44].

Several hereditary cancer syndromes have been observed that predispose patients to UL, such as HLRCC, tuberous sclerosis complex, and Birt-Hogg-Dubé syndrome. Interestingly, a genetic linkage has been shown with all three of these disorders and renal cell carcinoma [46]. HLRCC (MIM605839) in particular has been widely studied in relation to UL, and is known to be an autosomal dominant disorder with symptoms including smooth muscle tumors of the skin and uterus and papillary type II renal cell carcinoma [47–49].

Other related syndromes, such as angioleiomyomata and disseminated peritoneal leiomyomatosis (DPL), have also been investigated in the gene discovery quest for UL. Also known as ‘‘angiomyxomas’’ or ‘‘vascular leiomyomata,’’ angioleiomyomata are painful but benign subcutaneous or deep dermal tumors most often seen in the extremities [50,51]. DPL on the other hand is a rare disease in females that involves nodular proliferations throughout the omental and peritoneal surfaces; histologically, DPL is comprised of benign smooth muscle similar to UL [52]. Besides their high degree of symptomatic and histologic similarity, these diseases, in addition to Reed’s syndrome and HLRCC, have shown overlap with UL cytogenetically.

Molecular approaches to deciphering genetic mechanisms

The heterogeneity of UL growth and development has been further established through molecular research. Clonality studies using glucose-6-phosphate-dehydrogenase (G6PD) isoenzyme analysis and those using androgen receptor (*AR*) gene assays have both found that UL are monoclonal-independent lesions, such that multiple tumors from the same uterus arise independently and may have distinct chromosomal abnormalities. These studies have been important in resolving that UL are clonal despite their cytogenetic mosaicism in some cases.

Clonality studies: glucose-6-phosphate-dehydrogenase analysis

UL were one of the original tumor types studied by G6PD isoenzyme analysis and proved by this method to be clonal tumors. One of the initial studies using

this technique involved using polymorphic isoenzymes of X-linked G6PD in independent tumors from seven women heterozygous for this enzyme. It was noted that both A and B type isoenzymes could be found within the same patient, therefore indicating that UL arise independently and are monoclonal [53–55]. Because mammalian females have essentially only one activated X chromosome and only one active *G6PD* allele in each cell, this result was expected for a clonal tumor, such as UL [56]. This method, however, is limited in the number of individuals who qualify for analysis because women must be heterozygous for the G6PD enzyme; this is due to the fact that G6PD isoenzyme analysis is not a particularly polymorphic marker system. Despite these constraints, G6PD isoenzyme studies were essential in displaying a random pattern of inactivation among multiple tumors, proving that multiple tumors within a single uterus arise independently, and establishing the monoclonal nature of UL [53,57].

Clonality studies: AR *gene analysis*

Assays based on the *AR* gene both confirmed and expanded on the G6PD clonality studies. In evaluating the highly polymorphic trinucleotide CAG repeat in the X-linked *AR* gene, this method proved superior to previous studies in expanding informativeness for analysis. Taking advantage of the fact that only one X chromosome is activated in mammalian females, as well as the methylation-sensitive restriction enzyme site upstream of the CAG repeats in the *AR* gene, oligonucleotide primer pairs were made to flank the CAG repeats for DNA amplification. The amplified DNA was then digested with a methylation-sensitive restriction enzyme, such as *Hha*I, in individuals with varying numbers of CAG repeats [54]. Monoclonality was determined in this way by observing a random pattern of X chromosome inactivation among multiple tumors from the same patient, such that individual UL expressed only one of two alleles [58]. If the tumors were instead polyclonal, both maternal and paternal X chromosome products would be found, as either X chromosome could be randomly inactivated [54]. It should be noted that UL growing within close proximity and sampled as a single tumor may appear to be polyclonal, but are in fact two independent, monoclonal neoplasms [59].

Evaluating clonality in 36 UL from 16 patients confirmed these expected results; only one *AR* allele was expressed in each tumor but both alleles were randomly present in the tumor population [54]. The AR assay not only confirmed clonality data from earlier research, but also provided a method in which to study clonality in chromosomally mosaic tumors. Many abnormal UL are in fact mosaic, in that they have a mixture of both chromosomally normal (46,XX) and abnormal cells in the same culture [54,60]. At Brigham and Women's Hospital, approximately 30% of 217 UL tumors analyzed were shown to have abnormal karyotypes coexisting with normal 46,XX cells [61]. Further, by independently establishing clonality and mosaicism in these tumors by the AR assay, it was proven that these two unique attributes occur together in UL. However, examination of clonality data in conjunction with the fact that most UL are chro-

mosomally normal suggests that cytogenetic abnormalities may be secondary to establishment of clonality in tumorigenesis of genetically predisposed cells [15]. Recent research examined the number of CAG repeats in the *AR* gene to ascertain a possible correlation with susceptibility to UL. In 159 women with UL and 129 women without UL, it was found that the number of CAG repeats ranged from 9 to 31 and women with 27 CAG repeats were reported to have a higher risk of UL pathogenesis [62].

Cytogenetic analysis of uterine leiomyomata

Only 40% of UL are karyotypically abnormal, exhibiting nonrandom and tumor-specific chromosomal aberrations [63,64]. Abnormal UL, when compared with normal UL, are generally more cellular, have a greater mitotic index and lower DNA content, and also fail to produce a decrease in DNA content after GnRH agonist therapy [65,66]. Abnormal karyotypes are often observed in chromosomally normal cells, implying that neoplastic transformation occurs in susceptible cells prior to any chromosomal changes [54]. The other 60% of UL are chromosomally normal [67], suggesting that genetic aberrations may be submicroscopic for these tumors; this observation reiterates the belief that cytogenetic abnormalities may be secondary changes in susceptible cells [15,61].

In concordance with the established clinical and pathologic heterogeneity of UL, these tumors also display a heterogeneous cytogenetic makeup. Prompting research examining the genotypic and phenotypic patterns present in UL, this cytogenetic diversity has been observed in the form of various translocations, deletions, and trisomies. The most prevalent types of chromosomal rearrangements found in UL include t(12;14)(q14-q15;q23-q24), rearrangement of 6p21, and del(7)(q22q32). Other less commonly observed cytogenetic abnormalities are rearrangements of 1p36, 10q22, 13q21-22, and of the X chromosome, partial deletion of 3q, and trisomy 12. The variety of these aberrations insinuates that multiple genetic mechanisms exist in UL tumorigenesis, which is in accord with the fact that these tumors are highly prevalent [68]. Cytogenetic studies strive to identify specific genes involved in chromosomal rearrangement of UL, and seek to understand the diverse genetic pathways leading to UL pathogenesis.

Genotypic and phenotypic correlations of uterine leiomyomata

In examining UL with abnormal karyotypes, certain correlations between tumor genotype and clinical phenotype have been observed. Anatomically speaking, only 12% of submucosal UL have chromosomal rearrangements, followed by subserosal UL (29%) and then intramural UL (35%) [69]. However, in spite of their low frequency of karyotypic rearrangement, submucosal UL are highly symptomatic and can cause severe menorrhagia because of their anatomic proximity to the endometrium [70].

Another established association is that between tumor size and type of karyotypic abnormality. UL with del(7) (approximately 5 cm) tend to be around the same size as karyotypically normal tumors (approximately 5.4 cm), but smaller than UL with t(12;14) rearrangements (approximately 8.5 cm). This study sample involved 73 karyotypically normal and 41 karyotypically abnormal tumors, but could only establish a trend rather than statistical significance [67]; however, a clearer pattern emerged among abnormal mosaic and nonmosaic tumors. Many mosaic UL, most with del(7) rearrangements, are smaller in size than their chromosomally normal counterparts, indicating that a loss of genetic material from chromosome 7 may impair UL growth [60]. It should be noted, however, that larger UL are more likely to be chromosomally abnormal than smaller UL [67].

Thus far, no correlation has been established in UL between type of cytogenetic aberration and patient age or parity [71]. However, future analysis of the relationship between genotype and phenotype in these tumors seeks to explore these areas further, as well as possible associations with race, ethnicity, fibroid recurrence, age of onset, and responsiveness to GnRH agonist therapy [56,61].

The t(12;14) subgroup

Twenty percent of UL with karyotypic rearrangements present as t(12;14)(q14-q15;q23-q24), making it the most common chromosomal translocation in these tumors (Fig. 1A) [72]. Most chromosome 12 translocations in UL involve chromosome 14 as a partner, a trait almost unique to this type of mesenchymal tumor, although chromosomes 2, 4, 22, and X have also been observed in these translocations [73]. Although this was the first cytogenetic aberration found to be associated with UL [72], the 12q region has long been established as a chromosomal anomaly in other mesenchymal tumors, such as angioleiomyomata [74], breast fibroadenomas [75], endometrial polyps [76], hemangiopericytomas [77], lipomas [78], pulmonary chondroid hamartomas [79], salivary gland adenomas [80], and lipoleiomyomas [81]. The implication of this region in so many mesenchymal tumors suggests that this area contains critical genes in tumorigenesis, and led to the focus on 12q15 in the first positional cloning projects used to locate genes involved in UL formation [61].

In pursuit of positional cloning data for chromosome 12 at the q15 breakpoint, a high-density physical map was developed. A yeast artificial chromosome was then identified by fluorescence in situ hybridization (FISH) analysis on tumor metaphase chromosomes. This yeast artificial chromosome, 981f11, bridged the translocation breakpoints in UL, pulmonary chondroid hamartomas, and lipomas and was crucial in pinpointing the specific area on chromosome 12 likely to contain genes critical in the development of these tumors [81]. A high-mobility group (HMG) gene, *HMGA2* (previously known as *HMGIC*), was mapped to the yeast artificial chromosome clone and became an attractive potential candidate gene in UL pathogenesis [82]. A homologous gene in mice on chromosome 10, *Hmga2* (previously known as *Hmgic*), was previously implicated in cell

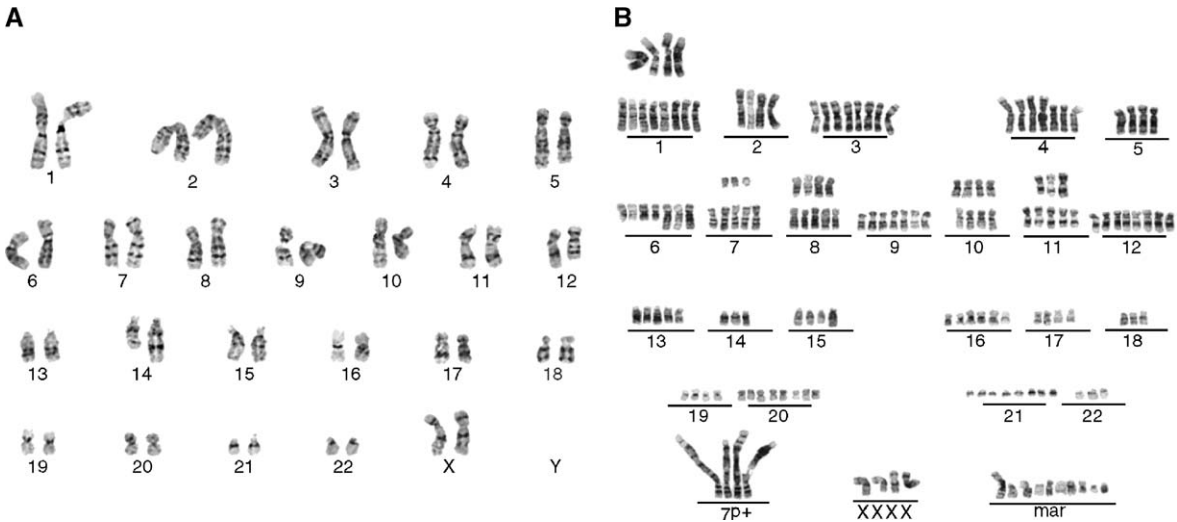

Fig. 1. Comparison of cytogenetically abnormal UL karyotype and leiomyosarcoma karyotype. (*A*) A t(12;14)(q14-q15;q23-q24), the most common translocation in UL, has been shown to result in elevated expression of *HMGA2*. (*B*) Uterine leiomyosarcomas are karyotypically more complex and more genetically unstable than UL.

proliferation and differentiation of mesenchymal tissues [83], pointing to the possible role of *HMGA2* in human mesenchymal tumor development; this is even more significant with the knowledge that 96% evolutionary conservation exists between mouse and human homologs [84]. A large gene with a large target for rearrangement, *HMGA2*'s involvement in chromosome 12q15 rearrangements has since been confirmed by FISH studies and molecular experiments on mesenchymal tumors [82,85].

HMGA2 codes for an architectural factor that is part of the heterogeneous HMG family of nonhistone DNA binding proteins [84]. Studies have indicated a relationship between elevated *HMGA2* expression and cellular proliferation, with in vitro experiments suppressing *HMGA2* expression and then observing a reversal of the tumorigenic phenotype in conjunction with inhibition of cellular transformation [86–88]. Structurally, *HMGA2* encodes three DNA binding motifs that includes AT hooks, regions that have been identified as having a crucial role in gene activity [84]. Several possible mechanisms of *HMGA2* dysfunction exist, and intragenic rearrangements can lead to disruption of regulatory sequences; however, most t(12;14) abnormalities in UL are caused by extragenic rearrangements of *HMGA2* [44,85].

To assess if dysregulation of *HMGA2* is a factor in tumor growth in a subgroup of UL, a Northern blot was performed on RNA from uncultured tissue of five UL with t(12;14) rearrangements and their normal matched myometrium. Gene expression was observed in four of the UL and none of the matched myometrium. *HMGA2* expression has also been noted to be elevated in UL with t(12;14) rearrangements when compared with karyotypically normal tumors [44].

Because most t(12;14) rearrangements occur outside of the *HMGA2* coding region, the entire gene is moved from existing "normal" regulatory regions to novel ones. FISH analysis of over 24 UL showed nearly all breakpoints mapping 10 to 100 kilobase (kb) upstream or 5′ of *HMGA2*, with a few UL exhibiting breakpoints mapping 3′ of the gene; all, however, left the coding region of *HMGA2* intact [44]. The exact molecular mechanism(s) involved in *HMGA2* dysregulation in UL remain unclear, although formation of fusion mRNA transcripts, protein truncation, and disruption of *HMGA2* regulatory sequences have all been observed in chromosome 12 translocation studies in UL and other benign mesenchymal tumors [61]. In one such case study, an 8-year-old boy with multiple lipomas presented with a pericentric inversion of chromosome 12, inv(12)(p11.2;q14.3), implicating *HMGA2* and exhibiting the first known constitutional rearrangement of this gene. Further clinical and genetic analysis of this unique case may provide clarity as to the role and mechanisms of *HMGA2* in human growth and development, as well as in benign mesenchymal tumorigenesis [89].

Although region 12q15 and *HMGA2* have been thoroughly studied, the genes on chromosome 14 implicated in t(12;14) rearrangements remain more elusive. Since the breakpoint region on chromosome 14 was initially identified, mapped, and cloned to q24 [90,91], several genes have been proposed to be involved in this translocation including the estrogen receptor β gene (*ESR2*) and *RAD51L1*

(also known as *RAD51B*, *hREC2*, and *R51H2*). Located on the long arm of chromosome 14 (14q23-q24) approximately 2 megabase (Mb) from the t(12;14) breakpoint, *ESR2* was considered as a potential candidate gene because of the responsiveness of UL growth to estrogen. However, expression analysis failed to indicate any difference in *ESR2* transcription levels between UL with and without t(12;14) rearrangements, making the *ESR2* gene unlikely to have a direct role in UL pathogenesis [92–94].

RAD51L1, on the other hand, has been found to be rearranged in some t(12;14) UL cases, albeit infrequently [44]. Also, mapping to chromosome bands 14q23-q24, *RAD51L1* is involved in DNA recombination repair, cell proliferation, cell cycle progression, and apoptosis [95,96], all pointing toward a possible role in tumorigenesis. Although fusion transcripts are rarely found in UL with t(12;14) rearrangements due to the extragenic nature of the breakpoint, fusion transcripts of *RAD51L1* and *HMGA2* have been observed in some t(12;14) UL. FISH analysis and reverse transcriptase polymerase chain reaction have both been used in trying to determine the expression of *HMGA2-RAD51L1* and *RAD51L1-HMGA2* fusion transcripts in UL cells, but the pathobiologic significance of this fusion is yet to be elucidated [97]. Partner genes for *HMGA2* other than *RAD51L1* have been shown in four UL, but not within the established 14q23-q24 breakpoint. These include *COX6C* at 8q22-q23 [98], *ALDH2* at 12q24.1 [99], *HEI10* at 14q11 [100], and the 3′ *RTVL-H* gene on chromosome 12 [101]. Although their exact role is unknown, it is possible that these genes are part of alternative translocations involving chromosome 12 or are part of more complex translocations involving both chromosomes 12 and 14 [71]; regardless, the genes on chromosome 14 involved in t(12;14) translocations merit further investigation.

The 6p21 rearrangement subgroup

Rearrangements of chromosome 6 at band p21 occur in less than 10% of karyotypically abnormal UL. Typically, these rearrangements involve translocations with chromosomes 1, 2, 4, 10, and 14, and specifically have been observed as t(1;6)(q23;p21), t(6;14)(p21;q24), and t(6;10)(q21;q22) [64,102–106]. It should be noted that rearrangements are rarely seen in UL between band 6p21 and the same region of chromosome 14 implicated in t(12;14) translocations. Other benign mesenchymal tumors, such as lipomas, pulmonary chondroid hamartomas, and endometrial polyps, also exhibit 6p21 rearrangements, and at a much higher frequency than UL; in particular, these aberrations most often appear as t(6;14) translocations with band 14q23-q24 involved as in UL t(12;14) rearrangements (Fig. 2A) [106–112].

Another HMG gene, *HMGA1* (previously known as *HMGIY*), has been identified as residing in band 6p21. Part of the same family as *HMGA2*, *HMGA1* is also an architectural factor gene coding for an HMG protein. After *HMGA2* was identified as having an association with t(12;14) UL, altered expression of *HMGA1* was recognized as having a role in UL with 6p21 rearrangements. This role was confirmed through FISH analysis, in which metaphases from a 46,XX,

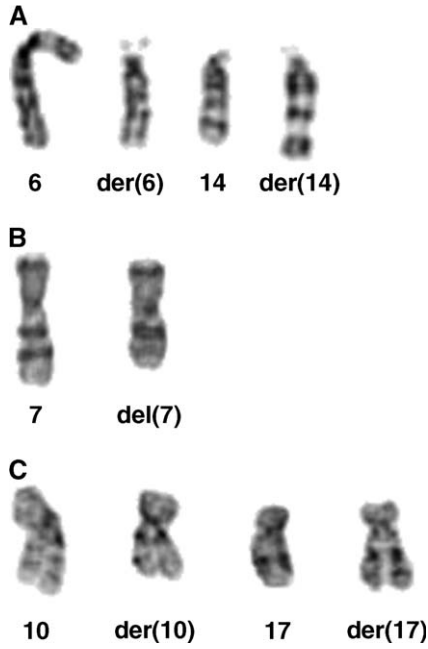

Fig. 2. Karyotypic representation of specific chromosomal aberrations in UL. (*A*) t(6;14)(p21;q24) has been observed in UL and other mesenchymal tumors, and implicates *HMGA1* at band 6p21. (*B*) Tumors with del(7)(q22q32) abnormalities are less common and generally smaller in size than tumors with t(12;14) translocations. (*C*) A minor cytogenetic subgroup of UL, t(10;17)(q22 ~ q24;q21 ~ q22), has been observed in a subset of tumors and involves the *MORF* gene at the 10q22 breakpoint.

inv(6)(p21q15) UL showed hybridization signals at 6p21 and 6q15 corresponding to a split in the clone containing *HMGA1* [113,114]. Electrophoretic mobility shift assay was also used in analysis of *HMGA1* expression in UL with 6p21 rearrangements, and elevated binding activity was detected in 9 of 16 UL examined. In contrast, no *HMGA1* activity was detected in any matched myometrial tissue [15]. Other research, however, has indicated some level of *HMGA1* expression in karyotypically normal UL, in karyotypically abnormal UL with rearrangements other than 6p21, and in matched myometrium, suggesting wider expression of *HMGA1* than *HMGA2* [68].

Comparison of HMGA2 *and* HMGA1

Although *HMGA2* and *HMGA1* are similar structurally and mechanistically, both contributing to the development of UL when disrupted or dysregulated, they differ in their expression patterns, function, and means of regulation. In a study of 17 UL, none showed both *HMGA2* and *HMGA1* expression, and expression of neither gene was observed in some UL; this indicates not only that the HMG proteins play a similar role in UL pathobiology, but also that another related gene

may exist that serves a parallel function [15]. The highest level of both genes is seen in tumor cells and in normally developing embryonic tissue, although *HMGA2* has been detected at low levels in adult kidney and lung tissues and the less restricted expression pattern of *HMGA1* shows low levels of the gene in many normal nonproliferating adult tissues [115,116]. This may suggest a more diversified role for protein HMGA1 beyond serving solely as a proliferation factor [56].

The HMG proteins, and specifically the HMGI proteins HMGA2 and HMGA1 encoded by *HMGA2* and *HMGA1*, respectively, are chromatin architectural and DNA-binding factors that are hypothesized to play a role in genomic stability [117]. By binding to the minor groove of AT-rich DNA through the AT hook, these proteins affect gene activity through various protein-protein and protein-DNA interactions [118,119]. Specifically, DNA conformation is modulated and access to transcription factors to target genes is regulated, although the proteins themselves appear to have no transcriptional activity. In general, HMGA2 and HMGA1 serve as proliferation factors in normal growing tissues, particularly those of mesenchymal origin, and also influence a variety of other cellular processes, such as differentiation, growth, and apoptosis [120,121]. Although it has been firmly established that the HMG proteins HMGA2 and HMGA1 play a role in UL pathogenesis, their exact function is yet to be determined; it remains unclear if binding of the HMG family transcription factors serves to induce gene expression or if binding prevents activation of tumor suppressor genes [122].

The del(7q) subgroup

Occurring in approximately 17% of karyotypically abnormal UL, del(7)(q22q32) is an interstitial deletion of chromosome 7 that usually occurs in mosaic UL with 46,XX normal cells (Fig. 2B) [60,123–125]. Although del(7)(q22q32) and translocations involving 7q22q32 have been observed in other mesenchymal tumors, such as lipomas and endometrial polyps, these aberrations are most commonly found in UL [76,124,126,127]. Translocations involving 7q22 are infrequently witnessed in UL relative to deletions, although their existence not only further implicates this region as being involved in UL pathogenesis but also serves as a valuable investigative tool in exploring predisposition genes on chromosome 7 [124]. The del(7q) abnormalities have also been seen in patients with primary acute nonlymphocytic leukemia (7.6%), myelodysplastic syndrome (19%), secondary acute myelocytic leukemia (26.8%), and secondary myelodysplastic syndrome (41%), and are often considered a poor prognostic factor associated with limited remission and resistance to therapy [128]. UL and other benign mesenchymal tumors with the same aberration, however, do not exhibit severe clinical features, possibly indicating that the deletion breakpoint is tissue specific or molecularly heterogeneous [61].

Of note is the fact that UL associated with del(7)(q22q32) abnormalities are smaller when compared with t(12;14) translocations, which may be caused by a

tumor suppressor gene present at 7q22 involved in regulating cell growth. Further, tumors with this deletion often suffer a loss of chromosomally aberrant cells in culture, suggesting tumor instability and again pointing to the possible presence of a tumor suppressor gene [60,67,117]. The del(7)(q22q32) abnormalities can be present alone or in conjunction with t(12;14) rearrangements and, as opposed to tumors with only del(7)(q22q32), UL with both aberrations are stable in culture and exhibit *HMGA2* expression. This suggests that the genes involved at 7q22q32 may not be essential in UL pathogenesis and that del(7)(q22q32) may be an early genetic event in UL evolution [60,122,129,130].

Mapping projects of the del(7q) region have been successful in narrowing down the breakpoint from q11.23-q36 to q22-q32, an area of less than 500 kb, although it remains difficult to isolate UL-specific genes because the region of focus still has a high density of genes [123–125,131–134]. FISH analysis has delimited a critical 2- to 3- Mb area on band q22, and recent molecular analysis has further identified a 10-cM (centimorgan) critical region on 7q22 [135–138]. Although further research strives to narrow the critical region on chromosome 7 to a 4-cM area [139], 7q22 can presently be said to be involved in growth and development for a subset of UL.

Specific gene discovery remains elusive in this chromosomal band, however, and no genes have as yet been identified as being involved in UL development for those tumors with del(7q) aberrations [61]. Genes located in 7q22 that are potentially involved in UL tumorigenesis include *CUTL1* (transcriptional repression), *ORC5L* (DNA replication), *PAI1* (hemostasis and smooth muscle cell and adipocyte migration), *PMS218* (DNA mismatch repair), *COL1A2* and *PCOLCE* (collagen metabolism), and *DLX5* and *DLX6* (developmental processes) [123,140–143]. *DOCK4*, a tumor suppressor gene mapping to 7q22-q31, has also been identified as a potential candidate gene and may provide a large target for deletion or mutation similar to *HMGA2* [144]. Although UL with chromosome 7 deletions have shown loss of heterozygosity or reduced gene expression of *CUTL1*, *ORC5L*, *PAI1*, and *PCOLCE*, no consistent gene deletions have been observed [145–147].

Chromosome 1 rearrangements and fumarate hydratase

Rearrangements of chromosome 1 often involve ring chromosome formation, such as r(1)(p34q32), although translocations t(1;6)(q23;p21) and t(1;2)(p36;p24) have also been observed. Ring chromosomes are usually only found in combination with other cytogenetic aberrations, although as such may be considered to be secondary changes in karyotypically abnormal tumors [148–152]. Interestingly, a member of the HMG gene family located on chromosome 1 at p35, *HMGI7*, was found to be deleted in a UL with a ring chromosome; however, a deletion implies that elevated expression of *HMGI7* does not play a role in UL development but instead possibly contributes to tumor formation through alternative mechanisms [153]. Other UL have shown nonrandom rearrangements at 1p36 [154] or a deletion of much of the short arm of chromosome 1 along

with monosomy 19 or 22 [155]. In addition, a recently discovered subset of UL was shown to contain chromosome 1 deletions exhibiting transcriptional profiles parallel to those of leiomyosarcomas [156]; this suggests that leiomyosarcomas may arise from a specific subset of UL [22], although further investigation and comparison of the molecular events leading to UL and leiomyosarcoma development is necessary. Karyotypes of the two tumors, however, are distinctly different, with leiomyosarcomas exhibiting much more complex chromosomal abnormalities than those of cytogenetically aberrant UL (Fig. 1A, B).

More attention has recently been put on rearrangements of chromosome 1 at bands q42-q44 in UL because of the identification of the *FH* gene in that region as a pathogenetic factor in both HLRCC and Reed's syndrome [49,157,158]. *MCUL1* has also been identified as a predisposing gene for Reed's syndrome in the same bands at 1q42.3-q43, although the region as a whole has seldom been observed to be involved in nonsyndromic UL cytogenetic abnormalities [47,159,160]. FISH analysis has shown loss of function of *FH* in some UL with 1q42 rearrangements, however, indicating that mutations of this gene, including protein-truncating deletions, large germline deletions, missense mutations, and in-frame deletions, may be important in the development of a subset of UL [71,158]. A housekeeping gene coding for an enzyme in the citric acid cycle, *FH* is important in energy metabolism and also appears to act as a tumor suppressor [48,159]. Aberrations of *FH* have thus far rarely been seen in patients with nonsyndromic UL, as shown by an analysis of 797 karyotyped ULs in which only six 1q42-q44 rearrangements (approximately 0.008%) were observed; further, *FH* mutations were only observed in UL of white women [158,160].

Other research examined 123 families with at least one affected sister pair, and performed linkage analysis on patient DNA to evaluate the role of *FH* mutations in predisposition of UL. This analysis confirmed the involvement of *FH* in a subset of nonsyndromic UL, and also found evidence suggesting earlier age of onset of UL is correlated with *FH* gene mutations. Because of the limited statistical power of this study, however, evaluation of a larger sample and use of second-stage markers closer to or within *FH* could more definitively determine if this gene serves as a predisposition factor for UL [158]. Another recent study used direct DNA sequencing analysis to screen for *FH* germline mutations in 21 patients with HLRCC and their families, while also evaluating the clinical presence of renal tumors, cutaneous leiomyomata, and UL. *FH* germline mutations were detected in 100% (21 of 21) of the families, with 62% (13/21) exhibiting renal cancer and 76% (16/21) displaying cutaneous leiomyoma varying in severity; UL were observed in 100% (22 of 22) of female *FH* mutation carriers in 16 families [161].

Cytogenetic characteristics of heritable diseases related to uterine leiomyomata

Because of the proven benefits of comparing UL with related Mendelian disorders, examination of some cytogenetic characteristics of diseases, such as

Reed's syndrome, angioleiomyomas, and DPL, may serve to provide clues in UL gene discovery. A possible locus of interest has been identified on the short arm of chromosome 18 in a Reed's patient, with the specific chromosomal aberration observed between chromosomes 9 and 18, resulting in partial trisomy 9p and partial monosomy 18p [162]. Angioleiomyomas have demonstrated a possible cytogenetic relationship to UL in the presence of tumors with abnormalities, such as del(6p) [163] or aberrations of the X chromosome [164,165]. Of particular interest was one angioleiomyoma exhibiting t(8;12)(p12;q15), because akin to many UL, the region 12q15 was implicated and *HMGA2* expression was altered [166]. X-inactivation studies of DPL have shown the pathogenesis of the disease to be parallel to that of UL [52]; one tumor showed t(7;18)(q22;p11.3), important because of the observation of similar 7q22 aberrations in UL, whereas another showed an addition to the long arm of chromosome 12, potentially affecting *HMGA2* expression [162].

Minor cytogenetic subgroups in uterine leiomyomata

Less common karyotypic abnormalities found in UL include those of chromosomes X, 3, 10, 13, and trisomy 12 [148,154,167–171]. Although the long and short arms of chromosome X can both be rearranged, the region Xp11-p22 appears to be preferentially involved [153]. This region has, in fact, been shown to contain an *HMGA1*-like sequence, *HMGIYL1*, but further assessment is needed of potential aberrant expression of this gene in UL [172]. Specific aberrations that have been observed include del(X)(p11.2), t(X;12)(p22.3;q15), -X, der(5)t(X;5)(p11;p15), del(X)(q12), del(X)t(X;3)(p22.3;q11.2), and inv(X)(p22q13) [133,167,173–176].

As for chromosome 3, rearrangements can occur alone or with rearrangements on other chromosomes. Insertions, long and short arm deletions, and translocations with chromosome 7 have all been found in UL, and specifically appeared as ins(2;3)(q31;p12p25), del(3)(p14), del(3)(q24), and t(3;7)(p11;p11) [176–178]. Chromosome 10 aberrations occur in approximately 5% of karyotypically abnormal UL, with most rearrangements appearing as translocations between 10q22 and chromosomes 4, 6, or 12. Deletions, such as del(10)(q22q24), however, have also been observed in UL as has monosomy 10. No specific candidate gene on chromosome 10 has yet been found to contribute to UL pathogenesis, but two tumor suppressor genes, *PTEN/MMAC1* at 10q23.3 and *DMBT1* at 10q25.3-26.1, both map to the long arm of this chromosome [169,177,178]. In addition, 10q22 breakpoints were recently found within gene *MORF* in four UL, with three of the tumors exhibiting a t(10;17) (q22~q24;q21~q22) translocation (Fig. 2C) [179].

Aberrations of the long arm of chromosome 13 have been observed in a subgroup of UL and in lipomas, whether alone or in conjunction with other rearrangements [61,155]; it is thought that deletions of 13q as the sole abnormality may play a primary role in the formation of some UL [63,170,180]. While deletions such as this generally result in a loss of gene expression,

trisomies, such as trisomy 12, usually increase gene expression because of an elevated gene dosage [61]. For this reason, the presence of an extra copy of chromosome 12 may increase the level of *HMGA2* and increase the gene product that is involved in UL development [64,68].

Future direction of uterine leiomyomata research

The future path of UL research seeks to continue exploring the epidemiologic, molecular, and cytogenetic aspects of the disease as well as employ new technology to expand knowledge about the genetic pathways and mechanisms of UL. Epidemiologic research strives to study women with UL and their similarly affected first-degree relatives to more efficiently locate the genetic loci involved in tumorigenesis [117]. In a study underway at the Center for Uterine Fibroids in Boston, Massachusetts (www.fibroids.net), affected sister pairs are currently being analyzed for identification of predisposition genes; the approach is a genome-wide screen examining known polymorphic markers in the genome. In addition, further study of patients with diseases related to UL, such as Bannayan-Zonana syndrome and Cowden syndrome, is also desirable, as these pathogenetically related disorders may give insight into the molecular mechanisms of UL development [61]. Another molecular pathway that merits examination is that of leiomyosarcomas, followed by an analysis of what differentiates this malignant tumor from its benign counterpart [15].

Many different angles exist in approaching future cytogenetic research of UL, including examination of the exact role of *HMGA2* and *HMGA1* in UL pathobiology, evaluation of the significance of t(12;14) and del(7q) appearing both together and independently, identification of candidate genes on chromosomes X, 3, 10, and 13, and performance of linkage analysis on the candidate region of chromosome 1 important in HLRCC and Reed's syndrome in nonsyndromic UL [56,61,68]. Novel technologic approaches will no doubt be available for use in pursuit of these research endeavors, and a number of studies using transcriptional profiling have been performed [68]. This multigene approach to gene identification has only been made possible with the use of data from the Human Genome Project, and UL are excellent candidates for this type of analysis because of the ability to control for environmental and hormonal influences by obtaining multiple tumors from the same patient [61,68]. Protein analysis is another potential direction for research through proteomics, an expanding field used to relate gene expression to protein function, and specifically mass spectophotometry. By forming protein arrays and making profiles of the proteins present in diseased and healthy tissues, mass spectophotometry allows for analysis of protein expression and function in UL [181,182]. Animal models, such as mice, guinea pigs, and Eker rats, have been widely used in past UL studies, but problems, such as inefficient production of tumors or the production of tumors histologically different from human UL, have limited this venue for research [183–185].

Summary

Research investigating the genetics of UL has already been successful in gathering epidemiologic evidence for heritability, establishing the clonal and mosaic nature of these tumors, correlating genotypic and phenotypic characteristics, defining cytogenetic subgroups, and identifying specific genes involved in tumorigenesis. Although UL are known to be benign tumors, the impact they have on the lives of so many women can only be described as ''malignant''. For this reason, continuing the quest to ascertain the genes, functions, and mechanisms integral to UL development is absolutely imperative. Genetic tests

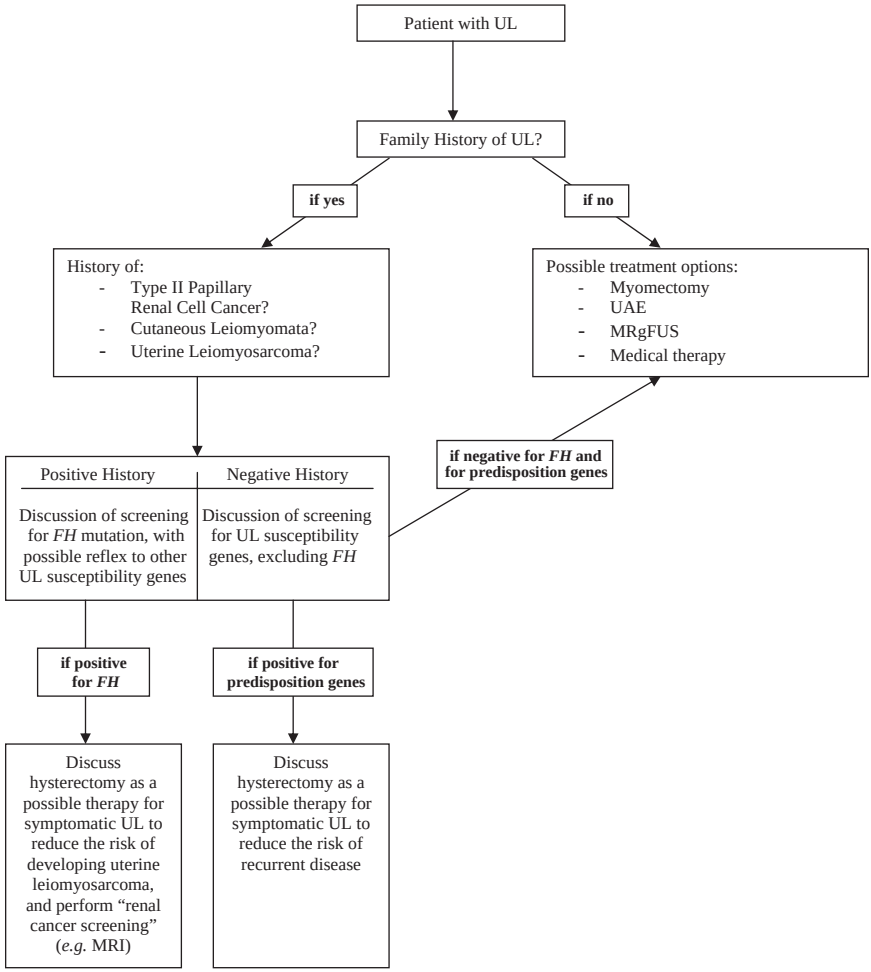

Fig. 3. Proposed schema for management of patients with UL, incorporating various treatment options based on family history of the disease and subsequent genetic testing. MRgFUS, MRI-guided focused ultrasound surgery; UAE, uterine artery embolization; UL, uterine leiomyomata.

for personalized medical management of women with fibroids is at the threshold for providing the most appropriate treatments (Fig. 3), and combined with developing less invasive therapies portends a brighter future for a major health problem for women.

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Cellular Biology of Myomas: Interaction of Sex Steroids with Cytokines and Growth Factors

Ibrahim Sozen, MD[a,*], Aydin Arici, MD[b]

[a]*Department of Obstetrics and Gynecology, Anadolu Health Center, Anadolu CAD No: 1, Cay.rova mevkii, Gebze, 41400 Kocaeli, Turkey*
[b]*Division of Reproductive Endocrinology, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA*

Uterine leiomyomata are the most common benign tumors in women of reproductive age, clinically diagnosed in 20% to 30% of women and established at autopsy in an additional 20% to 30% of women [1]. Growth of these tumors is believed to depend on ovarian hormones; however, in vitro studies in human tissues aiming to demonstrate a direct growth-promoting action of ovarian hormones has shown inconsistent or indirect results. This suggests the presence of intermediate elements, such as cytokines and growth factors, through which the ovarian hormones may be exerting their growth-stimulatory effects on leiomyomas. Estrogen and progesterone may regulate gene expression of these cytokines and growth factors, which in turn modify the transcription of other genes. The result of this abnormal production of cytokines and growth factors may be an increase in cell proliferation, accumulation of extracellular matrix (ECM), or a combination of these phenomena.

More recently, another potential mechanism, decreased apoptosis, was proposed by Matsuo and coworkers [2], who found that Bcl-2 protein, an apoptosis-inhibiting gene product, was abundantly expressed in leiomyomata relative to that in normal myometrium. In this study, Bcl-2 protein expression in leiomyoma cells was up-regulated by progesterone, but down-regulated by estradiol. The same group reported up-regulation of expression of proliferating cell nuclear antigen (PCNA) in leiomyomas by progesterone and estradiol. They also showed [3] that gonadotropin-releasing hormone antagonist (GnRH-a) cetrorelix down-regulates PCNA and up-regulates apoptosis.

* Corresponding author.
E-mail address: ibrahim.sozen@anadolusaglik.org (I. Sozen).

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This article reviews the current evidence pointing out the pivotal roles of cytokines and growth factors in the pathophysiology of leiomyomata at the cellular level, updating a previous review published in 2002 [4]. First discussed are the two most common mechanisms involved in the pathogenesis of leiomyomata, and then reviewed are the individual growth factors and cytokines that have been implicated in leiomyoma.

Cell proliferation

Leiomyoma, like myometrium, mainly consists of smooth muscle. Unlike the quiescent myometrium, however, leiomyoma exhibits elevated rates of mitotic activities and S phase fractions [5,6]. At least one mechanism responsible for leiomyomas undergoing extensive enlargement is the increased rate of cell proliferation.

The important observation by Kawaguchi and coworkers [5] that the mitotic activity of leiomyomas rises at the beginning of the luteal phase and remains high until menses, points to the pivotal role of progesterone in the cellular proliferation of these tumors. Lamminen and coworkers [7] studied the same proliferation activity through the expression of PCNA. They, too, demonstrated that leiomyomas proliferated most actively during the luteal phase of the cycle.

Through in vitro studies using PCNA, a study published in 1998 confirmed that progesterone and estradiol up-regulate the cell-proliferating activity in leiomyoma cell cultures [8]. This finding was also reported earlier by Cramer and coworkers [9], who used other in vitro methods. Agreeing with this pattern of hormonal regulation is the report that leiomyomata from women who have received GnRH-a demonstrated lower cellularity [10]. Additionally, leiomyomas showed significantly higher mitotic activity in women treated with progestins compared with women not treated with steroid hormones [11]. Finally, regression of leiomyomata in response to the antiprogesterone mifepristone was reported, but it is not known whether regression was the result of the decreased cell proliferation.

Other clinical and in vitro studies argue with the reports that indicate a growth-promoting role for progesterone in leiomyoma. Two clinical studies suggested that treatment with high-dose progestin could cause a decrease in the size of the uterus in women with leiomyomas, although it was not determined whether this decrease in size was caused by decreased cellularity [12,13]. Similarly, two case reports have described the regression of pulmonary nodules of so-called ‘‘benign metastasizing leiomyoma’’ in response to high-dose progesterone [14,15]. Kawaguchi and coworkers [16], the same investigators who observed the increased mitotic activity of leiomyoma cells during the luteal phase, found that in cultures with media containing progesterone, both leiomyoma and myometrial smooth muscle cells failed to increase in number.

The overall evaluation of all these studies suggests that progesterone (and possibly the up-regulation of progesterone receptors by estrogen) plays a sig-

nificant role in the cellular proliferation of leiomyoma. Because the evidence for a direct mitogenic action of progesterone is incomplete, however, one may conclude that progesterone probably exerts its action by elevating the expression of mitogenic cytokines and growth factors in leiomyomas. This hypothesis is consistent with the autocrine model of growth regulation described by Sporn and Todaro in 1980 [17], which was originated as a concept to explain the abnormal growth of tumor cells.

This model hypothesizes that affected cells (ie, those exposed to ovarian hormones) overproduce a stimulatory growth factor to which they respond, resulting in sustained, self-stimulated proliferation. If this is the case in leiomyomas, the increase in the expression of these cytokines and growth factors should be most obvious during the luteal phase when progesterone dominates in the presence of estrogen, and when leiomyomas proliferate most actively. Progesterone alone and coupled with estrogen should also be shown to induce the expression of these cytokines and growth factors in cell cultures in vitro.

Extracellular matrix accumulation

One distinctive feature of leiomyomata is the presence of abundant fibrous connective tissue elements and ECM [16]. It is clear that this overexpression of collagen [18], fibronectin [19], and glycosaminoglycans [20] contributes to the formation and growth of the bulk of the tumor. It is also thought that this overproduced ECM itself may play a dynamic role in the metabolic processes leading to tumor growth, by influencing cellular proliferation and differentiation and serving as a repository for biologically active growth factors and cytokines [21].

Neoplasia are composed of two discrete compartments: tumor cells and stromal connective tissue. In general, the latter constitutes a significant proportion of the tumor mass. This is even truer for leiomyomas; these are called ‘‘fibroids’’ because of their fibrotic nature, which develops as a result of deposition of abundant ECM. Fujita [22] reported that leiomyomas contain 50% more ECM than the corresponding myometrium. The ECM of leiomyomas consists primarily of collagen, fibronectin, and proteoglycans. Puistola and coworkers [23] and Stewart and coworkers [18] reported relative overexpression of collagen by leiomyomas as compared with corresponding myometrium. The latter study observed this increased expression of collagen only in leiomyoma samples from women who were in the follicular phase of the menstrual cycle. Although they could not find a differential expression of fibronectin in leiomyoma versus myometrium, it has been shown that, in all women with leiomyoma studied, fibronectin expression was higher in the leiomyoma than in the autologous myometrium [19]. Glycosaminoglycans and their protein-bound forms, proteoglycans, have also been observed to be increased both in leiomyomas compared with myometrium and during leiomyomatous growth process [20].

Normal connective tissue is under continuous remodeling that requires both breakdown and resynthesis of the ECM components. Because ECM accumulation is the most consistent feature of all fibrotic conditions, the basis for tissue fibrosis possibly involves not only increased connective tissue deposition but also decreased ECM degradation. Matrix metalloproteinases (MMPs) are the enzymes believed to be the primary contributors to the process of degradation of ECM. In vivo, net matrix degradation is caused by the balanced activity of these enzymes and their endogenous inhibitors, known as ''tissue inhibitors of metalloproteinases'' (TIMPs). In addition to their MMP-inhibiting activity, TIMPs have been implicated in processes involving cell growth and have growth factor–like activities in some cell types [24].

Expression and hormonal regulation of MMPs and TIMPs, and their interactions with cytokines in leiomyomata and other uterine tissues, have been a recent interest of investigation. Therapy with GnRH-a was shown to result in a significant decrease in TIMP-1 and an increase in MMP mRNA in leiomyoma compared with untreated tumors [25]. More recently, transforming growth factor (TGF)-β1 was shown to exert the opposite effect in myometrial cells: it was found to increase TIMP-1 and decrease MMP-1 and MMP-3 [26], favoring an antidegradation state of ECM. In another recent article, Palmer and coworkers [27] published their finding of increased expression of MMP-11, which degrades fibronectin, in leiomyoma compared with myometrium.

