Uterine leiomyomas are extremely common neoplasms that by the age of 50 are found in the uterus of almost 70% of white women and more than 80% of women of African ancestry. Growth of leiomyomas is largely dependent on female gonadal steroids, especially estrogens and progesterone, and following menopause they spontaneously regress.

The majority of women who harbor leiomyomas do not experience symptoms such as infertility or abnormal uterine bleeding (AUB), leading to the conclusion that the vast majority of leiomyomas are asymptomatic. A corollary notion is that in the presence of symptoms such as AUB, infertility, pain, and pressure, identified leiomyomas may or may not contribute to the symptom complex. Therefore, faced with a patient with both symptoms and leiomyomas, it is incumbent upon the clinician to determine which if any of the leiomyomas contribute to the symptoms and which do not and are functioning as “innocent bystanders.”

In the United States it is estimated that leiomyomas account for 30% to 40% of the approximately 600,000 hysterectomies performed annually, most of which are...
accomplished by laparotomy (66%), an expensive and typically cosmetically impactful procedure that has substantial incumbent morbidity. The last two decades have witnessed the development or increased use of procedures designed to reduce morbidity associated with leiomyoma-related therapy, ranging from hysterectomy without laparotomy (vaginal and laparoscopic hysterectomy) to less invasive and uterine-sparing interventions such as laparoscopic or hysteroscopic myomectomy, to image-guided techniques like uterine artery embolization and myoma ablation with cryotherapy, radiofrequency electricity, or focused ultrasound. Finally, whereas this article is included in a publication dedicated to less-invasive therapeutic procedures, it is important for the clinician to understand not only the known factors impacting growth and development of leiomyomas, but also the potential role of medical management of these highly prevalent lesions.

LEIOMYOMA GROWTH AND DEVELOPMENT

To understand medical therapy of leiomyomas requires some understanding of the myriad genetic factors and growth and steroid hormones that potentially influence leiomyoma development and growth. Unfortunately, estrogens have been perceived by many as the key, and even only stimulators of myoma growth, largely because the volume of a leiomyoma typically decreases following menopause. On the surface, this process seems to be simply related to hypoestrogenemia, even though the endocrinologic milieu of the postmenopausal woman is typified by other changes in the circulating levels of gonadal steroid hormones including the relative absence of progesterone. This relationship is particularly interesting in the context that progesterone receptor concentrations in leiomyomas are much higher than in normal myometrium. Progesterone has been demonstrated to upregulate factors associated with leiomyoma growth including Bcl-2 protein, proliferating cell nuclear antigen and epidermal growth factor. There is evidence that progestins may result in growth of leiomyomata and that antiprogestational agents have the opposite effect. Other evidence exists for the role of progesterone in myoma growth. Gonadotropin-releasing hormone agonist (GnRH-a)–treated patients enter a temporary “medical” menopause, frequently requiring that estrogen and/or progestin add-back therapy be provided to treat vasomotor symptoms or vaginal atrophy and to protect against osteopenia. Women so treated have been subjected to randomized trials comparing progestin-only add-back to estrogen-progestin regimens. In most instances myoma growth or lack of volume reduction has been demonstrated only in association with progestin use and is not seen with estrogen-progestin therapy. Another clue to the influence of progestins on myoma growth is that antiprogestational therapy has been demonstrated to reduce myoma volume in conjunction with reductions in progesterone receptor levels despite estradiol levels remaining normal. All of these findings suggest that progestins play a significant if not dominant role in the growth of leiomyomas, and that estrogens are important, but in themselves, are unlikely to directly cause growth of leiomyomas.

Leiomyomas may be present in a number of locations in the uterus; features that have been incorporated into the design of the Federation International d’Obstetrique et Gynecologie (FIGO) classification system of causes of AUB in the reproductive years and called the PALM-COEIN system (Fig. 1). The acronym is pronounced palm-coin, with each letter uniquely representing one of the classification categories. Generally, the PALM group represents entities that are currently clearly definable by gross and/or histopathologic evaluation. On the other hand, the COEIN group includes entities that are not definable structurally or histopathologically; they may occur in a structurally normal uterus. The one exception is the Not Classified (N)
category that includes rare or ill-defined entities such as arteriovenous malformations and endometritis. The leiomyoma category is subdivided into SM or O, depending on the presence of at least one submucous myoma (Lsm) and those with myomas that do not impact the endometrial cavity (Lo). When used in information notation, the letters AUB are followed by a hyphen in front of each identified entity - eg, AUB-P, -O denotes an individual with abnormal uterine bleeding in the presence of an endometrial polyp but that is also thought to occur in the context of an ovulatory disorder. (Reproduced from Munro MG, Critchley HO, Broder MS, et al. The FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in non-gravid women in the reproductive years, including guidelines for clinical investigation. Int J Gynaecol Obstet 2011;113:3–13; with permission.)

Fig. 1. Basic FIGO classification system for causes of AUB in the reproductive years. The system includes four categories that are defined by visually objective structural criteria (PALM: polyp, adenomyosis, leiomyoma, malignancy or hyperplasia); four unrelated to structural anomalies (COE; coagulopathy, ovulatory dysfunction, endometrial, iatrogenic); and one (N) that includes entities not yet classified. The leiomyoma category (L) is subdivided into those patients who have at least one submucous myoma (Lsm) and those with myomas that do not impact the endometrial cavity (Lo). When used in information notation, the letters AUB are followed by a hyphen in front of each identified entity - eg, AUB-P, -O denotes an individual with abnormal uterine bleeding in the presence of an endometrial polyp but that is also thought to occur in the context of an ovulatory disorder.