Although one expects to find a decreased level of MMPs in leiomyoma, the finding of an increased expression of MMP-11, along with the previously reported elevation of the same MMP in dermatofibroma [28] (a fibrotic tumor with a phenotype similar to leiomyoma), may indicate a unique role for this MMP in leiomyoma. The same applies to MMP-2 and 9, which were found to be increased in the uterine cavity of those patients with leiomyoma [29]. Dou and coworkers [30], however, identified the expression of MMP-1, 2, 3, and 9 in both myometrium and leiomyoma and found their expression to be lower in leiomyomata. They also noted that this expression was maximal during the progesterone-dominated luteal phase. Earlier studies in the endometrium, however, had revealed the opposite, that progesterone was a potent repressor of MMP activity both in vivo and in vitro [21]. The regulation of MMPs is quite different in the endometrium and myometrium-leiomyomata.

Transforming growth factor-β

TGF-β, a dimeric polypeptide composed of identical 112-amino acid subunits, is probably the most extensively studied growth factor in leiomyoma within recent years. This polypeptide is a member of a family of polypeptide growth factors that exist in three isoforms (TGF-β1, 2, 3) encoded by separate genes in humans. They are considered to be the prototype of multifunctional cytokines, and their primary role seems to be to modulate cell development, and conse-

quently cell proliferation, acting both as inhibitors and stimulators depending on the type of tissue [31]. Moreover, they up-regulate the synthesis of many of the components of the ECM leading to fibrosis [32]. Recently, as many as 310 genes were found to be differentially expressed and regulated in leiomyoma and myometrial smooth muscle cells by TGF-β [33]. Gene ontology assigned these gene functions as cell cycle regulators, transcription factors, signal transducers, tissue turnover, and apoptosis.

The presence of TGF-βs and their receptors in human myometrium and leiomyoma was first shown in 1994 by Chegini and coworkers [34] and Arici and coworkers [35]. Although the first group could not determine a menstrual cycle variation in TGF-β expression, Arici and Sozen [19] found a significantly increased expression of TGF-β3 in luteal phase leiomyoma samples, most pronounced in the midluteal samples. This observation suggests a potential stimulatory role for progesterone (possibly in combination with estradiol, which up-regulates progesterone receptors) in the expression of TGF-β3. Chegini and coworkers [36] confirmed this pattern of hormonal regulation through in vitro experiments where progesterone and estradiol up-regulated the production of TGF-β1. In addition, they demonstrated that GnRH-a inhibited the proportion of TGF-β1 released in an active form. Arici and Sozen [37] showed that leiomyomatous myometrium in the follicular and luteal phase secreted a higher proportion of active TFG-β1 compared with the samples from women using GnRH-a. Chegini and coworkers also showed that GnRH-a resulted in lowering TFG-β receptors [38] and TGF-β receptor intracellular signaling molecules [39].

The only growth factor so far that has been shown to be overexpressed in the luteal phase leiomyoma samples is TGF-β [19], which is also up-regulated in leiomyoma cell cultures exposed to progesterone [36]. The up-regulatory effect of progesterone on TGF-β production was also observed in human endometrial stromal cells [40]. The finding that TGF-β3 expression in leiomyoma samples was 3.5-fold higher than in the myometrial samples [19] indicates a possible role for TGF-β3 in the pathogenesis of leiomyomata. This possible role for TGF-β3 is further strengthened by the recent duplication of this finding by Lee and Nowak [41], who found fivefold higher levels of expression of TGF-β3 in leiomyoma than in autologous myometrium.

There is also sufficient evidence to suggest that ovarian hormones may exert their mitogenic effect on leiomyoma cells through up-regulation of TGF-β, which itself has been shown to stimulate the monolayer growth of cells of mesenchymal origin [42]. The dominant isoform in the cells of mesenchymal origin, including smooth muscle cells, is TGF-β3 [43]. Two groups of investigators have found that, in both leiomyoma and myometrium, TGF-β3 at low concentrations leads to a significant increase in cell proliferation [19,41]. It is interesting that, at high concentrations, TGF-β3 does not have this mitogenic effect. In a similar fashion another isoform, TGF-β1, at lower concentrations, induces an increase in leiomyoma cell proliferation that disappears at higher concentration [37,44].

These findings are consistent with the common observation of a bimodal effect of TGF-βs on cell proliferation. For example, Battegay and coworkers [45] have

shown that low concentrations of TGF-β enhance DNA replication in human vascular smooth muscle cells, whereas this effect disappears at higher concentrations. Similarly, Tang and coworkers [46], in their study investigating the presence and mitogenic effects of all three isoforms in myometrial cells, concluded that all three isoforms had stimulatory effects on cellular DNA synthesis at low concentrations; these effects were lost at higher concentrations. It is interesting that they found TGF-β3 to be the least expressed among the three isoforms in myometrium. This is in parallel with the finding of TGF-β3 levels being up to fivefold higher in leiomyoma samples than in myometrial samples. Battegay and coworkers [45] in investigating the mitogenic role of TGF-β [45] reported that TGF-β may induce bimodal proliferation of mesenchymal cells through the induction of other mitogenic growth factors, such as platelet-derived growth factor (PDGF). This relation between TGF-β and PDGF was reported in leiomyoma by Arici and Sozen [37].

MMP genes are expressed during the times in the cycle when progesterone concentrations are low (during the follicular and menstrual phases of the cycle). During the luteal phase when progesterone concentrations are high, the expression levels of most MMP family members decrease. Of significance is the observation that, when treated with progesterone, human endometrial stromal cells up-regulate the production of TGF-β, which then represses MMP-3 and MMP-7 production [40]. Both of these MMPs play a role in the degradation of fibronectin. In leiomyoma, a similar pattern is observed where progesterone up-regulates TGF-β3, which in turn stimulates fibronectin expression [19].

Studies [26,40] suggest that this fibronectin-promoting role of TGF-β could at least be partially explained on the basis of its inhibitory effect on MMP-3 and MMP-7, whose function, in turn, is to degrade fibronectin. There is evidence that TGF-β causes an increase in the expression of TIMPs in tissues, including myometrium. TIMPs in turn inhibit MMPs and the degradation of ECM [26,47].

Among the cytokines and growth factors already reviewed for their potential roles in the cellular proliferative process of leiomyoma growth, only TGF-β has been shown also to play a significant role in the accumulation of ECM [32]. The authors have studied the effect of TGF-β on fibronectin expression in leiomyoma [19] because among the ECM components, it is fibronectin that seems to play the most crucial role. It mediates cell attachment to collagen [48], and also is functionally involved in mediating the cellular responses to TGF-β. The stimulatory effect of TGF-β on fibronectin expression in leiomyoma cells has also been shown in many different cell lines, including fibroblasts [32]. In those experiments, in addition to enhancing fibronectin production, TGF-β also increased the ability of chick fibroblasts to incorporate fibronectin into the matrix. Moreover, it has been reported that TGF-β causes an increase in the expression of fibronectin receptor [49]. Also, TGF-β was found to increase the expression of collagen and increase its incorporation into ECM [32]. Indeed, a recent report showed that treatment of leiomyoma and myometrial cells with the TGF-β immunoneutralizing antibody for 24 hours caused a 45% to 60% reduction in

collagen type-1 and type-3 mRNA levels [41], suggesting that endogenous TGF-β is important for collagen production. In addition to this increase in the matrix material, there possibly is a change in the composition of the ECM in response to TGF-β.

To identify genes involved in the formation of leiomyomas, Catherino and coworkers [50] used global expression profiling to compare clonal tumors with normal myometrium. Contrary to expectation, genes involved in estrogen action were not differentially expressed between leiomyoma and normal myometrium. Instead, genes encoding ECM proteins were predominantly featured. Expression of collagen-binding protein dermatopontin was found to be consistently decreased in leiomyoma and in keloids, suggesting a molecular link between leiomyomas and keloids. Moreover, reduction in dermatopontin was associated with an increase in TGF-β3 mRNA levels in leiomyomas, whereas other genes involved in dermatopontin signaling were not differentially expressed.

Epidermal growth factor

Probably one of the earliest growth factors investigated in myometrium and leiomyoma was epidermal growth factor (EGF). EGF is a 53-amino acid polypeptide shown to have mitogenic activity in various reproductive tissues [51,52]. Studies on EGF and its receptor in leiomyoma date back to 1984 when Hofmann and coworkers [53] reported the presence of EGF binding sites in human myometrium and leiomyoma. EGF mRNA, detected both in leiomyoma and myometrial cells [54], does not seem to demonstrate a clearly defined differential level of expression in these tissues. Dixon and coworkers [55] showed that there were significantly decreased levels of EGF in leiomyoma tissue compared with matched myometrium.

In contrast, an earlier study reported higher levels of EGF in leiomyoma tissue than in myometrium, but only in luteal phase samples [56]. In line with this observation, more recently, studies revealed an up-regulation of EGF in leiomyoma culture cells treated with progesterone [8,57]. Likewise, EGF receptor levels show neither menstrual cycle variation nor differential level of expression in leiomyoma and myometrium [53,58]. Shimomura and coworkers [8], however, reported an up-regulation of EGF receptor levels in leiomyoma cells treated with estrogen. In line with this is the finding of reduced levels of EGF receptors in leiomyoma samples from women treated with GnRH-a [58]. Because hormonal regulation of this growth factor or its receptor could not be shown clearly in vivo, it may be speculated that GnRH-a might also have a direct action on the leiomyoma, where GnRH-a receptors are present [36], in reducing the EGF receptor levels. EGF has also been implicated in leiomyoma growth because the selective EGF receptor blocker AG1478 was shown to block leiomyoma cell proliferation [59].

Platelet-derived growth factor

Levels of PDGF, a 125-amino acid polypeptide and another potent mitogen for mesenchymal tissues, were not found to differ in leiomyoma versus myometrium [60]. Although PDGF receptor sites in leiomyomata outnumbered those in myometrium, the binding affinity for PDGF of those sites in leiomyoma tissue was lower than those in myometrium [61]. Hormonal regulation of PDGF is implicated through demonstration of down-regulation of PDGF in GnRH-a–treated women [62,63]. Addition of PDGF to myometrial or leiomyoma cell cultures results in a significant increase in DNA synthesis [61,37]. PDGF has recently been identified as the main growth factor involved in the proliferation response of leiomyoma cells to estradiol stimulation [64].

Insulin-like growth factors

Insulin-like growth factor-1 (IGF-1) is a 70-amino acid polypeptide with structural similarity to insulin. Three studies have shown higher levels of IGF-1 and its receptor in leiomyoma tissue than in myometrium [65–68]. Two more recent studies, however, have shown no difference between the levels of this cytokine in leiomyoma versus myometrium tissues [69,70]. That IGF-1 mRNA is expressed at the highest amounts in the follicular phase [71] indicates possible hormonal regulation; indeed, progesterone is found to inhibit IGF-1 expression in leiomyoma through in vitro studies [57,72]. Estrogen, however, seems to up-regulate IGF-1 gene expression [73]. IGF-2 is a mitogen with structural similarity to IGF-1. In fact, most of IGF-2's action is transmitted through IGF-1 receptor. The mRNA levels of IGF-2, but not IGF-2 receptor levels, were also reported to be higher in leiomyoma tissue than in myometrium [65,66]. Hormonal regulation of this factor, however, has not been shown in vivo or in vitro. IGF-1 seems to promote mitotic activity [74] and PCNA expression [75] preferentially in leiomyoma cell cultures. IGF has also been shown to up-regulate Bcl-2 expression, suggesting a role in inhibition of apoptosis [75].

Basic fibroblast growth factor

Basic fibroblast growth factor, a 155-amino acid polypeptide, stimulates mitogenesis and differentiation of a variety of mesodermal cells including fibroblasts and smooth muscle cells [76]. This factor was identified in abundance in myometrium [77] and in even higher amounts in leiomyoma [78]. GnRH-a treatment has been shown to decrease its expression, suggesting a potential hormonal regulation [62,79,80]. Rauk and coworkers [77] reported that both myometrial and leiomyoma cells showed significant thymidine incorporation, indicating elevated mitogenesis in response to basic fibroblast growth factor.

Parathyroid hormone–related peptide

Parathyroid hormone–related peptide is a tumor-derived factor occurring as three isoforms of 139, 141, and 173 amino acids. It was initially identified in tumors associated with hypercalcemia of malignancy. Its expression in leiomyoma was found to be increased compared with myometrium [81]. This differential expression was found to be most marked in tissues from women in the follicular phase. A study by Thiede and coworkers [82], which showed a sixfold to eightfold increase in the levels of parathyroid hormone–related peptide mRNA in ovariectomized rat uterus when stimulated by a single dose of estradiol, implies a similar "estrogen-mediated effect." The investigators did not specify, however, in which layer of the uterus they observed this response to estrogen. Nonetheless, neither menstrual cycle variation of expression nor in vitro regulation of parathyroid hormone–related peptide by estrogen and progesterone in women has been shown. Parathyroid hormone–related peptide receptors in leiomyomata have recently been characterized [83]. A study investigating the presence of parathyroid hormone–related peptide in leiomyoma [84] concluded that expression of parathyroid hormone–related peptide in leiomyomas correlated positively with cell proliferation.

Prolactin

Another widely studied hormone in leiomyoma is prolactin. In 1984, Daly and coworkers [85] reported prolactin production in leiomyoma tissue from women in the follicular phase. Relatively high levels of prolactin in these samples are indicative of estrogen's stimulating effect in vivo. Progesterone was shown to have a suppressive effect on prolactin expression in myometrium and leiomyoma cultures [86,87]. When the leiomyoma cultures were obtained from women who had been previously treated with GnRH-a, once again there was a decreased amount of prolactin produced [87], implying an inhibition of estrogen by GnRH-a, which may have a promoting effect on prolactin production. More recently, experiments using antiprogestins, such as mifepristone [88] and onapristone [89], also demonstrated suppressed levels of prolactin production in leiomyoma when cultures were treated with these antiprogestins.

The apparent inconsistency that both progesterone and antiprogestins have suppressive action on prolactin expression may possibly be explained by the antiprogestins sometimes acting as agonists, as shown in the endometrium of monkeys [90] and breast cancer cell lines [91]. None of these investigations, however, have concluded whether prolactin is expressed in higher amounts in leiomyoma than in myometrium. Hormonal regulation of prolactin in leiomyoma cells has not been determined fully either. In addition, there have been no reports of the presence of prolactin receptors in leiomyomas.

Prolactin also was implicated as a stimulator of the proliferation of leiomyoma cells by the mitogen-activated protein kinase cascade [89]. Moreover, a signifi-

cant decrease in leiomyoma and myometrial cell number was observed after treatment with antiprolactin antibody [92].

Heparin-binding epidermal growth factor

Heparin-binding EGF is a 22-kd growth factor that is mitogenic for fibroblasts and smooth muscle cells [93]. It is known to be a more potent mitogen for smooth muscle cells than EGF and has a greater affinity for EGF receptors. Heparin-binding EGF, however, was found to have a decreased expression in leiomyoma compared with normal myometrium [78], a finding that essentially argues against a possible role for this factor. Indeed, heparin-binding EGF was found to stimulate the proliferation of both leiomyoma and myometrial cells, but because the proliferative potential of the myometrial cells responded better to heparin-binding EGF than that of leiomyoma cells, it has been concluded that heparin-binding EGF may play a more vital role in myometrial growth than leiomyoma growth [94].

Monocyte chemotactic protein-1

Monocyte chemotactic protein-1 (MCP-1) is a 76-amino acid polypeptide that is a potent chemoattractant for monocytes and is known to have antitumor properties in various tissues [95]. The authors have investigated the presence of MCP-1 in leiomyomata and found its expression to be significantly higher in normal myometrium compared with leiomyoma [95]. Myometrial MCP-1 mRNA levels showed menstrual cycle variation, the levels of luteal phase samples being higher than those of follicular phase samples. In this study, the highest MCP-1 levels were found in samples from women using GnRH-a. Consistent with this, in vitro experiments revealed that estradiol, alone and in combination with progestins, down-regulated MCP-1 expression.

A subsequent study attempted to answer the question whether this increased MCP-1 expression in myometrium, especially pronounced in those samples from GnRH-a users, was accompanied by a concurrent increase in macrophage infiltration by means of chemoattraction [96]. Although this immunohistochemical study confirmed the significant up-regulatory effect of GnRH-a on MCP-1, it did not demonstrate a parallel increase in the macrophage count. It was concluded that this protective-appearing role of MCP-1 might work through a direct effect rather than by means of tumor-associated macrophages. MCP-1 receptors, however, so far have not been investigated in myometrium or leiomyoma.

MCP-1 seems to be the only peptide attributed a protective role against leiomyoma growth [95]. Indeed, there was an observed increase in the proliferation of leiomyoma cells treated with anti–MCP-1 neutralizing antibody blocking the MCP-1 action. Besides other antitumorigenic roles in various tissues, MCP-1 was also reported to inhibit the growth of rat vascular smooth muscle cells [97].

Endothelin-1

Endothelin-1 was first isolated from cultured endothelial cells as a potent vasoconstrictor, but later was also found to have a stimulatory effect on DNA synthesis, cell division, and hypertrophy in myocytes and fibroblasts [98]. Messenger RNA for endothelin and its receptors have been shown in leiomyoma, where the endothelin receptor$_A$ level was found to be significantly higher than in myometrium [99]. A recent French study [100] reported that endothelin-1 exerted a more potent mitogenic effect on leiomyoma cells than in normal myometrial cells and that it was more efficient than PDGF and EGF to stimulate proliferation. Endothelin-1 itself, however, has not been shown to be overexpressed in leiomyoma or to be under any hormonal regulation either in vivo or in vitro.

Vascular endothelial growth factor

Vascular endothelial growth factor is a primary regulator of angiogenesis and has also been studied in leiomyoma, although results are somewhat inconsistent. Gentry and coworkers [101] reported a higher expression of vascular endothelial growth factor in leiomyomas compared with the adjacent myometrium, indicating that local angiogenesis may be important in the development and growth of these tumors. Another British study [102], however, found that leiomyoma did not have significantly different levels of vascular endothelial growth factor mRNA compared with normal myometrium. The same study also did not show different levels of vascular endothelial growth factor in leiomyoma from women treated with GnRH-a compared with leiomyoma from untreated women, whereas in another study [62] vascular endothelial growth factor was found to be decreased in the leiomyoma of treated women. Chen and coworkers [103] found a significant decrease in serum vascular endothelial growth factor levels after hysterectomy of leiomyomatous uterus. These levels did not correlate, however, with uterine fibroid volume.

Human chorionic gonadotropin

The most recently reported hormone with regards to leiomyoma pathophysiology is human chorionic gonadotropin, which may be responsible for the rapid enlargement of leiomyomata during pregnancy. Horiuchi and coworkers [104] demonstrated the presence of human chorionic gonadotropin–luteinizing hormone receptor, but not human chorionic gonadotropin protein, in both cultured myometrial and leiomyoma cells. Human chorionic gonadotropin has been shown to increase the cell proliferation and the expression of cell cycle-related

proteins, such as PCNA, cyclin E, and cdc2, in both myometrial and leiomyoma cells [104].

Interleukin-8

The most recently reported cytokine with regard to leiomyoma physiology is interleukin-8, a potent chemoattractant cytokine expressed in a variety of human tumors [105]. High levels of interleukin-8 and its receptor have been demonstrated in myometrium immediately surrounding leiomyoma. It has also been reported that cell proliferation in the leiomyomatous uterus is inhibited when interleukin-8 was blocked by a neutralizing antibody, suggesting a possible mitogenic role for interleukin-8 [105].

Pituitary tumor–transforming growth factor-1

The most recently reported growth factor in the pathophysiology of leiomyoma is pituitary tumor–transforming growth factor-1 [106]. The expression of this gene is significantly elevated in leiomyoma compared with myometrium. The expression is independent of menstrual cycle. Basic fibroblast growth factor seems to stimulate pituitary tumor–transforming growth factor-1, which results in increased cell proliferation.

Summary

Many investigators who have been trying to delineate the pathophysiology of leiomyomata believe in the autocrine-paracrine model of tumor growth, where ovarian hormones act as regulators of gene expression in cells. These affected cells overproduce the stimulatory and fibrogenic cytokines and growth factors to which they respond, resulting in sustained, self-stimulated proliferation and fibrogenesis.

A number of cytokines and growth factors have been investigated in leiomyomata to determine which cytokines or factors may be responsible for mediating the growth-promoting effects of ovarian hormones. A review of the literature reveals that TGF-β is the only growth factor shown to be overexpressed in leiomyomata versus myometrium, hormonally regulated both in vivo and in vitro, and both mitogenic and fibrogenic in these tissues.

The authors believe that, given the extent and depth of the current research on the cellular biology of leiomyoma, the cellular mechanisms responsible in the pathogenesis of leiomyoma will be identified clearly within the foreseeable future. This will enable researchers to develop therapy directed against

the molecules and mechanisms at the cellular level, which undoubtedly will have a major impact on the number of hysterectomies being performed for a ''fibroid uterus.''

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Steroid Hormones and Leiomyomas

Erica E. Marsh, MD, Serdar E. Bulun, MD*

Division of Reproductive Biology Research, Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Robert H. Lurie Medical Research Center, 303 East Superior Street, 4-123, Chicago, IL 60611, USA

Uterine leiomyomas or fibroids are benign, hormonally responsive, smooth muscle tumors that have been reported to affect 20% to 40% of premenopausal women making them the most common solid tumor of the pelvis [1]. They are more common in African-American women and have a polygenic inheritance pattern [2,3]. Their clinical presentation is variable in that they can cause a range of symptoms including irregular and excessive uterine bleeding, pressure sensation in the lower abdomen, pain during intercourse, pelvic pain, recurrent pregnancy loss, infertility, and compression of adjacent pelvic organs, or be totally asymptomatic. Because of this range of symptoms, leiomyomas are responsible for over 200,000 hysterectomies per year in the United States. Given their prevalence and associated morbidity, there is significant interest in their etiology and growth.

Despite the prevalence of leiomyomas, relatively little is understood about their development and growth. Based on glucose-6-phosphate dehydrogenase studies and cytogenetic studies, it is thought that each leiomyoma is the product of clonal expansion of a single myocyte [4,5]. Like other neoplasms, there are likely multiple genetic "hits" that lead to the dysregulation of a smooth muscle cell and lead to its transformation into the common phenotype of the leiomyoma cell.

Although little is known about what specific events lead to the development of leiomyomas, what has been known for several decades is that they are hormonally responsive neoplasms. Case reports and studies dating back to the 1960s and 1970s reported the observations that myomas appear during the reproductive

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* Corresponding author.
E-mail address: s-bulun@northwestern.edu (S.E. Bulun).

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years, increase in the setting of taking sex steroids, and regress after menopause. The role of steroids or other growth factors in the initiation and growth of these tumors, however, is not completely understood. The neoplastic transformation of myometrium to leiomyoma likely involves somatic mutations of genes involved in proliferation and apoptosis in normal myometrium and the complex interactions of sex steroids and growth factors [6–9]. These observations, however, have given researchers a window into their pathophysiology and were the initial clues of the ovarian steroid-dependent growth potential of these tumors.

This article reviews and summarizes what is known about the roles of hormones in leiomyoma growth. Primarily discussed are the roles of the sex steroid hormones estrogen and progesterone in leiomyoma pathophysiology and the relationship between these hormones and known leiomyoma growth factors. Also discussed are the lessons learned about leiomyoma growth from the sex steroid receptor modulators and antagonists and their potential therapeutic benefits.

Estrogen, selective estrogen receptor modulators, and leiomyomas

It is widely accepted that the growth of uterine leiomyomas is up-regulated by estrogen and its receptors (ERα, ERβ), which reside in the nucleus. This finding has been born out in clinical studies and basic science and translational studies. Leiomyomas develop only after the commencement of menstrual cycles and become symptomatic usually in the 30s or 40s. At the time of menopause, leiomyomas start to regress in most patients. The ovary is thought to be the major source of sex steroids for leiomyoma growth.

A large body of experimental and clinical evidence shows that estrogen stimulates the growth of uterine leiomyomas [10–12]. Observational studies and case reports in the 1960s and 1970s detail the growth of fibroids in patients who were taking estrogens and clomiphene and who had recurrence or growth of fibroids during the highly estrogenic state of pregnancy [10,12–14]. The discovery in 1976 that leiomyoma cells have ERs further fueled the hypothesis that leiomyomas are estrogen-driven tumors [15]. Studies then began to quantify these receptors and found that there were increased numbers of ERs in leiomyomas versus normal myometrium [16–18].

In the setting of the clinical observations noted previously and the finding that myomas not only had ERs, but that they had increased numbers of ERs relative to normal myometrium, the obvious next question is how estrogen results in increased growth of these tumors. There is no complete answer to that question but clinicians are developing some understanding of mechanisms of action of estrogen. Estrogen may directly increase proliferation of leiomyoma cells or indirectly increase growth by enhancing progesterone action in human leiomyomas [11,19–21]. In an in vivo rat model, uterine leiomyomas were shown to be dependent on estrogen for growth [11,22]. Estrogen induces leiomyoma growth by possibly altering the expression of a large number of genes and growth factors [11,23]. These include but are not limited to estradiol-dependent

increases in epidermal growth factor and epidermal growth factor receptor expression in leiomyoma cells [23], and an increase in transforming growth factor-β1 expression in response to estradiol treatment [24,25]. Additionally, human ERα polymorphisms have recently been reported to be associated with uterine leiomyomata [26]. Recently, a negative cross-talk was uncovered between ER and peroxisome proliferator-activated receptor signaling pathways [27]. These data confirm a strong relationship between estrogen and pathogenesis of leiomyomata.

Although the mechanistic details of the role of estrogen in myoma growth are still elusive, the potential therapeutic benefit of agents that interrupt ovulation provided important clues. Coddington and coworkers [28] first reported the use of gonadotropin-releasing hormone (GnRH) agonists in the treatment of fibroids in 1986 and showed a significant reduction in fibroid size by ultrasound and pelvic examination. Since that time, numerous studies have confirmed these findings using various protocols and modes of delivery.

The roles of selective ER modulators in the treatment of fibroids are less clear. Unlike GnRH agonists, which after the flare on initiation of treatment have primarily hypoestrogenic effects, different selective ER modulators have varying mixes of estrogenic and antiestrogenic effects. This was first noted in the report by Frankel and Benjamin [14] of a patient with the rapid enlargement of a uterine fibroid after initiation of therapy with the selective ER modulator clomiphene citrate. Subsequent studies of tamoxifen in the Eker rat model in which reproductive tract leiomyomas arise with high frequency show a pure antagonist effect on leiomyoma [29,30]. Interestingly, the results with tamoxifen in humans are not nearly as clear. Some reports show solely no evidence of shrinkage [31,32], versus other case reports, which show rapid growth of leiomyomas on tamoxifen [33,34]. Presumably because of the case reports that noted growth of fibroids on tamoxifen, there have been no randomized controlled studies investigating its potential as a treatment for myomas.

Raloxifene has shown more promising results in the treatment of fibroids. In early studies of its effect on Eker rat myoma cell lines it was shown to inhibit cell proliferation [30]. In vivo studies in the guinea pig fibroid model showed rapid regression of myomas with raloxifene [35]. In 2001, Palomba and coworkers [36] published a randomized controlled trial of raloxifene treatment of fibroids in postmenopausal women, which resulted in a significant decrease in overall uterine size and in the size of the fibroids. When the study was repeated in a randomized, controlled trial in premenopausal women, however, these results were not replicated (ie, there was no significant decrease in size of fibroids in response to the treatment) [37]. This difference in responses can likely be explained by the fact that the antiestrogen effects of raloxifene were strong enough to counteract the low levels of background estrogen seen in postmenopusal women, but were not sufficient enough to counteract the substantial estrogen levels seen in women with intact and functioning ovaries. This was supported by a subsequent study from the same group that investigated combination therapy with GnRH agonist and raloxifene versus GnRH plus placebo in a randomized,

controlled trial in premenopausal women and found that the group taking GnRH and raloxifene had a significant decrease in uterine and myoma size in comparison not only with pretreatment size but also in comparison with the GnRH plus placebo group [38]. This and subsequent long-term studies by this group reveal a role for raloxifene as an add-back agent in conjunction with long-term GnRH treatment of myomas in the premenopausal population [39].

Aromatase and leiomyomas

In 1994, Bulun and coworkers discovered the presence of aromatase in leiomyomas [42] and ultimately, in addition to endocrine estrogen from the ovary, the contribution of in situ estrogen production to leiomyoma growth was reported, namely estrogen synthesized in leiomyoma cells. Leiomyomas express aromatase at strikingly higher levels than the surrounding myometrium and are able to synthesize estrogen [40–43]. The tissue concentrations of estrogen are elevated in leiomyoma nodules compared with levels in surrounding myometrium [44,45]. Moreover, it was shown in vitro that estrogen synthesized in leiomyoma smooth muscle cells in culture is sufficient to promote proliferation in an intracrine fashion, because the stimulation of aromatase activity increased cellular proliferation, whereas the addition of an aromatase inhibitor inhibited proliferation [43].

Local estrogen biosynthesis in intact leiomyoma tissue explants and cultured leiomyoma smooth muscle cells has been demonstrated [42]. The incubation of these cells with labeled androstenedione gives rise to significant conversion of this precursor steroid to estrone. Estrone is weakly estrogenic and needs to be converted to estradiol to exert full biologic activity. Estrone is further reduced to the biologically active estrogen estradiol by 17β-hydroxysteroid dehydrogenase activity in leiomyoma tissue [43]. This is verified by significant stimulation of proliferation of leiomyoma smooth muscle cells by androstenedione to the same extent as estradiol [43]. The addition of an aromatase inhibitor blocked the stimulatory effect of androstenedione [43]. These results indicate that androstenedione is locally converted to biologically significant quantities of estrone and further to estradiol by leiomyoma smooth muscle cells. Moreover, aromatase seems to be the key enzyme in this process, because the inhibition of aromatase activity blocked proliferation. Aromatase activity was significantly stimulated by a cAMP analogue, prostaglandin E_2, or a combination of a glucocorticoid and a cytokine (interleukin-1β) [42,46].

Aromatase mRNA was detectable by quantitative reverse transcriptase polymerase chain reaction in 91% of 35 leiomyomata from 26 women [42,43]. Aromatase mRNA was also detectable in 75% of normal-appearing myometrial tissues (N=24) biopsied at 2 cm from a leiomyoma. Aromatase mRNA was not detectable in myometrial tissues from disease-free uteri (N=8).

There was no correlation between aromatase mRNA levels and leiomyoma size, uterine weight, or patient age in these studies, although there was a positive

trend between advancing age and aromatase mRNA levels. For example, the highest mRNA levels were detected in patients above age 45, and leiomyoma tissue from a 65-year-old patient contained moderately high aromatase mRNA levels [42,43]. These data suggest that local aromatase expression may be important for the availability of estrogen to leiomyoma tissue despite severely decreased circulating estrogen levels in perimenopausal or postmenopausal women.

Published and unpublished observations indicated that cAMP-responsive promoters I.3 and II (86%) are primarily used for aromatase expression, whereas the glucocorticoid-responsive promoter I.4 (14%) plays a less important role [42]. In contrast, a Japanese group of investigators recently reported that promoter I.4-specific aromatase mRNA species were predominantly present in most leiomyoma tissues (N = 6) [46]. A glucocorticoid plus interleukin-1β stimulated aromatase enzyme activity and mRNA levels maximally in cells isolated from these specimens [46]. These investigators also demonstrated that glucocorticoids and interleukin-1β regulated aromatase expression by promoter I.4. The discrepancy between these results may be attributed to race-dependent differences, because samples from United States base studies were obtained from African-American and white patients, whereas all patients in the Japanese study were of Asian origin [42,46].

A preliminary piece of clinical evidence for the significance of local aromatase expression was published recently [47]. These authors described the shrinkage of a large leiomyoma in a 53-year-old menopausal woman using an aromatase inhibitor [47]. Because the patient did not have ovarian function, the therapeutic effect was postulated to be mediated by inhibition of local aromatase activity in the leiomyoma. This case report provides limited but promising evidence for a role of aromatase in the biology of uterine leiomyomata and future use of aromatase inhibitors to treat these tumors.

Progesterone, progestins, antiprogestins, and leiomyomas

Traditionally, estrogen has been considered the major promoter of myoma growth. Recent biochemical, histologic, and clinical evidence are suggestive of an important role for progesterone in the growth of uterine leiomyomas. Biochemical and clinical studies suggest that progesterone, progestins, and the progesterone receptors (PR-A and PR-B) might enhance proliferative activity in leiomyomas [9].

Much as in the case with ERs, the absolute quantities of PR-A and PR-B and the PR-A/PR-B ratio are significantly different in leiomyoma tissues compared with normal myometrium [48,49]. Progesterone has been shown to induce proliferation and up-regulate growth factors and antiapoptotic proteins (eg, epidermal growth factor, bcl-2) in leiomyoma smooth muscle cells [50]. It seems that the promoters of certain key genes that regulate apoptosis (*bcl-2*) and proliferation (*c-myc*) contain functional progesterone response elements and are up-regulated by PRs in the presence of a progesterone agonist [51,52]. Both *bcl-2*

and *c-myc* genes are expressed in leiomyomas [53,54], and *bcl-2* levels tend to be higher in leiomyoma tissues (versus normal myometrium) during the secretory (versus proliferative) phase [53]. Interestingly, progesterone has been shown to inhibit tumor necrosis factor-α and insulin-like growth factor-1, suggesting that it may have both inhibitory and stimulatory effects in leiomyoma [55,56].

Given these findings antiprogestins were turned to as a potential therapeutic tool against myoma. RU486, the high PR affinity antiprogestin created by Roussel-Uclef in France, is the most studied antiprogestin [57]. In 1993, Murphy and coworkers [58] published a clinical trial showing 49% regression at 12 weeks of uterine myoma in response to 50 mg/d RU486. A subsequent systematic review published in 2004 of six clinical trials reported reduction in leiomyoma size and improvement in symptoms [59]. Cell culture studies by Chegini and coworkers [24] suggested that the antiprogestin-induced leiomyoma regression seen with both RU486 and the antiprogestin ZK98299 are mediated in part through a pharmophysiology that involves suppression of transforming growth factor-β production and altered cell growth.

Preliminary data indicate that recently introduced selective PR modulators or mesoprogestins with mixed agonist-antagonist activity may be effective in decreasing or eliminating uterine bleeding and decreasing the volume of uterine leiomyomata [60]. These compounds possibly interact with PR-A, PR-B, and progesterone target genes in a distinct manner to exhibit their therapeutic effects in uterine leiomyoma smooth muscle cells. Ongoing studies are expected to elucidate their mechanism of action.

Summary

The sex steroid hormones play an important role in myoma maintenance and growth as evidenced by clinical, molecular, biological, and pharmacological models. It is hoped that the next phase of research will elucidate better the mechanisms through which these hormones modulate myoma growth and how they interact with the as yet unidentified other factors that play a role in myoma development and growth.

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Clinical Features of Myomas

Orhan Bukulmez, MD[a,*], Kevin J. Doody, MD[a,b]

[a]*Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390–9032, USA*
[b]*Center for Assisted Reproduction, 1701 Park Place Avenue, Bedford, TX 76022, USA*

Uterine myomas are among the most frequent entities encountered in gynecologic practice. Myomas are the most common solid pelvic tumors in women, occurring in 20% to 40% of women during reproductive years [1]. Uterine myomas are the fifth leading cause of hospitalizations for gynecologic conditions unrelated to pregnancy in women aged 15 to 44 years [2]. They are the primary indication for hysterectomy, accounting for over 200,000 hysterectomies annually in the United States, and the cause of significant morbidity from profuse menstrual bleeding and pelvic discomfort to reproductive problems [3].

Because routine ultrasound screening for myomas is not indicated, the exact prevalence of myomas is not known. The clinically recognized uterine myoma substantially underestimates the true occurrence of these tumors. A study involving hysterectomy specimens identified myomas in 74% of serially sectioned specimens of premenopausal women and in 84% of specimens from postmenopausal women [4]. A recent study screening randomly selected women provided different estimates [5]. The estimated cumulative incidence of uterine fibroids detected by ultrasound in randomly selected members of an urban health plan (N = 1364 women) by age 50 has been >80% for black women and nearly 70% for white women.

In terms of harboring myomas, black women have two to three times the risk of white women, and earlier ages at first diagnosis and more numerous and symptomatic tumors at the time of diagnosis [5–7]. An earlier survey revealed that in 1.7 million hysterectomies performed in the United States between 1988 and 1990, uterine myoma was the primary diagnosis for 29% of white and 61%

* Corresponding author.
E-mail address: Obukul@parknet.pmh.org (O. Bukulmez).

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of black women [8]. The rates of uterine myomas increase with age throughout the reproductive years. The prevalence of clinically significant myomas peaks in the perimenopausal years and declines after menopause [9].

Most uterine myomas cause no symptoms [4,10]. It is estimated that only 20% to 50% of women with one myoma or more experience symptoms that can be directly attributed to the tumor itself [11].

Approximately 62% of women with symptomatic myomas present with multiple symptoms [12]. The symptoms of uterine myomas usually correlate with their location, number, size, or concomitant degenerative changes [13]. This article reviews the clinical manifestations of uterine myomas, as listed below.

Asymptomatic
Abnormal uterine bleeding
- Menorrhagia
- Anemia

Pelvic mass
Pelvic pressure
- Urinary frequency
- Urinary incontinence
- Difficulty in urination
- Hydronephrosis
- Constipation
- Tenesmus
- Rectal pressure

Pelvic pain
Reproductive dysfunction
- Infertility

Pregnancy related
- Myoma growth
- Red degeneration and pain
- Spontaneous miscarriage
- Obstetric complications

Malignancy
Rare associations
- Ascites
- Polycythemia
- Familial syndromes with renal cell carcinoma
- Benign metastasizing uterine myoma
- Intravenous leiomyomatosis

Abnormal uterine bleeding

Excessive menstrual bleeding is often the sole symptom produced by myomas. The bleeding pattern most characteristic of myomas is menorrhagia or hyper-

menorrhea [14]. Metrorrhagia is not characteristic of myomas, and it should be worked-up to rule out endometrial pathologies (Table 1). The heavy bleeding can eventually cause iron deficiency anemia. In addition, it leads to social isolation and loss of productivity because some patients need to change sanitary protection frequently.

The reason why these tumors cause excessive menstrual bleeding is not clear. In one study that evaluated premenopausal women with and without abnormal bleeding, women with abnormal bleeding were significantly more likely to have either intramural (58% versus 13%) or submucosal myoma (21% versus 1%) when compared with asymptomatic women [15]. Submucosal myomas, those in or partially protruding into the endometrial cavity, are most likely to cause menorrhagia.

The cause of excessive bleeding associated myomas has been related to vascular alterations of the endometrium. The obstructive effect on uterine vasculature created by intramural myomas leads to endometrial venule ectasia [16,17], which results in the congestion of myometrium and endometrium leading to profuse menstrual bleeding . Another contributing factor may be the increased size of the uterine cavity and the surface area of the endometrium caused by the presence of myomas [1]. Hypermenorrhea may also be enhanced by the presence of an endometritis, which is a frequent histologic finding within the endometrium overlying submucous myomas. Excessive menstrual bleeding has also been related to the dysregulation of local growth factors and aberrant angiogenesis [18]. Although a rare occurrence, a pedunculated submucosal myoma may prolapse through the cervix and undergo necrosis, resulting in severe bleeding.

Myomas commonly regress after menopause, which is accompanied with an atrophic endometrium and cessation of uterine bleeding. Postmenopausal women on hormone therapy, however, may experience persistence of abnormal uterine bleeding. It has been reported that postmenopausal women with submucosal myomas using hormone therapy experience a twofold increase in the incidence of abnormal bleeding as compared with the women with no submucosal myomas [19].

Pelvic mass symptoms

The diagnosis of myomas is often suspected on the basis of palpation of an enlarged irregular uterine contour on pelvic examination. The size of the myomatous uterus is described in menstrual weeks as is a pregnant uterus. A myomatous uterus of more than 12- to 20-week size may be palpated on abdominal examination [14]. In a study of 2623 healthy, asymptomatic volunteers (mean age, 51 years; range, 25–92 years) who underwent pelvic examination as part of an ovarian cancer screening program, a bulky or fibroid uterus was detected in 12.9% of women [20].

Pelvic pressure arises when the uterine size is increased. In fact, the pressure and increased abdominal girth cause by the mass effect of myomas are more

Table 1
Differential diagnosis of uterine myomas

Condition	Characteristics	Remarks for diagnosis
Endometrial polyp	Abnormal uterine bleeding.	Thickened endometrial stripe on ultrasound, easily detected by hysterosonography or hysteroscopy, final pathologic specimen needed to confirm diagnosis.
Endometrial hyperplasia or carcinoma	Abnormal uterine bleeding.	Thickened endometrial stripe on ultrasound, diagnosed by endometrial biopsy.
Adenomyosis	Abnormal uterine bleeding, pelvic pain, pressure, globally enlarged uterus.	On ultrasound there is no pseudocapsule or no well-delineated mass. On MRI, adenomyosis appears as an ill-defined, homogenous low-signal intensity area embedded with sparse high-intensity spots. Myomas are well-circumscribed masses with a spectrum of signal intensity.[a]
Dysfunctional uterine bleeding	Variety of bleeding manifestations of anovulatory cycles in the absence of any uterine pathology or medical illness. Frequent in adolescence and perimenopause.	Endometrial biopsy is needed to rule out endometrial hyperplasia or cancer. Rule out coagulopathies in adolescents.
Endometriosis	Frequent cause of chronic pelvic pain in the reproductive period. Endometriotic cysts of ovaries can mimic myomas.	Gold standard of diagnosis is laparoscopy or laparotomy with pathologic evaluation of the specimen.
Ovarian tumors	Benign or malignant, may present with abnormal uterine bleeding if the tumor is functional or may cause pelvic pain with torsion, rupture, or spill of its contents into the peritoneal cavity.	Best noninvasive diagnosis is made by transvaginal ultrasound. Persistent or complex or solid ovarian masses need surgical exploration and pathologic diagnosis.

Pelvic inflammatory disease	May cause adhesions, tubo-ovarian abscess, or pseudocysts. Women may present with pelvic pain, tender pelvic mass, abnormal uterine bleeding.	History and pelvic examination, cervical cultures, transvaginal ultrasound, laparoscopy or laparotomy.
Cervical lesions	Cervical polyps present with abnormal bleeding and diagnosed by speculum examination. Cervical malignancies may present with abnormal bleeding, and in advanced stages with pelvic pain.	PAP smear detects cervical preinvasive and invasive malignancies and colposcopy-directed biopsies confirm the diagnosis.
Urinary causes	Urinary tract infections, chronic urethral syndrome, interstitial cystitis, bladder neoplasms, and detrusor instability are frequent causes of urgency, suprapubic pain.	Single-digit pelvic examination of anterior vaginal wall to reveal urethral or trigonal tenderness. Urine cultures, urinary sediment to check for any urinary tract infections. Urodynamic studies to rule out detrusor muscle instability, cystoscopy to rule out any bladder neoplasm and interstitial cystitis.
Gastrointestinal causes	Recurrent or persistent pelvic and abdominal pain, usually accompanied by intermittent or chronic diarrhea, constipation, bloating.	Refer to gastroenterologist to rule out irritable bowel syndrome, inflammatory bowel disease, diverticulitis, colorectal cancer, ischemic colitis. Patients may need stool studies, barium enema radiography, colonoscopy.
Musculoskeletal causes	Chronic abdominal and pelvic pain originating in the abdominal wall.	Single-digit palpation of the abdominal wall may reveal trigger points.
Miscellaneous causes of infertility and recurrent pregnancy loss	Etiologies of infertility and recurrent spontaneous miscarriage.	Exclude male, ovulatory, and tubal factors; uterine defects other than myomas (mullerian anomalies, intrauterine synechiae, cervical incompetence); genetic factors; thrombophilias; and antiphospholipid syndrome before considering myomas as the cause of reproductive failure.

[a] *Data from* Togashi K, Ozasa H, Konishi I, et al. Enlarged uterus: differentiation between adenomyosis and leiomyoma with MR imaging. Radiology 1989;171:531–4.

commonly encountered than pain. These symptoms develop insidiously and are often less apparent. As the tumors grow, pressure is exerted on adjacent organs, especially the urinary tract and rectosigmoid. The associated urinary tract manifestations include frequency, outflow obstruction, and ureteral obstruction with hydronephrosis [21]. Constipation or tenesmus may be the result of a posterior wall myoma exerting pressure on the rectosigmoid. Rectal pressure may occur because of the incarceration of the myomatous uterus in the cul-de-sac or with the presence of a large posterior uterine myoma. In women presenting with pelvic mass appropriate differential diagnoses other than myomas should also be considered (see Table 1).

Pain

Although dysmenorrhea may be present when menstrual flow is increased, pain as a symptom of uterine myomas is not frequent. When pain does occur, it is usually associated with torsion of the pedicle of a pedunculated myoma; cervical dilatation induced by a submucosal myoma; or red (carneous) degeneration, which is mostly associated with pregnancy [1]. Pain is usually acute onset in these conditions and creates a challenge to rule out other acute abdominal emergencies, such as ectopic pregnancy, adnexal torsion, appendicitis, or acute pelvic inflammatory disease. Some type of intermittent subacute to chronic type of pain may occur if there is associated adenomyosis or endometriosis, which should be included in the differential diagnosis (see Table 1). Rarely, myomas in the broad ligament may cause unilateral lower abdominal pain, or may cause sciatic nerve pain.

Uterine myomas as large as 100 lb have been reported. These large myomas may outgrow their blood supply, leading to ischemia and necrosis with the tumor. This degeneration is usually associated with severe acute pain, which may necessitate surgical exploration.

Reproductive dysfunction

Infertility

Currently in industrialized countries, the age at which a first pregnancy planned is increasing from the thirties to the forties. When this fact is combined with the 15% to 30% recurrence rate of uterine myomas after a myomectomy, myomas can be expected as a common occurrence in women seeking pregnancy.

Uterine myomas have been reported in 27% of infertile women. Fifty percent of women with unexplained infertility become pregnant after myomectomy [22]. Per The American Society of Reproductive Medicine, uterine myomas are

associated with infertility in 5% to 10% of cases [23]. When all other causes of infertility are excluded, however, myomas may be responsible for only 2% to 3% of infertility cases.

The role of uterine myomas as a possible cause of infertility is still a matter of debate. Many potential mechanisms have been proposed to justify biologic plausibility, as listed next.

- Alteration of endometrial contour, which may interfere with implantation
- Alterations of uterine and subendometrial blood flow caused by myomas may negatively affect endometrial receptivity
- Adverse affect on the overlying endometrium creating vascular disturbances, inflammation, ulceration, thinning, and atrophy impairing implantation
- Alteration of the biochemical environment-dysregulation of cytokines and growth factors-impairing implantation
- Enlargement and deformity of the uterine cavity interfering with sperm transport
- Cervical displacement induced by myomas may reduce exposure to ejaculated sperm
- Generation of dysfunctional and altered uterine contractility hindering gamete transport and embryo implantation
- Persistence of endometrial blood clots may interfere with embryo implantation and sperm transport
- Tubal ostia may be obstructed or altered by mass effect of myomas
- Large posterior myoma may interfere with tubo-ovarian relationship

Infertility may be associated with myomas in the presence of submucosal myoma [24,25] or a markedly distorted endometrial cavity induced by big intramural myomas, which both may interfere with embryo implantation or sperm transportation [26]. Intramural myomas may also obstruct the tubal ostia or the intramural segment of the tubes. It has been hypothesized that large myomas may impair the rhythmic uterine contractions that facilitate sperm motility through the uterus [27]. Concerning the effects on embryo implantation, a histologic study demonstrated that endometrium overlying a submucosal myoma was atrophic possibly because of compression, whereas the endometrium adjacent to the tumor was hyperplastic possibly because of the increased vascularity [28]. Reported venous dilatation in the endometrium overlying and adjacent to myomas may be another factor disturbing endometrial receptivity [17].

In an earlier systematic review of observational studies, it has been concluded that infertility patients with myomas that impinge on the endometrial cavity have poorer reproductive outcomes than those infertile patients without uterine myomas or infertile women with subserosal or intramural fibroids [29]. Moreover, removal of the submucosal myomas seems to be of benefit when compared with those women without myomas but with similar infertility factors. In a recent review, it has been concluded that myomas immediately adjacent to or impinging on the endometrial cavity can negatively impact in vitro fertilization (IVF) outcome [30].

Assisted reproductive technologies provide an opportunity to examine the effects of myomas on implantation and pregnancy rates. The data regarding the impact of intramural fibroids on the success of assisted reproductive technologies, however, are still conflicting [29,30]. Some studies suggested that the implantation and pregnancy rates were not impaired in patients with intramural or subserosal myomas not distorting the uterine cavity [31–36]. Other studies, however, reported that the patients with intramural myomas had significantly reduced implantation and pregnancy rates when compared with those without myomas or only with subserosal myomas [37–39]. Two prospective controlled observational studies have suggested that intramural myomas smaller than 5 cm in diameter can negatively affect IVF outcome [39,40].

In a recent small prospective study, patients with and without intramural myomas had similar pregnancy and implantation rates [41]. Both groups in that study, however, had similar endometrial and subendometrial three-dimensional power Doppler flow indices. In an earlier study, patients with myomas who did not get pregnant had lower uterine artery pulsatility and resistance Doppler indices on the day of oocyte retrieval [42]. Some subset of patients with intramural myomas not distorting the uterine cavity may achieve lower IVF pregnancy rates if the condition affects the uterine blood flow.

In a prospective nonrandomized observational study, the effect of intramural myomas on IVF outcome has been evaluated in women with normal endometrial cavities [40]. Women with intramural myomas smaller than 5 cm in diameter were compared with control women. The authors found no statistically significant differences between the group with and without myomas. Looking at the figures, however, the women with intramural myomas had lower implantation (13.6% versus 20.2%), pregnancy (34.4% versus 47.5%), and delivery (22.9% versus 37.7%) rates. The miscarriage rate was also higher in women with myomas as compared with control women (33.3% versus 20.7%).

In one recent retrospective controlled report, although no correlation was found between location and number of myomas and IVF outcome, women with intramural myomas larger than 4 cm had significantly lower pregnancy rates as compared with those with myomas smaller than 4 cm. This study suggested that subserosal and intramural myomas of 4 cm or less in size did not affect outcome in assisted reproduction cycles and a negative influence could be expected if the size of the myoma is bigger than 4 cm [43].

In a prospective study of tubal factor infertility patients with uterine myomas, IVF outcome was compared in women who opted to undergo laparoscopic myomectomy before IVF with those who declined surgery. All patients enrolled had one to five myomas with at least one above 5 cm in diameter, none of them being submucosal. Patients who underwent surgical removal of myomas before IVF had a cumulative clinical pregnancy rate of 33%, whereas the patients without previous myomectomy had a clinical pregnancy rate of 15% [44].

The studies on the affects of myomas on fertility suffer many flaws. Many of them excluded women with large myomas or did not provide exact size and the location of the tumors [30].

A causal relationship between infertility and intramural or subserosal myomas not disturbing the uterine cavity has not been established clearly. Ideally, prospective studies with adequate power and appropriate methodology are needed to compare the pregnancy rates between women with and without uterine myomas. The IVF model seems to indicate that pregnancy rates are decreased in the presence of submucosal fibroids and can be negatively affected with large intramural myomas or myomas distorting the uterine cavity.

The affects on pregnancy

Because the uterine myomas are the most common female genital tumors, they may often coexist with pregnancy. The reported incidence of myomas during pregnancy ranges from 0.1% to 12.5% [45–48].

There are several confounding factors in analyzing the effects of uterine myomas on pregnancy. Pregnant women with myomas are more likely than controls to be over 35 years of age, primigravida, and black [48,49]. Only 42% of myomas in pregnancy are detected clinically, usually when they are large. The rate of detection falls to 12.5% with myomas less than 5 cm in diameter [50].

Pregnancy and the growth of myomas

There is controversy about whether myomas increase, decrease, or remain the same size during pregnancy. When an increase in size is detected, most of the growth takes place in the early pregnancy after which either they remain stable or decrease in size [51]. In a series of 113 pregnant women, myomas less than 5 cm in diameter increased in size and larger myomas decreased in size during the second trimester, and all the myomas got smaller in the third trimester [51]. Another study reported that 63% of myomas decreased in size, especially those less than 5 cm in diameter [52]. Some myomas do increase in size rapidly during pregnancy, however, such as a reported increase in size of a myoma from 7 to 22 cm at 25 weeks of gestation [53].

Thirty-six pregnant women with a single uterine myoma were followed by ultrasound every 2 to 4 weeks [54]. An increase in volume during pregnancy was observed in 31.6% of cases. A statistically significant change in volume was noted between the first and the third trimesters ($P < .001$). The greatest increase in volume of myomas occurred before the tenth week of gestation.

A total of 134 pregnant women with uterine myomas were followed by ultrasound at 2-week intervals until 20 weeks of gestation, and monthly thereafter. Most myomas 5 cm or less in average diameter could no longer be seen during pregnancy. Most myomas greater than 5 cm in diameter tended to remain stable or decrease in size during pregnancy. Multiple myomas were less likely to disappear than solitary myomas [52].

In a prospective study, 32 myomas of 29 pregnant women were examined by ultrasound every 3 to 8 weeks. No increase in size was observed in 25 myomas (78%). Only seven (22%) increased in size but by no more than 25% of the initial

volume [55]. It seems that the growth of myomas is usually seen in the first trimester, and many uterine myomas, particularly large ones, often get smaller late in pregnancy [51].

Red degeneration and pain

Although the incidence of symptoms related to the degeneration of myomas is low [23], uterine myomas mainly cause pain during pregnancy [45,47,48]. Pain is mostly related to the red degeneration (necrobiosis) of myomas, although it may be the result of torsion or fibroid impaction. In one study it has been shown that abdominal pain was more common in pregnant women with myomas and was associated with myoma volumes over 200 cm^3, the presence of heterogeneous echo patterns within the myoma, or the presence of cystic areas [45]. Although most patients respond well to analgesics, in some patients symptoms may be severe enough to perform myomectomy [56].

Miscarriage

Uterine myomas may increase the risk of spontaneous miscarriage during the early pregnancy. An earlier review evaluated the pertinent literature and assesses the reports of 4714 myomectomies and records of 59 personal cases in terms of symptoms, natural history, indications, and types of treatment. In 1698 cases of myomectomy preoperative symptoms were reported and 30% of patients had menstrual abnormalities. In 59 personal cases the same number was 29%. In 1941 cases of myomectomy in which preoperative and postoperative abortion rates were recorded, it was revealed that spontaneous abortion was reduced from 41% preoperatively to 19% after myomectomy [10]. Furthermore, uterine myomas have also been implicated in recurrent pregnancy loss in recent reports [57,58].

Obstetric complications

In a retrospective review of 6706 pregnancies, uterine fibroids were identified in 93 patients, and patients with uterine fibroids were compared with matched control women [46]. Women with fibroids were more likely to be older than age 35, nulliparous, or black. The proximity of the fibroid to the placental implantation site and the size of the fibroid seemed to increase the obstetric complications.

In a population-based study, the authors evaluated a large sample of women located in one state; included a control group; and controlled confounding factors, such as maternal age, race, previous cesarean delivery, maternal weight gain, diabetes, and hypertension [49]. Pregnant women with myomas who were more likely to be older than age 35, nulliparous, and black, were found to be at increased risk for first-trimester bleeding, premature rupture of membranes, placental abruption, breech presentation, prolonged labor, cesarean section, low Apgar scores, and low birth weight.

It is estimated that in women with myomas, premature labor occurs in 15% to 20%, intrauterine growth restriction in 10%, and malpresentation in 20% [59]. The location of the myomas may be important in terms of their effects on

pregnancy. Uterine myomas located adjacent to the placental site were associated with an increased risk of bleeding, abruption, and premature rupture of membranes [46,50].

Evidence-based guidelines indicate that concern about possible complications related to myomas in pregnancy is not an indication for myomectomy, except in women who have experienced a previous pregnancy with complications related to these myomas. Women who have myomas detected in pregnancy may require additional fetal surveillance when the placenta is implanted over or in close proximity to a myoma [60].

Malignancy

Malignant transformation of myomas is extremely rare. Although it has been debated whether myomas and leiomyosarcomas are part of a disease continuum, cytogenetic studies have demonstrated that leiomyosarcomas arise de novo and may be unrelated to benign myomas [61,62]. Recent microarray data, however, identified a rare subset of myomas with deletions of chromosome 1 that have transcriptional profiles that cluster with those of leiomyosarcomas [3], suggesting that some rare leiomyosarcomas may arise from a specific subset of myomas.

An earlier pathologic study of presumed myomas reported 0.29% of tumors to be malignant [63]. Another clinicopathologic study even reported a rate of 0.13% [64]. These figures were quoted for the myomas that had been removed by surgery. Because many myomas are not operated on, the real figures may be expected to be lower.

The size of some uterine myomas may be significant and the growth rate may be rapid. The rapid growth of uterine myomas was arbitrarily defined as a gain of 6 weeks or more in gestational size within an interval of a year or less. In the past, the rate of myoma growth was considered as a risk factor for transition to leiomyosarcoma. Recent data have not supported an association between rapid growth of a myoma and an increased risk for malignancy.

A retrospective study reviewing 1332 women operated on for uterine myomas showed that leiomyosarcoma incidence was less than 2% in postmenopausal women and 0.23% in premenopausal women. One out of 371 women operated on for rapidly growing myomas was found to have a leiomyosarcoma [65]. In another study, after surgery, leiomyosarcoma was found in only 3 (0.17%) of 1815 pathologic specimens [10]. The mean age of patients with uterine leiomyosarcoma was 51 and patients were usually symptomatic. The diagnosis of uterine sarcoma should be considered in those postmenopausal women with a pelvic mass, abnormal bleeding, and pelvic pain.

The preoperative diagnosis of leiomyosarcoma may be a challenge and many different techniques have been suggested. In a prospective cohort study, 130 patients with degenerated uterine myomas and 10 with leiomyosarcoma underwent MRI and serum lactate dehydrogenase determinations before their treatment

[66]. Sixty seconds after the administration of the contrast, an enhancement was detected in all 10 leiomyosarcoma patients, whereas the contrast enhancement was absent in 28 of 32 degenerated uterine myoma patients. Both total lactate dehydrogenase and lactate dehydrogenase isozyme type 3 levels were elevated in all 10 patients with leiomyosarcoma. The authors concluded that the combined use of dynamic MRI and serum lactate dehydrogenase isozymes might be helpful in differential diagnosis of leiomyosarcoma from degenerated uterine myomas before any treatment decisions were made.

As a part of the preoperative planning, the needle biopsy of the uterine soft tissue tumors has been suggested to be helpful if there is a concern regarding the presence of a leiomyosarcoma. In a prospective study, transcervical needle biopsy was performed in 435 patients with presumed uterine myomas. Seven patients had uterine sarcomas and four of these were diagnosed with needle biopsy alone [67].

The telomerase activation is thought to be essential for immortality of malignant cells. The telomerase activity in needle biopsy samples is another potential useful diagnostic marker to distinguish uterine sarcoma from myoma. In a prospective study, 62 women with suspected uterine sarcomas based on clinical and MRI findings underwent preoperative transcervical ultrasound-guided needle biopsy. At a cutoff value of 20 units for telomerase activity, sensitivity, specificity, positive predictive values, and negative predictive values for detecting uterine sarcoma were 86% (95% confidence interval, 59%–100%), 100% (94%–100%), 100% (54%–100%), and 98% (95%–100%), respectively [68].

Needle biopsy combined with MRI screening may reduce the number of patients undergoing unnecessary surgery with the sole concern of leiomyosarcoma, although more studies are needed.

Rare associations

Myomas may attach to omentum (parasitic myoma) whose eventual blood supply is derived solely from the omental vessels. Floating myomas may result in torsion or obstruction of these vessels, which in turn may lead to transudation of fluid and the development of ascites. Rarely, a secondary polycythemia is detected in women with uterine myomas. This entity is related to elevated levels of erythropoietin. The polycythemia resolves following hysterectomy.

There are several reports of familial clustering of uterine myomas, which have suggested that myomas are fourfold to fivefold more common in first-degree relatives of women with myoma compared with the general population [69,70]. In addition, some inherited disorders associated with myomas have been defined. Reed's syndrome, a rare inherited disorder, is characterized by the appearance of multiple myomas in skin, uterus, or both [71]. Recently, reports of several families in Finland and England with multiple uterine and cutaneous myomas and papillary renal cell carcinoma were linked to mutations in the fumarate hydratase

gene [72]. Furthermore, mutations in the tuberous sclerosis 2 tumor suppressor gene leading to renal angiomyolipomas, cysts, and carcinoma in humans are frequently associated with uterine myomas in the Eker rat animal model, which may have clinical implications [73]. The finding of cutaneous myomas in a woman should prompt screening of the patient and her family not only for renal cell carcinoma but also for uterine sarcomas, which are more frequent in those patients and their immediate relatives.

Benign metastasizing uterine myoma is characterized by myoma-like lesions, usually in the lungs, in women with myomas [3]. Intravenous leiomyomatosis is a hormonally responsive disease that manifests as vermiform extensions originating in the uterus that can extend as far as the heart.

Changes in symptoms over time

There are few long-term longitudinal studies available to help assess the changes in symptoms that occur with uterine myomas over the course of time. In a 12-month follow-up study, of the women with uterine myomas (N = 229) who were managed either by observation (68%), nonsteroidal anti-inflammatory agents (18%), or sex steroids (14%) 40% experienced vaginal bleeding, 43% reported pain, and 48% described fatigue [74]. In newly diagnosed patients it is prudent to re-evaluate patients with asymptomatic uterine myomas with clinical examination in 3 to 6 months and then as needed to exclude rapid growth and development of symptoms.

Summary

Uterine myomas are the most common solid pelvic tumors in women and the primary indication for hysterectomy. Most of the myomas are asymptomatic. The most common symptoms associated with uterine myomas are abnormal uterine bleeding and pelvic discomfort mostly caused by the mass effect. Vaginal bleeding may lead to iron deficiency anemia. Uterine myomas have a significant role in reproductive dysfunction, although a causal relationship between infertility and intramural or subserosal myomas not disturbing the uterine cavity has not been established clearly. Nevertheless myomas, especially the tumors distorting the uterine cavity, are associated with infertility and spontaneous miscarriage. In addition, the myomas may be the potential cause for numerous obstetric complications, especially if they are located adjacent to placenta. The transformation of myomas to leiomyosarcomas is a very rare event. Leiomyosarcomas may be suspected in postmenopausal women with rapidly growing symptomatic solid pelvic mass. Despite the high prevalence of these tumors, there is paucity of data available regarding the natural clinical history of myomas.

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Diagnostic Imaging of Myomas

Danielle Vitiello, PhD, MD*, Shirley McCarthy, PhD, MD

Department of Obstetrics and Gynecology, Yale University School of Medicine, 333 Cedar Street, TE-2, P.O. Box 208042, New Haven, CT 06520-8042, USA

Uterine leiomyomas are the most common gynecologic neoplasm. They occur in 70% of women and are believed to be symptomatic in approximately 30% of women who are older than 30 years of age [1,2]. Often, their presence is heralded by worsening menstrual irregularities, pelvic pain, and reproductive dysfunction. Bimanual examination has been the diagnostic standard with confirmatory imaging studies. Historically, the mainstay treatment approach has been surgical. Hysterectomy was the therapy of choice; a myomectomy was performed if uterine preservation was of issue. The sophistication of more conservative treatment options commands that we be able to localize, map, and characterize leiomyomas in an effort to provide patients with a treatment approach that is best suited to their needs. Therefore, it is essential that imaging techniques be able to differentiate benign conditions that are amenable to alternative therapies from potentially malignant conditions that necessitate surgical intervention.

Leiomyoma may be solitary neoplasms; however, they most often appear as multiple, separate entities that vary in size and location throughout the myometrium. The overwhelming majority of leiomyomas are found within the uterine corpus with a minority located in the cervix and broad ligament. Uterine leiomyomas are categorized according to location: intramural, submucosal, and subserosal (which may be broad-based or pedunculated).

The etiology of uterine leiomyomas has not been defined precisely. Each discrete fibroid is composed of a clonal population that is derived from a single, progenitor myometrial cell [3]. Approximately 40% of these progenitor cells demonstrate aberrant cytogenetic alterations. Such chromosomal mutations may enhance the cellular response to steroids and other growth factors, and thus, alter

* Corresponding author.
E-mail address: vitiello69@yahoo.com (D. Vitiello).

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their growth potential when compared with myometrial cells under appropriate cell-cycle control [4,5].

Macroscopically, they are firm, circular, whorllike bundles of smooth muscle that are encapsulated by a discrete fibrinous pseudocapsule. Their growth capacity is determined by their vascular supply. In general, the arterial tributaries are in the base of the myoma and supply less blood to the myoma then would be supplied to a comparable normal myometrium. As it outgrows its vascular support, the leiomyoma undergoes degeneration.

The severity of the discrepancy between supply and demand determines the degree of degeneration incurred. The mildest form is hyaline degeneration, where cellular detail is replaced by dense, fibrous tissue. Small blood vessels within the area of hyaline necrosis undergo similar histologic change [6]. Degenerative changes within the fibroid blood vessels is one of the sentinel characteristics that is used in differentiating benign, degenerating leiomyomas from the coagulative necrosis that is seen in leiomyosarcomas where vessels are preserved [7]. Further benign variants include myxoid degeneration with or without a cystic component and the more symptomatic red degeneration of the acutely infarcting fibroid. Carneous, or red degenerating fibroids are soft, and appear pink and homogenous immediately after infarct of venous tributaries. With time, they become uniformly white and calcify [6].

Imaging

Continued pathologic–radiologic correlation serves to enhance our ability to diagnosis and to treat pathologic conditions of the female reproductive tract. Knowledge of pathology-induced anatomic changes is essential in optimizing information that is gained from imaging technology. Because each modality has strengths and limitations, the most appropriate choice of imaging study promotes accurate diagnosis, improves management, and reduces the need for unnecessary intervention.

Transvaginal ultrasonography

The gold standard for imaging of the female pelvis is transvaginal ultrasound (TVUS). Secondary to its availability, ease of use, and relative low cost, it continues to be an effective initial means of assessment [8]. The efficacy of this technique is highly operator dependent [9] and can vary from 65% to 99% [10,11]. The sensitivity of sonography continues to improve with the use of higher frequency probes and the development of intrauterine probe placement [12]. The mapping accuracy does decrease in larger uteri and in those that contain multiple fibroids. Furthermore, smaller fibroids and subserosal fibroids may not be detected by TVUS (Fig. 1). More importantly, transvaginal sonography is

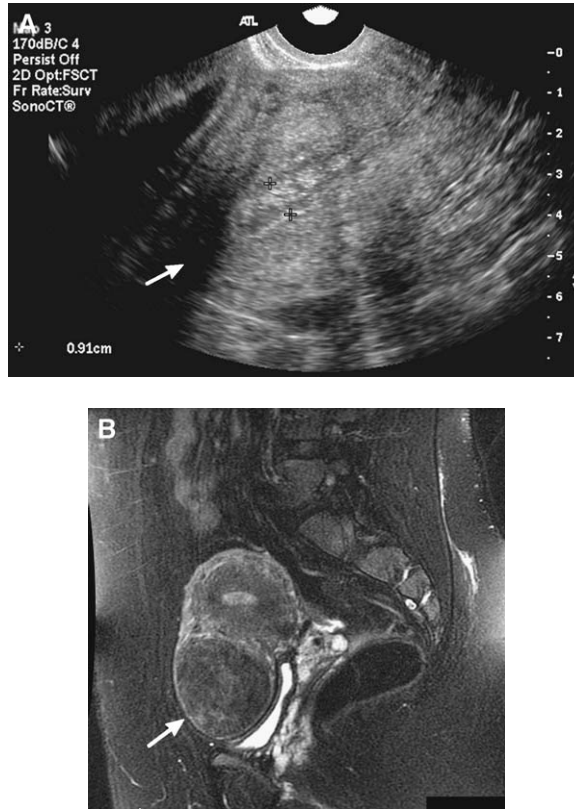

Fig. 1. (*A*) TVUS does not demonstrate a subserosal fibroid adequately (*arrow*). (*B*) Sagittal T2-weighted MRI demonstrates large subserosal fibroid (*arrow*) emanating from the anterior wall of the uterus. Note the bladder compressed posteriorly.

imprecise in distinguishing leiomyomas from leiomyosarcomas [13] and adenomyosis [14,15].

The addition of sonohysterography (SHG) to TVUS greatly improves the sensitivity in detecting submucosal fibroids [16–18]. The sensitivity and specificity for the detection of focal endometrial lesions is 70% and 96%, respectively [19]. Adjunct SHG increased the sensitivity to 90% and the specificity to 93% [19].

Few studies have compared imaging modalities and accuracy directly in leiomyoma diagnosis using pathologic specimens. Dueholm and colleagues [10] used a double blinded study in which the accuracy of measurement and mapping of leiomyomas, using MRI and TVUS, were verified by pathologic specimen after hysterectomy. In brief, 106 consecutive, premenopausal women who were scheduled for hysterectomy were enrolled. Indications for hysterectomy included: abnormal uterine bleeding (48%), symptomatic myomas (33%), pelvic pain (16%), and previous borderline ovarian tumor (3%). Before hys-

terectomy, myomas were mapped to uterine wall embedment (subserosal, transmural or submucosal) and uterine zones (anterior, posterior wall; corpus, fundus; left, right, or medial) and then compared with the hysterectomized uterus en bloc.

They found that the sensitivities of these techniques were equally accurate in their detection of myomas; however, MRI was superior in leiomyoma mapping. In addition, when uterine volume exceeded 375 mL, or when the number of myomas increased, the efficacy of TVUS decreased markedly (73%). Acoustic shadows, larger uteri that extended outside of the visual field, and myomas that obscured other myomas accounted for the increased inaccuracy.

CT

There is no role for CT in the work-up of leiomyomas; however, myomas can be seen incidentally on CT scans that are performed for other reasons. The most common finding is uterine enlargement or contour deformity. Myomas exhibit a range of enhancement. Although calcification is seen in less than 10%, it is the most specific finding. CT cannot distinguish myomas from other uterine or cervical masses reliably [20].

MRI

In addition to the benefits of sonography in uterine fibroid detection, MRI affords precise spatial resolution [21] and provides information with regard to morphologic subtypes [22]. It is the most accurate imaging modality for the diagnosis, mapping, and characterization of leiomyomas [13]. The use of

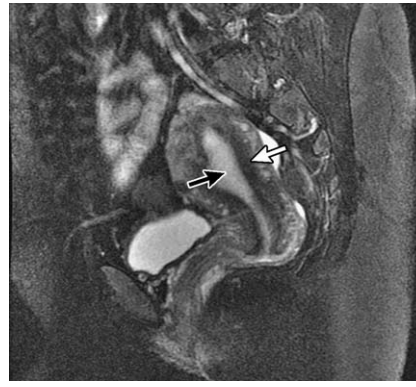

Fig. 2. Sagittal T2-weighted scan demonstrating the zonal anatomy visualized with MRI. The endometrium and endocervical canal are a bright or hyperintense (*black arrow*), whereas the junctional zone (the inner myometrium) is a dark surrounding band (*white arrow*).

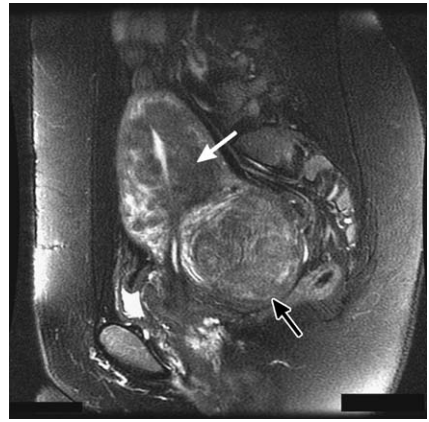

Fig. 3. Sagittal T2-weighted image shows large subserosal fibroid emanating from the posterior wall (*black arrow*) with a thin peripheral rim (dilated veins or lymphatics). The thickened junctional zone indicates adenomyosis (*white arrow*).

T2-weighted sequences provides the contrast resolution that is necessary to delineate detailed pelvic anatomy and makes MRI far superior to CT.

Three distinct uterine zones are noted on T2-weighted images (Fig. 2). The endometrium is of high signal intensity. The surrounding low-signal band is called the junctional zone, which represents inner myometrium where there is an increased nuclear ratio of condensed myometrial cells, decreased water content, and extracellular matrix [23–25]. The junctional zone is histologically indistinct from the remainder of the myometrium [26], which is intermediate in signal [27].

Nondegenerated leiomyomas display characteristic features on MRI. On T2-weighted pulse sequences, they appear as low signal intensity (Figs. 3 and 4). In approximately 30% of fibroids that are imaged compression of the surrounding

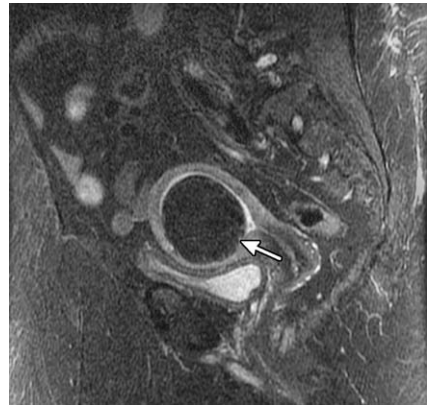

Fig. 4. Sagittal T2-weighted scan demonstrates large submucosal fibroid (*arrow*) that is low signal, which is typical of hyaline change.

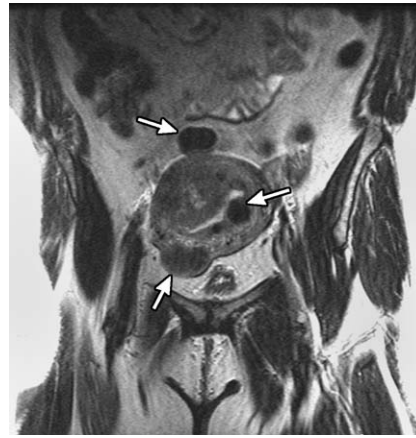

Fig. 5. Coronal T2-weighted scan shows three myomas: one submucosal and two subserosal (*arrows*). Heterogeneity in the posterior wall is adenomyosis.

myometrium by neighboring cells often results in a thin, hyperintense rim that is composed of dilated veins, lymphatics, or edema [28]. There is clear demarcation in signal intensity between the leiomyoma and that of the higher intensity myometrium (Fig. 5).

MRI has a 70% accuracy rate in the diagnosis of benign histologic subtypes of fibroids [22]. Cellular leiomyomas contain compacted smooth muscle with little collagen, and as a result, they have a higher signal [29]. Degenerated fibroids have variable appearances on MRI. In contrast, the appearance of a calcified or hyalinized leiomyoma is comparable to a nondegenerated one. Cystic changes

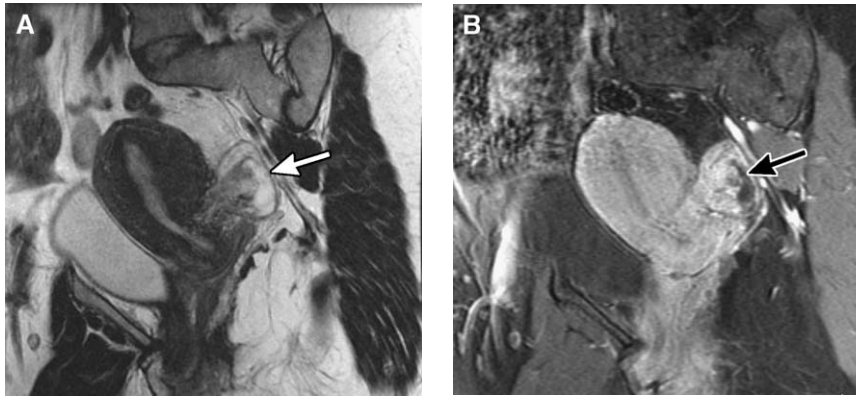

Fig. 6. (*A*) Sagittal T2-weighted scan demonstrates a primarily hyperintense mass arising from the lower corpus/upper cervix (*arrow*). (*B*) Sagittal T1-weighted scan after intravenous gadolinium demonstrates a pattern of enhancement that is indicative of myxomatous degeneration of a myoma.

within the leiomyoma appear hyperintense and do not enhance after intravenous contrast. Myxoid degeneration also demonstrates areas of high signal intensity, but there are linear or septated regions of contrast enhancement (Fig. 6) [30]. Lipoleiomyomas can be diagnosed on MRI with the use of chemically selective fat-suppression sequences (Fig. 7) [31].

Necrotizing leiomyomas may have components of necrotizing or coagulative necrosis, and thus, display variable signal intensities on T1- and T2-weighted images. Acutely infarcting fibroids exhibit high signal intensity on T1-weighted images, whereas they often are of variable intensity, sometimes with a surrounding hypointense rim, on T2-weighted scans [30,32]. These carneous fibroids are accompanied by fever and the acute onset of abdominal pain, which assist in the diagnosis (Fig. 8).

Obvious concern is for the ability to delineate benign from malignant conditions, particularly when such signaling variability exists among the different

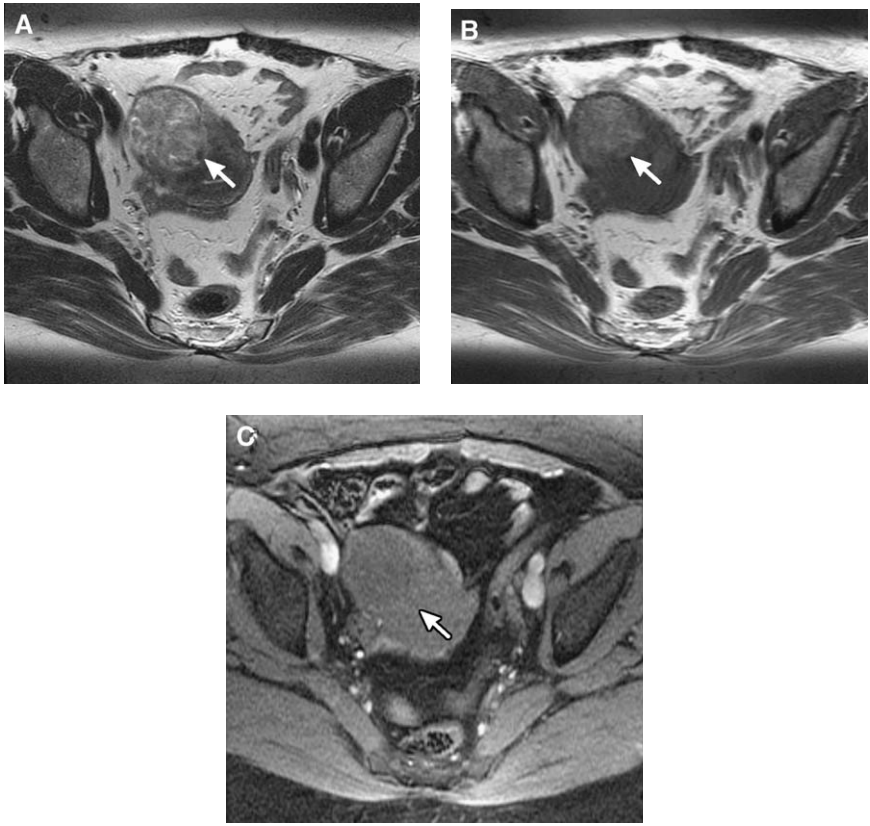

Fig. 7. (*A*) Axial T2-weighted scan exhibits a subserosal myoma (*arrow*) that has internal signal that is isointense with fat. (*B*) Axial T1-weighted image also shows internal signal that is isointense with fat (*arrow*). (*C*) Fat-suppressed sequence proves that high signal is fat because it suppresses (*arrow*) and, therefore, the mass is a lipoleiomyoma.

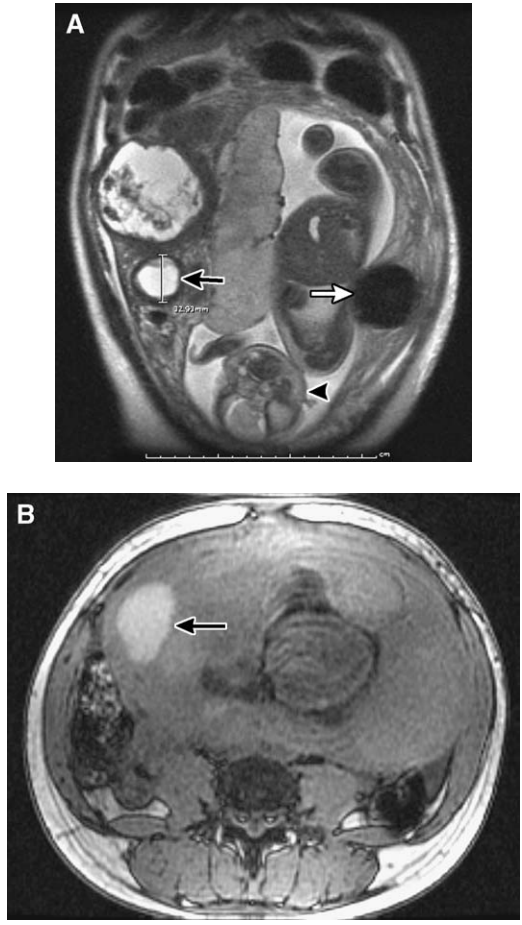

Fig. 8. (*A*) Pregnant woman with acute right flank pain. Coronal T2-weighted scan demonstrates two hyperintense myomas on the right that are degenerated; the more inferior one (*black arrow*) measures approximately 3 cm and exhibits a dark rim. The hypointense myoma (*white arrow*) in the left uterine wall is not degenerated. (*B*) Axial T1-weighted image shows the smaller myoma is hyperintense (*black arrow*) because of hemorrhage, and therefore, has infracted acutely and accounted for the patient's pain.

subtypes. Other than in carneous degeneration, hemorrhage and necrosis within leiomyomas are rare and should alert the reviewer to the possibility of more formidable disease [32].

Cellularity and degree of atypia are used morphologically to define smooth muscle neoplasms on the pathologic specimen. Moreover, such a diagnosis can be challenging to the pathologist's eye. MRI lacks the microscopic sensitivity to differentiate localized, increased mitotic indices; however, regions of higher cellularity can translate into hyperintense signal on T2-weighted images [29].

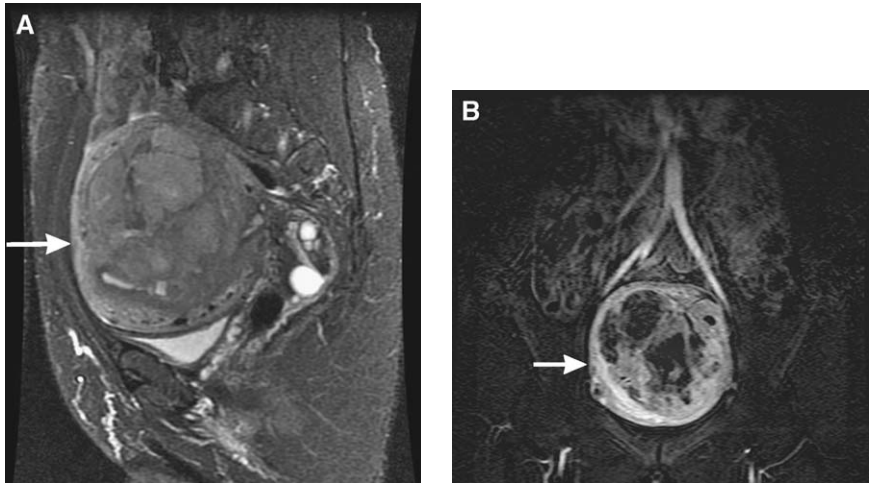

Fig. 9. (*A*) A middle-aged woman who was believed to have uterine enlargement from a myoma. Sagittal T2-weighted scan shows a mass (*arrow*) primarily in the posterior wall that is heterogeneous and ill-defined. (*B*) Following intravenous gadolinium, coronal image shows areas of necrosis that are consistent with leiomyosarcoma.

There are suggestive MRI findings that elicit further investigation. Leiomyosarcomas tend to be larger, heterogenous masses that harbor regions of hemorrhage and coagulative necrosis [7,33]. Hemorrhage within necrotic foci increases T1-weighted signal intensity [34]. The solid component of the sarcomas are enhanced markedly and the margins are ill-defined in contradistinction to benign myomas, which exhibit a well-defined margin because of their pseudocapsule (Fig. 9). Sadhev and colleagues [35] demonstrated that 25% of histologically confirmed uterine sarcomas demonstrated endometrial masses that more closely resembled MRIs of endometrial cancer. Along with patient demographics, history, and clinical presentation, these criteria allow radiologists to confirm the diagnosis with confidence.

Summary

As treatment options become less invasive and more sophisticated it is imperative that benign myomas be distinguished from potential malignant conditions without falter. The radiologic–pathologic correlations have been integral to our ability to characterize and to localize uterine leiomyomas with accuracy. TVUS remains the standard assessment tool. Its usefulness may be enhanced by SHG or transabdominal ultrasound in certain circumstances; however, it falls short in its ability to map multiple myomas or those in large volume uteri. MRI has become ultrasound's complement and far exceeds ultrasound's technical limitations in precise fibroid mapping and characterization.

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Options for Medical Treatment of Myomas

Beth W. Rackow, MD, Aydin Arici, MD*

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, & Reproductive Sciences, Yale University School of Medicine, P.O. Box 208063, New Haven, CT 06520-8063, USA

Uterine myomas are the most common benign tumor in women of reproductive age, and affect 20% to 50% of this population. The prevalence of these tumors increases with age [1–4]. Symptoms associated with these smooth muscle cell tumors include pelvic pressure and pain, dysmenorrhea, abnormal bleeding, dysfunction of adjacent organs such as bowel and bladder, and reproductive dysfunction including infertility; however, many patients are asymptomatic [1,4–7]. Approximately 30% of women who have myomas experience menstrual abnormalities, and menorrhagia is the most common abnormality [1]. The presence or severity of symptoms depends on the number, size, and location (subserosal, intramural, submucosal, or intracavitary) of the myomas [5]. In the United States, 600,000 hysterectomies are performed annually, and myomas are the indication for almost 40% of these surgeries [8]. For women who are affected by uterine myomas and prefer conservative management, several medical therapies are available. Most current medical therapies target myomas by manipulating their hormonal environment.

It is well established that myomas are hormonally responsive, and myoma growth has some dependence on the ovarian steroid hormones estrogen and progesterone [5,9]. The growth patterns of these benign neoplasms are influenced by the hormonal milieu. They rarely are observed before puberty; are most prevalent and tend to grow during the reproductive years; can grow during times of elevated steroid levels, such as in pregnancy; and typically regress during menopause [5]. Risk factors for myoma development include obesity, early age of first menarche, race, and infertility, whereas protective factors include smoking, exercise, oral contraceptive use, and parity [6,10,11]. Certain protective factors,

* Corresponding author.
E-mail address: aydin.arici@yale.edu (A. Arici).

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such as oral contraceptives and pregnancy, are associated with high estrogen and progesterone concentrations, thus nonhormonal factors also must be involved with myoma development [6].

Numerous studies have investigated factors that contribute to the development and growth of uterine myomas. Current knowledge about the factors involved in the control of myoma development and growth is a complex topic, and only hormonal factors are briefly reviewed. Studies have identified estrogen and progesterone receptors within myomas, receptor concentrations varied with the menstrual cycle, and both receptors had higher concentrations in myomas than in the surrounding myometrium [12,13]. One study identified that leiomyoma and myometrial smooth muscle cell DNA synthesis was stimulated by estrogen and progesterone, and was inhibited by estrogen and progesterone antagonists [14]. Furthermore, in myomas the proliferative activity and mitotic count were higher in the secretory phase [13,15,16], and mitotic activity was significantly higher with progestin therapy [17]. Aromatase P450, an estrogen synthetase, also has been identified within myomas and likely enables myomas to synthesize their own estrogen and promote myoma cell growth [18,19]. Other studies noted endometrial gland hyperplasia located at the periphery of submucosal myomas; this finding suggests a localized hyperestrogenic environment [20,21]. Thus, evidence suggests that myoma proliferation is controlled, at least in part, by the ovarian steroid hormones estrogen and progesterone [10,13,16]. Maruo and colleagues [22] further studied this complex interaction and suggested that progesterone has a dual effect on myomas; progesterone stimulates leiomyoma cell growth by up-regulating epidermal growth factor and Bcl-2 protein while down-regulating tumor necrosis factor α, and inhibits myoma cell growth by down-regulating insulin-like growth factor-I expression. Thus, local growth factors are involved in myoma growth and may mediate the growth-promoting effects of estrogen and progesterone on the uterus [6,23]. Genetic factors, vascular abnormalities, and response to injury also may play roles [24], but these topics are beyond the scope of this article.

This article discusses available therapies for the medical management of myomas and the risks and benefits of each medication, and considers future therapy options.

Estrogen and progestin therapy

Estrogen and progestin therapy, in combination or progestins alone, often are the first-line of treatment for patients with uterine myomas and abnormal uterine bleeding. Although these therapies may manage myoma-associated bleeding or abnormal uterine bleeding successfully by producing endometrial atrophy and stabilization, this is a temporary measure, and they have not been shown to reduce myoma size [5,25]. In vitro evidence suggests that estrogens and progestins can function as growth stimulants for myomas; therefore, these therapies should be used judiciously in patients with symptomatic myomas [26].

Few studies have investigated the effects of oral contraceptives or progestins alone on myoma growth; most studies have evaluated these medications in conjunction with gonadotropin-releasing hormone (GnRH) agonists. One estrogen-progestin study investigated a self-selected group of 82 women with symptomatic myomas who opted for conservative management [27]. In this nonrandomized study patients took a low-dose monophasic oral contraceptive for 12 months or no hormones. Oral contraceptives were associated with a significantly decreased mean duration of menstrual flow from 5.8 to 4.4 days, increased mean hematocrit from 35.8% to 37.8%, and no significant difference in mean uterine size as noted by bimanual examination or ultrasound at 12 months [27]. Despite selection bias, lack of blinding, and small size, this study demonstrated that oral contraceptives may improve menorrhagia in the setting of myomas, and might not cause uterine or myoma growth. Another study used data from the Nurses' Health Study II to investigate any association between oral contraceptive use and incidence of myomas; only women who first used oral contraceptives at 13 to 16 years of age had a significantly elevated risk for developing myomas [11].

Progestin studies have shown mixed results in the treatment of myomas. Several studies documented a decrease in the size of a myomatous uterus during progestin therapy [4]. One study administered medroxyprogesterone acetate (Depo-Provera), 150 mg/mo for 6 months, to 20 premenopausal women who had symptomatic myomas [28]. The results were significant for a 30% amenorrhea rate, 70% resolution or improvement in bleeding, 15% mean increase in hemoglobin levels, and a reduction in mean uterine (48%) and mean myoma volumes (33%) [28]. Although larger randomized studies are indicated, this therapy may be valuable in regions of the world where other therapies are not available [28]. In contrast, other small studies and case reports showed a marked enlargement of myomas during progestin therapy, an effect that reversed after the therapy was discontinued [29,30]. Furthermore, several studies that used GnRH with hormonal add-back therapy to treat myomas determined that estrogen-progestin add-back caused no change in myoma growth; however, significant myoma growth occurred with the use of progestins [31–33]. In vitro data support this clinical finding; the mitotic activity in myomas was significantly greater with progestin therapy, whereas mitotic activity with estrogen-progestin therapy and in controls was the same [17]. The limited data on estrogens, progestins, and myomas reveal that estrogen plus progestin may have minimal effect on myoma growth, whereas there is significant potential for myoma growth with progestin therapy.

Steroid synthesis inhibitors

Gonadotropin-releasing hormone agonists

GnRH's are the most established, most successful therapy for the medical management of myomas [9]. They effectively down-regulate GnRH receptors at the level of the pituitary, and cause profound reductions in follicle-stimulating

hormone (FSH), luteinizing hormone (LH), and ovarian steroid hormones, and thus, produce a hypoestrogenic state [3,9]. This results in amenorrhea and a rapid decline of uterine and myoma size by 35% to 65%; the decrease in size is most pronounced within 3 months of treatment [3]. Although a significant decrease in uterine volume is expected, individual myomas are heterogeneous, and thus, demonstrate a variable response to GnRH's, with a 0% to 100% reduction in volume [23]. GnRH's also suppress the expression of aromatase P450, an estrogen synthetase found in myoma cells, which decreases in situ estrogen production and may contribute to myoma shrinkage [19]. Myoma symptoms, such as bleeding, pelvic pressure and pain, and distortion of adjacent organs, are known to improve with GnRH therapy [7]. The benefits of GnRH's, however, are tempered by significant side effects due to hypoestrogenism—hot flushes, headaches, vaginal dryness, depression, and bone demineralization that leads to osteoporosis [2,4,5,9,23]. Furthermore, after discontinuation of therapy, myomas tend to grow back to their original size or larger over several months [2,3,7,9,23,34,35]. Although the side effects of GnRH's can be alleviated by add-back therapy using estrogen, progestin, or both, the addition of hormones can limit the effectiveness of this therapy in reducing uterine and myoma size [31–33]. Therefore, when treating myomas, this therapy is not appropriate for prolonged use in premenopausal patients, and is best suited for the perimenopause or a preoperative period [2–4,7].

Several studies documented the regression of uterine myomas in response to GnRH's, and the benefits of GnRHa use before surgery [31–34,36,37]. One double blind, placebo-controlled study used monthly administration of leuprolide acetate depot (Lupron), for 24 weeks, and MRI identified a 30.4% decline in myoma volume, a 42.7% decline in nonmyoma volume, and an improvement in myoma-related symptoms [35]. Another randomized, controlled trial of preoperative leuprolide acetate depot noted that at 12 weeks the median uterine volume decreased by 31% to 39%, and the median myoma volume decreased by 23% to 27% [38]. Vercellini and colleagues [37] also conducted a randomized, controlled trial to compare abdominal myomectomy with and without preoperative GnRH therapy for 2 months. A 22% reduction in myoma volume was noted in the group that received GnRH's; however, at surgery there was no significant difference in blood loss, duration of surgery, postoperative morbidity, and hospital stay between the groups. Six months after surgery, a trend toward higher rates of myoma recurrence were noted in the group that received GnRH's. The investigators concluded that anemia was the only indication for preoperative GnRH use. Before this study, Lethaby and colleagues [36] performed a systematic review of 26 randomized, controlled trials that evaluated the use of GnRH's in patients before hysterectomy or myomectomy. These investigators concluded that GnRH's effectively increased preoperative hematocrit in anemic patients, significantly reduced uterine and myoma volume, enabled the use of a transverse incision instead of a vertical incision, allowed the conversion from an abdominal hysterectomy to a vaginal approach, and reduced intraoperative blood loss. Because of inadequate data, the study was unable to assess the effects of GnRH's on

the risk for myoma recurrence after myomectomy. Overall, the available data demonstrate that GnRH agonists significantly reduce uterine and myoma volume, and are considered a valuable preoperative therapy for patients who have anemia or large myomas.

In contrast, studies of GnRH use with hormonal add-back therapy demonstrated different results. Friedman and colleagues [32,33] studied leuprolide acetate depot with daily estrogen and cyclic progestin, or daily progestin in 51 premenopausal women with myomas. Both groups received GnRH's alone for 3 months, and mean uterine volume decreased by 40%. The group that received estrogen-progestin add-back demonstrated no further change in uterine volume; however, mean uterine volume increased to 87% of pretreatment size by 12 months and 95% by 24 months in the group that received progestin add-back. Bone mineral density decreased by 3% overall after 3 months of GnRH's alone, and did not change significantly with either add-back regimen. Furthermore, amenorrhea persisted, hemoglobin and hematocrit increased, and menopausal symptoms improved with both add-back regimens. A similar study investigated the effectiveness of GnRH's with concomitant versus delayed medroxyprogesterone acetate (MPA) [31]. The predominant effect of GnRH's was on nonmyoma uterine volume; this finding also was noted in another study [35]. Nonmyoma volume refers to the difference between total uterine volume and myoma volume, the calculated volume of the myometrium [31,35]. The addition of MPA at the start of the GnRH therapy inhibited the decline in total uterine volume that was expected with GnRH's, and the addition of MPA after 12 weeks of GnRHa therapy caused a significant increase in uterine volume [31]. Despite the beneficial effects of GnRH's on uterine and myoma volume, the addition of progestins, and possibly the addition of estrogen and progestin, reduces the effectiveness of the GnRH's on both parameters.

Gonadotropin-releasing hormone antagonists

GnRH antagonists also have been used to treat myomas, often before surgery. Unlike the GnRH's, which initially stimulate gonadotropin release, GnRH antagonists block pituitary GnRH receptors and cause an immediate decline in FSH and LH. This rapid effect enables a shorter duration of treatment and related side effects, and pituitary function normalizes upon cessation of treatment [39–42]. Studies that investigated the effects of two GnRH antagonists (ganirelix and cetrorelix) in women with symptomatic myomas identified an overall reduction in myoma and uterine volume [40–42]. One recent study used ganirelix to treat 20 premenopausal women who were scheduled for surgery for symptomatic myomas [41]. The median reduction in myoma volume was 43% by ultrasound and 29% by MRI, the median decrease in uterine volume was 47% by ultrasound and 25% by MRI, and the median duration of treatment to achieve maximal myoma size reduction was 19 days (range, 1–65 days). Thus, within 3 weeks of GnRH antagonist therapy, a 25% to 40% regression in myoma volume was noted. This degree of myoma reduction is comparable to that achieved with GnRH

therapy, but the time course was much shorter, and surgery was able to be scheduled sooner. Common side effects were hot flushes and headaches, and both improved after discontinuation of the medication [41]. Although GnRH antagonists may treat symptomatic myomas effectively, larger studies are needed to evaluate preoperative use, to investigate how myomas behave after discontinuation of this therapy, and to compare myoma response to GnRH antagonists and GnRH's directly.

Aromatase inhibitors

Aromatase inhibitors directly inhibit ovarian estrogen synthesis and rapidly produce a hypoestrogenic state [18,50]. Serum estrogen levels decrease after 1 day of treatment [51]. This can be contrasted with GnRH's which indirectly inhibit ovarian estrogen synthesis, cause an initial flare-up period with resulting hyperestrogenism, and then produce a hypoestrogenic state [18,50]. Myomas are known to overexpress aromatase, an estrogen synthetase, which suggests that myomas may produce their own estrogen [18,19], and that aromatase inhibitors can target this local source of estrogen. One case report discussed the use of fadrozole to treat a 53-year-old woman with a 20-weeks-pregnant size myomatous uterus that caused acute urinary retention [50]. Myoma volume declined by 61% at 4 weeks and 71% at 8 weeks, and the urinary retention resolved by 14 days [50]. Fadrozole may have caused myoma regression by targeting local aromatase activity. Aromatase inhibitors are a promising therapy for myomas because of their rapid hypoestrogenic effect, and the possibility of initiating therapy at any time in the menstrual cycle. This class of medication may be developed to have a differential effect on ovarian and myoma estrogen production, and thus, could act preferentially to cause myoma shrinkage without causing hypoestrogenism and the related adverse effects [18]. Further research on aromatase inhibitors as a therapy for uterine myomas is necessary in the reproductive-aged population.

Steroid receptor modulators

In the search for a myoma therapy with beneficial effects that are equal to those of GnRH's without the side effects, investigators have studied other medications that manipulate estrogen and progesterone. Several therapies that target estrogen or progesterone have proven effective in managing uterine myomas. Although estrogen has long been considered a factor in the development of myomas, there is increasing evidence that progesterone plays a critical role in this process.

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) are nonsteroidal agents that bind to the estrogen receptor and exhibit estrogen agonist or antagonist effects,

depending on the target tissue [10]. Tamoxifen is a SERM that acts as an antagonist in breast tissue, and has agonist effects on bone, cardiovasculature, and endometrium. The agonist action on the endometrium causes an increased risk for endometrial hyperplasia and cancer [10]. Sadan and colleagues [43] performed a small prospective study to investigate tamoxifen's effects on the symptomatic myomatous uterus over 6 months. The study determined that tamoxifen did not affect uterine size, although menstrual blood loss and intensity of pelvic pain improved with this therapy. The side effects of the treatment were significant; the study group experienced ovarian cyst formation, hot flushes, dizziness, and endometrial thickening, of which all biopsies were negative. The investigators concluded that this therapy had marginal benefit for treating symptomatic myomas, but unacceptable side effects.

Raloxifene, another SERM, has been studied further as a treatment for uterine myomas. This SERM, unlike tamoxifen, has no agonist activity on endometrium and subtle antiestrogenic effects [10,44]. Palomba and colleagues [45] studied postmenopausal women with uterine myomas who were treated with raloxifene, 60 mg/d, or placebo for 12 months. The patients who received raloxifene demonstrated significantly decreased uterine and myoma size at 6, 9, and 12 months, and the treatment seemed to target the myomas with less effect on normal myometrium. Raloxifene showed promise in premenopausal women with asymptomatic uterine myomas, but a higher dosage of medication was required. One study noted that dosages up to 180 mg/d did not affect uterine or myoma size significantly, disrupt normal ovarian cycling, or affect the length or severity of bleeding [46]. However, myoma growth may have been inhibited by the 180-mg dosage; subjects in the groups that received the 60-mg dosage or placebo had new myomas diagnosed during the study [46]. A similar, smaller study noted a nonsignificant decrease in myoma size in the study group (raloxifene, 180 mg/d for 3 months) compared with the ''no treatment'' control group, and the control group experienced an increase in myoma volume [47]. Again, there was no myoma growth in the treatment group.

This early data on raloxifene and myomas, especially the marked effects that were noted in postmenopausal women [45], led to further studies that used concomitant GnRH's to decrease endogenous estrogen levels. Palomba and colleagues [48] studied 100 premenopausal women with symptomatic myomas and received GnRH's plus raloxifene, 60 mg/d, or GnRH's with placebo for 6 months. Both groups demonstrated a significant decrease in uterine, myoma, and nonmyoma sizes, and myoma symptoms improved overall; however a significantly greater decrease in myoma size occurred in the group that received raloxifene compared with the placebo group [48]. When the study group's treatment was extended to 18 months, the group that received GnRH's plus raloxifene demonstrated stable suppression of uterine and myoma size—with no further decrease compared with the 6-month data—and myoma symptoms remained improved [49]. Furthermore, bone mineral density did not change significantly from baseline to 18 months in this group. Raloxifene was well tolerated in all studies, and after 18 months there was a low rate of bleeding and no proliferative effect on

the endometrium; the main side effect was hot flushes [49]. Thus, the combination of GnRH's with raloxifene had a marked effect on uterine and myoma size—an effect superior to either therapy alone—without adverse effects on bone or endometrium [3].

Progesterone receptor modulators

Mifepristone

Antiprogestins are considered progesterone receptor modulators with primarily antagonist action [3,52]. High concentrations of progesterone receptors have been identified in myomas compared with the surrounding myometrium [12,13]. This class of medication targets and reduces the number of progesterone receptors, and effectively produces amenorrhea and myoma suppression [7,52,53]. Furthermore, mifepristone decreases the number of progesterone receptors in myomas and myometrium, inhibits ovarian cyclicity, maintains a hormonal state similar to the early follicular phase, and affects the vascular supply of myomas [52–54].

Small studies that used mifepristone, 12.5 mg to 50 mg/d, noted a 40% to 50% reduction in myoma volume and a high prevalence of amenorrhea; vasomotor symptoms were the most common side effect [9]. One small study treated 10 patients who had myomas with mifepristone, 50 mg/d, for 3 months [53]. Mean myoma volume decreased by 22% at 4 weeks, by 40% at 8 weeks, and by 49% at 12 weeks. Overall, 80% of the subjects had at least a 25% decrease in myoma volume, and bone mineral density was stable after the therapy. Six of the 10 patients had a myomectomy or hysterectomy after the study, and progesterone receptor—but not estrogen receptor—immunoreactivity was reduced significantly in myoma tissue and myometrium compared with normal controls. This finding suggests that mifepristone achieves myoma regression through a direct antiprogesterone effect [53]. Another study evaluated low doses of mifepristone, 5 to 10 mg/d for 6 months, to treat premenopausal women with symptomatic myomas [55]. Myoma volume decreased by 48% in the group that received 5 mg, and by 49% in the group that received 10 mg; both groups demonstrated a decrease in myoma symptoms and a rate of amenorrhea of 60% to 65%. Overall, there was a similar prevalence of hot flushes and simple endometrial hyperplasia without atypia (28% of subjects overall). The investigators concluded that mifepristone, 5 mg, had efficacy comparable to the 10-mg dose and may cause fewer hot flushes; however, this study was limited by a small sample size [55].

Steinauer and colleagues [52] reviewed six clinical trials of mifepristone treatment for symptomatic myomas. A total of 166 premenopausal subjects was treated for 3 to 6 months with 5 to 50 mg/d of mifepristone. Although these studies were few, small, not placebo-controlled nor blinded, varied in the amount of subject information presented, and overall were heterogeneous, they consistently demonstrated that daily administration of mifepristone resulted in significantly decreased mean myoma volume (26–74%) and uterine volume (27–49%); up to a 75% reduction in myoma symptoms, including menorrhagia, dysmen-

orrhea, and pelvic pressure; and a 91% rate of amenorrhea. There was no consistent correlation between mifepristone dosage and myoma response. Significant side effects included hot flushes (38%, no correlation with dose), elevated hepatic enzymes, and endometrial hyperplasia. The endometrial biopsy data [55] were reevaluated, and the number of cases of simple hyperplasia identified was reduced from 10 (28%) to 5 (14%), all in the group that received 10 mg [52]. Thus, studies highlight that mifepristone therapy effectively achieves myoma regression while maintaining stable bone density [9,53,54]; however, endometrial hyperplasia may limit the long-term use of this medication. Further studies are warranted, including direct comparisons with GnRH's [9,55].

Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs), like SERMs, exhibit agonist and antagonist activity with a high degree of progesterone receptor specificity and tissue selectivity [5,56]. This therapy directly targets the endometrium, and acts differently than do progestins or antiprogestins [5,56]. Early clinical studies with asoprisnil identified a dose-dependent suppression of menstruation, likely due to suppression of endometrial proliferation, but no change in basal estrogen concentration, no effects on ovulation, and no significant breakthrough bleeding [5,56]. One recent study investigated three dosages of asoprisnil (5 mg/d, 10 mg/d, 25 mg/d) and placebo in women with myomas [57]. The two higher doses effectively decreased myoma size, reduced pressure symptoms, suppressed uterine bleeding, and increased hemoglobin levels, and the 25-mg dosage had an amenorrhea rate of 80%. All doses were well tolerated [57]. Thus, data show that the SPRM asoprisnil is capable of suppressing normal and abnormal uterine bleeding, inhibiting myoma growth, and acting without affecting ovarian steroid production; however, the mechanisms for these inhibitory effects are unknown [5]. Further studies of this novel therapy are indicated.

Androgen therapy

Two androgenic medications, danazol and gestrinone, also have been studied for the treatment of uterine myomas. Danazol is a 19-nortestosterone derivative that inhibits pituitary gonadotropin secretion and ovarian steroid production, and suppresses endometrial growth [3,26,58]. The effects of danazol are mainly androgenic, with moderate progestogenic, antiprogestogenic, and antiestrogenic properties [58,59]. Danazol effectively decreased myoma volume. One study treated 20 women with myomas with danazol, 400 mg/d for 4 months, and noted a 24% average decrease in myoma volume by 4 months. With this therapy, all patients experienced significant improvement in myoma symptoms. Myoma volume had increased slightly by 6 months after the end of danazol treatment, but remained lower than the baseline volume [58]. A similar small study used danazol, 100 mg/d for 6 months, to treat 15 women with symptomatic myomas

[59]. During the study 3 patients experienced amenorrhea, and at 6 months significant reductions were noted in overall uterine volume (29% decrease) and mean myoma volume (38% decrease). This therapy also was associated with a significant increase in uterine artery impedance to blood flow, and this increase in the uterine artery pulsatility index correlated with the reduction in uterine volume [59]. Thus, danazol's efficacy in the treatment of myomas may be related to hormonal and vascular effects, and the effects persist after a course of therapy.

Gestrinone is a derivative of ethinyl-nortestosterone, and has antiestrogenic and antiprogestogenic properties [23]. Like danazol, this therapy effectively induced amenorrhea and decreased myoma volume [26]. Studies have used oral and vaginal gestrinone, with dosages ranging from 2.5 to 5 mg, two to three times weekly, for 4 to 24 months [60,61]. Uterine volume was significantly reduced by 40% at 6 months, and this change in uterine volume persisted for at least 18 months after the discontinuation of gestrinone [61]. Furthermore, dyspareunia and chronic pain symptoms improved with gestrinone therapy. An advantage of this therapy is the lasting effect on myomas that endures after discontinuation of the medication. Gestrinone is not available in the United States [26].

Although effective in treating myomas, the androgenic side effects of danazol and gestrinone are their most prominent disadvantages. The most common side effects associated with danazol include weight gain, edema, decreased breast size, acne, oily skin, hirsutism, a deepened voice, headache, hot flushes, altered libido, and muscle cramps [9,58]. More serious, but rare, side effects include mild to moderate hepatocellular damage, marked fluid retention, and spontaneous pregnancy loss if conception occurs within 3 months of discontinuing danazol [9]. Similarly, gestrinone is associated with weight gain, seborrhea, acne, myalgias, and arthralgias, and less commonly with hirsutism, hoarseness, and changes in libido [9,60,61]. Although danazol is available in the United States, these side effects often preclude its use.

Progestin-containing intrauterine contraceptive devices

Progestin-containing intrauterine contraceptive devices (IUDs) have been studied as a local treatment for menorrhagia and symptomatic myomas. The levonorgestrel intrauterine system (LNG-IUS) has been studied extensively; it is a proven, effective, reversible treatment for menorrhagia which functions by inducing endometrial atrophy and inactivity [62,63]. Studies showed a significant reduction in mean menstrual blood loss—at times exceeding a 90% reduction after 3 to 12 months of use—with few side effects and high patient satisfaction [62,63]. Documented side effects include irregular bleeding, headache, nausea, mastalgia, acne, functional ovarian cysts, depression, weight gain, and lower abdominal pain [63]. A myomatous uterus with an enlarged or distorted uterine cavity or a submucosal myoma is a contraindication for LNG-IUS use [26].

Initial investigation into LNG-IUS use for the local management of symptomatic uterine myomas involved small clinical trials and several case series, all

of which demonstrated a significant reduction in menorrhagia and a reduction in myoma size [62]. Subsequently, Grigorieva and colleagues [64] studied 67 premenopausal women with myomatous uteri that measured 12-weeks-pregnant size or less and who desired the LNG-IUS for contraception, 39% of whom had menorrhagia. A profound, significant reduction in menstrual blood loss was noted by 3 months—which persisted for the 12-month duration of the study—with concomitant increases in hemoglobin and ferritin values. The amenorrhea rate was 10% at 3 months, 20% at 6 months, and 40% at 12 months. Although statistically significant decreases in mean uterine volume and total myoma volume were observed during the study, these changes were small and were considered not clinically significant [64]. The investigators concluded that the LNG-IUS is an effective treatment for menorrhagia due to uterine myomas for patients who desire conservative management and contraception. A second study compared the LNG-IUS with hysterectomy for the treatment of menorrhagia [65]. Of 119 subjects who used the LNG-IUS, 38 (31.9%) had myomas, with an average size of 2.9 cm. The LNG-IUS did not affect the uterine nor myoma size, but was associated with decreased endometrial thickness. Several subjects who had the LNG-IUS underwent a hysterectomy during the study, and this outcome was more likely in the subjects with myomas. Additionally, the study noted that asymptomatic functional ovarian cysts occurred in 17.5% of patients who used the LNG-IUS, and most cysts resolved spontaneously [65]. Although both studies demonstrated that the LNG-IUS did not cause myoma regression, the use of a control group would help to identify if the LNG-IUS prevents myoma growth.

Thus, few studies have evaluated the management of symptomatic myomas with the LNG-IUS. Earlier, the authors reviewed the effects of progestins, antiprogestins, and SPRMs on myoma growth, and discussed that progestins seem to stimulate myoma growth, whereas progestin antagonists have the opposite effect [31–33]. In contrast, the LNG-IUS data do not show myoma growth, and this therapy may prevent myoma growth. Results from Maruo and colleagues [22] revealed that the LNG-IUS may have variable effects on uterine myomas based on the balance of growth factors in the local environment [62]. Clearly, the effect of the LNG-IUS on a myomatous uterus needs to be studied further.

Future directions

Tremendous effort is ongoing to better understand uterine myomas and the effects of current medical therapies, and to develop new methods for the conservative management of myomas. No medication is approved for long-term administration for myoma treatment [5]. Furthermore, it is unclear how long-term medical therapy for myomas may impact future fertility [3]. Compared with surgical management, the possibility of myoma regrowth always exists with medical therapy, and some portion of the myoma always is retained; thus, definitive treatment is not achieved [9]. Therefore, surgery remains the treatment standard for large symptomatic myomas in patients who desire future fertility [3].

Although long-term data about medical therapies for myomas are needed, long-term data about myoma response after a therapy is discontinued also are important. To minimize side effects, some therapies may be amenable to intermittent use, especially if the positive results, such as myoma regression, persist upon discontinuation of the medication [52]. GnRH's are considered the gold standard therapy for myomas, especially in the preoperative period, and although they have the most evidence to support their use, they have significant side effects. Studies are needed to compare GnRH's and other effective therapies, such as mifepristone and aromatase inhibitors, directly. These targeted hormonal therapies may be more selective in their actions, with fewer side effects [25].

Current medical therapies for myomas involve systemic manipulation of the ovarian steroid hormones estrogen and progesterone, as well as local therapy with the LNG-IUS (Table 1). These therapies affect other steroid-responsive tissues, such as breast and bone, and systemic side effects may limit use of certain medications [66]. An ideal medical therapy would have limited systemic side effects, as well as minimal to no effect on follicular development, ovulation, implantation, and embryo development [3]. Other possibilities for future therapies include inhibition of the transformation of a myometrial cell into a leiomyoma cell; targeting growth factors that are involved in angiogenesis or fibrosis; enabling gene regulation; interference with myoma growth; or local therapy, such as IUDs, vaginal creams, or pessaries [9,66,67]. Pirfenidone is an antifibrotic agent that is being investigated for use in patients with pulmonary fibrosis—it inhibits production of transforming growth factor-β and collagen, and in vitro results reveal a decrease in leiomyoma cell proliferation—however, cell death is not achieved [9,23,66–68]. There are no published clinical data on the use of pirfenidone in women with myomas. Further research into similar nonsteroidal myoma therapies is warranted.

As we look to the future, we need to consider the quality of available evidence on the medical management of myomas. Myers and colleagues [69] reviewed all published studies on uterine myomas from 1975 to 2000. A total of 1084 studies was identified, of which 115 studied invasive therapies, and 51 were trials of medical therapies (21 were randomized). GnRH's were the primary therapy investigated in 33 of the medical therapy studies. Compared with the evidence for hysterectomy, there is little high-quality evidence on which to base medical treatment strategies [69]. When the non-GnRH medical therapies were evaluated, no consistent conclusions could be made about the effectiveness or risks of these therapies. Most evidence comes from small nonrandomized studies that do not permit definitive conclusions about the likelihood of good or bad outcomes. The investigators recommended longer-term, prospective, controlled studies of all available myoma treatments, with attention to detailed data collection about patient characteristics, myomas, and response to the therapy [69]. Furthermore, many studies reviewed in this article selected patients from an asymptomatic, or less symptomatic, population of women with myomas; excluded patients with large myomas (uterine size greater than 12-weeks-pregnant); and some studies were nonrandomized (patients decided whether to have surgery or a trial of

Table 1
Medical treatment options for myomas

Medication	Effect on myomas	Effect on myoma symptoms	Side effects that limit use	Benefits of therapy
Estrogen/progestin	May stimulate or stabilize growth	Improves menorrhagia		Treats menorrhagia, provides contraception
Progestin	May stimulate growth, some studies show decrease in size	May cause amenorrhea, may improve bleeding symptoms		May improve menorrhagia
GnRH agonist	Decreases size	Causes amenorrhea, pressure symptoms improve	Hypoestrogenic side effects: hot flushes, vaginal dryness, bone demineralization; side effects may be managed with add-back hormones; higher postoperative recurrence rate	Preoperative therapy for anemia and large myomas, may enable transverse surgical incision
GnRH antagonist	Decreases size	Symptoms may improve, likely depends on duration of therapy	Hypoestrogenic side effects	Shorter duration for preoperative therapy, no initial flare effect
Aromatase inhibitor	Decreases size	Needs to be studied further; symptoms may improve	Hypoestrogenic side effects	No initial flare effect, needs to be studied further
SERM: raloxifene	Decreases size, most pronounced with addition of GnRH	Symptoms improve	Hot flushes, irregular bleeding	Maintains stable bone density
Mifepristone	Decreases size	May cause amenorrhea; symptoms improve	Endometrial hyperplasia	Maintains stable bone density
SPRM: asoprisnil	Decreases size	May cause amenorrhea; symptoms improve		Action does not affect ovarian steroid production
Androgens	Decreases size	Symptoms improve	Androgenic side effects	Decrease in myoma size persists after medication is discontinued
Progesterone-containing IUD	May stabilize myoma growth	Improves menorrhagia, may cause amenorrhea	Irregular bleeding, ovarian cysts	Local therapy, menorrhagia improves, provides contraception

medical therapy). These study designs led to significant bias in the results; the symptomatic patients are underrepresented, and these are the patients who most need treatment. Future studies should consider these concerns about the quality of current data on medical therapies for myomas.

Summary

It is evident that complex biochemical interactions are involved in the regulation of myoma growth, and ovarian steroid hormones have significant influence on this process. Current myoma therapies manipulate the hormonal environment to achieve myoma regression and control of bleeding. Although several of these therapies achieve some level of success, further studies are necessary to evaluate the current and long-term effects of these therapies. In clinical medicine each patient must be evaluated thoroughly, and the decision for medical therapy or surgery—and for which medical therapy—needs to be individualized. If one medical therapy does not work, several other effective therapies are available.

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Conservative Surgical Management of Uterine Myomas

David L. Olive, MD*, Steven R. Lindheim, MD,
Elizabeth A. Pritts, MD

Department of Obstetrics and Gynecology, University of Wisconsin School of Medicine, 600 Highland Avenue, Madison, WI 53792-6188, USA

Uterine leiomyomata, also referred to popularly as fibroids, are among the most common of uterine pathologies. Approximately 1.6 million women in the United States are diagnosed each year, and the prevalence may be more than 25% of all reproductive age women. Symptoms that are associated with the tumors include bulk symptoms, such as pelvic pressure and pain, urinary frequency, constipation, abnormal uterine bleeding, and infertility.

The traditional treatment for uterine fibroids has been surgical; hysterectomy is the predominant procedure that is offered to women who have completed their childbearing. Of the approximately 600,000 hysterectomies that are performed annually in the United States, about half involve a diagnosis of uterine myoma. It has become apparent, however, that increasing numbers of women would very much like to avoid this procedure, despite the definitive result. Justification for requesting alternative approaches include a desire to maintain childbearing potential, fear of major surgery, and even the wish to maintain the uterus for psychologic reasons.

Given this increasing demand for a more conservative approach to the patient who has fibroids, it is incumbent upon the practicing gynecologist to be aware of the many treatment alternatives to hysterectomy. Therapeutic options are available that preserve the uterus in situ and allow an attempt at conception if

* Corresponding author.
E-mail address: dlolive@facstaff.wisc.edu (D.L. Olive).

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the patient so desires. This article focuses upon the surgical options that are available to preserve the uterus in the face of symptomatic uterine fibroids.

Myomectomy

Uterine myomectomy, or removal of the uterine fibroids from the uterus and surrounding structures, was the first surgical approach to attempt to conserve the uterus. The approach is variable and depends upon fibroid location. Submucous myomas frequently (although not invariably) may be approached transvaginally and removed by way of hysteroscopy or vaginal surgery, whereas other locations generally necessitate an abdominal approach. Furthermore, either approach frequently can be accomplished endoscopically, provided the fibroids are accessible and the surgeon has sufficient skill with this instrumentation.

Abdominal myomectomy

Abdominal myomectomy is the most common surgical approach to conserve the uterus in the face of myomas. The approach is one within the capability of all gynecologic surgeons, and therefore, has sustained a high degree of popularity, despite the advent of several alternatives. Abdominal myomectomy remains the conservative surgical treatment of choice for all gynecologists when large (>10 cm) myomas are present, when large numbers of fibroids must be removed, or if concomitant pathology that involves major surgery is encountered.

The technique of abdominal myomectomy involves an abdominal incision that facilitates access to the uterus and tumors. A midline incision may be required for very large myomas, but a transverse approach frequently is satisfactory. Very small incisions may be attempted and used if the myomatous uterus is not adherent to surrounding structures, and can be mobilized and delivered through the abdominal incision. Frequently, this facilitates surgery by avoiding obfuscation of the surgical field by surrounding abdominal structures and improves the surgeon's access to the fibroids and uterine blood supply.

Achieving a relative hemostasis before uterine incision is a vital part of this procedure, and can be achieved in a variety of ways. The use of vasopressin, injected into the site of incision, the utero–fibroid junction, or the lower uterine segment near the entrance of the uterine arteries is performed frequently. This technique often provides significant reduction of blood loss during the procedure. Disadvantages include the inadvertent injury of a large blood vessel and possible systemic adverse effects of the drug. Another approach is the use of a tourniquet around the lower uterine segment. This can be placed after creating windows in the broad ligament bilaterally and lateral to the uterine vessels. Although effective, this technique has proven inferior to vasopressin for the reduction of blood loss [1]. A third technique is to clamp the parametrium directly with an atraumatic instrument, such as a rubber-shod clamp, similar to the ap-

proach that is used to grasp bowel during intestinal surgery. Clamps may be placed low in the paracervical tissue to occlude the uterine artery, and on the infundibulopelvic ligament or utero-ovarian ligament to prevent flow from this route. For long procedures, it may be advantageous to release these clamps periodically to ensure an absence of thrombosis in the vessels. Although this technique is used by many gynecologic surgeons, its advantages, disadvantages, and complications have not been evaluated.

After reasonable hemostasis can be expected, an incision is made in the uterus. For solitary fibroids the incision usually is made over the tumor, preferably in a transverse direction. If numerous fibroids are to be excised, a single incision may be attempted with removal of the myomas through this large, central incision. The anterior uterine surface is preferred to the posterior, in an attempt to minimize adhesions to adnexal structures. The incision should be deep enough to enter the fibroid, and allow clear delineation of fibroid tissue from the surrounding pseudocapsule of myometrium. After the myoma is identified, it is grasped and the surface is bluntly and sharply dissected free of myometrium. It can be removed by rotating the tumor gently while continuing the dissection circumferentially until the complete myoma is freed. Frequently, large blood vessels may be identified at the base of the fibroid; these are clamped, ligated, and incised.

After all myomas that are intended for removal are extirpated, closure of the uterine incision becomes critical. Generally, this is performed with a multilayer closure using a large suture for deep layers and a small suture for the peritoneal surface. Hemostasis and excellent approximation should be the goals. If the uterine cavity has been entered, closure of the endometrium and adjacent myometrium with fine sutures in an interrupted fashion is traditional, but no evidence has been accumulated to clarify the optimal approach for this or any aspect of closure.

Adhesion prevention adjuvants should be used to cover the uterine incision after closure. Three such adjuvants, Preclude (W.L. Gore, Newark, Delaware), Seprafilm (Genzyme, Cambridge, Massachusetts), and Interceed (Gynecare, Somerville, New Jersey), have been used for this purpose, and resulted in better adhesion prevention or minimization than no covering in randomized trials [2–4]. In the only comparative trial, Preclude membrane outperformed Interceed [5].

Following myomectomy the risk of recurrence is substantial; 50% of women demonstrate a myoma on transvaginal ultrasonography within 5 years [6]. The rate of symptomatic recurrence is 15% to 30% per 10 years, and 10% of women require further surgical treatment [7]. Predictors of recurrence include the presence of multiple fibroids and nulliparity [8].

When compared with hysterectomy, myomectomy had a similar rate of perioperative morbidity [9]; however, myomectomy had a higher rate of febrile morbidity within the first 48 hours after the procedure [10].

Pregnancy rates after myomectomy are highly variable and depend upon the number, size, and location of myomas that are removed. Overall, reports show a pregnancy rate of approximately 50%, with a range across reports from 10% to 75%. The risk of uterine rupture following myomectomy is unknown. Estimates have ranged from 0.002% to 5% [10a,b].

Laparoscopic myomectomy

In some instances, a myomectomy can be performed laparoscopically. The potential advantages of this approach are obvious, in that the patient has a much more rapid recovery; however, the skill level that is required to perform this procedure traditionally has been so great that it has not been used on a widespread basis. With advances in instrumentation and increasing levels of endoscopic competency, the laparoscopic myomectomy is a procedure that is now within the capability of most gynecologic surgeons.

To determine the role of laparoscopic myomectomy in clinical practice, it must be compared with the abdominal myomectomy, based on several parameters: time, blood loss, complications, cost, adhesion formation, and future fertility. Procedural time has been studied retrospectively and prospectively. Early trials suggested that the procedure was considerably longer than its open counterpart; however, more recent studies suggested only a slightly longer and nonsignificant increase in procedure duration. Blood loss also was comparable [11]. Limited data exist regarding complication rates, but evidence from a single randomized study suggests that laparoscopy results in fewer transfusions and less postoperative fever [12]. No cost or charge analysis has been performed.

Because most women undergo conservative procedures in an attempt to preserve future fertility, the pregnancy rate after laparoscopic myomectomy is of critical importance. A summary of uncontrolled trials showed that pregnancy rates were similar for the two procedures, although the quality of the included data is highly variable [12]. One randomized, prospective clinical trial exists; 131 women who had otherwise unexplained infertility were given a laparoscopic myomectomy or underwent an open procedure [13]. Requirement for inclusion was the presence of one to three fibroids that were larger than 5 cm. Results indicated no difference in pregnancy rates, miscarriage rates, pregnancy complications, or mode of delivery (Table 1).

Table 1
Laparoscopic versus abdominal myomectomy: outcomes

	Abdominal myomectomy	Laparoscopic myomectomy
Pregnancy rate (%)	55.9	53.6
Abortion rate (%)	12.1	20
Ongoing pregnancies	2	3
Ectopic pregnancies	0	1
Deliveries	27	20
Preterm deliveries (%)	7.4	5.0
Vaginal deliveries (%)	22.2	35.0
Caesarean sections (%)	77.8	65
Uterine rupture	0	0

Data from Seracchioli R, Rossi S, Govoni F, et al. Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy. Human Reprod 2000;15(12):2663–8.

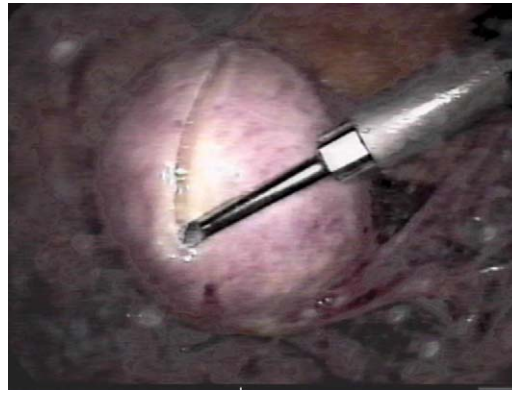

Fig. 1. Using the hook tip harmonic scalpel, an incision is made in the uterus to begin the laparoscopic myomectomy.

Laparoscopic myomectomies are performed in the same fashion as are open procedures with few exceptions. Because tourniquet application is difficult laparoscopically, hemostasis is enhanced by the use of dilute vasopressin injected into the uterus [7]. An incision is made over the surface and the fibroid. This incision can be performed with any cutting instrument, although the harmonic scalpel hook tip seems to be ideal for incising and achieving hemostasis with minimal lateral damage (Fig. 1). The incision is usually horizontal in an attempt to avoid most incoming blood vessels. After an incision has been made through the overlying myometrium into the fibroid, it is grasped by a large grasper or myoma screw to stabilize it. Sharp and blunt dissection is performed around the periphery of the structure with traction applied constantly. Eventually, the myoma is dissected completely free, which leaves a large crater in the myometrium. Removal of the myoma from the peritoneal cavity is performed by electromechanical morcellation, at the rate of approximately 25 g/min (Fig. 2).

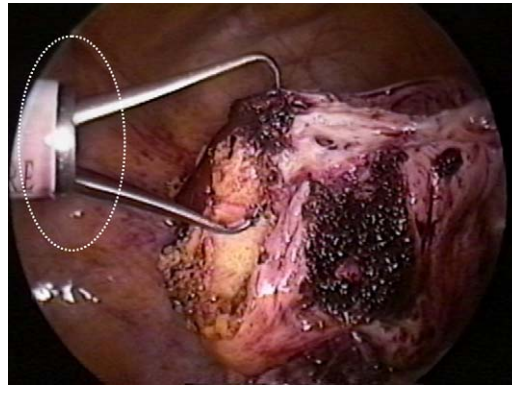

Fig. 2. Morcellation can be accomplished laparoscopically with an automated morcellator and a laparoscopic single-tooth tenaculum. Dashed oval denotes the blade of the morcellator.

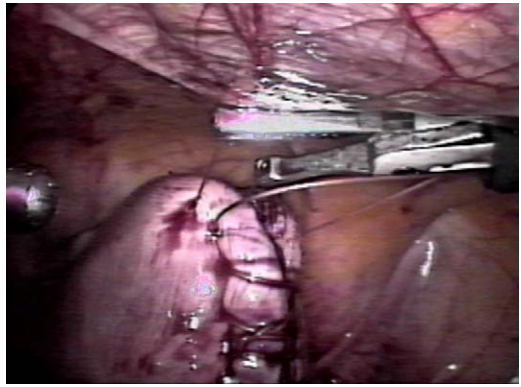

Fig. 3. Suturing the myomectomy incision can be accomplished by the use of the Endo-stitch laparoscopic suturing device.

When closing the uterine defect after myoma removal, it is critical to perform the procedure exactly as if the surgery were laparotomy; thus, multilayer suturing is preferred. Closure can be performed by traditional laparoscopic suturing or with the use of specifically designed laparoscopic suturing devices, such as the Endo-Stitch (U.S. Surgical Corporation, Norwalk, Connecticut) (Fig. 3). This instrument can be an impressive time saver, especially when combined with dissolvable suture clips, such as the Lapra-tye (Ethicon Endo-Surgery, Cincinnati, Ohio), and allows for two- or three-layer closures in less than 15 minutes. After completion of the closure, the uterine incision is covered by an adhesion prevention adjuvant, three of which have been demonstrated to reduce adhesion formation (Fig. 4).

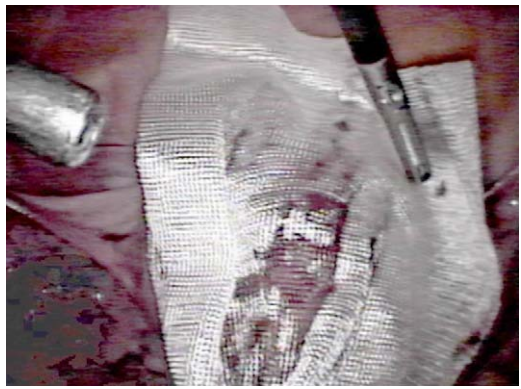

Fig. 4. An adhesion prevention barrier is placed over the repaired uterine incision to reduce adhesions.

Hysteroscopic myomectomy

If a myoma is entirely or predominantly within the endometrial cavity, a hysteroscopic myomectomy is used frequently. This approach offers several major advantages. It is minimally invasive and no incision is required. Access to the cavity is achieved by dilating the cervix and inserting the hysteroscope. A second advantage is the lack of incisions on the exterior of the uterus. This reduces the likelihood of pelvic adhesions after resection. The hysteroscopic approach does have multiple unique issues, including the possibility of inadvertent perforation, bleeding, infection, and intracavitary adhesions.

The resectoscopic loop, which uses monopolar or bipolar electrosurgery, is the technique that usually is used to resect submucous myomas,. In some cases, vaporization can be performed, and mechanical removal by way of a morcellating device was developed recently. Uterine distension may be accomplished using electrolyte-poor low-viscosity solutions (glycine, sorbitol), isosmolar low-viscosity solutions (saline, Ringer's lactate), or high viscosity media (32% dextran-70, Hyskon [Pharmacia & Upjohn, Peapack, New Jersey]) [14]. Frequently, the choice depends upon the type of energy that is being used. For monopolar electricity, an electrolyte-poor low-viscosity solution is optimal, whereas bipolar energy can make use of saline or Ringer's lactate solutions [15]. Multiple problems can result from excessive absorption of these fluids. Hyponatremia, hyperammonemia, and cerebral edema can occur with the use of electrolyte-poor solutions. Isotonic solutions do not cause these problems, but either type of distension medium can produce fluid overload with resultant pulmonary edema. High-viscosity media, such as Hyskon, produce anaphylaxis, disseminated intravascular coagulopathy, and fluid overload.

Abnormal uterine bleeding and fertility disruption are the chief symptoms of submucous myomas. When bleeding is encountered, hysteroscopic resection is successful in remedying the problem in most cases. However, for fertility the evidence is much murkier. These fibroids have been linked to infertility and early pregnancy loss. A recent meta-analysis suggested that resection of submucous myomas increases fertility [16]. Although little data exist to support the assertion that fewer spontaneous abortions occur after conception, the available data suggest that the procedure is of value.

Myolysis

If the patient desires preservation of the uterus, the in situ destruction of tumors is an alternative to the removal of fibroids. This destruction can be performed laparoscopically by electrosurgical heat, laser energy, or cryotherapy. This procedure, termed "myolysis," can be accomplished by destruction of the tumor tissue or obliteration of the vasculature that supplies the fibroid.

Compelling reasons for performing this procedure include the ease and rapidity of surgery, the lack of concern for hemostasis, and the rapid recovery by

Table 2
Fibroid volumes before and after myolysis

	Pretreatment	Post GnRHa	3–6 mo postoperatively	7–12 mo postoperatively
Fibroid volume (mL)	193	83	25	30
Mean decrease (%)		57%	87%	84.5%

Abbreviation: GnRHa, GnRH-agonist.
Data from Phillips DR, Milim SJ, Nathanson HG, et al. Experience with laparoscopic leiomyoma coagulation and concomitant operative hysteroscopy. J Am Assoc Gynecol Laparosc 1997; 4(4):425–33.

the patient. Disadvantages include a delay in reduction of uterine size and an unknown risk for recurrence or regrowth.

The bipolar needle is the most commonly used instrument for myolysis [17]. This instrument coagulates an area of tissue that is approximately 5 mm in diameter. Originally, repeated application to the myoma was necessary, which resulted in complete tissue destruction after many insertions. A faster and simpler approach is to coagulate along the fibroid–uterine junction until an absence of blood flow is apparent. Results from both procedures have been promising; a reduction in myoma volume as great as 80% has been noted (Table 2) [18]. Adhesions have been a problem, especially with the neodymium: yttrium-aluminum-garnet laser and complete fibroid destruction. For this reason, alternative myolytic approaches have been sought.

Cryotherapy is one technique that is used in lieu of electrosurgery. Freezing the myoma usually can be accomplished by a single puncture into the lesion and insertion of the cryoprobe. Liquid nitrogen or proprietary gas mixtures can be used as a coolant; ice balls of up to 6 cm can occur with a single 5- to 8-minute freeze. After freezing and removal of the cryoprobe, a coagulation enhancer (Surgicel, Johnson & Johnson Medical Inc., New Brunswick, New Jersey) is placed within the cryoprobe tract and the hole is covered by an adhesion prevention adjuvant. A single preliminary report suggested that this technique may reduce fibroid size by approximately 40% [19]. No comparative trials exist for the various techniques of myolysis.

Uterine artery ligation and occlusion

Obstruction of the uterine arteries is a conservative technique that was developed recently. This technique has long been a method for stopping postpartum hemorrhage, and initially was applied to the treatment of fibroids by way of embolization by interventional radiologists. Recently, the surgical ligation of uterine arteries has been performed and evaluated. One report from South Korea described two vascular clips being applied to each uterine artery by way of laparoscopy [20]. A 46% decrease in fibroid volume was observed, and symptomatic improvement was noted in 78% to 95% of patients. Bipolar

coagulation of vessels also has been described, with symptomatic improvement in 87% of patients [21]. Other smaller cohort studies showed similar results. Park and colleagues [22] compared fibroid treatment in 23 women who underwent uterine artery embolization with 17 patients who underwent ligation of the uterine arteries; comparable amounts of fibroid shrinkage and symptomatic improvement were seen.

A simpler, more transient approach was described recently—temporary, transvaginal uterine artery occlusion. Doppler-directed clamp placement is performed with resulting obstruction of the vessels by squeezing the vaginal mucosa and uterine arteries against the lateral borders of the lower uterus. Occlusion is confirmed by cessation of the Doppler signal. After 6 hours, the clamp is removed. The entire procedure is performed best under epidural anesthesia (Fred Burbank, MD, personal communication, 2005). In a study of 75 women, 2 developed hydronephrosis that required temporary stenting (Fred Burbank, MD, personal communication, 2005). In a report that followed 51 women for 5 months, 80% had a decrease in uterine volume, with an average decrease of 24% in those who responded to treatment. Similarly, 81% of women who complained of menorrhagia reported some improvement, although the degree of improvement was not provided [23].

Virtually no data exist regarding the effect of these occlusive techniques on subsequent pregnancies. Thus, they cannot be recommended for women who desire to give birth.

Summary

Uterine fibroids are a major gynecologic problem in American women, and several alternatives have been developed. Conservative treatment, with the goal of treating the fibroid but retaining the uterus, is a frequent choice among women who require therapy during their early to middle reproductive years.

A variety of conservative surgical approaches exist; each has advantages and disadvantages for the clinician and the patient. Some are well-established techniques, whereas others are still in the investigational stage. None has been evaluated adequately for its effects on future fertility. To this end, it is imperative that investigators continue to evaluate these surgical procedures so that the clinician can provide accurate and comprehensive information when faced with a patient who desires one or more of these approaches. Furthermore, it is critical for the practitioner to stay informed about these procedures so that patients can be given a full complement of options.

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Uterine Artery Embolization as a Treatment Option for Uterine Myomas

Paul B. Marshburn, MD*, Michelle L. Matthews, MD, Bradley S. Hurst, MD

Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Carolinas Medical Center, P.O. Box 32861, Charlotte, NC 28232, USA

Uterine artery embolization (UAE) has been used successfully for refractory postpartum hemorrhage, bleeding after gynecologic surgery or pelvic trauma, and treatment of a pelvic arteriovenous malformation [1–3]. The desire for minimally invasive alternatives for the management of symptomatic uterine myomas prompted Ravina and colleagues [4] to propose UAE as an alternative to surgical treatment of uterine fibroids in 1995. The demand for UAE subsequently accelerated following other reports that symptoms of uterine bleeding and pelvic discomfort were improved without the need for surgery [5–10]. Despite the growing public demand for UAE in treating symptomatic uterine fibroids, no prospective randomized trials have been performed to determine the relative safety, effectiveness, and indications of UAE compared with conventional surgical and medical options. The gynecologist must partner with the interventional radiologist to establish optimal clinical guidelines for patient care, because preoperative consultation, diagnostic testing, and postprocedural follow-up may require treatment gynecologic services.

Technical overview of uterine artery embolization

The goal of UAE is to deliver particulate material—typically polyvinyl alcohol (PVA) particles, PVA microspheres, or gelatin-coated tris-acryl polymer microspheres—into both uterine arteries to produce ischemic change to myomas

* Corresponding author.
E-mail address: paul.marshburn@carolinas.org (P.B. Marshburn).

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without causing permanent damage to the uterus [11,12]. Aspects of the technical approach to UAE was summarized [13]. After intravenous analgesia or epidural anesthesia, a single femoral artery typically is catheterized and pelvic arteriography is performed to define the vascular tree (Figs. 1 and 2). A bilateral femoral approach is more cumbersome, but is preferred at some centers to reduce radiation exposure and procedural time [10]. When both uterine arteries have been identified using subtraction angiography, arteriography is performed to confirm that no vascular anomalies are present [7]. Technical difficulties in cannulating the arteries may occur as a result of anatomic variation, arterial spasm, or current use of a gonadotropin-releasing hormone agonist [14]. Failure also may occur because of uterine perfusion from collateral ovarian vasculature [15].

Initially, complete occlusion of both uterine arteries was the goal of UAE. Recent data with PVA or gelatin-coated tris-acryl polymer microspheres suggest that incomplete embolization of both arteries may produce effective infarction of myomas with less severe pain [16]. The procedure requires approximately 1 hour to perform, and radiation exposure is comparable to that received during 1 or 2 barium enemas [8,9,17]. Uterine cramping may be severe, but usually is reduced by nonsteroidal anti-inflammatory drugs. Most patients are admitted

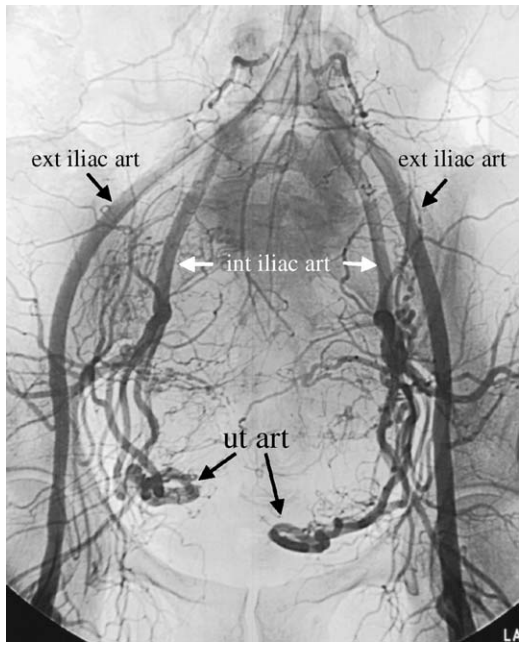

Fig. 1. Digital subtraction flush pelvic arteriogram. A 5-French flush catheter is placed from a right common femoral approach through the right external iliac artery (ext iliac art) and positioned with the sideholes just above the aortic bifurcation. Normal pelvic vasculature with hypertrophy of the uterine arteries (ut art) is seen, (int iliac art) internal iliac artery. (*From* Hurst BS, Stackhouse DJ, Matthews ML, et al. Uterine artery embolization for symptomatic uterine myomas. Fertil Steril 2000;74:858; with permission.)

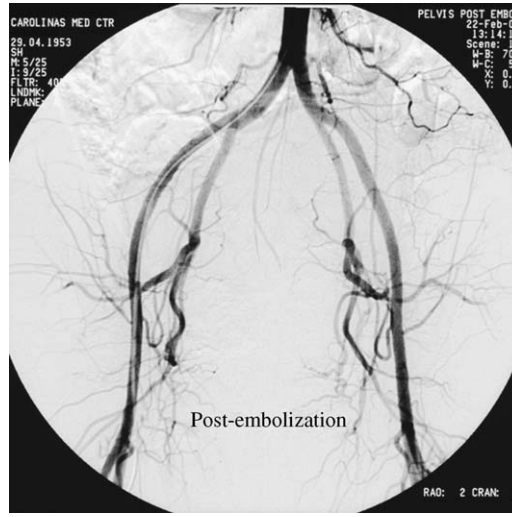

Fig. 2. Unsubtracted pelvic arteriogram after uterine artery embolization. (*From* Hurst BS, Stackhouse DJ, Matthews ML, et al. Uterine artery embolization for symptomatic uterine myomas. Fertil Steril 2000;74:862; with permission.)

overnight for pain control. In some circumstances, the hospitalization may require a 2- to 4-day extension to provide parenteral narcotics when pain is severe or extended.

Quality improvement guidelines and credentialing standards were published recently to ensure safe technical practices, identify the elements of appropriate patient selection, anticipate expected outcomes, and recognize complications in a timely manner after UAE [18,19].

Clinical outcomes for uterine artery embolization

An ideal conservative treatment for leiomyomata would eliminate symptoms, markedly reduce the size of myomas, limit recurrence of future myomas, and preserve fertility. UAE accomplishes some, if not all, of these goals. Within 2 to 4 months after embolization, a 40% to 60% reduction of uterine volume may be expected. One study showed that the uterine volume continues to shrink over time [10]; however, symptomatic improvement may be achieved without remarkable change in myoma size. An outline of treatment outcomes, length of postprocedural observation, and comments on complications for the major studies for UAE for uterine fibroids are summarized in Table 1.

The location of the myoma is the most important factor that contributes to myoma-induced menorrhagia [34]. In reviews of published data, the symptomatic improvement rate for menorrhagia was approximately 85% [13]. Most studies that reported relief from menorrhagia after UAE relied upon interviews or questionnaires from patients without additional objective measures, such as

Table 1
Outcome of uterine artery embolization for symptomatic leiomyomas

Reference	No. patients	Uterine volume (%↓)	Menorrhaghia (%↓)	Follow-up interval	Serious complications
Ravina et al, 1997 [20]	88	69	89	2–6 mo	1 hysterectomy due to necrosis 7 failures required hysterectomy or myomectomy 2 required D&C
Goodwin et al, 1997 [6]	11	40	20	6 mo	1 hysterectomy
Worthington-Kirsch et al, 1998 [9]	53	53	46	3 mo	1 hysterectomy 1 upper GI bleed due to vomiting
Bradley et al, 1998 [17]	8	51	80	3 mo	1 ovarian failure 1 fever—6 wk 1 delayed myoma passage by way of cervix
Goodwin et al, 1999 [7]	60	43	81	10 mo	6 hysterectomies 4 delayed myoma passage by way of cervix 1 ovarian failure
Spies et al, 1999 [10]	169	35	88%	12 mo	1 delayed myoma passage 1 hysteroscopic resection 1 D&C required 4 irregular cycles 2 hysterectomy—treatment failures 2 ovarian failure
Vashisht et al, 1999 [22]	1	N/A	N/A	N/A	Death due to sepsis
Hutchins et al, 1999 [23]	305	48%	86% 3 mo 85% 6 mo 92% 12 mo	12 mo	1 hysterectomy 4 puncture site hematoma 2 pain readmission

Ravina et al, 1999 [24]	184	87% of patients 6 mo	90%	29 months	1 hysterectomy with bowel obstruction 6 fibroid expulsion
Siskin et al, 2000 [25]	49	47.5% 6 mo	88.5%	-	1 hysterectomy for prolonged pain 1 prolonged fever 6 wk, resolved
Pelage et al, 2000 [26]	80	20% 2 mo 52% 6 mo	94%	-	1 hysterectomy for infection 4 amenorrhea 4 fibroid passage
Brunereau et al, 2000 [27]	58	23% 3 mo 43% 6 mo 51% 1 y	90% 3 mo 92% 6 mo 93% 1 year	12 mo	1 external iliac artery dissection
McLucas et al, 2001 [28]	167	49% 6 mo 52% 12 mo	82% 6 mo	6 mo	1 hysterectomy for infection 8 fibroid passage
Anderson et al, 2001 [29]	62	68% 6 mo	96%	6 mo	1 endometritis 2 fibroid expulsion
Spies et al, 2001 [30]	200	42% 3 mo 60% 1 y	86% 3 mo 88% 6 mo 90% 1 y	21 mo	2 endometrial Infection 1 fibroid expulsion 1 pulmonary embolus 1 DVT
Katsumori et al, 2002 [31]	60	55% 4 mo 70% 12 mo	98% 4 mo 100% 12 mo	-	2 fibroid expulsion 1 amenorrhea
Walker & Pelage 2002 [32]	400	64% by MRI 73% by U/S	84%	17 mo	3 hysterectomy for infection 26 amenorrhea 9 fibroid expulsion 13 chronic vaginal discharge
Pron et al, 2003 [33]	538	42%	83%	3 mo	21 amenorrhea

Abbreviations: D&C, dilation and curettage; DVT, deep vein thrombosis; GI, gastrointestinal; N/A not available; U/S, ultrasound.

posttreatment hemoglobin levels or control groups. For example, Worthington-Kirsch and colleagues [9] reported that 88% of interviewed subjects had less bleeding 3 months after embolization for fibroids. Other investigators who published case series since 2000 reported between an 84% and 93% reduction in menorrhagia at 1 year based upon patient impressions from interviews and questionnaires (see Table 1).

Patient selection for uterine artery embolization

Indications

The indications for UAE are not defined clearly, and there is not an established set of absolute and relative contraindications for the procedure. Pregnancy, active infection, and suspicion of uterine or ovarian cancer are absolute contraindications for UAE [18]. Relative contraindications include coagulopathy, immunocompromise, previous pelvic irradiation, and a desire to maintain childbearing potential. UAE may be the best treatment option for women who have symptomatic fibroids who are not candidates for surgery or who do not wish to accept the risks of an operative procedure. More knowledge is needed to determine if myoma location, size, or blood flow characteristics are important predictors of the response to UAE [34].

Some experts have questioned whether there is an upper limit for uterine size beyond which UAE should not be recommended. Potentially, UAE for symptoms of the massively enlarged uterus could be less effective because of more extensive collateral circulation. Additionally, extensive infarction of tissue could increase necrosis-related complications. Goodwin and colleagues [7], however, found no correlation between initial uterine volume and treatment outcome in 59 subjects. McLucas and colleagues [28] investigated factors that were associated with treatment failure in 167 patients who received UAE. Twelve percent of patients had treatment failures, defined as worsening of symptoms, subsequent hysterectomy, or less than 10% shrinkage of the primary myoma 6 months after UAE. Pretreatment uterine volume was not associated with poor outcome; however, failure was more likely when patients had undergone previous pelvic surgery. Results from one investigation indicated poorer results after UAE for myomas; blood flow demonstrated lower peak systolic velocity as determined by Doppler flow studies [35].

Submucous and subserosal myomas

No studies have determined the efficacy of UAE specifically for submucous myomas. Transcervical leiomyoma expulsion most commonly originates from detachment of submucosal myomas, and may be associated with uterine contractions, abdominal pain, fever, nausea, vomiting, vaginal bleeding, and discharge. It also is possible that some treatment failures with continued

abnormal uterine bleeding are due to submucous myomas. Until studies establish the safety, efficacy, and cost-effectiveness of embolization for this indication, hysteroscopic resection should be considered the preferable approach [8].

Generally, pedunculated subserosal myomas have been considered a relative contraindication for UAE, mainly because of the risk for detachment from the uterus after embolization [36]; however, at 2 years of follow-up, relief of bulk-related symptoms was achieved after UAE without complication in 12 patients who had pedunculated subserosal myomas with mean a diameter of 8 cm and a mean stalk diameter of 3 cm [37].

Adenomyosis

Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium, and may be associated with uterine enlargement, abnormal uterine bleeding, and dysmenorrhea [38]. Patients frequently present with symptoms of menorrhagia, dysmenorrhea, and bulk-related symptoms—a profile that overlaps with clinically symptomatic myomas. Pretreatment diagnostic studies indicate that ultrasound has a sensitivity of 80% for detecting adenomyosis [39,40]. MRI is superior to ultrasound in diagnosing adenomyosis [41]. Because definitive diagnosis is not possible with current imaging techniques, some women who have adenomyosis undergo UAE for suspected uterine fibroids. Preliminary reports have shown a high prevalence of treatment failures attributed to adenomyosis, confirmed by histocytologic methods after hysterectomy [7,42]. Because of adenomyosis-related treatment failures, some centers consider adenomyosis to be a relative contraindication to embolization.

Successful outcomes have been reported after UAE in women who had adenomyosis, however. In 1999, 3 women who had a preexisting diagnosis of adenomyosis achieved a successful outcome after UAE [7]. In 43 women who had MRI-documented adenomyosis, significant improvement of dysmenorrhea and menorrhagia was achieved and a reduction in adenomyotic volume was detected at 3.5 months of follow-up [43]. Experienced interventional radiologists have recommended that if adenomyosis is identified before embolization, that a lower success rate be given to patients [28]. On the basis of these limited reports, treatment of adenomyosis with UAE is less successful, but adenomyosis should not be considered a contraindication for UAE.

Uterine artery embolization as a surgical adjuvant

UAE before abdominal myomectomy has not reduced complications or improved long-term results following conservative surgery. In a prospective study of 42 patients who were scheduled for myomectomy, 20 were embolized immediately before surgery. There was no difference in the mean blood loss between the groups, although 4 patients in the group that was not embolized required transfusion [44]. Uterine healing might be compromised after combined embolization and surgical myomectomy, which increases the risk for uterine rupture during pregnancy. UAE has been proposed before hysterectomy to shrink

the fibroid mass and to reduce the incidence of intraoperative hemorrhage [8]. Although size reduction may allow hysterectomy by a transverse suprapubic incision, a combined approach is expected to increase treatment cost, with marginal treatment benefit. Hysteroscopic myomectomy to treat a focal intracavitary myoma, combined with UAE, was proposed to reduce bulk symptoms and reduce subsequent abnormal uterine bleeding and myoma extrusion [8]; however, there are no studies to support this approach. The usefulness of UAE as a surgical adjuvant has no proven benefit.

Risks of uterine artery embolization for uterine myomas

Major complications after UAE for uterine fibroids are estimated to occur in 1% to 5% of cases [32,45]. Chronic vaginal discharge after UAE affects 4% to 7% of patients [32]. The persistent vaginal discharge in these patients appears secondary to fluid accumulation within the cavity of infarcted myomas that communicated with the endometrial cavity [46]. In 94% of cases this resolves spontaneously; in the remainder, hysteroscopic resection of the necrotic fibroid is curative. Fibroid extrusion occurs in 10% of patients after UAE [7,10,47]. In some patients, hysteroscopy or dilation and curettage has been required after embolization to remove degenerating submucous myomas [10,20,21]. An overall review of studies estimates that 1% to 2% of subjects experience ovarian failure after this procedure [7,10,13]. Most of these cases occur in perimenopausal patients, but loss of ovarian function was reported for some women younger than 40 years old. Embolization of the ovaries through the collateral utero-ovarian artery is suspected.

Serious infectious complications affect 1% to 2% of cases, and this problem is encountered more frequently with embolization of larger fibroids [47,48]. Approximately one third of all patients develop postembolization fever. Fever and leukocytosis likely are the result of myoma infarction and necrosis and may be associated with nausea and vomiting, malaise, and anorexia. This "postembolization syndrome" may occur in as many as 15% of patients; they require readmission for monitoring of symptoms. Perhaps the most troubling aspect after embolization is that it may be difficult to distinguish between severe postembolization syndrome and a secondary infection.

Hysterectomy after UAE is necessary in approximately 1% of patients. The necrotic, degenerating myoma may become infected following embolization, especially if there is a large amount of devascularized tissue. Hysterectomy may be required when postembolization syndrome is severe (see Table 1). Overall, the rate of hysterectomy with UAE may be compared with the rate during attempted myomectomy, which ranges from 1 in 23 to approximately 1 in 128 cases [49–51]; however, some of the hysterectomies in myomectomy series were performed for previously undiagnosed conditions that were discovered at surgery (eg, extensive adenomyosis or leiomyosarcoma) and not because of intraoperative complications. A prospective study of UAE for symptomatic myomas in 85 patients indicated that six cases were immediate failures (one technical failure, one case of endometrial

cancer, 2 patients who had adenomyosis, 2 patients who had subserosal myomas), and there were eight late failures or recurrences [52]. Embolization therapy should not be performed if cancer is suspected. A typical pre-embolization evaluation includes a pelvic examination, Pap smear, endometrial biopsy for women older than 40 years, laboratory studies, and ultrasonography or MRI [53]; however, these studies do not aid in the diagnosis of leiomyosarcoma [8].

Three deaths have been reported after an estimated 15,000 UAE procedures worldwide [54]. Death due to sepsis after embolization for uterine fibroids has been reported [22]. Most radiologists use prophylactic antibiotics to reduce the risk for infection, but the efficacy of this approach is unknown. A second death after UAE was secondary to pulmonary embolism [55]. A massive pulmonary embolism was found at autopsy, and was attributed to a pelvic vein thrombosis secondary to the mass effect of the fibroids.

Although UAE complication rates seem to compare favorably with those after myomectomy or hysterectomy, no data from a prospective randomized trial is available to objectify this comparison.

Pregnancy outcome after uterine artery embolization

There are not sufficient data to conclude that UAE is a safe option for women who wish to retain their fertility [56]. Normal pregnancy and delivery can be achieved after UAE for uterine leiomyomata, as has been shown for postpartum hemorrhage [57]. Assessing the comparability of pregnancy outcome after UAE for leiomyomata is complicated by the size and location of myomata, and the fact that nonsubserosal leiomyomas reduce fertility [58]. UAE pregnancy outcomes are reduced most severely when submucous myomas cause endometrial distortion [59]. Reports do not document the number of women who attempted pregnancy after embolization; therefore, cycle conception and fecundity rates cannot be calculated.

The first report of pregnancy after UAE occurred in 1995 [4]. A total of 93 pregnancies was reported after UAE for leiomyomas; delivery outcome is provided for 52 of those pregnancies (Table 2). Overall, most pregnancies were delivered full term without complications. Despite these encouraging results, no randomized controlled trials (RCTs) have compared the effects of UAE and myomectomy on future fertility [34]. One retrospective study that assessed pregnancy outcome indicated an increased risk for preterm delivery and malpresentation after UAE compared with laparoscopic myomectomy [60].

Ovarian function may be compromised after UAE, and this result is likely to reduce fertility. Premature menopause secondary to dissemination of embolization materials to the ovarian blood supply has been documented. Additionally, decreased vascularity of the uterine myometrium and endometrium could affect embryo implantation. Theoretically, this may contribute to difficulties in embryo implantation or maintenance of pregnancy, or possible complications during labor and delivery. In fact, embolization particles have been identified after UAE in

Table 2
Pregnancy outcome after uterine artery embolization

Reference	No. UAE subjects	No. pregnancies	No. deliveries	Comments
Bradley et al, 1998 [17]	8	1	NS	First trimester viability
Pron & Simons, 1999 [61]	77	1	NS	First trimester viability
Nicholson & Ettles, 1999 [62]	24	1	1	1 term C/S
Forman et al, 1999 [63]	1000	14	NS	
Ravina et al, 2002 [64]	184	12	7	2 term SVD 2 term C/S 3 preterm (septicemia, twins + preeclampsia) 5 SAB
Vashist et al, 2001 [65]	NS	1	1	1 term C/S
Ciraru-Vigneron & Ravina 2001 [66]	NS	5	3	2 term SVD 1 term C/S 1 SAB 1 EAB
McLucas et al, 2001 [67]	400	17	10	2 term SVD 7 term C/S (2 breech) 1 preterm (previa, abruption) 5 SAB
Goldberg et al, 2002 [68]	NS	2	2	1 term C/S (twins) 1 preterm C/S (PROM, abruption)
Kovacs et al, 2002 [69]	NS	1	NS	Second trimester viability
Walker & Pelage, 2002 [32]	400	13	9	8 term 1 preterm (preeclampsia) 2 SAB 1 EAB 1 ectopic
D'Angelo et al, 2003 [70]	NS	1	1	1 preterm C/S (34 week twins)
Pron et al, 2005 [71]	555	24	18	9 term SVD; 5 term C/S -3 small for gestational age -2 previa + hemorrhage 4 preterm (htn, prior preterm delivery, previa + hemorrhage) 4 SAB 2 EAB
Total		93	52	41 term, 11 preterm

Abbreviations: C/S, cesarean section; EAB, elective abortion; htn, hypertension; NS, not stated; PROM, premature rupture of membranes; SAB, spontaneous abortion; SVD, spontaneous vaginal delivery.

structures adjacent to leiomyomas (eg, myometrium, parametrium, mesovarium) [72]. Most often, myometrium adjacent to embolized leiomyomas is spared from tissue necrosis. In addition, there generally does not seem to be any significant histologic impact on the endometrium, presumably because myometrial vessels trap particles before arrival in the endometrium [73]. Colgan and colleagues [73] reported cervical necrosis, necrotizing myometritis, endomyometritis, or acute endometritis in five of eight hysterectomy specimens that were performed for complications after 555 UAE procedures. Therefore, although the overall risk seems to be low, there is a concern that UAE could produce a deleterious impact on the myometrium and endometrium in some cases.

Theoretically, a uterus with areas of devascularized leiomyomata likely is structurally weaker or would exhibit contractile dysfunction during labor. The authors could find no documented report of uterine rupture during labor after UAE only. Based on the results of small studies it is difficult to determine if these risks are increased after UAE. The rate of fetal malpresentation, birth weight, and information regarding intrauterine growth restriction are not provided consistently in the available reports of pregnancy outcome after UAE. The rate of cesarean section after UAE seems to be higher than in the general population. Of the 33 patients with term deliveries that were reported thus far, 18 (54.5%) were delivered by cesarean section. The indications for cesarean section are not reported uniformly and could include common indications (eg, previous cesarean section, breech presentation). Residual fibroids and myometrial weakening from UAE may contribute to dysfunctional labor, and theoretically, may increase the risk for cesarean delivery. Therefore, it is premature to conclude that UAE increases the rate of dysfunctional labor that results in cesarean section.

It is unclear if patients who have undergone UAE have an increased risk for preterm delivery. Certainly, this population of patients has established risk factors for preterm delivery, including advanced age and residual fibroids [74,75]. Of 52 patients with delivery information, 11 preterm deliveries were reported (21%) which is higher than the expected rate for the general population. The causes for preterm labor include septicemia, preeclampsia, multiple pregnancy, previous preterm delivery, abruption, and hemorrhage secondary to placenta previa. These observations provide no insight into whether UAE increases the risk for those complications. It seems that there may be an increased risk for postpartum hemorrhage in patients after UAE. Pron and colleagues reported a possible correlation between UAE and abnormal placentation contributing to hemorrhage [71]. In their series of 18 deliveries, three cases of abnormal placentation with subsequent antepartum or postpartum hemorrhage were reported (two cases of placenta previa [one with accreta], and one case of accreta without previa). When considering the remainder of the available literature, 2 of 33 pregnancies (6%) were delivered prematurely because of abruption and hemorrhage, and one of those had placenta previa (see Table 2). It is reasonable to expect that this population may be at a higher risk for placental abnormalities compared with women who had previous uterine surgery for leiomyomas, submucous myomas, or advanced maternal age [76].

Could previous UAE be a predisposing factor for increased early spontaneous abortion? Of the original 93 pregnancies, several were terminated electively or outcome information is not available, which leaves a total of 72 pregnancies for consideration (see Table 2). There were 17 spontaneous losses reported for a spontaneous abortion rate of 23.6%. The average age of the patients who conceived is not provided in many reports, but the average age of embolization in two of the largest series was 41 to 42 years. Spontaneous abortion rates increase with age so it is difficult to determine the specific impact of embolization on miscarriage rates. In the largest study to date, Pron and colleagues [71] reported that the average age at delivery was 36 years, with a spontaneous abortion rate of 16.7%. This seems in accordance with the expected loss rate in the general population. Based on these small reports, the spontaneous abortion rate does not seem to be increased significantly after UAE.

In conclusion, based on small studies, uncomplicated pregnancy and delivery can be expected for most patients after UAE. There may be an increased risk for preterm delivery and placental abnormalities that contribute to an increased risk for antepartum hemorrhage. Patients should be advised of these potential risks and evaluated in pregnancy accordingly. In addition, women should be advised that UAE generally is not recommended for patients who are interested in pursuing future fertility. In patients who decide to pursue pregnancy after UAE, there is no known optimal time to achieve pregnancy. It seems that most reductions in myoma size occur by 6 months to 1 year. Women must consider the advantage of optimal myoma shrinkage with the disadvantages of possible new myoma formation as well as increasing maternal age.

In 1999, the Society of Interventional Radiology Foundation began the Fibroid Registry for Outcomes Data (FIBROID) to collect prospective data on a large number of women who undergo UAE. One of the goals is to collect data on long-term safety and to help patients and clinicians with decision making regarding treatment options for women who wish to become pregnant after embolization. More than 3000 patients are registered so far, and more than 700 report that they are considering future pregnancy. This database may provide invaluable information on fertility rates, miscarriage rates, and pregnancy outcome after UAE to counsel patients who are considering future fertility [77]. Spies and colleagues [10] reserve embolization for women who do not desire future fertility, but consider UAE for women who wish to maintain reproductive capability if hysterectomy or repeat extensive myomectomy are the only other options. Other groups have taken a more open approach, and now offer UAE to patients who desire future fertility [4,17,78].

Alternatives to uterine artery embolization

Conservative surgical alternatives to UAE should be considered for appropriate candidates who wish to preserve fertility. Broder and colleagues [79] compared the long-term outcomes of UAE and abdominal myomectomy for

symptomatic myomas. Patients who received UAE required more invasive treatments for myomas than did those who received myomectomy in the 3- to 5-year interval after the initial therapy. Patient satisfaction rates were high with both procedures (94% UAE, 79% abdominal myomectomy), however. Abdominal myomectomy resolves menorrhagia and anemia in 80% of cases [80]. Retrospective studies indicated that 40% to 45% of infertile couples conceive after myomectomy, and miscarriage rates are reduced after abdominal myomectomy [80,81]. Conclusive proof of the value of myomectomy in enhancing fertility has not been tested in prospective randomized trials. Table 3 shows the clinical factors that should be considered before selecting myomectomy or UAE.

Less is known about leiomyoma recurrence after UAE than after myomectomy, because long-term results after embolotherapy are limited. In both treatments, recurrence rates are affected by the patient's age, and the number and location of the myomas. The rate of recurrence that requires further surgery after myomectomy is estimated to be between 15% and 20% [80,82]. Fedele and colleagues [83] reported that new myomas could be identified by ultrasound in more than 50% of patients by 5 years after myomectomy. After excluding immediate treatment failures after UAE, Marret and colleagues [52] reported a symptom recurrence rate of 10% at approximately 2 years. Other investigators have questioned whether these reported late clinical failures were secondary to new fibroid growth or the progression of insufficiently devascularized myomas.

Complications from myomectomy are increased when large transmural myomas are encountered or when myomas are located in the broad ligament or the posterior cervical region. Myomectomy is associated with a higher morbidity than is hysterectomy [82,84], and the high rate of postoperative adhesion formation can cause small bowel obstruction or impairment of fertility [85].

Table 3
Indications for ablative therapy for uterine leiomyomata: abdominal myomectomy versus uterine artery embolization

Condition	Myomectomy	Uterine artery embolization
Multiple symptomatic subserosal, intramural, and submucous myomas	+	+
Rapidly enlarging myoma	+	0
Infertility	+	0
Desire to retain fertility	+	?
Does not desire future fertility, but wishes to retain uterus	?	+
Poor surgical risk	0	+
Hemodynamic instability due to hemorrhage	0	+
Diffuse multiple uterine leiomyomas	0	+
Hydrosalpinx	+	0
Adnexal mass	+	0

Abbreviations: +, indicated; ?, unknown; 0, not indicated.
From Hurst BS, Stackhouse DJ, Matthews ML, et al. Uterine artery embolization for symptomatic uterine myomas. Fertil Steril 2000;74:855–69.

Laparoscopic myomectomy is associated with shorter hospitalization, faster recovery, less postoperative morbidity, and comparable pregnancy and recurrence rates for selected patients when compared with abdominal myomectomy [86]. Pregnancies after UAE had higher rates of preterm delivery and malpresentation than did pregnancies after laparoscopic myomectomy [68].

Hysteroscopic myomectomy is reserved for patents who have predominantly submucosal myomas. UAE and hysteroscopic myomectomy are comparable for control of excessive uterine bleeding (85–90%), especially when hysteroscopic myomectomy is combined with endometrial ablation [87]. Hysteroscopic myomectomy, however, often does not result in a appreciable reduction in uterine size; this is a disadvantage when compared with UAE. Hysteroscopic myomectomy is a more accepted therapy for appropriate patients who desire fertility preservation, with conception in nearly 50% of patients after resection of a submucous myoma [88]. Combinations of operative approaches (eg, laparoscopic and hysteroscopic myomectomy) under a single anesthesia increase the rate of complete myoma resection. UAE also may be compared with hysterectomy. Hospitalization and the recovery time required are shorter for UAE than for hysterectomy [89]; however, hysterectomy is the only proven definitive treatment for symptomatic fibroids.

Myolysis involves placing laparoscopically directed electrical, thermal, or laser probes for coagulation of fibroids without resecting the fibroid. Initial results with myolysis produced a high rate of abdominal adhesions [90]; subsequent technique improvement with bipolar cautery needles reduced adhesion formation [91]. Although myolysis produced a reduction in mean fibroid volume and symptoms that were comparable to UAE, abdominal adhesions from myolysis present a clear disadvantage.

Medical therapies have not provided long-term treatment for uterine myomas, and no comparative trials of medical therapy with UAE for treating symptomatic myomas are available. Gonadotropin-releasing analogs with steroid hormone add-back, the levonorgestrel intrauterine system, aromatase inhibitors, progesterone receptor antagonists, selective progesterone receptor antagonists, and antifibrotic agents (eg, pirfenidone) offer promise to temporize symptoms from myomas, and may obviate the need for more invasive measures (see the article by Rackow and Arici elsewhere in this issue) [86].

Summary: collaborative management of symptomatic leiomyomata

Information is still being collected on the long-term clinical responses and appropriate patient selection for UAE. Prospective RCTs have not been performed to compare the clinical results from UAE with more conventional therapies for symptomatic uterine leiomyomata. At least three attempts at conducting such RCTs have been unsuccessful because of poor patient accrual that related to differing patient expectation and desires, clinical bias, insurance

coverage, and the tendency that patients who have exhausted other treatment options may be disposed more favorably to less invasive treatments. Other comparative studies have serious limitations. For example, the retrospective study that compared outcomes after abdominal myomectomy with UAE suggested that patients who received UAE were more likely to require further invasive treatment by 3 years than were recipients of myomectomy [79]. Lack of randomization introduced a selection bias because women in the group that underwent UAE were older and were more likely to have had previous surgeries. A prospective study of "contemporaneous cohorts," which excluded patients who had submucosal and pedunculated subserosal myomas, sought to compare quality of life measures and adverse events in patients who underwent UAE or hysterectomy [89]. The investigators concluded that both treatments resulted in marked improvement in symptoms and quality of life scores, but complications were higher in the group that underwent hysterectomy over 1 year. In this study, however, a greater proportion of patients who underwent hysterectomy had improved pelvic pain scores. Furthermore, hysterectomy eliminates uterine bleeding and the risk for recurrence of myomas. Despite the lack of controlled studies that compared UAE with conventional surgery, and despite limited extended outcome data, UAE has gained rapid acceptance, primarily because the procedure preserves the uterus, is less invasive, and has less short-term morbidity than do most surgical options.

The cost of UAE varies by region, but is comparable to the charges for hysterectomy and is less expensive than abdominal myomectomy. The evaluation before UAE may entail additional fees for diagnostic testing, such as MRI, to assess the uterine size and screen for adenomyosis [10]. Other centers have recommended pretreatment ultrasonography, laparoscopy, hysteroscopy, endometrial biopsy, and biopsy of large fibroids to evaluate sarcoma [8]. Generally, after UAE the recovery time and time lost from work are less; however, the potential need for subsequent surgery may be greater when compared with abdominal myomectomy [79].

Any center that offers UAE should adhere to published clinical guidelines, maintain ongoing assessment of quality improvements measures, and observe strict criteria for obtaining procedural privileges [18]. After McLucas [92] advocated that gynecologists learn the skill to perform UAE for managing symptomatic myomas, the Society of Interventional Radiology responded with a precautionary commentary on the level of technical proficiency that is necessary to maintain optimum results from UAE [19]. The complexity of pelvic arterial anatomy, the skill that is required to master modern coaxial microcatheters, and the hazards of significant patient radiation exposure were cited as reasons why sound training and demonstration of expertise be obtained before clinicians are credentialed to perform UAE.

A collaboration between the gynecologist and the interventional radiologist is necessary to optimize the safety and efficacy of UAE. The primary candidates for this procedure include women who have symptomatic uterine fibroids who no longer desire fertility, but wish to avoid surgery or are poor surgical risks (see

Table 3). The gynecologist is likely to be the primary initial consultant to patients who present with complaints of symptomatic myomas. Therefore, they must be familiar with the indications, exclusions, outcome expectations, and complications of UAE in their particular center. When hysterectomy is the only option, UAE should be considered. Appropriate diagnostic testing should aid in the exclusion of most, but not all, gynecologic cancers and pregnancy. Other contraindications include severe contrast medium allergy, renal insufficiency, and coagulopathy. MRI may be used to screen women before treatment in an attempt to detect those who have adenomyosis; patients should be aware that UAE is less effective in the presence of solitary or coexistent adenomyosis. Because some women may experience ovarian failure after UAE, additional studies to determine basal follicle-stimulating hormone and estradiol before and after the procedure may provide insight into UAE-induced follicle depletion.

UAE is a unique new treatment for uterine myomas, and is no longer considered investigational for symptomatic uterine fibroids. There is international recognition that data are needed from RCTs that compare UAE with surgical alternatives. Current efforts to provide prospective objective assessment of treatment outcomes and complications after UAE will help to optimize patient selection and clinical guidelines. FIBROID should provide critical data for the assessment of safety and outcomes measures for women who receive UAE for symptomatic uterine myomas [73].

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Myomas and Assisted Reproductive Technologies: When and How to Act?

Aytug Kolankaya, MD[a,*], Aydin Arici, MD[b]

[a]*Infertility and IVF Unit, Department of Obstetrics and Gynecology, Anadolu Health Center, Affiliated with Johns Hopkins Medicine, Anadolu Saglik Merkezi, Anadolu Cad. No: 1, Cayirova, Gebze, 41400 Kocaeli, Turkey*
[b]*Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06520, USA*

Uterine myomas are present in approximately one third of women of reproductive age [1]. Although 5% to 10% of cases of infertility are associated with myomas, they are estimated to be the sole factor for infertility in only 1% to 3% of cases [2,3].

The mechanisms by which myomas may affect reproductive outcome are as follows [4–6]:

Interference with sperm transport or access by: (1) anatomic distortion of the cervix; (2) enlarging or deforming the endometrial cavity; (3) altering the uterine contractility; and (4) obstructing tubal ostia.
Implantation failure by: (1) physically changing the shape of the endometrium; (2) preventing discharge of intrauterine blood or clots; and (3) altering the normal endometrial development.

The goal of this review of the literature is to answer two consecutive questions: Do the location and size of myomas reduce the success of assisted reproduction? If the answer of this question is yes, do different treatment modalities for myomas improve the reproductive outcome?

* Corresponding author.
E-mail address: aytug.kolankaya@anadolusaglik.org (A. Kolankaya).

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Myomas and assisted reproduction

Check and colleagues [7] investigated the effect of intramural myomas (≤5 cm in diameter and not compressing the uterine cavity) on in vitro fertilization–embryo transfer (IVF-ET) cycle outcome. The additional requirements were that the myomas did not have a submucosal component, the patient had not undergone previous uterine surgery for leiomyomata or other reasons, and no other uterine cavity abnormalities existed (eg, uterine septum or polyps). Sixty-one women who had myomas in their first IVF cycle were matched prospectively by age with 61 women who did not have leiomyomata. The maximum number of myomas in a given patient was seven. The outcome measurements were positive pregnancy test, clinical pregnancy, spontaneous abortion and live birth rates. Although the comparison of all results showed no significant difference between the study and control groups, the investigators indicated that a multicenter study is essential because the trend for increased miscarriage and decreased term delivery rates may become significant.

A letter to the editor by Nawroth and Foth [8] in response to the study by Check and colleagues [7] brought forth a discussion about the nomenclature of myomas. They stated that myomas that compress the uterine cavity with an intramural portion of more than 50% should be classified as submucous myoma type II. Therefore, intramural myomata per se do not compress the uterine cavity [9].

Hart and colleagues [10] investigated the outcome of assisted reproduction in women who had intramural myomas that were up to 5 cm in diameter, and reached totally different results than did Check and colleagues [7]. In this study, instead of case-matching, 112 women who had myomas were compared with 322 women who did not have any uterine pathology. Pregnancy, implantation, and ongoing pregnancy rates were reduced significantly and were 23.3%, 11.9%, and 15.1%, respectively, compared with 34.1%, 20.2%, and 28.3% in the control group. When the results of logistic regression were adjusted for the number of embryos transferred and the women's age, the odds ratio (OR) of an ongoing pregnancy in the presence of an intramural fibroid that was up to 5 cm in diameter was halved (OR, 0.46; CI, 0.24–0.88]), especially among women who were at least 40 years of age.

Ramzy and colleagues [11] aimed to study the success of IVF/intracytoplasmic sperm injection (ICSI) in patients who had subserous or intramural myomas that did not encroach upon the endometrial cavity. Among a total of 406 patients, 51 (12.6%) had myomas. Twelve of these were excluded from the study and were advised to have myomectomy—for submucous or intramural myomas that were deforming the endometrial cavity—before assisted reproduction. Because it was a mixed group and consisted mainly of patients who had subserous, rather than intramural, myomas (32 versus 12, respectively), the results are not definitive for the group that had intramural myomas. The mean diameters for both groups were 3 to 4 cm. No significant difference was found between the two groups for total pregnancies, clinical pregnancies, implantation

rate, abortions, preterm labor, or deliveries. The only significant finding was the increased incidence of myoma with increasing age, especially after 35 years. The investigators concluded that subserous or intramural myomas that do not encroach the endometrial cavity and are less than 7 cm in diameter do not affect the IVF/ICSI outcome.

An older case-matched study by Stovall and colleagues [12], which was performed between 1993 and 1995 and included 182 patients, also questioned the difference in pregnancy rates after assisted reproduction in nonmyomatous patients and in patients who had myomas [33]. Although the pregnancy rate for the former group was higher (52.7% versus 38.3%), several confounding factors may have altered the results. First, the mean age of the control group was younger, 35.9 years versus 36.8 years. Second, male factor infertility was lower in the control group (23.1% versus 31.1%). Finally, the mean number of embryos that was transferred in the control group was higher than in the study group (3.6 versus 3.2). Despite these differences in the two groups that were undergoing assisted reproduction, the investigators found a significant Mantel-Haenszel estimate of relative risk (RR) for the presence of myomas for lower pregnancy and delivery rates (RR, 0.71; CI, 0.51–0.98 and RR, 0.68; CI, 0.47–0.98, respectively).

In a retrospective case-controlled analysis, Surrey and colleagues [13] investigated the impact of intramural myomas on assisted reproduction. Three hundred and ninety-nine consecutive fresh IVF-ET cycles were grouped into four major groups and a subgroup. Groups that did and did not have myomas were divided according to age (<40 years and $\geq$40 years). A group that did not have myomas and was between the ages of 35 and 39 was used as another control subgroup. All patients had undergone hysteroscopy during the midfollicular phase within 6 months of the cycle, and all had normal endometrial cavities. In addition, a baseline precycle transvaginal ultrasound examination was performed in each case. For patients who were younger than age 40, the implantation rate was significantly lower in the group that had myomas compared with the group that did not have myomas or with the subgroup (21.4%, 57.5%, and 57.0%, respectively). For the patients who were at least 40 years of age, the presence or absence of myomas did not create a significant difference (11.6% versus 17.5%, respectively).

Eldar-Geva and colleagues [14] compared pregnancy and implantation rates in women who had myomas in different locations with women who did not have myomas. Women who had submucous myomas had the lowest pregnancy and implantation rates (10.0% and 4.3%, respectively). The group that had intramural myomas also had significantly reduced pregnancy and implantation rates compared with the groups that had subserous myomas or no myomas (16.4% and 6.4%, 34.1% and 15.1%, 30.1% and 15.7%, respectively). This is one of the rare studies in which cases of submucous myomas were included. The investigators made it clear that all submucous myomas caused cavity distortion, and that the intramural myomas were completely within the myometrium or had subserosal parts only.

Unless a myoma is purely subserous, surgery before assisted reproduction should be considered as an option. Most investigators suggest surgery for submucous and intramural myomas that depress the endometrial cavity [15]. There is no consensus for intramural myomas that do not encroach upon the cavity; however, most surgeons would agree to remove them if they are larger than 7 cm or are associated with multiple failed IVF cycles.

Treatment of myomas and the reproductive outcome

Hysteroscopic myomectomy

Although endoscopic visualization of the endometrial cavity has been performed for more than a century, the first hysteroscopic myomectomy was performed in 1957 by Norment [16,17]. Repeat procedures for incomplete resections, uterine perforation during surgery, and uterine rupture in a subsequent pregnancy are rare risks about which patients should be informed [18,19].

Emanuel and colleagues [20] showed a 46% conception rate after hysteroscopic myomectomy. Vercellini and colleagues [21] subgrouped submucous myomas, and reported conception rates after hysteroscopic surgery—over a 3-year period—of 49% for pedunculated myomas and 33% for myomas with intramural components. The benefit and efficacy of hysteroscopic myomectomy in cases of pedunculated myomas and myomas with more than 50% in the uterine cavity is generally accepted.

Abdominal myomectomy

A review by Vercellini and colleagues [22] in 1998 confirmed the fertility-improving effect of abdominal myomectomy. The 23 studies that were included in the review were highly heterogenous by all means (eg, type of study, location of myomas, causes of infertility, years of infertility). Cases in all studies, except 4, were followed for up to at least 12 months. Among the included studies, 564 infertile women underwent myomectomy, and 269 pregnancies (47.7%) occurred during the follow-up period. The pregnancy rate for the 9 prospective studies was 57% (CI, 48–65%). The overall conception rate among 7 prospective studies, in which only unexplained cases of infertility were included, was 61% (CI, 51–70%). The conception rates after myomectomy were 58%, 64%, and 70% in the three studies of women who had only intramural or subserous myomas [23].

Li and colleagues [24,25] performed myomectomy using microsurgical techniques on 51 women who had intramural or subserosal myomas, and no other significant infertility factors, and who wished to conceive. No myomas caused any deformity of the endometrial cavity. Before surgery there were 40 pregnancies among these 51 women and 24 pregnancies were lost among 19 women. Following myomectomy, there were 33 spontaneous pregnancies

among 29 women. The rate of pregnancy loss after myomectomy was significantly lower than before surgery (24% versus 60%).

In a retrospective analysis Marchionni and colleagues [24] evaluated the results of abdominal myomectomy for intramural and subserosal myomas that might influence the reproductive outcome. Seventy-two women were included in the study. There were 26 pregnancies before myomectomy and 68 pregnancies after myomectomy in 51 of these 72 women. The pregnancy loss rate was significantly lower (25%) after myomectomy compared with that before the operation (69%). The live birth rate also improved significantly after surgery (31% versus 75%).

Frederick and colleagues [26] performed a prospective cohort study of reproductive outcome after a second myomectomy for recurring myomas. Nine (15.5%) of 58 women became pregnant after the second surgery; however, only 5 (56%) had live births. The investigators constructed a model depending on the likelihood ratios of different parameters. The number of myomas present, was the third significant factor for a successful pregnancy outcome, where age and the presence of tubal adhesions were first and second, respectively.

Laparoscopic myomectomy

Laparoscopic myomectomy has been the subject of several studies since the late 1980s; however, data on reproductive outcome after this procedure have become of concern in the last decade [27–29]. Because it is a difficult procedure that requires advanced surgical skills, especially in endoscopic suturing, the use of this technique is limited.

In a study of the comparison of reproductive outcome after abdominal and laparoscopic myomectomy, Seracchioli and colleagues [30] treated 65 patients by abdominal technique and 66 patients by laparoscopic technique. Pregnancy rates were comparable (55.9% and 53.6%, respectively). Miscarriage rates were 12.1% and 20.0%, respectively, but this difference was not significant.

Fauconnier and colleagues [31] performed laparoscopic myomectomy on 91 infertile patients who had at least one subserous or intramural myoma that was larger than 2 cm. Eighty-one of these patients were followed-up for 2 years and 43 (53.1%) of them became pregnant. The spontaneous pregnancy rate was 44% (CI, 32–56%) for the same time period. In the multiple regression of prognostic factors for fertility after myomectomy, intramural myomas were significant in reducing the pregnancy rate (RR, 0.4; CI, 0.2–0.8), whereas, subserosal myomas did not affect the reproductive outcome.

Seinera and colleagues [32] reported 202 cases of laparoscopic myomectomy and 65 subsequent pregnancies in 54 patients. Twenty-one of these were after IVF, and 51 (78.5%) pregnancies were completed uneventfully.

Ribeiro and colleagues [33] performed laparoscopic myomectomy on 28 infertile patients, each of whom had at least one myoma that was larger than 5 cm in diameter. Two patients also underwent simultaneous hysteroscopic myomectomy. Eighteen (64.3%) of these patients, including one who also underwent

hysteroscopic myomectomy, became pregnant after the procedure and 14 delivered viable term babies.

Other techniques

Hutchins and colleagues [34] described selective uterine artery embolization for symptomatic uterine myomas with a high treatment effect. Goldberg and colleagues [35] investigated the reproductive outcomes after coagulation of uterine vessels (CUV) and laparoscopic myomectomy. A significantly increased risk for preterm delivery and malpresentation, as well as an increased risk for spontaneous abortion were found for CUV. Chen and colleagues [2] treated 142 women who had myomas by CUV; the myoma sizes were reduced significantly after the procedure. When a subgroup of 36 sexually active women that was not using contraception was followed after CUV, 15 (41.6%) became pregnant (17 total pregnancies); however, a high rate of miscarriages (7/17, 41.2%) occurred in this group. Therefore, the investigators advised that the procedure be reserved for women with no desire for pregnancy.

Laparoscopic coagulation of uterine myomas, namely myolysis and MRI-guided focused ultrasound surgery, are recent alternatives for the treatment of uterine myomas [36,37]. The accumulation of data about these procedures is scarce, and the safety of the procedures needs to be evaluated before the reproductive outcomes can be discussed [38–42].

Summary

The effect of myomas on reproductive outcome has been the subject of many studies; however, a definitive answer is still missing. Therefore, the authors have tried to outline some guidelines for the management of women who have uterine myomas and desire to conceive.

The location and size of the myomas are the two parameters that influence the success of a future pregnancy. Subserosal myomas seem to have little, if any, effect on reproductive outcome, especially if they are up to 5 to 7 cm in diameter. Intramural myomas that do not encroach upon the endometrium also can be considered to be relatively harmless to reproduction, if they are smaller than 4 to 5 cm in diameter. This is the ambiguous gray zone of the subject, and where research should be focused before a consensus can be established. Myomas that compress the uterine cavity with an intramural portion (submucous myoma type II) and submucous myomas significantly reduce pregnancy rates, and should be removed before assisted reproductive techniques are used.

Hysteroscopic myomectomy is the gold standard for the treatment of submucous myomas. For other myomas, abdominal myomectomy, or laparoscopic myomectomy—when the experience of the surgeon and the facilities are sufficient—are the best alternatives. In most of the literature, the pregnancy rates

were increased and the miscarriage rates were decreased after surgery with these two techniques. Other alternative treatment modalities, such as CUV, laparoscopic myolysis, or MRI-guided focused ultrasound, are to be monitored and evaluated thoroughly before they are applied as routine procedures.

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Obstetric Complications of Fibroids

David W. Ouyang, MD[a,*],
Katherine E. Economy, MD, MPH[a],
Errol R. Norwitz, MD, PhD[b]

[a]*Department of Obstetrics, Gynecology & Reproductive Biology, Brigham & Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA*
[b]*Department of Obstetrics, Gynecology & Reproductive Sciences, Yale-New Haven Hospital, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA*

Uterine fibroids (leiomyomas) are common benign smooth muscle tumors of the uterus. They are found in approximately 25% to 35% of reproductive age women [1], although detailed pathologic examination can identify fibroids in up to 77% of all hysterectomy specimens [2]. Uterine fibroids are seen more commonly in African American and older populations [3]. As more and more women choose to delay childbearing, the issue of fibroids in pregnancy is one that obstetric care providers are likely to face with increasing frequency. This article reviews in detail the current literature regarding the effect of uterine fibroids on pregnancy outcome, the mechanisms by which fibroids may complicate pregnancy, and the usefulness of medical and surgical interventions that are used to prevent and treat such complications.

Prevalence of fibroids in pregnancy

The reported prevalence of fibroids in pregnancy ranges from 0.09% to 3.9% [4–9]; however, most of these studies have been criticized because of the manner in which they selected their study populations. For example, many of these studies were published before the routine use of prenatal ultrasounds and, as such, included fibroids that were diagnosed primarily by physical examination, at

* Corresponding author.
E-mail address: douyang@partners.org (D.W. Ouyang).

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the time of laparotomy, or during manual removal of the placenta after delivery [5–9]. Such studies likely underestimated the true prevalence of uterine fibroids by failing to detect smaller, asymptomatic tumors. Some studies did use ultrasound, but only in selected patient populations, such as pregnant women with uterine size greater than dates, cases of vaginal bleeding or malpresentation, or women who presented for routine genetic testing [6,7]. Other studies simply used hospital discharge diagnosis codes to identify women who had uterine fibroids. It is not surprising, therefore, that these studies reported a prevalence of uterine fibroids of only 0.09% to 0.37% [1,4].

Only two publications used routine ultrasound examinations in consecutive women who presented for prenatal care to define the true prevalence of uterine fibroids in pregnancy [10,11]. Exacoustos and Rosati [10] reported that 4% of their pregnant patients had fibroids with a diameter greater than 3 cm. Strobelt and colleagues [11] identified 209 patients who had fibroids that were larger than 1 cm among 12,600 consecutive pregnant patients, which corresponded to a prevalence of 1.6%. Both of these studies were performed in tertiary care referral centers, which may have biased the cohort toward older parturients and, as such, selected out a population that was at higher risk for fibroids.

Natural history of fibroids in pregnancy

Contrary to popular belief, most longitudinal studies that were designed to measure the growth pattern of fibroids during pregnancy refute the commonly held belief that fibroids continue to increase in size throughout gestation [12]. A series of retrospective studies that was performed in the early 1980s was the first to dispel this myth; they demonstrated that approximately 90% of fibroids exhibited no significant change in size during pregnancy [13,14]. Three subsequent prospective studies confirmed that most uterine fibroids (49–60%) had a negligible change in volume throughout pregnancy (defined as <10%), whereas 22% to 32% exhibited an increase in growth, and 8% to 27% exhibited a decrease in size [5,15,16]. Another prospective longitudinal study of 134 patients reported that 62% of fibroids with a diameter of less than 5 cm that were diagnosed early in pregnancy were no longer visualized by ultrasound in the latter half of pregnancy [11].

In those fibroids that do increase in size in pregnancy, when does most of the growth occur and how large do they grow? The weight of evidence in the literature suggests that fibroid growth occurs most commonly in the first trimester, and that the second and third trimesters of pregnancy are associated with little, if any, further increase in size [5,15,16]. Larger fibroids (>5 cm in diameter) are more likely to grow, whereas smaller fibroids are more likely to remain stable in size [11]. If smaller fibroids do increase in size, they generally do so in the first and second trimesters and decrease in size in the third trimester [5]. The mean increase in fibroid volume during pregnancy is 12%, and few fibroids increase by more than 25% [15,16].

Complications of fibroids in pregnancy

Uterine fibroids have long been implicated as a cause of subfertility and adverse pregnancy events [17]. The complications of pregnancy that have been attributed to fibroids are summarized in Box 1. Review of the literature suggests that the presence of uterine fibroids in pregnancy is associated with an antepartum complication rate of 10% to 40%. Because uterine fibroids are common in reproductive-aged women, their presence at the time of prenatal ultrasound does not mean that they are related causally to the complication in question. In general,

Box 1. Complications associated with fibroids in pregnancy

Antepartum complications

- Spontaneous abortion
- Threatened abortion
- Preterm labor
- Premature rupture of membranes
- Placental abruption
- Pain
- Preeclampsia
- Intrauterine growth restriction
- Malpresentation
- Disseminated intravascular coagulation
- Radiculopathy
- Acute renal failure
- Uterine incarceration

Intrapartum/postpartum complications

- Dysfunctional labor
- Cesarean delivery
- Postpartum hemorrhage
- Retained placenta
- Postpartum sepsis

Fetal complications

- Decreased Apgar score
- Fetal anomalies
  - Limb reduction
  - Head deformities
  - Congenital torticollis

the literature tends to underestimate the prevalence of fibroids in pregnancy and overestimate the complications that are attributed to them. Individual complications of pregnancy that are attributed to uterine fibroids are discussed in detail below.

Pregnancy loss

The weight of evidence in the literature suggests that uterine fibroids increase the risk for spontaneous abortion and are a cause of recurrent pregnancy loss [5,14,18–20]; however, not all fibroids pose equal risk. Large submucosal fibroids that distort the uterine cavity consistently have been associated with pregnancy loss (Fig. 1) [3,20,21], whereas the data on smaller intramural and subserosal fibroids is less consistent [10,18,19]. For example, some investigators have reported that, when compared with women who have subserosal or no fibroids, even small intramural and submucosal fibroids that do not alter the contour of the intrauterine cavity are associated with failed implantation following assisted reproductive technology [22,23], whereas other investigators were unable to confirm these observations [24].

Several mechanisms have been suggested to explain the association between uterine fibroids and spontaneous pregnancy loss. A large submucosal fibroid that projects into the uterine cavity may compress the underlying endometrium and lead to endometrial dysfunction or it may distort the vascular architecture that supplies and drains the endometrium at that site. If the embryo chooses to implant at that site, the fibroid may interfere with normal placentation and development

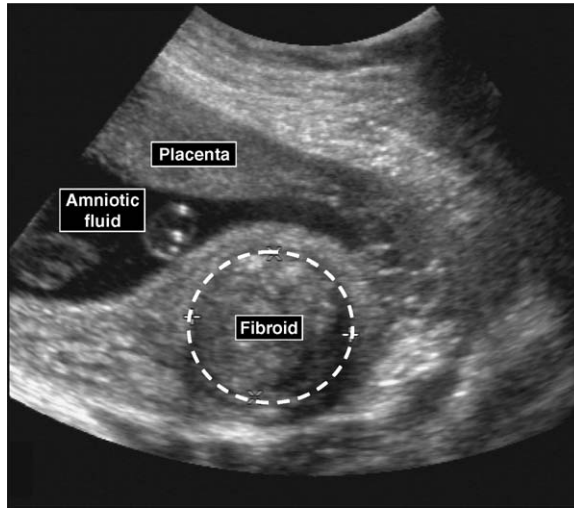

Fig. 1. Fibroid distorting the uterine cavity. A transabdominal ultrasound image of a 16-week pregnancy is shown. The placenta is located anteriorly. A large (4.8 × 4.3 cm) submucosal fibroid can be seen in the posterior uterine wall and is distorting the uterine cavity.

of the definitive uteroplacental circulation and lead to spontaneous pregnancy loss [25,26]. Alternatively, rapid fibroid growth with or without degeneration may lead to increased uterine contractility or altered placental oxytocinase activity [26,27], both of which may disrupt placentation and lead to spontaneous abortion.

Threatened abortion

Numerous studies reported that antepartum bleeding is significantly more common in pregnancies with uterine fibroids [4,10,13,14], although not all studies confirmed this association [5,28]. Exacoustos and Rosati [10], for example, reported that 17% of women who had uterine fibroids had a threatened abortion compared with only 10% of women who did not have fibroids. Similarly, Coronado and colleagues [4] reported that first trimester bleeding was more common in women who had uterine fibroids compared with those who did not (OR, 1.82; 95% CI, 1.05–3.20). Once again, the location of the fibroid in relation to the placenta may be an important determinant; 72% of patients who had retroplacental fibroids reported vaginal bleeding compared with only 9% of patients who had nonretroplacental fibroids (Fig. 2) [14,29].

Preterm labor and birth

The risk for preterm labor and delivery has been purported to increase in pregnancies with uterine fibroids [6,9,10,14,16,30,31]. For example, a statisti-

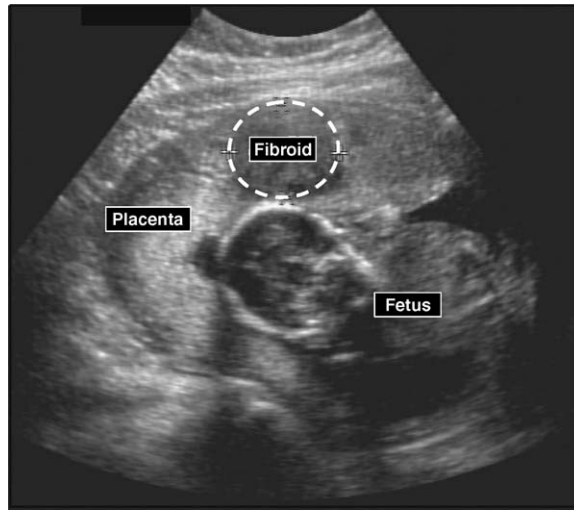

Fig. 2. Retroplacental fibroid. A transabdominal ultrasound image of an 18-week pregnancy is shown. The placenta is located anteriorly. The fetus is in the breech position. A large (3.6 × 3.3 cm) submucosal fibroid can be seen behind the placenta.

cally significant increased risk for preterm labor (defined as regular contractions at <37 weeks' gestation that required tocolysis) and preterm birth was reported with fibroids larger than 3 cm [32] and 6 cm in diameter [16] as compared with controls. This is especially true if multiple fibroids are present or if placentation occurs adjacent to or overlying a fibroid [5,14]. Not all studies showed an association between uterine fibroids and preterm labor and birth [8,10,28,33]. Yet other investigators demonstrated an increased risk for threatened preterm labor that required tocolysis in women who had uterine fibroids, although such women were not more likely to deliver preterm [10].

Various theories have been proposed to explain the biologic basis of preterm labor in the setting of uterine fibroids. Some investigators suggested that fibroid uteri are less distensible than are nonfibroid uteri, which leads to premature labor and delivery in the same way that women who have congenital Müllerian abnormalities are at risk for preterm labor [6,25]. Others noted decreased oxytocinase activity in the gravid fibroid uterus, which may result in a localized increase in oxytocin levels and predisposition to premature contractions [27].

Preterm premature rupture of membranes

Similar to preterm labor, the literature describing the association between uterine fibroids and preterm premature rupture of membranes (pPROM) is conflicting. In one study, Coronado and colleagues [4] reported that women who had uterine fibroids were almost twice as likely to have pPROM than were women who did not have fibroids (OR, 1.79; 95% CI, 1.2–2.69). A retrospective case-control study by Davis and colleagues [8] confirmed this association; 7% (6/85) of women who had uterine fibroids developed pPROM compared with 1% (1/85) of women who did not have fibroids. The greatest risk for pPROM seems to be in women in whom the fibroid is in direct contact with the placenta [13]; however, numerous other groups reported no increased risk for pPROM in women who had uterine fibroids [10,28,33].

Placental abruption

A retrospective analysis of 6706 consecutive pregnant patients identified 93 patients (1.4%) who had uterine fibroids [6]. Among these 93 patients, 14 (15.1%) had one or more fibroids that were retroplacental in location. Significantly, 8 of these 14 patients (57%) subsequently developed placental abruption, which resulted in the deaths of four fetuses. Among the remaining 79 patients whose fibroids were not retroplacental, placental abruption occurred in only 2 patients (2.5%), neither of which resulted in fetal death. Although this observational study has been criticized because ultrasounds were not performed routinely in all antepartum patients, other studies also showed an increased risk for abruption with fibroid pregnancies [4,10,31]. Exacoustos and Rosati [10], for example, performed routine ultrasound examinations in 12,708 consecutive pregnant patients and identified uterine fibroids in 492 patients (3.9%). Of these

492 women, 7.5% had an abruption compared with only 0.9% of the controls ($P < .001$). Subsequent subanalysis of the data suggested that submucosal and retroplacentally located fibroids and fibroids with volumes greater than 200 mL (corresponding to 7–8 cm diameter) had the highest risk for abruption. Not all studies confirmed an association between uterine fibroids and placental abruption [5,8,28,32,33].

The explanation for the increased risk for abruption in the setting of uterine fibroids likely is related to placental perfusion [6]. Using locally injected ^{133}Xenon to measure regional blood flow in the uteri of 11 nonpregnant patients who underwent laparotomy, Forssman [34] demonstrated that blood flow is reduced significantly in fibroids and in the myometrium adjacent to fibroids. Therefore, implantation in the endometrium overlying a fibroid may lead to placental ischemia and decidual necrosis, which makes it more susceptible to abruption.

Placenta previa

The presence of uterine fibroids was believed to lead to preferential placentation in the lower uterine segment; however, subsequent studies failed to show any association between uterine fibroids and placenta previa [4,5,8,32,33].

Pain

Pain is one of the most frequent complications of fibroids in pregnancy. Most studies suggest that 5% to 15% of women who have fibroids require hospitalization at some point during their pregnancy for management of abdominal pain [9,10,28,35]. This risk for pain increases with size, and is especially high in fibroids that are larger than 5 cm in diameter [6,10]. Fibroid pain likely results from decreased perfusion in the setting of rapid growth leading to ischemia and necrosis (degeneration) with release of prostaglandins (Fig. 3) [36]. This hypothesis is supported by the observation that fibroid pain typically presents in the late first or early second trimester, which corresponds to the period of greatest rate of fibroid growth. Traditional teaching tells us that fibroid degeneration is a clinical diagnosis with localized tenderness over the fibroid, mild leukocytosis, pyrexia, and nausea and vomiting [37]. Most patients who are admitted for fibroid pain have a relative absence of these symptoms, with the exception of localized pain [7].

The management of fibroid pain during pregnancy includes rest, hydration, and pain control with a standard analgesic (eg, acetaminophen) or, if necessary, narcotic analgesia [7]. Management of intractable fibroid pain that is refractory to this regimen has included nonsteroidal anti-inflammatory drugs (NSAIDs), antepartum myomectomy, and even termination of pregnancy [6,10,37]. Ibuprofen, a nonselective cyclooxygenase inhibitor, was reported to be an effective

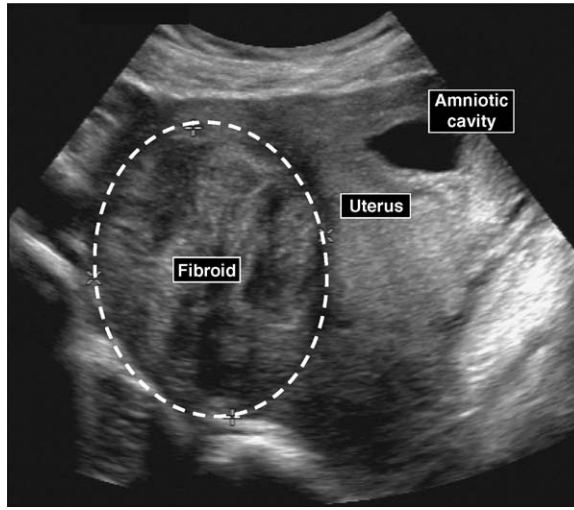

Fig. 3. Degenerating fibroid. A large (7.1 × 5.8 cm) intramural and subserosal fibroid is shown in the fundal region of a uterus that contains a viable 12-week intrauterine pregnancy. The patient presented with lower abdominal pain, low-grade fever, nausea, and localized tenderness over the uterine fundus, which suggested a diagnosis of a degenerating fibroid. The presence of a large fundal fibroid on ultrasound with echogenic irregularities that are suggestive of necrosis likely confirms the diagnosis.

agent for the management of fibroid pain in pregnancy, and resulted in a dramatic reduction in the length of hospital stay compared with narcotic analgesia [6]. Although most studies demonstrated no fetal complications that were attributable to NSAID use, it is not recommended beyond 32 weeks of gestation because of the possibility of premature closure of the ductus arteriosus, neonatal pulmonary hypertension, oligohydramnios, and platelet dysfunction [38]. Indomethacin (25 mg every 6 hours) also was reported to be useful in treating fibroid pain in pregnancy [37,39,40]. In a series of seven patients who had fibroid pain that was refractory to narcotic analgesia, all women achieved symptomatic relief within 48 hours of indomethacin administration. One of the seven patients developed transient constriction of the ductus and oligohydramnios, which resolved within 1 week after discontinuation of the indomethacin [39]. Although no permanent complications were attributable to indomethacin in this study, therapy should be limited to gestational ages of less than 32 weeks because of the increased prevalence of ductal constriction beyond that gestational age [39,40].

Preeclampsia

Most studies do not support an association between uterine fibroids and preeclampsia [4,8,28]. In the study by Roberts and colleagues [28], although there was no significant increase in the prevalence of preeclampsia in patients who had fibroids, women who had multiple fibroids were more likely to develop

preeclampsia than were those who had a single fibroid (45% versus 13%, $P < .05$). The investigators suggested that the increased risk was due to disruption of trophoblast invasion by the multiple fibroids, which leads to inadequate uteroplacental vascular remodeling, and ultimately predisposes the patient to the later development of preeclampsia.

Intrauterine growth restriction

Most of the recent literature suggests that uterine fibroids are not associated with intrauterine growth restriction (IUGR) [5,6,8,10,28,32,33], although a study by Rosati and colleagues [16] of 36 pregnant patients suggested that large fibroids (>200 mL) may be associated with delivery of small-for-gestational age infants (defined as less than the tenth percentile for gestational age). Two subsequent studies suggested an association between uterine fibroids and the delivery of low birth-weight infants (<2500 g); however, these studies were flawed because the women who had uterine fibroids delivered at earlier gestational ages than did the control group [4,32].

Fetal anomalies

Several case reports described an association between large submucosal uterine fibroids and fetal anomalies, including limb reduction defects, congenital torticollis, and head deformities [41–43]. To investigate the association between uterine fibroids and congenital anomalies, Matsunaga and Shiota [43] examined 3571 well-preserved human embryos that were collected from elective pregnancy terminations. The frequency of malformed embryos was 6.2% among 97 pregnancies from women who had known uterine fibroids, which was almost twofold higher than the 3.3% rate among 3474 pregnancies that were not complicated by fibroids. The dominant lesion in the fibroid cases was caudal dysplasia.

Malpresentation

Müllerian anomalies are known to be associated with an increased risk for malpresentation because they distort the shape of the uterine cavity [44,45]. In the same way, large submucosal fibroids that distort the uterine cavity have been associated consistently with fetal malpresentation [4,6,9,10,32]. Using a population-based cohort of 2065 women who had uterine fibroids who delivered singleton viable infants in Washington State (1987–1993) and controls that were matched (1:1) by year of delivery, Coronado and colleagues [4] reported a significant increase in malpresentation (primarily breech presentation) in women who had fibroids (OR, 3.98; 95% CI, 3.07–5.16). Other studies noted an increased prevalence of malpresentation only if the uterus had multiple fibroids or

if there was a fibroid located behind the placenta or in the lower uterine segment [5,6,35].

Dysfunctional labor

Fibroids have been postulated to decrease the force of uterine contractions or disrupt the coordinated spread of the contractile wave, and thereby, lead to dysfunctional labor [33,46]. Coronado and colleagues [4] reported a significant increase in the prevalence of dysfunctional labor (OR, 1.85; 95% CI, 1.26–2.72) and a decreased prevalence of precipitous labor (OR, 0.41; 95% CI, 0.21–0.81) in pregnancies that were complicated by fibroids. They also reported a trend toward prolonged labor, but this did not reach statistical significance (OR, 1.17; 95% CI, 0.80–1.71). Although several studies have reported similar findings [9,33], not all investigators have been able to confirm this association [28]. Higher rates of tachysystole (defined as more than five contractions in 10 minutes) also were reported in patients who had uterine fibroids, although these were not associated with a corresponding abnormal fetal heart rate pattern (hyperstimulation) [47].

Cesarean delivery

Studies that investigated the association between uterine fibroids and cesarean delivery rates are fraught with design bias. The most notable and obvious source of error is detection bias where fibroids are noted for the first time at cesarean delivery. In one such study, 72.5% of patients who underwent cesarean delivery had a diagnosis of fibroids made at the time of delivery, compared with 5% of women who delivered vaginally [4]. Other studies used ultrasound to identify fibroids before delivery, but did so selectively. Finally, an incidental finding of a large uterine fibroid at the time of routine ultrasound examination may decrease an individual clinician's threshold to proceed with an abdominal delivery rather than persist with an attempted vaginal birth under the presumption that the fibroid will lead to an obstructed labor.

Despite this bias, the literature generally is consistent in reporting that the presence of uterine fibroids is associated with an increased risk for cesarean delivery [4–7,9,32,33], although not all studies confirmed this association [10]. The proposed increase in cesarean delivery rate probably is due to such factors as an increased risk for malpresentation, dysfunctional labor, and placental abruption. For example, in a retrospective cohort study of 183 consecutive pregnant women with sonographic evidence of uterine fibroids at the time of routine second trimester ultrasound and matched controls who did not have fibroids, Vergani and colleagues [33] reported that cesarean delivery was significantly more common in women who had fibroids (23.4% versus 12.1%; $P < .001$). Moreover, within the group of women that had fibroids, the prevalence of

cesarean delivery was not different in cases of multiple lesions compared with solitary lesions, but it was significantly higher in cases of lower uterine segment fibroids compared with fundal fibroids (39% versus 18%; $P < .01$; OR, 2.4; 95% CI, 1.1–4.9) and when the mean diameter of the fibroid was larger than 5 cm (35% versus 17%; $P = .01$; OR, 2.9; 95% CI, 1.2–5.5). Other studies also noted an increased rate of cesarean delivery if the fibroids were located in the lower uterine segment [5].

Postpartum hemorrhage

As for other complications of pregnancy, the literature on the risk for postpartum hemorrhage in women who have uterine fibroids is controversial because of inherent design flaws. Several studies reported an increased risk for postpartum hemorrhage in pregnancies that were complicated by uterine fibroids [9,29], especially if the fibroids were large (>3 cm) and located behind the placenta [13,35,36]. The risk for postpartum hemorrhage in women who have uterine fibroids may be increased further in the setting of cesarean delivery [9]. Pathophysiologically, uterine fibroids may predispose to postpartum hemorrhage by decreasing the force and coordination of uterine contractions, which leads to uterine atony [46]. Numerous other studies found no association between fibroids and postpartum hemorrhage [5,28,33].

Fetal outcome

Several studies compared 5-minute Apgar scores in infants who were delivered by women who did and did not have uterine fibroids. Most of these studies found no significant difference between these groups [6,8,28], although one study reported that pregnancies with fibroids were more likely to be associated with infants who had a 5-minute Apgar score of less than 7 (OR, 2.49; 95% CI, 1.49–4.15) [4].

Rates of intrauterine fetal demise do not seem to be increased in pregnancies that are complicated by uterine fibroids [4,32].

Other complications

Several less common complications of pregnancy also have been attributed to the presence of uterine fibroids, including disseminated intravascular coagulation, spontaneous hemoperitoneum, uterine inversion, uterine incarceration, acute renal failure, and urinary retention [35,48–50]. L5 radiculopathy, limb reduction anomalies, and head deformities in the fetus also have been described in pregnancies that were complicated by uterine fibroids [35,41,42], although it remains unclear whether this association is causal.

Myomectomy and pregnancy

Myomectomy is indicated in nonpregnant women who have intractable fibroid pain or metro-menorrhagia that are unresponsive to medical therapy and who have not completed childbearing. Whether to recommend myomectomy in a patient who has subfertility or a poor obstetric history is controversial, and is a common problem that is faced by obstetrician-gynecologists. The lack of large, well-designed, randomized clinical trials that address these issues severely limits our ability to reach any definitive conclusions; however, many small retrospective studies have attempted to address these questions.

Preconception myomectomy

There is little data to guide the clinician in deciding whether to recommend elective preconception myomectomy to women who have recurrent pregnancy loss or a history of pregnancy complications that may be related to uterine fibroids (eg, preeclampsia, pPROM, placental abruption). In general, the literature suggests that large fibroids that are submucosal or retroplacental in location are more likely to be related to pregnancy complications; however, it is difficult, if not impossible, to predict which fibroids will grow in pregnancy or where the placenta will implant. As such, the decision of whether to recommend prophylactic myomectomy should be individualized with specific attention made to the patient's age and reproductive history, as well as the size and location of the fibroids.

A detailed review of the literature on the efficacy of prophylactic myomectomy on subsequent pregnancy outcome is beyond the scope of this article; however, the weight of evidence in the literature suggests that preconception myomectomy seems to improve the likelihood of a successful pregnancy in women who have recurrent pregnancy loss, especially when no other identifiable cause for the previous spontaneous abortions can be found [1,18]. In a retrospective review of 1941 women who underwent abdominal myomectomy, Buttram and Reiter [1] reported that the rates of spontaneous pregnancy loss decreased from 41% preoperatively to 19% postoperatively. In a more recent study, in which abdominal myomectomy was performed using microsurgical techniques in 51 women who had intramural or subserosal fibroids and wished to conceive, Li and colleagues [18] reported that the overall conception rate was 57% after myomectomy. The spontaneous pregnancy loss rate in this cohort was 60% (24/40) before myomectomy, which was reduced to 24% (8/33) after myomectomy ($P < .001$). Taken together, these studies suggest that myomectomy may improve significantly the reproductive performance of women who present with subfertility or pregnancy loss. Hysteroscopic resection of fibroids showed similar results and is the procedure of choice for submucosal fibroids, because it is associated with decreased blood loss, operative time, and adhesion formation, and obviates the need for subsequent cesarean delivery [20].

Antepartum myomectomy

Numerous case series suggested that myomectomy can be performed safely in the first and second trimesters of pregnancy in a carefully selected group of patients [1,7,33,51–53]. Although every effort should be made to avoid surgery during pregnancy, indications for myomectomy may include intractable fibroid pain that is refractory to rest, intravenous fluids, and NSAIDs or narcotic medications. Exacoustos and Rosati [10] described a case series of 13 women who had a myomectomy before 26 weeks' gestation. All women had a latency of at least 7 weeks from myomectomy to delivery. Eight women delivered at term and the remaining 5 women had preterm deliveries after 32 weeks' gestation. In another case series, Michalas and colleagues [54] reported the outcome of 18 myomectomies that were performed during pregnancy; there were two miscarriages and 16 uncomplicated term deliveries. A similar case series of 18 patients who had a myomectomy during the first or second trimester reported that 16 patients delivered healthy infants between 36 and 41 weeks' gestation, one patient had a spontaneous abortion on postoperative day one, and another patient was lost to follow-up [36]. Another retrospective study of 11 patients who had antepartum myomectomies reported that the rate of pregnancy loss was similar in patients who were managed surgically or expectantly [55].

Mollica and colleagues [56] enrolled 106 pregnant women who had uterine fibroids into a clinical protocol for operative or conservative management of fibroids. Surgical intervention was pursued in patients who had recurrent pain, a rapidly growing fibroid (defined as doubling in size over 8 weeks), or a fibroid that was larger than 5 cm that was located in the lower uterine segment or deformed the placental site. According to these criteria, 18 patients underwent myomectomy and 88 were managed conservatively. No spontaneous abortion occurred in the group that underwent surgery, whereas the spontaneous abortion rate was 13.6% (12/88) in the group that was managed conservatively. The preterm birth rate was 5.6% in the surgical cohort compared to 22.7% in those managed expectantly. The group that underwent myomectomy had a rate of cesarean delivery of 93.7% compared with 34% in the group that was managed conservatively; the rate of puerperal hysterectomy was 0% and 4.5%, respectively. Fetal outcomes were good in both groups. There was one perinatal death in a patient who declined to enter the surgical arm of the trial and ultimately delivered at 32 weeks of gestation.

Taken together, these data suggest that—in contrast to earlier recommendations [57]—myomectomy may a safe procedure to perform in pregnancy, if indicated. It should be kept in mind that the published literature on this topic likely is biased toward more favorable results, and most studies had a small number of patients and, as such, lack adequate statistical power to reach any definitive conclusions. A well-designed, prospective, randomized clinical trial probably will not be performed. In select patients who have pedunculated or subserosal fibroids, antepartum myomectomy is a reasonable option if fibroid pain is severe and refractory to medical management. If a myomectomy is

performed, the perioperative use of indomethacin may be of benefit in inhibiting preterm labor [38].

Intrapartum myomectomy

Performing a myomectomy at the time of cesarean delivery traditionally has been discouraged because of the reported high morbidity, primarily from hemorrhage [54]. The risk for excessive hemorrhage at the time of myomectomy is significantly greater at term than in the first or second trimesters of pregnancy. In the first trimester, the uterus receives only 2% to 3% of the cardiac output. At term, however, the uterus receives in excess of 17% of the cardiac output [25].

In a case series of nine patients who underwent myomectomy at the time of cesarean delivery, three patients (33%) had severe hemorrhage that required puerperal hysterectomy [10]. In another report of 25 myomectomies that were performed at the time of cesarean delivery, five patients (20%) received blood transfusions, although none required hysterectomy [58]. A similar study of 13 intrapartum myomectomies reported that only one case (8%) was complicated by severe hemorrhage that required blood transfusion and uterine artery ligation [1]. More favorable results have been reported with removal of pedunculated fibroids at the time of cesarean section. In a series of five myomectomies that were performed during cesarean section, the four pedunculated fibroids were removed without difficulty, whereas removal of the single nonpedunculated fibroid was associated with severe hemorrhage [9]. The decision to proceed with myomectomy at the time of cesarean section should be approached with caution, and probably should probably be limited to patients who have symptomatic pedunculated fibroids.

Summary

The effect of uterine fibroids on fecundity and pregnancy outcome is difficult to determine with any degree of accuracy; this is due, in large part, to the lack of adequate large clinical trials. In general, the literature tends to underestimate the prevalence of fibroids in pregnancy and overestimate the complications that are attributed to them. In contrast to popular opinion, most fibroids do not exhibit a significant change in volume during pregnancy, although those that do increase in size tend to do so primarily in the first trimester. Although most pregnancies are unaffected by the presence of uterine fibroids, large submucosal and retroplacental fibroids seem to impart a greater risk for complications, including pain (degeneration), vaginal bleeding, placental abruption, IUGR, and preterm labor and birth. Preconception myomectomy to improve reproductive outcome can be considered on an individual basis, but likely has a place only in women who have

recurrent pregnancy loss, large submucosal fibroids, and no other identifiable cause for recurrent miscarriage. Antepartum myomectomy should be reserved for women who have subserosal or pedunculated fibroids and intractable fibroid pain that are unresponsive to medical therapy and who are in the first or second trimester of pregnancy. Myomectomy at the time of cesarean delivery is associated with significant morbidity (hemorrhage) and should be pursued with caution and only in select patients.

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Borderline Smooth Muscle Tumors of the Uterus

Naciye Mulayim, MD*, Fatih Gucer, MD

Department of Obstetrics and Gynecology, Anadolu Health Center, Gebze, Kocaeli, Turkey

Uterine leiomyomas are the most common neoplasms of the female genital tract. As much as 77% of the cases of hysterectomy specimens removed for all indications demonstrate uterine leiomyomas [1]. In addition to the unambiguous usual uterine leiomyomas and uterine leiomyosarcomas, there is a spectrum of intermediate or borderline uterine smooth muscle tumors with overlapping features that can be challenging even for the most experienced pathologist to diagnose. Despite several reports that have indicated the coexistence of classical, cellular, and atypical leiomyomata and leiomyosarcoma in the uterus, it is not clear whether these intermediate tumors reflect a transition from the one extreme end of common benign leiomyoma to the other extreme end of uterine leiomyosarcoma at the pathogenetic level [2,3]. The spectrum of intermediate smooth muscle cells of the uterus has been most extensively studied by Kempson and coworkers [4–8] over almost four decades. The clinicopathologic data derived from a series of 213 problematic cases of uterine smooth muscle cases and other meticulous studies from the same group of pathologists currently comprise the main source to guide clinical management in this challenging group of neoplasms [4,9].

Evaluation of smooth muscle neoplasms of the uterus ought to start with determination of whether the cells in the neoplasm show smooth muscle differentiation or endometrial stromal differentiation. A diagnosis of uterine smooth muscle tumor is usually reached without difficulty when neoplastic cells resemble normal myometrial cells with their typical eosinophilic fibrillary cytoplasm. In some cases, however, smooth muscle cells lose their characteristic appearance

* Corresponding author.
E-mail address: mulayin2@hotmail.com (N. Mulayim).

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and resemble endometrial stromal cells. Architectural features, such as fascicular alignment of tumor cells and the presence of thick-walled vascularity, favor a smooth muscle tumor. The vessels in endometrial stromal tumors are mainly thin-walled capillaries in arching pattern. In difficult cases, immunohistochemical staining with desmin, CD-10, and caldesmon may aid in determining whether the cells are of smooth muscle or endometrial stromal origin [9]. The distinction between a uterine smooth muscle tumor and an endometrial stromal tumor is particularly crucial in tumors in which infiltration of the myometrium or vessels is encountered. In endometrial stromal tumors, this finding indicates malignant behavior [10]. In smooth muscle tumors, clinical course may be benign despite the infiltrative pattern.

The next challenge after a diagnosis of uterine smooth muscle tumor has been made is to categorize it into a prognostic category. Caution should be exercised before labeling a uterine smooth muscle tumor benign or malignant for the following two reasons.

First, histopathologic and clinical attributes of benign and malignant do not necessarily correlate. Morphologic features are as valuable as their ability to predict clinical outcome within an acceptable range of reliability. In most cases, uterine smooth muscle neoplasms with usual histologic patterns are easily categorized as benign (eg, usual leiomyoma and leiomyoma with increased mitotic figures) or malignant (eg, leiomyosarcoma). In these cases, morphologic features predict clinical behavior in a dependable manner. In other cases, however, correlating morphologic appearance with clinical prognosis becomes a complex task. In a significant number of cases, the neoplasm appears unusual or malignant by its microscopic or macroscopic appearance and may even show spread beyond the organ, yet clinical course is quite innocuous. At the other extreme, some tumors do not have to demonstrate the conventional morphologic features of malignancy to be able to behave in a malignant fashion. Benign metastasizing leiomyomas comprise a prime example of the issue of morphologic and clinical discrepancy. These uterine tumors have the classical features of a leiomyoma and have no histologic features of malignancy, such as coagulative necrosis, significant atypia, or increased mitotic index (MI), yet they do metastasize. They are accompanied by clonally related nodules in the lung, lymph nodes, or other sites with microscopic appearance similar to the original tumor, and in other cases with morphologic features of a leiomyosarcoma or smooth muscle of uncertain malignant potential (STUMP) [11–14]. Unlike leiomyosarcomas, the clinical course of benign metastasizing leiomyomas is relatively nonaggressive. The interval between myomectomy or hysterectomy and the diagnosis of pulmonary nodules averages 15 years. The median survival after the excision of metastases is 94 months [15].

Second, there is a wide spectrum of clinical behavior between an obviously benign and an overtly aggressive clinical outcome. A tumor may be relatively benign or malignant depending on where it takes place between these two extremes. In line with modern understanding of the biology of cancer, there is no guarantee that a tumor will behave totally innocuous from the time of diagnosis to

the very end. Similarly, projecting that a tumor invariably results in fatality is a rather simplistic and prejudiced approach. It is more realistic to view tumor behavior as wide spectrum of disease and evaluate a variety of factors: Does the tumor invade or metastasize, and if so, how does this affect prognosis? Does the tumor recur? If it does recur, what is the time to recurrence? What does the recurrence entail? How efficacious is the currently available treatment modalities? Most importantly, how do these data contribute to the quality of life and survival rate?

The terms ''high malignant potential'' and ''low malignant potential'' have now come to be used for a variety of human tumors to reflect the need to describe various tumor behavior. Precision in describing tumor behavior is of utmost relevance when managing patients in whom organ or fertility preservation is desired. In gynecologic oncology, borderline (low malignant potential) tumors of the ovary are the first and most studied example of this concept. The same notion is coming to be applied to a variety of uterine smooth muscle tumors as data are being gathered. Parenthetically, some tumors are so rare that clinical data are not adequate to come to a clear conclusion. These tumors are appropriately called ''tumors with limited experience.''

In the initial classification systems, the main criterion to prognosticate biologic behavior of uterine smooth muscle tumors was the number of mitotic figures in a tumor (MI) [6,16–19]. As more experience was gained, however, other significant morphologic markers of prognosis have been discovered. It is now accepted that using multiple predictors increases accuracy in the decision-making process. This multivariate approach starts with making note of how easily the leiomyoma is enucleated during surgery. Difficulty experienced during enucleation raises a red flag about infiltration and the possibility of malignant nature. Gross evidence of necrosis and fleshy texture are other intraoperative observations suspicious for malignancy. These findings prompt a vigilant surgeon to seek for intraoperative frozen section.

Microscopic features that are significant predictors of clinical outcome are as follows:

1. Coagulative tumor cell necrosis. Presence of coagulative tumor cell necrosis is a solid predictor of malignancy. Tumor cell necrosis is characterized by an abrupt transition between viable cells and an area of necrosis. Other features include ghost outlines of tumor cells and degenerating, hyperchromatic, and pleomorphic nuclei. Tumor necrosis is of such importance that it should never be ignored, but it should also be differentiated from other types of innocuous morphologic changes, namely hyalinizing necrosis, necrosis associated with superficial ulceration of submucous leiomyomas, and hemorrhage within leiomyomas (apoplectic leiomyomas) not uncommonly encountered in pregnancy and hormone use [20,21].
2. Atypia. Cytologic atypia has been well established as an important criterion for clinical outcome for smooth muscle tumors of the uterus. Determination

of the severity of atypia may be subjective and highly dependent on the experience of the examining pathologist. Hendrickson and coworkers [9] suggest dividing atypia into significant (moderate to severe atypia) and nonsignificant (absent to mild) categories to improve reproducibility. Significant atypia is featured by the presence of pleomorphism and nuclear hyperchromasia obvious on low-power field examination. Atypia can be diffuse or focal.

3. Mitotic Index. MI denotes definite mitotic figures (mf) per 10 high power field (hpf) [22]. It may be best to reserve counting of mitotic figures until the end because, in some cases, decision can be readily made on the basis of tumor cell necrosis and atypia and without the need to resort to absolute number of mitotic figures.
4. Differentiation. Some smooth muscle tumors may demonstrate epithelioid or myxoid differentiation. The type of differentiation is a significant prognosticator. The previously mentioned criteria of coagulative necrosis, atypia, and MI are used differently when a uterine smooth muscle shows standard versus unusual differentiation.

Evaluation of smooth muscle tumors with standard differentiation

Assessment of key features in a smooth muscle tumor with usual differentiation comprises evaluating the key prognostic markers discussed previously: (1) determination of whether coagulation necrosis is present, (2) assessment of whether moderate to severe atypia exists, and (3) evaluation of MI. Only after completing this checklist can one start to categorize uterine smooth muscle tumors into clinically relevant groups (Table 1).

Table 1
Criteria and diagnostic terms for uterine smooth muscle tumors with standard differentiation

Diagnosis	Coagulative necrosis	Significant atypia	Mitotic index
Leiomyoma	No	No	<5
Highly cellular leiomyoma	No	No	<5
Leiomyoma with increased MI	No	No	≥5 and <20
Leiomyoma with increased MI but LE	No	No	≥20
Atypical leiomyoma with low risk of recurrence	No	Yes (diffuse)	≤10
Leiomyoma with atypia but LE	No	Yes (focal)	≤10
Leiomyosarcoma	No	Yes (diffuse)	>10
Leiomyosarcoma	Yes	Yes	Any
STUMP	Yes	No	≤10

Abbreviations: LE, limited experience; MI, mitotic index; STUMP, smooth muscle tumors of uncertain malignant potential. (*Data from* Kempson RL, Hendrickson MR. Smooth muscle, endometrial stromal, and mixed mullerian tumors of the uterus. Mod Pathol 2000;13:328–42.)

If there is neither tumor necrosis nor moderate to severe atypia, the tumor consists of typical bland smooth muscle cells, and mitotic index is less than 20 mf/10 hpf, the clinical course is benign

Leiomyoma

If the MI is less than 5 mf/10 hpf, the tumor is labeled as leiomyoma. The usual leiomyoma is grossly well circumscribed and white. At the microscopic level, the tumor cells resemble surrounding myometrial cells except for the fact that they are usually more crowded and larger with bigger nuclei. They are arranged in a whirled trabecular fashion. The pathogenesis, cytogenetics, diagnosis, and management of these common neoplasms are extensively studied and reviewed [23–27].

Highly cellular leiomyomas

It is not unusual for a leiomyoma to deviate from its typical appearance, and the most commonly encountered change in form is an increase in cellularity. Highly cellular leiomyomas are free of any morphologic features of malignancy. Although the clinical course of these tumors is no different than that of usual leiomyomas, making a correct diagnosis is crucial for the fact that highly cellular leiomyomas resemble low-grade stromal sarcomas and stromal nodules [28]. The presence of large thick-walled, nonarborizing vessels favors a smooth muscle neoplasm. Endometrial stromal neoplasms, in contrast, exhibit an arborizing vasculature with thin-walled vessels.

Considering the differential diagnosis of a cellular mesenchymal proliferation is of particular importance in cases where the specimen has been recovered by endometrial sampling. In cases where the diagnosis is not obvious, management depends on whether or not a hysterectomy is considered acceptable. If a hysterectomy is desired, the problem is resolved because the uterus becomes available for thorough examination. In situations where hysterectomy is being avoided, such methods as imaging studies and hysteroscopy may be used to aid in the decision-making process [29]. One also needs to be cautious when making a diagnosis of hypercellular mesenchymal tumor in a prolapsed leiomyoma, because these neoplasms and endometrial stromal sarcomas have similar features [30].

Mitotically active leiomyoma (leiomyoma with increased mitotic index)

If a grossly and microscopically bland leiomyoma contains more than 5 but less than 20 mf/10 hpf, the tumor is referred to as ‘‘mitotically active leiomyoma’’ [4,31]. These tumors may be cellular. The diagnosis should not be made if the neoplasm harbors areas of coagulative necrosis, moderate to severe nuclear atypia, or abnormal mitotic figures. Thorough sectioning and meticulous examination of the specimen is essential. Clinically, easy and complete removal of the leiomyoma during myomectomy strongly favors a benign nature.

Mitotically active leiomyomas demonstrate a clinically benign course. In Bell’s series [4], there were no recurrences in 87 patients. In 34 of these patients, the leiomyomas contained 10 to 20 mf/10 hpf.

When increased MI is encountered in a uterine smooth muscle neoplasm, attention should be paid to the clinical history. In contrast to leiomyosarcomas, mitotically active leiomyomas almost invariably occur in women of reproductive age. Some submucous myomas and myomas obtained from women during the secretory phase of the menstrual cycle, during pregnancy, or from women who have been on progestins may contain high mitotic counts [20,21,32,33]. In these cases, zones of hemorrhage may be encountered (apopletic leiomyomas) and should not be interpreted as an indication of coagulative tumor cell necrosis.

If there is no tumor cell necrosis but focal or diffuse moderate to severe cytologic atypia on low-power examination, prognosis depends on the mitotic count

Atypical (symplastic) leiomyomas with low risk of recurrence

Tumors with cytologic atypia with a MI of less than 10 mf/10 hpf but no tumor cell necrosis are called ''atypical leiomyomas.'' Enlarged, multinucleated giant cells are frequently encountered. Most often, moderate to severe atypia is diffuse. These tumors exhibit a low risk of recurrence. In Bell's series [4], 1 out of 46 patients with diffuse atypical leiomyomas showed extrauterine recurrence at 60 months' follow-up. According to Hendrickson and coworkers [9], these tumors tend to have a slower rate of progression even if they do recur. Patients with such tumors are candidates for uterine preservation after myomectomy provided that vigilant clinical and radiologic follow-up is performed.

Leiomyoma with atypia but limited experience

Leiomyomas with focal atypia are less common and there is less experience regarding their prognosis. These tumors are appropriately denoted as ''leiomyoma with atypia but limited experience.''

Leiomyosarcoma

When the MI is counted to be greater than 10 mf/10 hpf, malignant behavior is frequent enough that the neoplasm is denoted as leiomyosarcoma.

Tumor necrosis favors malignancy in most cases

Leiomyosarcoma

Tumor necrosis accompanied by moderate to severe atypia is approached as leiomyosarcoma regardless of MI.

Tumors of uncertain malignant potential

Difficulty arises when tumor necrosis is encountered but there is no atypia and the MI is less than 10 mf/10 hpf. Because experience regarding these tumors is limited, these tumors should be regarded as STUMP.

Evaluation of smooth muscle tumors with unusual differentiation

Epithelioid (clear cell) differentiation

If few foci of epithelioid smooth muscle cells are seen to blend with typical areas of smooth muscle cells, the diagnosis is made in favor of a smooth muscle neoplasm. Immunostaining studies with keratin, actin, EMA, CD10, caldesmon, and desmin may aid in differential diagnosis. If the tumor is determined to be smooth muscle tumor with epithelioid differentiation, caution should be given to the fact that information on the clinical behavior of these tumors is limited (Table 2):

1. Epithelioid leiomyoma (limited experience). Tumors with less than 5 mf/10 hpf, no or minimal atypia, and no necrosis may be considered benign based on the experience with seven cases [34].
2. Epithelioid leiomyosarcoma (limited experience). A MI of equal to or more than 5 mf/10 hpf, despite absent tumor necrosis or cytologic atypia, is alarming for an ominous prognosis. Tumors with significant atypia and tumor cell necrosis also behave aggressively regardless of MI [4].
3. Tumors of uncertain malignant potential. Tumors with moderate to severe atypia but no necrosis and a MI of less than 5 mf/10 hpf are denoted as STUMP because of lack of clinical data.

Myxoid differentiation

Myxoid differentiation denotes smooth muscle tumors with myxoid stroma. These tumors are grossly myxoid. Their clinical behavior depends on the characteristics of the cells that constitute the tumor (see Table 2): myxoid leiomyoma, where there is presence of no or mild atypia, and a MI of less than

Table 2
Criteria and diagnostic terms for uterine smooth muscle tumors with unusual differentiation

	Diagnosis	Coagulative necrosis	Significant atypia	MI
Smooth muscle tumors with epithelioid differentiation	Epithelioid leiomyoma (LE)	No	No	<5
	Epithelioid LMS (LE)	No	No	≥5
	Epithelioid LMS (LE)	Yes	Yes	Any
	STUMP	No	Yes	<5
Smooth muscle tumors with myxoid differentiation	Myxoid leiomyoma	No	No	<5
	Myxoid LMS	Any	Yes	Any

Abbreviations: LE, limited experience; LMS, leiomyosarcoma; MI, mitotic index; STUMP, smooth muscle tumors of uncertain malignant potential. (*Data from* Kempson RL, Hendrickson MR. Smooth muscle, endometrial stromal, and mixed mullerian tumors of the uterus. Mod Pathol 2000;13:328–42.)

5 mf/10 hpf, indicating a benign tumor; and myxoid leiomyosarcoma. Moderate to severe atypia, enlarged cells, and infiltration of the surrounding normal myometrium predicts a dismal prognosis regardless of the MI or absence of coagulative necrosis [35,36].

Molecular markers of prognosis

Ancillary immunohistochemical techniques have been investigated to assess cases with uncertain histology. Multiple studies suggest that the immunoprofile of STUMP is much closer to leiomyomas than to that of leiomyosarcomas, correlating with the clinical behavior of these tumors [37]. Immunostaining for Ki-67 can be useful in discriminating leiomyosarcomas from STUMP and uterine leiomyomas [37–39]. In a recent study, Mayerhofer and coworkers [40] detected Ki-67 in 50% of paraffin-embedded tissues from 20 patients with uterine leiomyosarcoma, whereas only 8% of the 25 cases of leiomyomas and none of the 22 cases of STUMP demonstrated Ki-67. The difference regarding the frequency of Ki-67 expression between leiomyosarcomas and STUMP and leiomyosarcomas and leiomyomas was highly significant (P=.0001 and P=.002, respectively). Cell cycle regulatory proteins other than Ki-67 were also investigated in several studies. The expression of the cyclins (E and A) and cdks (cdk2 and cdc2) were markedly increased in leiomyosarcomas compared with leiomyomas and STUMP [38]. Similar observations were made for p16 protein, progesterone receptor, and matrix metalloproteinase-2 [41–43]. The study by Layfield and coworkers [44] is noteworthy for its findings. The authors assayed 45 smooth muscle neoplasms for DNA ploidy, silver-staining nucleolar organizer regions, percent nuclear proliferating cell nuclear antigen, p53, Her-2/neu, and MDM-2 protein and compared their value in predicting clinical outcome with traditional histopathologic criteria of mitotic rate and nuclear grade proposed by Kempson and Bari [6]. Significantly, in a multivariate analysis, the criteria of Kempson and Bari [6] were the strongest predictors of prognosis.

The studies investigating molecular markers of prognosis in uterine smooth muscle all suffer from low number of cases. The other common denominator in these studies is that all cases between leiomyomas and leiomyosarcomas are collectively analyzed under STUMP and not subdivided like in the more precise schema proposed Kempson and coworkers [4–9]. Further studies are needed before molecular markers can be used safely in clinical practice.

Summary

At present, decision regarding where to place a uterine smooth muscle tumor that deviates from the most obvious leiomyoma and leiomyosarcoma groups still

depends on time-honored conventional criteria. The focus of categorization should be the clinical outcome and not nosology. To improve accuracy in predicting clinical behavior, a multivariate approach is needed. This involves combining background clinical information, intraoperative and gross findings, multiple relevant morphologic criteria, and immunohistochemical studies. The authors believe that in future, as the number of cases with intermediate clinical outcome and morphologic features increases, and as molecular markers of prognosis are studied, managing these tumors will become more objective.

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Malignant Transformation of Myomas: Myth or Reality?

Peter E. Schwartz, MD*, Michael G. Kelly, MD

Department of Obstetrics, Gynecology and Reproductive Sciences,
Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA

Uterine leiomyosarcomas are malignant tumors of the uterus that are composed entirely of smooth muscle. They represent the most common pure sarcoma of the uterus. Their incidence has been estimated at 0.67 per 100,000 women per year [1]. The median age of a woman with leiomyosarcomas is 50 to 55 years old, about 10 years older than that of a woman with a leiomyoma [2,3]. The incidence of leiomyosarcoma in women undergoing hysterectomy for presumed fibroids is 0.2% for women age 31 to 40 years, 0.9% for those age 41 to 50 years, 1.4% for those age 51 to 60 years, and 1.7% for those age 61 to 81 years [4]. A recent review of the surveillance, epidemiology, and results (SEER) data reports that leiomyosarcomas are significantly more common in black women (1.51 per 100,000) than in white women (0.91 per 100,000) ($P < .01$) [5]. Schwartz and coworkers [6] has related the risk for uterine leiomyosarcomas to the use of oral contraceptives. Leiomyosarcomas may occur more frequently in women who are receiving tamoxifen therapy [7,8].

Approximately 55% of women with uterine leiomyosarcoma present with stage I disease (limited to the uterine corpus) as compared with 80% of those with uterine adenocarcinomas [5]. The 5-year relative survival for a stage I uterine sarcoma was 73.2% for white women and 63.2% for black women ($P < .05$). The 5-year relative survival for stage II (cervix involvement) disease was 43.3% for white women and 35% for black women. For stages III (disease involving the adnexa or other pelvic sites) and IV (extrapelvic spread), the 5-year relative survival was 32% for white women and 37% for black women.

The main presenting symptoms of uterine leiomyosarcomas are abnormal vaginal bleeding, lower abdominal pain, and a pelvic or abdominal mass [2,9–12]. Most patients with uterine leiomyosarcoma present with disease confined to the

* Corresponding author.
E-mail address: peter.schwartz@yale.edu (P.E. Schwartz).

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uterine corpus or cervix [5,13,14]. These tumors grossly are more likely to be solitary than leiomyomas [15]. Macroscopic features that are suspicious for malignancy in a smooth muscle tumor include a loss of the whorl pattern typical of a leiomyoma, a homogeneous texture, ill-defined margins, a yellow color, a softer less resilient tumor, and an absence of a bulging surface when one cuts into the tumor [15]. Rarely, a leiomyosarcoma grossly resembles a leiomyoma [16]. Leiomyomas may frequently resemble a leiomyosarcoma grossly, however, because of benign degenerative changes [16].

Microscopically, mitotic activity, nuclear atypia, and coagulative tumor cell necrosis have been identified as the critical elements in diagnosing leiomyosarcoma [17]. In addition, the degree of histologic differentiation, presence of giant cells, vascular space invasion, and invasion of the surrounding myometrium are also important in the diagnosis of this disease [10,18].

Within stage I (disease confined to the uterine corpus) tumor size is an important prognostic factor [9,10,19]. Leiomyosarcomas of less than 5 cm in diameter rarely demonstrate aggressive behavior [10]. There are no reports of leiomyosarcomas less than 3 cm demonstrating an aggressive behavior. Additional clinical and histologic features associated with a poor prognosis for patients with leiomyosarcomas include being of an older age and having anaplastic tumors with evidence of vascular invasion [10,18]. Radiation and chemotherapy rarely influence the long-term prognosis [10,18,20–23]. A Gynecologic Oncology Group randomized clinical trial of adjuvant doxorubicin therapy included 48 patients with stage I or II uterine leiomyosarcomas [21]. There was no statistical difference in recurrence rates between those who received the chemotherapy and those who did not [21]. Although local regional control seems to be improved with radiation therapy, statistically significant survival differences from controls could not be demonstrated in several studies [2,3,9,10]. There is lack of consistency among studies, however, regarding prognostic features and survival [16,24].

Two particular forms of smooth muscle tumors of the uterus that are quite problematic for clinicians are smooth muscle tumors of uncertain malignant potential (STUMP) and epithelioid leiomyoma, which include leiomyoblastoma and clear cell leiomyoma [15–17,24]. Although the latter group of tumors is mainly benign, the behavior of the epithelioid tumors that contain two of the following four features makes their behavior uncertain: a large size (> 6 cm); having a mitotic count between two and four mitoses per high power field; significant cytologic atypia; and tumor cell necrosis. STUMP in turn are composed of smooth muscle tumors where the degree of the smooth muscle differentiation is uncertain and the microscopic criteria of malignancy are borderline [17].

Can asymptomatic rapidly growing fibroids be observed or must they routinely be removed?

A classic indication for recommending a hysterectomy in reproductive age or postmenopausal women with a fibroid is rapid growth of the fibroid. Although

this has been routinely taught for decades, its relevance has been challenged in a study by Parker and coworkers [25] who reviewed 1332 women who underwent a hysterectomy for presumed uterine leiomyoma at two community hospitals and the indications for the operations. Only 1 of 371 women operated on for a ''rapidly growing fibroid'' proved to have a leiomyosarcoma [25]. When rapid uterine growth was defined as an increase by 6 weeks gestational size over a 1-year period, none of the 198 patients who met that published definition of rapid growth were found to have a uterine sarcoma [25]. Two women were found to have an endometrial stromal sarcoma. The 30-year-old woman with the only leiomyosarcoma in this study had a normal uterus by physical examination 22 months before being admitted for management of a 16-week size uterus. Because this patient had not been seen within the preceding year, she did not meet the published criteria for rapid growth used in the study [25]. None of the 198 patients who met the criteria for rapid growth had a leiomyosarcoma, a mixed mesodermal tumor, or an endometrial stromal sarcoma. None of 17 postmenopausal women admitted for rapid uterine growth proved to have a sarcoma. Ten of the latter women were noted to be on estrogen-replacement therapy. Another study revealed that leiomyosarcoma is not more prevalent (< 0.5%) in women with rapidly growing fibroids [4].

In the authors' experience rapidly growing fibroids may be observed as long as they are asymptomatic and their diagnostic imaging studies are consistent with a leiomyoma. Symptomatic fibroids, however, require prompt evaluation and treatment. A recent review of a 20-year experience at the Mayo Clinic reported that among 208 women with leiomyosarcomas treated at that institution, the most common presenting symptoms were abnormal bleeding in 56% (117) of the patients; a pelvic mass in 54% (112) of the patients; and pain in 22% (46) of the patients [10].

The Society for Obstetricians and Gynecologists of Canada issued guidelines regarding management of postmenopausal women with fibroids who experience bleeding and pain [26]. The guidelines indicate that these women should be investigated in the same way as a woman without fibroids. The guidelines go on to state, however, that there is currently no evidence to substantiate performing a hysterectomy for an asymptomatic leiomyoma for the sole purpose of alleviating the concern that it may be malignant [26].

Can diagnostic imaging distinguish leiomyosarcomas from uterine leiomyomas?

Major advances in cross-sectional imaging have occurred during the past three decades. Unfortunately, the diagnostic imaging criteria for distinguishing leiomyosarcoma from benign leiomyomas remain vague and ill-defined [27–30]. It is unlikely on a routine basis that diagnostic imaging techniques can distinguish leiomyosarcoma from uterine leiomyomas. It is routine to find necrosis in leio-

myomas greater than 10 cm in diameter and this criteria alone is not diagnostic of a leiomyosarcoma.

MRI has become the imaging technique of choice in the evaluation of uterine leiomyosarcomas because it can demonstrate the number, size, precise location, and extent of degeneration as opposed to other imaging techniques [30]. MRI can distinguish ovarian versus uterine origins of adnexal masses better than ultrasound. MRI criteria are being developed, but at present one should be skeptical about routinely distinguishing a leiomyoma from a leiomyosarcoma using diagnostic imaging criteria alone. Schwartz and coworkers [29] reported that smooth muscle tumors with ill-defined margins were significantly more likely to be leiomyosarcomas because those with well-defined margins were characteristically benign. Only four patients with leiomyosarcomas were evaluated in the latter study, however, none of whom presented with rapid growth. Tanaka and coworkers [30] have reported that if more than 50% of a uterine smooth muscle tumor has a high-signal on T2-weighted images and any small high-signal areas are present on T1-weighted images, this is consistent with a MRI suggestive of a smooth muscle tumor of uncertain malignant potential or a leiomyosarcoma.

The combined use of dynamic MRI and serum lactate dehydrogenase levels may be the most useful tool in distinguishing leiomyosarcomas from leiomyomas. Lactate dehydrogenase is elevated in patients with leiomyosarcoma and its isozymes, particularly lactate dehydrogenase isozyme type 3, might be produced by leiomyosarcoma cells [31]. Goto and coworkers [32] performed MRIs, dynamic MRIs with enhancement by gadopentetate dimeglumine, and serum lactate dehydrogenase levels on 10 patients with leiomyosarcoma and 32 patients with degenerated leiomyoma. The sensitivity for determination of leiomyosarcoma was 100% with each of these modalities. The specificity, positive predictive value, and negative predictive value, however, were 93%, 53%, and 100% with MRI alone; 94%, 83%, and 100% with dynamic MRI alone; and 100%, 100%, and 100% with combined use of lactate dehydrogenase and dynamic MRI, respectively. Solid tumors, such as smooth muscle tumors of the uterus, can be enhanced with gadopentetate dimeglumine. The most contrasted images are usually obtained 40 to 60 seconds after the administration of gadopentetate dimeglumine.

Can a leiomyosarcoma be identified preoperatively using gonadotropin-releasing hormone analogues?

Uterine leiomyomas contain steroid receptor proteins and are known to be hormonally sensitive [33]. Uterine leiomyomas routinely shrink in menopause, whether the menopause is spontaneous or medically induced. The gonadotropin-releasing hormone analogue challenge test has been reported as a way of identifying a leiomyosarcoma preoperatively [34]. The concept of the

gonadotropin-releasing hormone analogue challenge test is that the leiomyosarcoma should not routinely shrink in response to gonadotropin-releasing hormone analogue therapy, whereas leiomyomas do respond by shrinking. The authors have reported on a case where this seemed to work well in the diagnosis of a uterine leiomyosarcoma [34]. In other patients the overall size of the uterus remained stable as the normal smooth muscle shrunk, whereas the dominant fibroid (ie, the leiomyosarcoma) grew. The authors have also seen patients on gonadotropin-releasing hormone analogues with leiomyosarcomas where the tumor grew very rapidly, and earlier than planned surgical intervention was necessary. There is at least one case report, however, of uterine leiomyosarcomas shrinking in size after treatment with gonadotropin-releasing hormone agonist [35]. This is biologically plausible because uterine leiomyosarcomas have been shown to express estrogen receptor (ER) and progestin receptor (PR). The authors suggest caution when using the gonadotropin-releasing hormone analogue test to determine if a rapidly growing fibroid may be a leiomyosarcoma.

Which fibroid has the leiomyosarcoma?

Uterine leiomyosarcomas are much more commonly not associated with fibroids than with fibroids [15]. Nevertheless, in a patient with a multilobulated fibroid uterus the question arises whether a frozen section can identify which fibroid has the leiomyosarcoma. In a study of 21 consecutive patients operated on at Yale-New Haven Hospital who had uterine leiomyosarcomas, in 20 the leiomyosarcoma was in a dominant (ie, the largest or the only) fibroid [36]. In the remaining case, the leiomyosarcoma involved both the largest and the second largest fibroid. In requesting a frozen section during surgery for a uterine smooth muscle tumor, the surgeon should routinely request the pathologist to evaluate carefully the largest of the uterine leiomyomas.

Are frozen section examinations at the time of surgery reliable in diagnosing uterine leiomyosarcoma?

A clinician cannot routinely rely on a frozen section examination to diagnose a uterine leiomyosarcoma. Data currently available suggest most patients with uterine leiomyosarcomas are not recognized at the time of frozen section [4,36]. This diagnosis often is made only on permanent section. In most medical centers frozen section is not the final histologic technique for diagnosis. Only one to three slides of a so-called ‘‘fibroid’’ may be routinely evaluated at the time of frozen section examination. It is more common than not to miss the diagnosis of a uterine leiomyosarcoma on frozen section [4,36].

Is it necessary to remove ovaries in premenopausal women if a diagnosis of leiomyosarcoma is established by frozen section?

There are very limited data on the value of prophylactic oophorectomy at the time of a hysterectomy for what seems to be leiomyosarcoma confined to the uterus.

Two studies reported no pathologic involvement of the ovaries by uterine leiomyosarcoma when the ovaries were grossly normal [19,37]. Larson and coworkers [9] compared 31 premenopausal patients who had residual ovarian tissue following treatment for a uterine leiomyosarcoma with 19 premenopausal women who underwent bilateral salpingo-oophorectomy. There was no difference in survival between the two groups [9]. Gadducci and coworkers [2] showed no difference in survival in women with stage I disease, younger than age 50, who had preservation of ovaries compared with those who underwent bilateral salpingo-oophorectomy.

The currently available data suggest that in disease limited to the uterus (ie, stage I) it is not necessary to remove the ovaries in a premenopausal patient because it has no impact on survival [1,2,10]. In one study patients who did not undergo a bilateral salpingo-oophorectomy had a better diseases-specific survival than those who had their ovaries removed [10]. In the latter study, a Cox proportional hazards model revealed that having a high-grade tumor, an advanced stage, and removal of the ovaries significantly influenced disease-specific mortality ($P < .05$). An alternative model revealed that older age ($\geq$51 years) significantly impaired survival. Alternative models that included tumor size revealed a significant correlation with this increased risk of recurrence. When 25 cases were matched by stage, grade, and age to 25 controls that underwent bilateral salpingo-oophorectomy, the 25 cases with ovarian preservation showed no significant difference in disease-specific survival compared with the controls that underwent an oophorectomy. In a Gynecologic Oncology Group study only 3.4% of patients with the leiomyosarcoma grossly confined to the uterine corpus or cervix had adnexal involvement [3]. The authors recommend routinely removing the ovaries in women with more advanced disease (ie, disease that seems to be invading beyond the uterus) and in postmenopausal women. There seems to be no survival advantage, however, to removing the ovaries in premenopausal women with small (<5 cm) leiomyosarcomas limited to the uterus.

Can fertility be preserved following a myomectomy for a leiomyosarcoma?

The data for fertility preservation following removal of a leiomyosarcoma are extremely limited. Patients who should do best with conservative management are those with small (<5 cm), histologically low-grade leiomyosarcomas [10]. Bonney [38] presented the first large series of women who underwent

abdominal myomectomies for preservation of fertility. Bonney [38] reported in 1937 on 632 cases of abdominal myomectomies. Only 1 of the 632 patients was found to have a sarcoma. Unfortunately, that tumor rapidly recurred following the myomectomy with peritoneal spread leading to the patient's death. Friedrich and coworkers [39] reported on two premenopausal women with leiomyosarcoma who underwent fertility-preserving surgery who subsequently became pregnant. The patients were alive without evidence of disease 3 and 6 years after the surgical resection. An Italian series presented eight nulliparous women who underwent abdominal myomectomies and were found to have a leiomyosarcoma confined to a leiomyoma in their surgical specimen [40]. All eight had fertility preservation. With a median follow-up of 42 months, three of the eight subsequently became pregnant and two spontaneously delivered healthy babies [40]. Seven of the eight patients remain alive and well. The remaining patient was diagnosed to have recurrence at the time of a cesarean section and, despite additional therapy, died 26 months following the initial diagnosis of the leiomyosarcoma.

Van Dinh and Woodruff [41] reported on six patients who were found to have leiomyosarcomas in myomectomy specimens. With a median follow-up of 4 years, five of the six were clinically free of disease and three had subsequent pregnancies. One of the 6 recurred, however, 2 years following the myomectomy. Davis [42] identified five cases of uterine leiomyosarcoma in 1150 patients who had undergone myomectomy. All five patients were followed without additional treatment. All five patients remain free of disease. Three patients became pregnant [42]. Finally, Spies and coworkers [43] reported on a patient who underwent a uterine artery embolization for management of what was believed to be a single, large intramural leiomyoma. The leiomyoma decreased in size and her symptoms disappeared. Thirteen months later the patient began attempts to become pregnant. Thirty-one months after the embolization she underwent a myomectomy that proved the mass to be a leiomyosarcoma. The patient refused hysterectomy. Nine months later she underwent a second myomectomy to further reduce the bulk of the residual mass which pathologically was a leiomyosarcoma. At 46 months after the original emobolization the patient was free of symptoms from the disease.

Kagami and coworkers [44] reported on a successful pregnancy in a woman initially diagnosed to have a myxoid leiomyosarcoma of the uterus in a myomectomy specimen at age 20. At age 23 the patient had a massive recurrence of the disease, again underwent fertility-saving surgery, and became pregnant 2 years later. At the time of a cesarean section, recurrent disease was present. The patient was alive and well 1 year later. Bekkers and coworkers [45] reported on a patient who became pregnant 4 years after a uterine mass was removed that was thought to be a leiomyoma. Three years after the initial operation a second mass was removed and also was thought to be a leiomyoma. During her pregnancy the patient had rapid growth of four uterine masses. At the time of cesarean section she was found to have an epithelioid leiomyosarcoma. The patient ultimately underwent a total abdominal hysterectomy, bilateral salpingo-

oophorectomy, and aggressive cytoreduction. The patient had no recurrence of tumor growth based on a CT scan 6 months following the surgery. It was believed that the removal of both ovaries in this patient, whose tumors contained ER and PR, was probably responsible for the fact the tumor had not recurred at that point [45].

In counseling a patient regarding fertility preservation when a leiomyosarcoma has been found in a myomectomy specimen, both the patient and her family must be made aware that preservation of fertility carries with it severe risks, including death. The routine follow-up for a woman who has undergone a myomectomy and found to have a low-grade leiomyosarcoma who wishes to preserve fertility includes obtaining serial MRI of the uterus and pelvis to rule out a recurrence at the primary site and serial chest radiographs to rule out pulmonary metastases. Once the patient has completed child-bearing, removal of the uterus should be considered.

Does morcellation of a leiomyosarcoma influence management?

Uterine morcellation is a very common operation for the management of leiomyomas and allows the patient to preserve fertility [46]. The authors have limited experience with this scenario, and only know of one patient whose final pathology was consistent with leiomyosarcoma after undergoing a laparoscopic assisted vaginal hysterectomy with uterine morcellation for a presumed fibroid uterus. Her disease was confined to the uterus (stage I) and she declined adjuvant therapy. Unfortunately, she recurred 10 months after her initial surgery and died of her disease 6 months later.

Corson and Brooks [47] reported on 92 consecutive patients undergoing resectoscopic myomectomy. Two of the 92 were subsequently identified to have leiomyosarcomas. Both patients underwent hysterectomy. No residual disease was present in one of the hysterectomy specimens. Unfortunately, no follow-up was available in the article.

Morice and coworkers [48] reported on 57 women who underwent uterine morcellation for the management of what proved to be uterine leiomyosarcomas. These morcellation procedures included a hysterectomy with morcellation clearly indicated in the surgical report, myomectomy, operative hysteroscopy with resection, or a simple biopsy of the uterine tumor. The authors recognized that the prognosis for leiomyosarcoma is poor, with most patients recurring within 2 years following the initial treatment. They chose to study the rate of local recurrence within 3 months following the surgical procedure as a possible indication of inadequate surgical management rather than to study the natural evolution of the disease [48]. In this study none of 17 patients recurred at 3 months who underwent morcellation. None of the 36 patients recurred at 3 months who did not undergo morcellation. At 6 months 1 (7%) of 15 of the patients undergoing morcellation recurred compared with 5 (14%) of 36 who underwent no morcellation.

The difficulty with recommending additional therapy for a woman with a newly diagnosed leiomyosarcoma is that there is no adjuvant therapy that is particularly effective [10,18,20–23]. On a routine basis delaying therapy until recurrence presents has been as effective as giving adjuvant therapy because of the relative insensitivity of leiomyosarcoma to currently available chemotherapy. If gross contamination of the peritoneal cavity occurs as a result of morcellation of a leiomyosarcoma, however, the authors recommend adjuvant therapy.

Is it always necessary surgically to stage patients with leiomyosarcomas?

Surgical staging of uterine cancers in general includes a total abdominal hysterectomy; bilateral salpingo-oophorectomy; pelvic and para-aortic lymphadenectomies; and, in addition, for uterine papillary serous cancers, an omentectomy and multiple peritoneal biopsies are performed.

Uterine leiomyosarcomas, when found grossly confined to the uterus, are not routinely associated with microscopic metastases to the lymph nodes. A Gynecologic Oncology Group study reported that only 3.5% of patients with disease confined to the uterine corpus or cervix (stage I or II disease) who underwent lymph node sampling at the original surgery had positive lymph nodes [3]. Indeed, in a large study from Memorial-Sloan Kettering Cancer Center, no stage I or II uterine leiomyosarcomas were associated with pelvic or para-aortic lymph node spread [13]. For more advanced-stage disease, however, lymph node spread has been described [10,13,14]. In general, if lymphatic dissemination has occurred the pelvic nodes are involved before the para-aortic nodes. In two series, no para-aortic nodes were involved if the pelvic nodes were free of disease [12,49]. Even when lymphadenectomy is performed and is negative for metastatic disease, a high proportion of patients develop recurrence of the leiomyosarcoma [14].

Finally, a recent study from the Mayo Clinic reported that 4 of 36 women who underwent pelvic lymphadenectomies as part of the surgical staging of uterine leiomyosarcomas were found to have enlarged lymph nodes, two of which had metastatic disease in the nodes [10]. Only 1 of 32 patients with clinically unremarkable nodes had metastatic tumor in the lymph node–bearing tissue. Within stage I, patients who underwent a negative lymph node sampling or lymphadenectomy were compared with those who did not undergo lymph node sampling and whose nodes were assumed to be uninvolved. The disease-specific survival curves were not statistically different [10].

In the authors' experience early stage disease in premenopausal women with tumors <5 cm in diameter does not require lymphadenectomy. On several occasions the author has noted that metastases to the retroperitoneum were identifiable by palpation of the pelvic sidewalls and para-aortic areas at the time of surgery. Whenever a nodule or mass is detected in the retroperitoneum in the presence of a uterine leiomyosarcoma (regardless of the size of the sarcoma), it

is appropriate to remove it. These retroperitoneal nodules or masses, in the author's experience, are metastases that may not always be in lymph nodes.

If more advanced disease is found at surgery, optimal cytoreduction is performed. In a recent review of the Massachusetts General Hospital experience with uterine leiomyosarcomas, the only therapy associated with improved overall survival, including chemotherapy and radiation treatment, was optimal cytoreduction [50].

In the event that a leiomyosarcoma is found in a hysterectomy specimen after the surgery has been completed, the authors routinely obtain a CT scan of the chest, abdomen, and pelvis. If no abnormalities are found, additional surgical staging is not performed. If lesions are found on the CT scan and they seem to be surgically resectable, additional surgery is performed. If the patient is not a candidate for additional surgery, a fine-needle aspiration biopsy or a diagnostic imaging-guided core biopsy is performed to confirm the nature of the lesion.

Can molecular biology be used to determine the biologic aggressiveness of leiomyosarcomas?

Currently, there are only limited reports studying the molecular biology of leiomyosarcomas to determine their biologic aggressiveness [51–53]. The expression of *bcl*-2, an apoptosis-inhibiting gene product, in leiomyosarcomas reflects biologic virulence [51]. It generally is well expressed in leiomyomas and less often in STUMP and leiomyosarcomas. *Bcl*-2–positive leiomyosarcomas that showed less vascular space invasion were associated with a longer overall survival. Other markers include p53, which tends to be overexpressed in uterine leiomyosarcomas and is associated with an increased recurrence risk in early stage disease [54].

There are several biologic markers that are differentially expressed in leiomyosarcomas compared with STUMP or leiomyomas and normal myometrial tissue. This information may lead to the development of novel therapeutics aimed at these differentially expressed targets, and novel markers capable of distinguishing leiomyomas from STUMP and leiomyosarcomas preoperatively and during pathologic examination.

One recent series looking at the expression of proto-oncogene c-*kit* revealed that c-*kit* was expressed in 12 of 16 leiomyosarcomas but was not detected in any of the eight leiomyomas studied [53]. The authors suggested that studies using c-*kit* may help distinguish leiomyosarcomas from benign leiomyomas particularly in uterine tumors that have uncharacteristic features. The study also creates the prospect of treating leiomyosarcomas with tyrosine kinase inhibitors.

Cyclins and cyclin-dependent kinases are differentially expressed in leiomyosarcomas compared with leiomyomas and normal myometrial tissue [55]. Cyclins interact with cyclin-dependent kinases to inactivate tumor-suppressor gene products, thereby increasing the likelihood of malignant transformation. Zhai and coworkers [55] have shown that cyclins E and A, and cyclin-dependent

kinases cdk2 are minimally expressed in normal myometrium and leiomyomas but overexpressed in leiomyosarcomas. Furthermore, these authors determined that in leiomyosarcomas, cyclin A expression was associated with decreased overall survival [55]. Novel therapy targeting cyclins and their respective kinases may be effective in treating leiomyosarcomas.

PR calponon h1 and mitogen-inducible gene-2 expression may help distinguish STUMP from leiomyosarcomas. Bodner and coworkers [56] determined the PR expression in 26 patients with leiomyomas, 24 patients with STUMP, and 21 patients with leiomyosarcomas. Each group of patients had a distinct and characteristic PR expression pattern. Calponin h1, a cytoskeletal protein, is underexpressed in leiomyosarcoma compared with STUMP, leiomyoma, and normal myometrium [57]. Down-regulation of mitogen-inducible gene-2 may be a marker for leiomyosarcoma. Kato and coworkers [58] have demonstrated, compared with normal myometrium and leiomyoma, the expression of mitogen-inducible gene-2 is significantly less in leiomyosarcoma.

Novel therapies targeting matrix metalloproteinase-2 and vascular endothelial growth factor may be effective in treating leiomyosarcoma. Matrix metalloproteinase-2 likely plays an important role in tumor invasion and metastasis in uterine leiomyosarcoma. Bodner-Adler and coworkers [59] have shown that matrix metalloproteinase-2 expression is correlated with lymph vascular space involvement and shorter disease-free survival. Vascular endothelial growth factor, the most potent angiogenic factor induced in ischemic and inflamed tissues, is not expressed in normal uterine smooth muscle, but is present in most uterine sarcomas [60].

Should all women with stage I uterine leiomyosarcomas receive postoperative adjuvant chemotherapy?

There is a dearth of information regarding the value of adjuvant chemotherapy in the management of early stage uterine sarcomas [10,18,20–23]. One prospective randomized trial compared adjuvant doxorubicin therapy with observation in 156 patients who underwent surgery for stage I and II uterine sarcomas [21]. Although there was a trend toward a reduced recurrence rate and improved survival in the chemotherapy group, the subgroup analysis of patients with stage I disease did not reveal any benefit to chemotherapy in this population. Additionally, several studies have shown that the use of adjuvant therapy, either chemotherapy or radiation therapy, does not improve overall survival when the leiomyosarcoma is confined to the uterus [10,18,20–23]. Although intuitively treating potential microscopic metastases makes sense in the management of women with uterine leiomyosarcomas of all stages, there is no clear justification for the use of adjuvant chemotherapy in early stage uterine sarcoma [61].

In contrast, there are some data supporting the role of adjuvant therapy in advanced (extrauterine) or recurrent disease. A review of the SEER database from 1989 to 1999 showed that adjuvant therapy improved overall survival in

uterine sarcomas that had spread beyond the uterus [5]. Standard chemotherapeutics only have limited activity, however, in leiomyosarcomas. The combination of ifosfamide and doxorubicin has produced the best overall response rate (ORR=30%) in a trial conducted by the Gynecologic Oncology Group [62]. Other chemotherapeutics have only demonstrated modest activity in advanced leiomyosarcoma: liposomal doxorubicin (ORR=15%); paclitaxel (ORR=9%); and etoposide (ORR=0%) [63–65]. Likewise, novel therapeutics have shown little activity in advanced leiomyosarcoma; trimetrexate had no activity and the overall response rate of amonafide was 4% [66,67].

Alternatively, hormonal therapy may be effective in treating uterine and extrauterine leiomyosarcomas. Most uterine leiomyosarcomas express ER and PR and 25% and 13% of extrauterine leiomyosarcomas express ER and PR, respectively [68]. Additionally, the expression of PR and AR (androgen receptor) is associated with a decreased risk of recurrence in uterine leiomyosarcoma [69]. Antiestrogens, such as tamoxifen, antiprogestins, such as mephisterone, and antiandrogens may have a role in treating uterine and extrauterine leiomyosarcomas.

Can hormone-replacement therapy be safely given to a woman following treatment for a leiomyosarcoma?

There is almost no information on the role of hormone-replacement therapy in women who have been previously treated for leiomyosarcoma. It is well established that ER and PR proteins may be present in uterine leiomyosarcoma [33,51,68]. Leitao and coworkers [33] reported that androgen receptor was present in 40% of leiomyosarcomas studied immunohistochemically. Kelley and coworkers [68] demonstrated significant immunohistochemical staining for ER (13 [87%] of 15) and PR (12 [80%] of 15) in uterine leiomyosarcomas. Most extrauterine leiomyosarcoma studied in the latter series did not express ER or PR. Low-grade leiomyosarcomas have been reported to be hormonally sensitive. When they metastasize and ovaries are in place, these tumors may respond to prophylactic oophorectomy [69]. In one epidemiologic study hormone-replacement therapy and obesity were each associated with an increased risk for uterine leiomyosarcomas, but cigarette smoking reduced the risk of uterine leiomyosarcoma [6].

One report presented two women who received hormone-replacement therapy after the diagnosis of a uterine leiomyosarcoma was confirmed and they had received treatment [70]. One patient underwent surgery only and subsequently had been on hormone-replacement therapy for 61 months without complications. The second was treated postoperatively with cytostatic and radiation therapy because of locally widespread disease. Ten months after the initial diagnosis and 3 months after beginning hormone-replacement therapy she was found to have recurrent cancer. The patient stopped the hormone-replacement therapy, underwent two additional operations, and was alive and clinically free of disease at the time of the report [70].

The authors of a second report, one in which a 15 year old underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy for management of a uterine leiomyosarcoma, also supported the idea of giving hormone-replacement therapy to young women who lose ovarian function as part of the management of uterine leiomyosarcoma [71]. In the latter report the patient received only estrogen-replacement therapy and the follow-up was limited to 7 months. These authors indicated that hormone-replacement therapy can help develop secondary sexual characteristics of young girls and improve their psychologic status in addition to the benefits of preventing bone loss, atrophic genital symptoms, and cardiovascular disease [71].

Malignant transformation of leiomyomas: myth or reality?

The overwhelming data strongly suggest that uterine leiomyosarcomas are isolated lesions and are not routinely found in association with uterine leiomyomas. If malignant transformation of uterine leiomyomas occurs, it is a rare event [18,24,72–76]. For example, none of the 71 cases of leiomyosarcoma accumulated over a 10-year study in an Austrian multi-institutional study could be documented to arise from a leiomyoma [18]. On a molecular level, however, the transformation from leiomyoma to leiomyosarcoma is biologically plausible. An accumulation of genetic alterations in tumor suppressor genes probably accounts for tumorogenesis and progression of uterine leiomyosarcoma. Zhai and coworkers [77] investigated the loss of heterozygosity at nine loci (p53, RB1, DCC, NNM23, WT1, D14S267, p16, DPC4, PTCH) within or close to tumor suppressor genes in 20 patients diagnosed with uterine leiomyosarcoma. Nineteen of these 20 patients had at least one instance of loss of heterozygosity and 11 of the 20 cases exhibited two or more instances of loss of heterozygosity.

A review of the literature suggests, however, that only a limited number of case reports have demonstrated a histologic transition of a benign leiomyoma into a leiomyosarcoma [24,72,76]. The hypothesis that uterine leiomyosarcomas arise from or are a result of the malignant transformation of benign leiomyomas has not been proved.

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Future Directions in Myoma Research

Pavna K. Brahma, MD, Kristina M. Martel, BS,
Gregory M. Christman, MD*

Department of Obstetrics and Gynecology, University of Michigan Health System, University of Michigan Medical School, 6422 Medical Science I, 1150 West Medical Center Drive, Ann Arbor, MI 48105, USA

Our knowledge regarding the pathogenesis, genetics, and improved treatment of uterine fibroids has expanded exponentially over the past decade. Science is poised for exciting opportunities to target specific patients for therapy based on genetic diagnosis, and to use minimally invasive techniques that are based on the latest technology with impressive effectiveness. Approximately 3 to 5 billion dollars are spent annually in the diagnosis and treatment of uterine leiomyomas, also known as fibroids or myomas. A surge in public and industrial research funding has contributed to the development of innovative treatment modalities. In the future, the goals of fibroid therapy will evolve from simple surgical removal of the affected organ to targeting tissue-specific promoters to decrease symptoms without side effects. Some of the most compelling new information stems from a better understanding of the genetic factors that contribute to myoma development. Future therapies for myomas likely will be developed around molecular diagnostic tools and genetic and targeted pharmacologic intervention.

Uterine leiomyomata are one of the most common clinical conditions that affect women. Nearly 50% to 80% of women will develop fibroids, and they are the reason for more than 200,000 hysterectomies annually [1]. Symptoms that are caused by fibroids include dysmenorrhea, recurrent miscarriage, pelvic pain and pressure, and obstetric complications. Current medical and surgical innovations are expanding to target these sequelae better. The epidemiology of fibroids parallels the reproductive changes in progesterone and estrogen over the life span.

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* Corresponding author.
E-mail address: growthh@umich.edu (G.M. Christman).

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Therefore, leiomyoma are present in 25% of reproductive-aged women; symptoms cease at the time of menopause. Nearly 80% of surgically excised uteri have myomas [2]. Genetic predispositions and racial differences in fibroid prevalence are evident. The relative risk for having fibroids is two to three times higher in African American women than in white women [3,4]. Investigating the basis for this disparity had led to a better understanding of the molecular contributions that predispose to fibroid development.

Fibroids are classified by their location in the uterus. Intramural fibroids develop from within the uterine wall and are more likely to enlarge and distort the uterine cavity. Submucosal fibroids develop from myometrial cells below the endometrium and protrude into the uterine cavity. Subserosal fibroids, which originate from the serosal surface of the uterus, can have a pedunculated base or can extend into the ligaments of the uterus. Methods of treating myomas vary based on location, size, and presenting symptoms.

The following pages highlight our current knowledge of fibroids and addresses future directions for fibroid research and treatment over the next decade. The authors discuss the available data on cytogenetics, in addition to discoveries into signaling pathways and second messenger molecules in leiomyomas. Furthermore, the authors summarize current medical management and surgical trends and the barriers to transition to minimally invasive procedures. Innovations in genetic diagnosis and interventional radiologic-aided therapies may revolutionize therapy for certain populations of women who have fibroids. From tissue-specific medical management, to minimally invasive surgical techniques, to pharmacogenetics, the current directions of fibroid research are leading us to an exciting new frontier.

Etiology

Risk factors

Many risk factors for the development of uterine leiomyomas have been examined. None of these risk factors is linked definitively by causality to leiomyomas, but they reflect the importance of the hormonal milieu in the pathogenesis of uterine leiomyomas. It is not a novel idea that these risk factors interplay and contribute to overall risk for the development of leiomyomas [5].

Increased prevalence of leiomyomas with increasing age is noted in epidemiologic studies [5]. Studies that restricted diagnosis to surgical pathology showed increases in leiomyoma diagnosis in women who were in their forties [5]. This statistic may be related more to increases in the prevalence of surgery during the fifth decade, rather than an actual increase in disease. Early menarche is suggested to be a risk factor for the development of fibroids later in life [5,6]. A significant inverse association is noted between women who experienced menarche at age 12 or younger versus women who experienced menarche at age 16 or older [5]. Additionally, much evidence exists to support the fact that

postmenopausal women have a 90% reduced risk for developing fibroids [6]. Studies of postmenopausal patients showed a reduction in leiomyomas that required surgery [5] as well as a reduction in the size and number of leiomyomas [6]. One study that examined uteri that were sectioned at 2-mm intervals noted a similar prevalence of leiomyomas in pre- and postmenopausal patients (74% and 84%, respectively), but noted smaller leiomyomas in the postmenopausal uteri [5].

Parity has long been discussed as a factor for leiomyoma development, with nulliparous women having a greater risk for fibroids than parous women [5,6]. A further decrease in risk is associated with increasing pregnancies [5,6]. In animal models, pregnancy was protective against leiomyoma growth, with an inverse relationship between leiomyoma growth and number of pregnancies [7]. Exogenous hormone therapy also has been examined for leiomyoma risk. The role of oral contraceptives in the pathogenesis of uterine leiomyomas is unclear, and some studies suggested an increased risk, whereas others noted no risk [5,6]. Hormone replacement therapy (HRT) was scrutinized, and estrogen-only HRT is associated with an increase in leiomyoma-related surgery [5] and hospitalization [5,6]. Other studies showed that transdermal and injectable forms of progestin-estrogen combinations, but not oral forms, resulted in an increase in the size of leiomyomas [5]. Two studies suggested that oral HRT may inhibit normal menopausal regression of fibroids [5]. Tamoxifen inhibits estrogen-stimulated growth of Eker rat–derived uterine leiomyoma cells in vitro, but clinical studies reported enlargement of uterine leiomyomas in patients who had breast cancer and were receiving tamoxifen therapy [5].

Few studies have examined the role of diet as a risk factor in leiomyoma growth. One case-control study from Italy noted that women who had leiomyomas reported more frequent consumption of beef, other red meat, and ham and less frequent consumption of green vegetables, fruit, and fish [8]. The investigators also noted an inverse trend associated with leiomyoma risk and increased fish consumption; however, this study only focused on the frequency of intake, and neglected total calories consumed and calories consumed from each food source.

Increasing body mass index (BMI) is associated with an increased risk for uterine leiomyomas [5,6]. The Nurses' Health Study II (NHSII) showed an increased risk for leiomyomas with increasing BMI [9]. Although more than 95% of the women in the NHSII were white, similar results were obtained in the Black Women's Health Study [10]. Ethnicity is an important factor in fibroid development, independent of BMI. Numerous studies have reported an increased prevalence of tumors, increased size of tumors, and younger age of myoma tumor development in African American women compared with white women [5,6].

Finally, current smoking is associated with a decreased risk for leiomyomas in several studies, yet this relationship does not exist in studies of former smokers [5,6,9,11]. There have been some reports of an inverse relationship between fibroid risk and amount of cigarette smoking, but other studies noted no relationship [5,6].

Genetics

Analysis of multiple leiomyomas from a single uterus showed that different tumors possess different chromosomal changes that suggest that each tumor develops separately. This idea was confirmed with glucose-6-phosphate dehydrogenase isoenzyme analysis that showed the clonal origin of several leiomyomas in a single uterus [12,13]. Further examination of CAG repeat polymorphisms in the X-linked androgen receptor gene, X-linked phosphoglycerokinase alleles, and androgen receptor DNA produced similar findings [13].

It is estimated that 40% to 50% of uterine leiomyomas have karyotypic or cytogenetic abnormalities that are nonrandom and tumor specific [13]. Although a myriad of chromosomal changes has been noted, several broad subgroups occur with greater frequency [13]. These subgroups include t(12;14)(q15;q23~q24), del(7)(q22q32), rearrangements at 6p21 and 10 q, trisomy 12, and deletions of 3q [13]. One study found a positive correlation between cytogenetic abnormality and anatomic tumor location, and noted that intramural and subserous leiomyomas were more likely to be cytogenetically abnormal than were submucous tumors [13]. Greater mitotic indices are found in karyotypically abnormal fibroids than in chromosomally normal neoplasms [13].

Several genes have been implicated in the molecular pathogenesis of leiomyomas. Chromosomal rearrangements in leiomyomas and other benign soft tissue tumors have been noted in the High Mobility Group I proteins, including those encoded by *HMG2A* (formerly *HMGIC*) and *HMG1A* (formerly *HMGIY*) [13]. High levels of these closely related, low molecular mass proteins are detected in leiomyomas but not in the adjacent myometrium [13]. Furthermore, several genes of heritable disorders predispose to the development of leiomyomas. Genetic studies of families who had multiple cutaneous and uterine leiomyoma (MCUL) revealed 20 distinct germline mutations at the fumarate hydratase gene (*FH*) [14]. Members of this same group found evidence of MCUL linkage to chromosome 1q42.3-q43 [15]. Another study noted 18 novel mutations in *FH* and 2 known mutations in 35 families in North America [16]. Two distinct mutations in *FH* also were associated with the MCUL variant: hereditary leiomyomatosis and renal cancer syndrome [14].

Basic science of leiomyomas

Sex steroids

Many studies have detailed the effect of steroid hormones on leiomyoma and myometrial growth. Estrogen is believed to be the main regulator of leiomyoma growth, because fibroids grow only after menarche, may increase in size during pregnancy, and shrink during menopause [5,17,18]. Furthermore, women who have increased estrogen production (eg, obese women) or exposure to unopposed estrogen (eg, nulliparous women) have an increased risk for the development of

leiomyomas [5,18]. Gonadotropin-releasing hormone (GnRH) agonists reduce the size of leiomyomas and the uterus by mimicking the estrogen-depleted state of menopause [5,18,19].

Through binding of specific nuclear receptors, estrogen exerts its effects on target cells. These receptors form heterodimers that bind to the estrogen-responsive element (ERE) in the cell's DNA to exert estrogen's effect (Fig. 1). One recent study evaluated a gene therapy strategy for the treatment of fibroids with a dominant-negative estrogen receptor (ER) gene that was based on the principle that the transcripts from the negative gene would create heterodimers with the native ER transcripts to prevent binding to the ERE [20]. The investigators showed increased apoptosis in leiomyoma cells and sustained arrest of tumor growth without functioning ERs [20].

There are two subtypes of ER: α and β. These receptors are similar in their homology at the DNA-binding domain and the ligand-binding domain [19]. ER-α and -β are expressed in myometrium and leiomyoma during all phases of the menstrual cycle [5,19]. One study showed that ER-α and -β levels in the

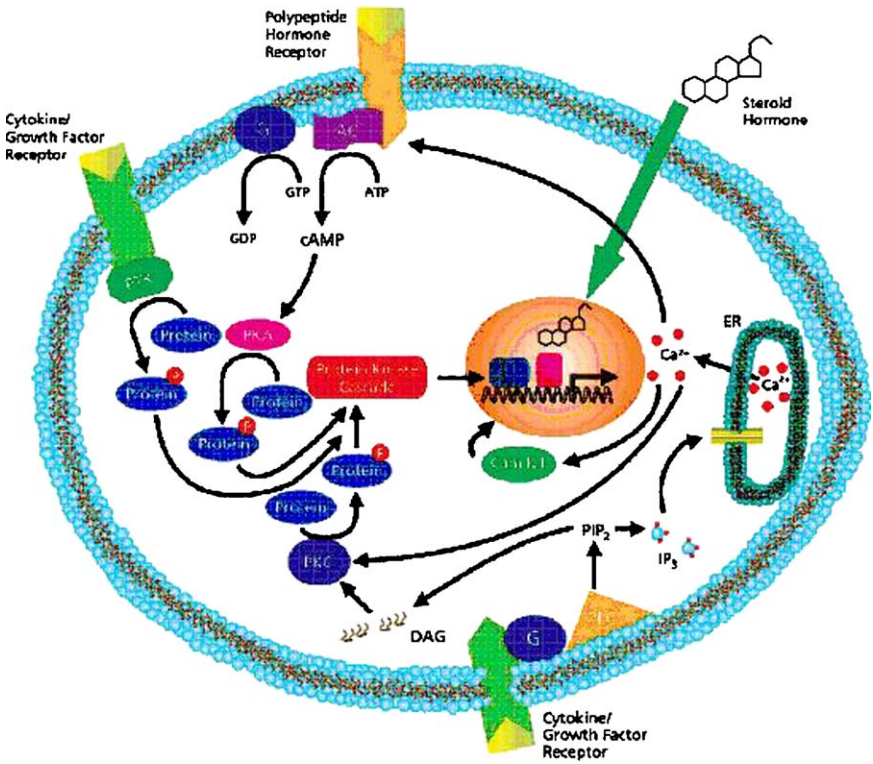

Fig. 1. Sex steroid hormone action. Estrogen and progesterone exert action through binding of specific receptors, which then bind to DNA at specific response elements. Binding of estrogen and progesterone at a variety of genes has different effects in various cells. Courtesy of Sigma-Aldrich Co., St. Louis, MO, © 2006. Used with permission.

myometrium change in a similar manner during the myometrial cycle, but that ER-α levels predominate over ER-β levels [19]. This assertion remains controversial, because other studies showed no difference in ER-α and -β mRNA expression between leiomyomas and the corresponding myometrium in perimenopausal women [21]. Andersen [22] noted that ER-α is greater than ER-β in nonpregnant women, and high levels of ER-β are expressed in term myometrium. This investigator also noted low levels of ER-β expression in nonpregnancy myometrium and leiomyoma tissues as compared with term myometrium. ER-β levels in myometrial and leiomyoma tissues vary similarly during the menstrual cycle, with the lowest levels at midcycle [22]. In another study, however, the same investigator and colleagues found that ER-α was increased in leiomyomas versus matched myometrium in all phases of the menstrual cycle, particularly during the follicular phase [23]. Agonist-bound ER-α increased transcription of activator protein (AP)-1 through heterodimers of the Jun and Fos families, which, in turn, increased the expression of connexin43 [22]. This does not rule out an important role for ER-β, because the ER-β gene, *ESR2*, maps to 14q22-24, an area close to the breakpoint site of a common genomic rearrangement that is found in leiomyomas [5].

Progesterone also plays an important role; its presence increased mitotic activity in leiomyomas, especially during the secretory phase of the menstrual cycle when progesterone levels are at their highest [5,17,18]. Increases in mitotic activity were noted with the administration of medroxyprogesterone acetate [19]. Transdominant suppression of ER by progesterone receptor (PR) ligands was demonstrated in experiments with leiomyoma cell lines that were derived from Eker rats [24]. Progestins can inhibit GnRH agonist–induced tumor shrinkage [19]. This suggests that cross-talk occurs between ER and PR in leiomyomas, and disruption of this cross-talk by agents, such as mifepristone (RU486), may affect proliferation negatively [24].

Progesterone receptor also exists in two forms, PR-A and PR-B. These receptors also function as ligand-activated transcription factors with distinct biologic functions. There seems to be a greater concentration of each subtype in leiomyomas versus matched myometrium, with PR-A greater than PR-B. This is a controversial claim, however, because there is evidence that there is no difference in PR expression between leiomyomas and myometrium. An increase in PR mRNA and protein levels has been associated with elevated proliferation-associated antigen Ki-67 in leiomyomas versus adjacent myometrium, which suggests progestin-mediated signaling in leiomyoma growth [19]. Several studies showed that progesterone antagonism with RU486 results in a decrease in leiomyoma size and symptomatology, probably through down-regulation of progesterone receptors [25]. Also, GnRH agonist therapy down-regulates PR-A and PR-B expression, and PR-A and PR-B mRNA levels in leiomyoma [19].

In addition to its responsiveness to endogenous sex steroids, leiomyoma tissue is a source of estrogen. Leiomyoma tissue produces its own aromatase, a microsomal enzyme that catalyzes the conversion of androgens to estrogen, whereas normal myometrium does not [26]. Exogenous estrogen that is produced

by leiomyomas likely promotes growth in an autocrine or intracrine fashion [27]. Estrogen production in leiomyomas is inhibited by GnRH agonist therapy in situ [28] and in vivo [29] through suppression of aromatase activity [28]. Shozu and colleagues [30] found that leiomyoma size correlated directly with aromatase mRNA expression among leiomyomas within the same uterus. This correlation did not hold true for aromatase mRNA levels compared among several individuals who had large leiomyomas [30]. Conversion of estrone to estradiol is increased threefold in leiomyoma tissue compared with matched myometrium; this corresponds to a higher expression of 17β-hydroxysteroid dehydrogenase (HSD) type I mRNA [30]. This enzyme, 17β-HSD, catalyzes the interconversion between androstenedione and testosterone and also estrone and estradiol, and plays an important role with aromatase. Overexpression of aromatase in leiomyomas was linked to promoter I.4, with evidence for the role of the glucocorticoid-response element in the transcription of aromatase [28]. The investigators postulated that a factor that acts in concert with cortisol may upregulate aromatase transcription in situ, but they were unable to isolate this factor.

Cytokines, growth factors, and growth factor receptors

Leiomyomas express many types of growth factors. Insulin-like growth factor (IGF)-1, the product of an estrogen-regulated gene, mediates the biologic effects of growth hormone (GH) in many tissues. It exerts its mitogenic action by increasing DNA synthesis, accelerating the progression of the cell cycle from G1 to S phase, and inhibiting apoptosis. A study of women in the proliferative phase of the menstrual cycle, in whom estrogen is the predominant hormonal influence, showed that mean IGF-1 expression was not statistically significant in leiomyomas versus myometrium [31]; however, increased expression of IGF-1 was noted in some tumors [31]. Previous studies indicated increased expression of IGF-1 mRNA and higher tissue concentrations of IGF-1 protein in leiomyomas versus corresponding myometrium [32]. Minimal to moderate focal immunolocalization of IGF-1 peptide in myometrial and leiomyoma smooth muscle cells also was noted, along with intense expression of IGF-1 peptide in epithelioid and fibroblast cell types within the perivascular and extracellular matrix (ECM) [31]. An increase in the levels of IGF-1Rβ, an IGF-1 receptor, also was noted [31]. The investigators noted that these data support a possible paracrine mechanism for IGF-1–induced growth in leiomyomas [31]. Other data showed an inverse relationship between IGF-1 expression and IGF-1 receptor (IGF-1R) expression, which suggested that overproduction of IGF-1 by leiomyomas resulted in an activation of signaling pathways downstream from the IGF-1R [33]. Immunocytochemical staining also demonstrated that IGF-1 treatment in vitro results in an increase in the expression of proliferating cell nuclear antigen (PCNA), a DNA polymerase-associated protein that is manufactured in DNA replication [34]. Furthermore, IGF-1 treatment also improves cell survival, possibly by increasing levels of Bcl-2, an apoptosis inhibitor [34]. Hormonal influences can cause IGF-1 expression to vary, with decreased expression in postmenopausal women and

those who are treated with GnRH agonists [32,35,36]. Estrogen levels correlated directly with IGF-1 mRNA expression in leiomyomas and the corresponding myometrium [32]. Estrogen-treated cells had increased *IGF-1* gene transcription [37]; however, the use of levonorgestrel, a progestin, caused a down-regulation of IGF-1 mRNA and protein expression in vitro [38]. Studies of IGF-II showed overexpression of IGF-II in leiomyomas versus myometrium, but no significant difference in IGF-II receptor expression in these two tissues [17].

The epidermal growth factor (EGF) family of proteins are autocrine regulators for fibroblasts and smooth muscle cells. This family includes EGF, heparin-binding EGF-like growth factor (HB-EGF), transforming growth factor (TGF)-α, and several others (Fig. 2). In cultured leiomyoma cells, EGF caused an increase in the percent of PCNA-positive cells, but this effect was not additive with estrogen. Furthermore, progestin-treated leiomyoma cells in vitro had increased EGF expression versus control cultures, whereas estrogen addition resulted in a lower expression of EGF in cultured cells. Immunocytochemical analysis showed up-regulation of EGF receptor (EGFR) with estrogen treatment compared with

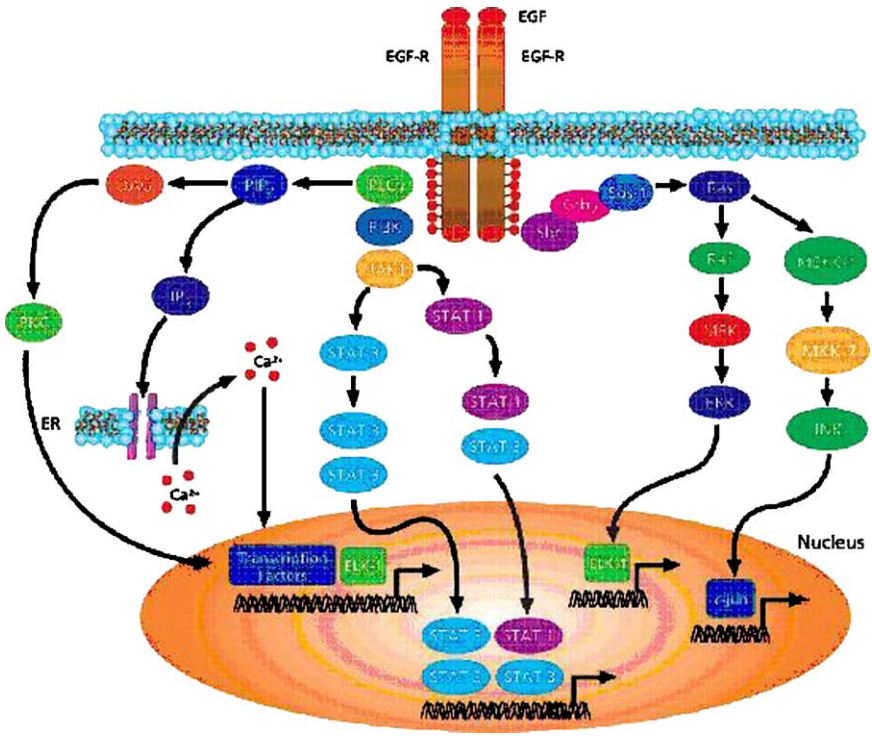

Fig. 2. EGF receptor signaling transduction pathway. In leiomyoma cells, EGF increases the percentage of PCNA-positive cells. Progestin increases EGF expression in leiomyoma cells, whereas estrogen decreases EGF expression. Estrogen in leiomyoma cells up-regulates EGFR, but progesterone does not have this effect. Courtesy of Sigma-Aldrich Co., St. Louis, MO, © 2006. Used with permission.

control cultures, but no effect on EGFR expression with progestin [34]. These investigators postulated that progestin and estrogen work together to promote growth by enhancing EGF protein and EGFR expression in leiomyoma cells. One study of leiomyoma tissue taken from women in the proliferative phase of the menstrual cycle demonstrated no difference in the amount of EGF mRNA in leiomyomas and normal myometrium, and no statistically significant difference in EGFR between leiomyomas and myometrium [31]. Cultured cells that were treated with HB-EGF increased the Ki-67-positive rate and PCNA expression of leiomyoma cells and myometrial cells in a dose-dependent manner [39]. Treatment of cultured leiomyoma cells with the GnRH antagonist cetrorelix significantly decreased PCNA expression, EGF mRNA, and EGF protein in a dose- and time-dependent manner [40]. Also, the selective EGF receptor blocker AG1478 inhibited leiomyoma cell growth in vitro by inducing cell cycle arrest without cytotoxicity or apoptosis [41].

TGF-β isoforms seem to play a significant role in the increased cellular proliferation and excessive accumulation of ECM that characterize leiomyomas (Fig. 3). Studies of TGF-β1 demonstrated an overall increased expression in leiomyomas versus myometrium [42]. These results are controversial, because

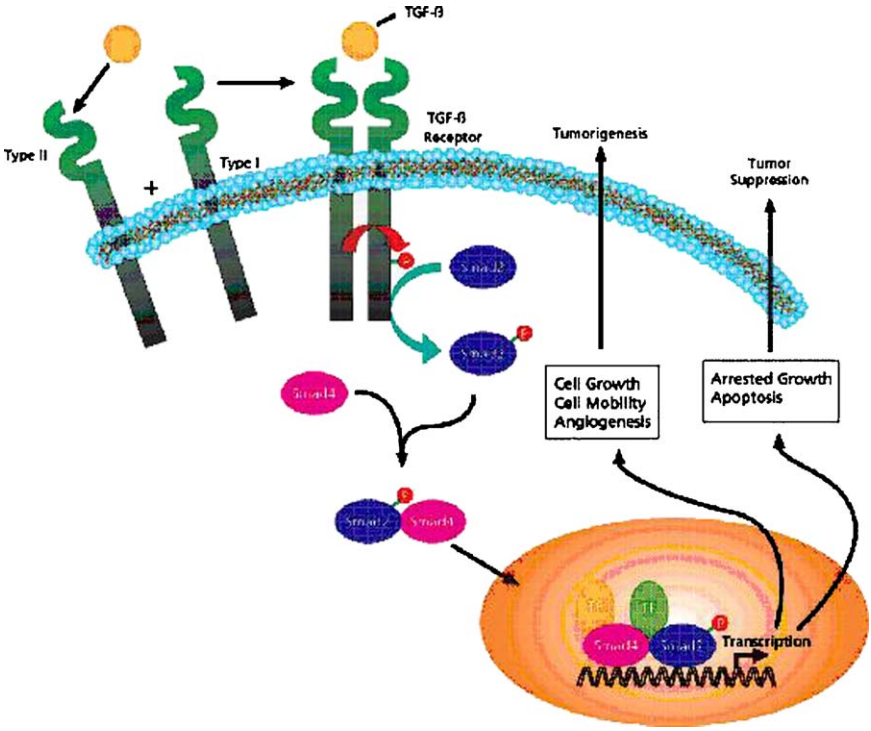

Fig. 3. Signaling pathway of TGF-β. TGF-β plays a significant role in cellular proliferation and excessive accumulation of ECM in leiomyomas. Isoforms TGF-β1 and -β3 play important actions in leiomyoma cells. Courtesy of Sigma-Aldrich Co., St. Louis, MO, © 2006. Used with permission.

other studies showed no difference in TGF-β1 expression between leiomyomas and myometrium [43]. Furthermore, although levels of total TGF-β1 did not vary throughout the menstrual cycle, levels of active TGF-β1 in the myometrium and leiomyoma during follicular and luteal phases are significantly higher than are levels observed in myometrium from women who were treated with GnRH agonists; this suggests a stimulatory role for sex hormones in the action of TGF-β1 [42]. Leiomyoma cells also show increased expression of TGF-β3 mRNA versus the matched myometrium [43,44]. One study noted the highest levels of TGF-β3 expression in leiomyomas in the midsecretory phase of the menstrual cycle versus the proliferative phase [44]. Treatment with TGF-β3 increased the expression of fibronectin mRNA [44].

Several other growth factors have been implicated in the pathogenesis of uterine leiomyomas. Basic fibroblast growth factor (FGF) usually is present in the basement membrane and the subendothelial ECM of blood vessels. Its expression was increased in leiomyomas versus myometrium in the proliferative phase of the menstrual cycle. Its expression decreased after treatment with GnRH agonists, [45] which contrasts with the results of previous studies [31]. Staining for FGF receptor (FGFR)-1 in leiomyomas revealed that it was homogeneous throughout the menstrual cycle, and it increased after GnRH agonist therapy [45]. No differences in FGFR-2 were noted between leiomyoma or myometrium in any phase of the menstrual cycle [31,45]. Expression of vascular endothelial growth factor, a growth factor that correlates with angiogenic activity, was no different in leiomyoma versus normal myometrium [31,46]. Platelet-derived growth factor (PDGF) was not different in leiomyomas versus myometrium. Although PDGF receptor sites in leiomyomas outnumbered those in myometrium, the binding affinity for PDGF at those sites was lower [47]. Expression of parathyroid hormone–related peptide, a hormone that is identified in tumors that are associated with hypercalcemia of malignancy, was elevated in leiomyoma versus myometrium, especially in women during the follicular phase of the menstrual cycle [47]. Endothelin-1—a potent vasoconstrictor with a stimulatory effect on DNA synthesis and hypertrophy of monocytes and fibroblasts—mRNA, and receptor mRNA levels were increased in leiomyoma versus myometrium, but endothelin-1 was not overexpressed in leiomyoma or under hormonal variation [47]. The expression of monocyte chemotactic protein (MCP)-1, a monocyte chemoattractant and antitumor agent in many tumors, was significantly higher in myometrium versus leiomyoma [47]. Myometrial MCP-1 levels showed menstrual cycle variation, with higher levels during the luteal phase than during the follicular phase and highest levels during GnRH agonist therapy [47].

Extracellular matrix

Leiomyomas consist of smooth muscle cells and an abundant ECM, which can be up to 50% greater than in the corresponding myometrium [47]. This ECM consists mostly of collagen, fibronectin, and proteoglycans. Its presence probably plays an important role in the pathogenesis of uterine leiomyomas because it can

serve as a biologically active repository for cytokines and growth factors; collagens, fibronectin, and proteoglycans bind these molecules tightly [47].

Collagen fibrils within leiomyomas are overexpressed relative to normal myometrium, especially during the follicular phase of the menstrual cycle [47]. In leiomyomas, mRNA from types I and III collagen are overexpressed [48]. Furthermore, the collagen within leiomyomas is abnormal in structure and orientation in contrast to the myometrium, regardless of tumor size or menstrual cycle phase [49]. The investigators could not account for why the collagen structure was abnormal, but they suggested that proteoglycans might account for the abnormal structure. The diameter of collagen fibrils was not significantly different between leiomyomas or myometrium [49]. Transfection of leiomyoma cells in vitro with p53 inhibited collagen type I production, whereas transfection with p21 did not influence collagen type I production in leiomyomas [50]. There was no significant difference in the amount of total collagen or glycosaminoglycan in uterine leiomyomas from homozygous negative individuals and heterozygous individuals who had type IV Ehlers-Danlos syndrome (EDS-IV), an autosomal dominant disorder that is characterized by decreased type III collagen in the ECM [51]. Leiomyomas from women who had EDS-IV showed reduced type III collagen content, which is consistent with the disease phenotype [51]. Growth factors and hormones also affect the expression of ECM; TGF-β and GnRH increase the expression of type I collagen and fibronectin, probably through downstream expression of the mitosis associated protein kinase/estrogen receptor kinase signaling cascade [52].

Proteoglycans, glycosylated proteins with covalently linked sulfated glycosaminoglycans, also are part of the leiomyoma structure. Wolanska and colleagues [53] found low concentrations of hyaluronic acid in leiomyomas versus myometrium, and noted higher proportional amounts of sulfated glycosaminoglycans (GAGs). These investigators noted that heparan sulfate is the major GAG component in normal myometrium and leiomyomas, whereas other studies noted that chondroitin sulfate and dermatan sulfate were the main GAGs [54,55]. Dermatan sulfate is found in greater concentrations than is chondroitin sulfate, and it is found in a D-glucuronic acid–rich form that migrates between dermatan sulfate and chondroitin sulfate [54]. Although the content of hyaluronic acid did not change during tumor growth, the content of sulfated GAGs, including heparan sulfate, keratin sulfate, chondroitin sulfate, and heparin, increased [53]. Differences in GAG sulfation patterns also were noted between leiomyomas and myometrium, with a decreased percentage of disulfated dermatan sulfate chains in leiomyomas [55].

Many other proteoglycans are found in leiomyomas. Decorin is a member of the leucine-rich repeat protein family, and its N-terminal has a binding site for dermatan sulfate. It also interacts with specific regions of types I and II collagen fibrils, and thus, plays an important role in the organization and assembly of collagen fibrils. Decorin is expressed in leiomyoma and myometrium, but it has a higher molecular weight in leiomyomas [56]. The distribution patterns of decorin and collagen also are different in leiomyomas versus myometrium;

decorin is found in regions that contain type I collagen but not type IV collagen [56]. Dermatopontin, an extracellular protein that binds small dermantan sulfate molecules and decorin, also was expressed in leiomyomas; however, dermatopontin mRNA was decreased when compared with myometrium [57]. Matrix metalloproteinases (MMPs), which break down the ECM, and their tissue inhibitors (TIMPS) also are important in the discussion of the ECM. Myometrium is known to express the mRNA of several forms of MMPs as well as TIMPs; the expression of this mRNA is cycle-dependent, with greatest expression during the secretory phase of the menstrual cycle [58]. Furthermore, MMP and TIMP protein and mRNA also are expressed in leiomyoma, but at much lower levels than in myometrium, with maximal expression in leiomyoma during the progesterone-dominated secretory phase [58].

Advances in the medical therapy of myomas

Treatment of leiomyomata varies, and is based on the magnitude of symptoms and the size and location of the myoma. Other important factors include the patient's age and proximity to menopause. The patient's desires for future fertility and obstetric history contribute significantly to the decision about therapeutic options. The main goal of therapy is the relief of symptoms. Because abnormal uterine bleeding often has several possible etiologies, a trial of medical therapy is warranted before surgical intervention.

Gonadotropin-releasing hormone agonists

GnRH agonists are the mainstay of medical therapy for uterine fibroids. These drugs cause a down-regulation of endogenous luteinizing hormone and follicle-stimulating hormone production, which leads to a hypogonadotrophic, hypogonadal state that resembles menopause. A significant reduction in uterine size—between 35% and 60%—typically is seen within 3 months of initiating therapy [1–4]. GnRH agonists typically induce amenorrhea, and improvements in hematocrit and symptoms; however, the severe hypoestrogenism that results from GnRH administration leads to bone loss and osteoporosis over time [1]. For these reasons, GnRH agonist therapy typically is limited to 6 months and can be used to temporize until surgery or impending menopause. Preoperative administration of GnRH agonists increases hematocrit and may decrease the need for blood transfusion [59,60]. In addition, decreasing uterine volume preoperatively may facilitate a less invasive procedure, including possible vaginal or laparoscopic approaches. Smaller surgical incisions, shorter hospital stays, and a faster recovery also contribute significantly to potential benefits. To help minimize the long-term effects of GnRH agonist use, add-back therapy with low doses of estrogen and progesterone can be given. Low doses of estrogen (eg, 0.625 mg of conjugated equine estrogen) maintained amenorrhea and decreased

uterine volume. Add-back therapy can be initiated after the initial phase of down-regulation to ensure a decrease in uterine volume [61].

Mifepristone

Antiprogestin therapy with mifepristone (RU486) showed efficacy in reducing uterine volume that was comparable to GnRH agonists [62,63]. One study showed a reduction in symptoms and a reduction in overall volume by 26% to 74% [64]. Mifepristone is being studied in the United States at a dosage of 5 to 50 mg/d for 3 to 6 months for fibroid treatment, compared with the 200-mg dose that is used for termination of pregnancy. The marked regression of leiomyomas with RU486 highlights the importance of progesterone on fibroid tumors.

Uterine artery embolization

Over the past 10 years, uterine artery embolization (UAE) has been developed as an alternative to the surgical treatment of fibroids (Fig. 4). It is based on the hypothesis that decreased myometrial blood flow results in the infarction of fibroids, and decreased symptoms with the loss of volume [65–68]. Although more than 15,000 cases of UAE have been performed in the United States, long-term success rates remain unknown. A study by Worthington-Kirsch and colleagues [69] in 1998 reported on 53 patients who underwent UAE for fibroids; 88% had improvement in menorrhagia, 94% had improvement in pressure symptoms, and the mean reduction in uterine volume was 46%.

Although UAE is emerging as an effective alternative to hysterectomy and myomectomy for symptomatic fibroids, no long-term data are available [70]. Generally, treatment failure is defined as a lack of demonstrable clinical benefits after successful bilateral embolization of right and left uterine arteries. Possible reasons for treatment failure include luminal recanalization, large fibroid size, and coexisting disorders (eg, adenomyosis, uterine leiomyosarcoma, extensive collateralization of the arterial blood supply). Specific guidelines in patient selection are not well defined; however, candidates for UAE should have symptoms from their fibroids, and wish to avoid invasive surgery and retain their uterus. UAE is not indicated in patients who would be excellent candidates for hysteroscopic myomectomy, patients who have heavily calcified myomas, or patients who desire future fertility. A preprocedure MRI is useful in identifying the presence of pedunculated submucosal or serosal fibroids, and in excluding other disease processes, such as ovarian tumors or extensive adenomyosis. Pedunculated tumors do not respond as well to UAE, and they are associated with an increased risk for complications, including torsion [71]. Generally, short-term outcomes of UAE have been favorable, and the average reduction in uterine volume seems to be approximately 40% [68,71–76]. Spies and colleagues [77] reported a 90% improvement in menorrhagia and a 91% improvement in bulk symptoms at 1 year in 200 women who underwent UAE. Another series of 400 women found

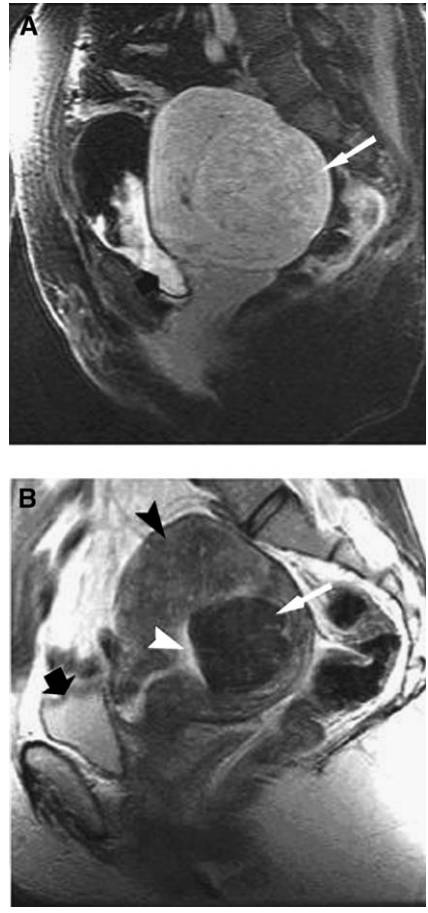

Fig. 4. (*A*) Sagittal T1-weighted spoiled gradient echo image before embolization shows heterogeneous enhancement of the leiomyoma (*white arrow*). (*B*) Sagittal T2-weighted image of the uterus 5 months after embolization shows shrinkage and homogeneous low signal intensity of the leiomyoma (*white arrow*), (*top black arrow*, uterus; *left black arrow*, bladder). (*From* Mueller GC, Gemmete JJ, Carlos RC. Diagnostic imaging and vascular embolization for uterine leiomyomas. Semin Reprod Med 2004;22(2):135; with permission.)

an 84% improvement in menorrhagia and a 90% improvement in pressure symptoms at 16.7 months [75].

Although serious complications are rare, other complications do not seem to be related to uterine or myoma size. Up to 40% of women experience postembolization syndrome—a constellation of diffuse abdominal pain, nausea, vomiting, low-grade fever, and leukocytosis [70]. Generally, this is self-limiting, but may contribute to the 3.5% readmission rate after UAE [74]. Infection, including pyometria, endometritis, tubo-ovarian abscess, and infected myomas, has been reported in 1.0% to 1.8% of cases [70]. Persistent pain is seen in

5% to 10% of women, and hysterectomy for postembolization pain occurs in up to 2% of women within 6 months of embolization [78,79]. Transient and permanent ovarian dysfunction occurs in up to 15% of women after UAE. Although the specific factors that lead to ovarian dysfunction are unclear, women aged 50 and older have a 41% risk for this complication [80–83]. The main hypothesized cause is unintentional embolization into the ovarian arteries; however, cases of endometrial atrophy with functioning ovaries have been reported. For women who desire future fertility, no prospective study has examined ovarian reserve after UAE.

Regarding future pregnancy after UAE, little information is available regarding outcomes. Concerns include possible ovarian dysfunction, endometrial atrophy, intrauterine adhesions, and possible subendometrial scarring. A recent report of 10 women who wished to conceive after UAE demonstrated that intrauterine adhesions were seen in 4 women, subendometrial scarring was seen in 1 woman, and yellowing of the endometrium was seen in 3 women; however, 5 of the 10 women eventually conceived [84]. No long-term data exist regarding pregnancy outcomes after UAE. Current recommendations state that UAE is appropriate for women who desire future fertility only if myomectomy has failed, if they are poor surgical candidates for myomectomy, or if they fully understand the lack of long-term information on UAE and the possibility of ovarian damage.

Innovations in surgical management

Surgical treatment is the mainstream therapy for leiomyomas. Hysterectomy represents the only definitive therapy; however myomectomy, endometrial ablation, and myolysis are increasing in frequency as alternative procedures. Indications for surgical intervention include failure to respond to medical treatment, worsening vaginal bleeding, suspicion of malignancy, or treatment of recurrent pregnancy loss. In postmenopausal women who have an enlarging pelvic mass and abnormal bleeding, surgery should be considered strongly. In this population, the prevalence of a sarcoma is higher than in the premenopausal population (~1–2%) [85].

Hysterectomy

Approximately 30% of hysterectomies in the white population and 50% of hysterectomies in the African American population are performed secondary to leiomyomas [86]. Because hysterectomy eliminates current symptoms and the risk for recurrence, it can be an attractive option among patients who have completed childbearing. A 2-year follow up study that evaluated women who underwent hysterectomy for benign conditions showed that greater than 90% of women experienced significantly less symptoms, depression, and anxiety [87]. The morbidity of hysterectomy in the setting of a solitary or pedunculated myomas has led to the popularity of less invasive procedures, including myo-

mectomy. Total laparoscopic hysterectomy and laparoscopic-assisted vaginal hysterectomy are emerging as minimally invasive options in the appropriate patient populations; however, the technical education that is needed to perform advanced laparoscopy limits the available surgical expertise.

Myomectomy

Myomectomy is an effective option for women who desire future pregnancies or who desire to retain their uterus. Despite its effectiveness in reducing menorrhagia and pelvic pressure, the main disadvantage of myomectomy is the risk for recurrence. The risk for new myomas forming from clones of preexisting myomas is high, and approximately one third of women who undergo abdominal myomectomy have a second surgical procedure within a decade [88]. Another study found that 50% to 60% of patients had new myomas detected by ultrasound 5 years after abdominal myomectomy. In this study, 10% to 25% of patients required a second major surgery [89–93].

Risk factors for subsequent procedures include uterine size less than 12 weeks size at time of myomectomy, and weight gain in excess of 14 kg after the age of 18 years. Overall, operating on a small uterus (prophylactic myomectomy) increases the risk for needing a second procedure [88]. The degree of weight gain after adolescence may correlate with peripheral estrogen exposure. Other studies, however, reported a higher risk for recurrence in women who had larger uterine sizes and multiple fibroids [92]. Generally, laparoscopic myomectomy is considered an option in women who have less than a 17-weeks size uterus with a few subserosal or intramural fibroids. Factors that increase the risk for conversion to an open procedure include fibroids that are at least 5.0 cm, intramural location, preoperative GnRH agonist use, and anterior location of fibroids [94]. Potential benefits to minimally invasive myomectomy include shorter hospital stays, decreased blood loss, and shortened recovery time.

The reported rates of the risk for uterine rupture after abdominal myomectomy are biased by the routine practice of recommending elective cesarean section in women who have undergone a transmural approach [95,96]. This bias included, the risk for rupture before labor after myomectomy is low (~0.002%), compared with the risk for rupture after classic cesarean section (~3.7%) [97]. It remains unclear whether reapproximation of the myometrium by way of laparoscopic suturing yields the same uterine wall strength as does a multilayer closure by way of laparotomy. This remains an area of controversy until further data are made available [95,98,99]. Hysteroscopic myomectomy offers several advantages when dealing with submucous myomas. The location of these tumors makes them readily accessible to an operative hysteroscope inserted through the cervix. Other benefits include outpatient surgery, possible use of local anesthesia with sedation, and a short recovery period. Overall, excellent success is described with this approach, and one large series noted that less than 16% of patients had a second surgery performed in a 9-year follow-up period [100]. For these reasons, hysteroscopic myomectomy is the preferred conservative surgical treatment

for women who have intracavitary fibroids that are suitable for hysteroscopic resection.

Endometrial ablation

Endometrial ablation has been described alone or in combination with hysteroscopic myomectomy as therapy for women who do not desire future fertility. It may alleviate symptoms of menorrhagia with minimal invasiveness. Most of the case series that investigated endometrial ablation excluded women who had large myomas [100]; however, given the large number of commercial devices that are available for ablation, it is important to evaluate the size and shape of the endometrial cavity.

Myolysis

Myolysis is a laparoscopic procedure that involves cauterization or cryoablation of myomas. By not requiring intracorporeal or extracorporeal suturing, this procedure is less technically challenging than is laparoscopic myomectomy; however, long-term implications for fertility and the risk for uterine rupture in pregnancy are unknown. Given the localized tissue destruction without repair, there may be a theoretic increased risk for adhesion formation or uterine rupture during pregnancy [101].

Treatment innovations for the future

MRI-guided focused ultrasound therapy

Recent advances in the field of ultrasound have led to the development of focused ultrasound surgery (FUS). FUS unites two technologies—therapeutic ultrasound and diagnostic MRI—and provides a noninvasive procedure that aims to destroy fibroid tissue in a precise and controlled manner. By placing an ultrasound transducer on the surface of a patient and focusing energy at a specific, controllable depth and position, tissue is destroyed within the focal zone (Fig. 5). The therapeutic ultrasound is monitored by MRI, which records the temperature elevation from heat generated over time. Once the temperature reaches 57°C for 1 second, tissue is destroyed within the focal zone. Tissue within 2 mm to 3 mm of the focal zone is unaffected because of the precise demarcation between normal and destroyed tissue.

MRI-guided focused ultrasound surgery as a therapy for leiomyoma treatment received U.S. Food and Drug Administration approval in October 2004. FUS is the first technology to be approved for fibroid therapy as its primary indication. General patient selection criteria include fibroids that are between 4 cm and 10 cm, maximum depth of subcutaneous tissue to the fibroid of less than 12 cm, completion of childbearing, premenopausal status, and fibroids that are visualized

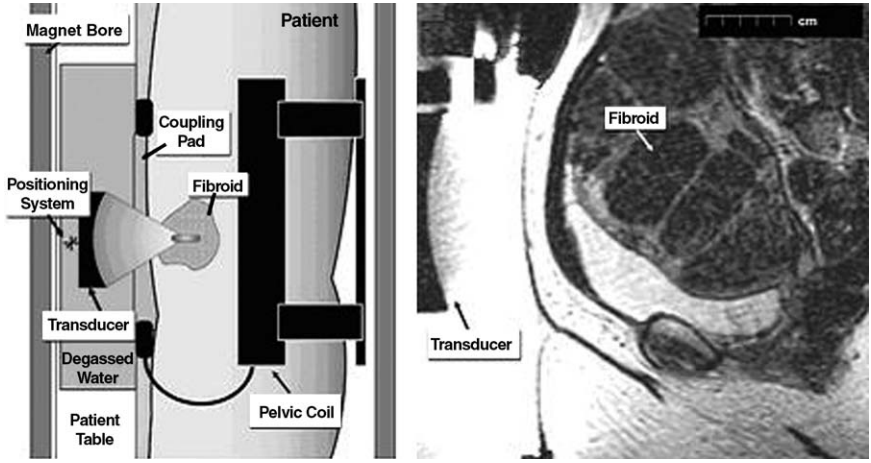

Fig. 5. (*Left*) Side-view diagram of the focused ultrasound system and patient positioning. (*Right*) Sagittal T2-weighted fast spin-echo MRI obtained with the patient in position for treatment. (*From* Tempany CMC, Stewart EA, McDannold N, et al. MR imaging–guided focused ultrasound surgery of uterine leiomyomas: a feasibility study. Radiology 2003;226:897; with permission.)

clearly on MRI. Based on results of a 6-month follow-up study, mean fibroid reduction volume was 13.5 cm^3, and the mean volume of nonperfused tissue was 51.2 cm^3. Furthermore, 79.3% of patients reported a greater than 10-point reduction in symptoms and improvement in quality of life measures based on the questionnaires that were used in the study [102]. Adverse events included minor skin burns in 4% of patients, worsening menorrhagia in 4% of patients, hospitalization for nausea in 1% of patients, and nontargeted sonication of uterine serosa in 1% of patients [103].

Somatostatin analogues

There is increasing evidence that growth factors clearly play a role in the generation and growth of fibroids. Recent studies indicate that IGF-I and -II messenger RNA are present in uterine tissue [104]. Estrogen stimulation increases levels of these messenger RNAs. Although myometrium and leiomyomas express IGF-I and IGF-II, leiomyomas contain more binding sites for IGF-I than does normal myometrium [105,106]. Explants of myometrial tissue and myomas also secrete IGF-1 [107]. Lanreotide is a long-acting somatostatin analog that reduces GH secretion [108]. It was shown recently that acromegaly—a disorder in which patients have high levels of GH—is associated with a prevalence of 81% for uterine leiomyomata. Administration of the somatostatin analog lanreotide reduced uterine volume and myoma volume in fertile women [109]. Using the 30 mg depot formulation of lanreotide, the mean reduction in total uterine volume was 24% and the mean reduction in myoma volume was 41.6%

[110]. The antiproliferative effect of somatostatin is believed to work indirectly by inhibiting growth factors and angiogenesis, and directly by binding to somatostatin receptors 2 through 5 and by decreasing IGF-I and -II production [111].

Selective progesterone receptor modulators

Asoprisnil is an antiprogestin with high tissue selectivity; it binds to the progesterone receptor with a threefold greater binding affinity than progesterone. It was the first selective progesterone receptor modulator to reach advanced stage clinical trials for the potential treatment of endometriosis and symptomatic leiomyomata. Studies showed that asoprisnil reduced uterine volume by a median of 16.1% in the first 4 weeks and by 26.5% in 8 weeks [112]. Other notable benefits included a relief in pressure symptoms and increased hemoglobin concentration because of a dose-dependent induced amenorrhea. Specific benefits of asoprisnil are secondary to its high degree of uterine selectivity. It is a selective inhibitor of endometrial proliferation and targets endometrial vasculature specifically to induce amenorrhea. Unlike other progestins (eg, mifepristone), asoprisnil does not terminate pregnancy effectively in animal models. Furthermore, it has not been shown to induce breakthrough bleeding or premenstrual symptoms like progestins. In general, asoprisnil seems to be safe and effective in decreasing fibroid volume and in reducing menorrhagia. Although two dosages of the drug (5 and 10 mg) were investigated, women who took the lower dosage had fewer hot flashes [113]. Long-term risks, including the possible risks for endometrial hyperplasia, have not been studied. It should be anticipated that alternative selective progesterone receptor modulators will be developed and studied in the near future.

Aromatase inhibitors

Ovarian steroid hormones and aromatase are essential for the progression of leiomyomata. Aromatase, the key enzyme that is responsible for estrogen biosynthesis, has an abnormally high expression in leiomyoma tissue when compared with normal myometrium. Data suggest that leiomyoma cells synthesize estrogen in situ, which explains the advantage of their growth over surrounding myometrium. The aromatase gene is expressed in extragonadal sites in a tissue-specific manner, and the primary promoter region for aromatase expression in uterine leiomyoma is likely promoter 1.3/II. Preliminary cases that investigated the use of aromatase inhibitors showed improvement in urinary retention and reduction in the ultrasound estimates of leiomyoma volume by 71% after 8 weeks of treatment [114]. Theoretically, aromatase inhibitors offer several advantages over GnRH agonists. First, serum levels of estrogen tend to decrease rapidly with aromatase inhibition. This leads to rapid onset of symptom alleviation, including

bulk-related symptoms [114]. Further, aromatase inhibitors do not have an initial flare-up period that is associated with hyperestrogenism, as GnRH agonists do. Additionally, aromatase inhibitors are effective, even in obese women who may fail to respond to GnRH therapy. By working to inhibit estrogen synthesis in the ovary and peripheral tissues simultaneously, aromatase inhibitors effectively decrease growth in morbidly obese women who have estrogen-dependent tumors [115]. The long-term safety of this approach needs to be addressed before widespread clinical application.

Future directions in myoma research

The next frontiers in fibroid research and treatment will pose unique challenges. Specifically, the risk and treatment of myoma recurrence after non-definitive surgical therapy present new diagnostic and interventional challenges. As diagnostic imaging continues to produce more innovative technology, the standards of care for monitoring treatment will be reinvented. Newer innovative surgical and medical therapies may have unanticipated long-term side effects on the integrity of myometrial tissue or side effects outside of the reproductive tract. As newer treatment options are enacted, the patient's overall quality of life, relief of symptoms, rate of subsequent pregnancy, and subsequent pregnancy outcomes must be investigated thoroughly. As with all genetically driven information, establishing proven links to a genetic predisposition to fibroid development may introduce ethical and social conflict.

Understanding the genetics and molecular biology of uterine leiomyomas will be the basis of new treatment options. In the United States, more than 200,000 hysterectomies are performed annually with the primary indication of symptomatic fibroids. These result in significant health costs to society and a tremendous loss of productivity for affected individuals and families. Increasingly, women are seeking minimally invasive alternatives because of their desire to maintain fertility and have shorter recovery periods; this trend will continue and grow. Current medical therapy, including GnRH agonists or progesterone antagonists, always will be limited to short-term use because of their known potential side effects that are related to steroid suppression. Therefore, the development of specific and effective medical, minimally invasive, and eventually, preventative therapies have the potential to impact the lives of many women.

Upcoming strategies will use the available map of the human genome project as a tool to guide research and treatment options. Microarray analysis will enable us to test many genes for differential expression, and formulate experimental hypotheses for testing. Targeting specific genes that are involved in the formation of fibroids will provide new therapies that are aimed at prevention and early intervention. Treatments in the future probably will target tissue-specific inhibitors that are unique to leiomyomas, with more favorable side effect profiles. The current surge in recent epidemiologic, basic, and translational clinical

fibroid research sheds exciting light on one of the most common medical conditions that affect women. These steps bring us closer to the ultimate goal of fibroid therapy for the future: prevention.

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