With regard to leiomyosarcoma, misperceptions of the risk of malignancy in leiomyomas may have a profound impact on the decision-making of women contemplating the spectrum of therapeutic approaches to their clinical problem. First, it is important for both clinicians and women to understand that leiomyosarcoma likely represents a de novo neoplasm and is not a result of malignant transformation of a benign tumor. Leiomyosarcoma is extremely rare, particularly in premenopausal
women, even in the context of rapid enlargement. It is more frequently encountered in the sixth or seventh decade of life in which it has been reported to occur in 1.4% to 1.7% of women undergoing hysterectomy.\textsuperscript{13,14} For premenopausal women, understanding that a myoma is almost certainly benign should allow for the consideration of expectant medical approaches, minimally invasive procedures, or myomectomy, without undue concern for the presence of malignancy. However, for those women who are postmenopausal with a diagnosed enlarging myoma, malignancy is a distinct possibility, making medical or conservative surgical procedures inappropriate.

Fig. 2. FIGO classification system including the leiomyoma subclassification. The classification of leiomyomas categorizes the submucous (sm) group according to the Wamsteker system\textsuperscript{12} and adds categorizations for intramural, subserosal, and transmural lesions. Intracavitary lesions are attached to the endometrium by a narrow stalk and are classified as type 0, whereas types 1 and 2 require that a portion of the lesion is intramural with type 1 being 50% or less and type 2 more than 50%. Type 3 lesions are totally extracavitary but abut the endometrium. Type 4 lesions are intramural leiomyomas that are entirely within the myometrium with no extension to the endometrial surface or to the serosa. Subserosal (types 5–7) myomas include type 5, which are more than 50% intramural; type 6, which are 50% or less intramural, and type 7 being attached to the serosa by a stalk. Lesions that are transmural are categorized by their relationships to both the endometrial and serosal surfaces. The endometrial relationship is noted first whereas the serosal relationship is second (eg, type 2–5). An additional category, type 8, is reserved for myomas that do not relate to the myometrium at all and include cervical lesions, those that exist in the round or broad ligaments without direct attachment to the uterus, and other so-called parasitic lesions. (\textit{Reproduced from Munro MG, Critchley HO, Broder MS, et al. The FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in non-gravid women in the reproductive years, including guidelines for clinical investigation. Int J Gynaecol Obstet 2011;113:3–13; with permission.})
HOW DO LEIOMYOMAS CAUSE SYMPTOMS?

Abnormal Uterine Bleeding

The mechanisms involved in leiomyoma-associated AUB are only beginning to be understood. First, leiomyomas themselves are typically and strikingly solid and relatively avascular, so bleeding from the myoma itself is probably rare. On the other hand, the myoma may be surrounded by a relatively rich vasculature. When hysteroscopy demonstrates submucous leiomyomas (Lsm) in women with heavy menstrual bleeding (HMB), in most instances the tumors are covered by endometrium, whereas in others endometrium seems thin or even absent with a variable amount of perimyoma vasculature overlying the tumor.15

The search for biochemical mechanisms of leiomyoma-associated uterine bleeding has demonstrated a number of differences between myoma cells and normal myometrium. The smooth muscle cells that comprise leiomyomas release angiogenic and growth factors such as vascular endothelial growth factor, basic fibroblast growth factor, and transforming growth factor (TGF-β) as well as plasminogen activators and inhibitors.16 There is evidence from Yale University that TGF-β may have a direct impact on factors that impair local endometrial hemostasis.17 It seems that when leiomyomas are adjacent to endometrium, elevated levels of TGF-β compete at the level of the endometrial stromal cell membrane for the receptor to a substance called bone morphogenetic protein-2 (BMP-2), which is normally responsible for the production in the nucleus of factors such as plasminogen activator inhibitor, antithrombin III, and thrombomodulin. The impact of reduced BMP-2 activity is a reduction in these substances and a corresponding impairment of local hemostatic processes in the endometrium.

Leiomyoma matrix metalloproteinase (MMP) 2 and 11 activity have been demonstrated to be increased, but MMP 1 and 3 remain unchanged. Unfortunately, the relationship of these findings to myoma-related AUB remains unclear.18,19

Still, the overwhelming clinical impression is that those myomas that cause bleeding are submucous in location and that the site of bleeding is usually the adjacent and/or overlying endometrium or, less commonly, the blood vessels that surround the tumor. This observation makes careful evaluation of the endometrial cavity important in determining the cause of AUB. Clinically obvious myomas, such as those detected by manual palpation, may have nothing to do with the bleeding, whereas submucous tumors not detectable on manual examination may be the responsible pathologic entity. Among the myriad questions facing investigators and clinicians is the role of FIGO type 3 lesions in the genesis of AUB.

Infertility and Recurrent Pregnancy Loss

Leiomyomas can be implicated in the genesis of infertility and early pregnancy loss, but not all myomas have this deleterious manifestation. A 2009 systematic review reported on the effects of leiomyomas on fertility and the performance of myomectomy on fertility and early pregnancy outcomes.20 Of 347 studies initially evaluated, 23 were included in the data analysis but only four provided data that allowed evaluation of the impact of submucous fibroids (types 0–2) on fertility. The investigators concluded that women with submucous fibroids, compared with infertile women without such fibroids, demonstrated a significantly lower clinical pregnancy rate (four studies), implantation rate (two studies), and ongoing pregnancy/live birth rate (two studies).20

Further evidence regarding the impact of submucous myomas on fertility can be found in studies evaluating the fertility-related results of resectoscopic myomectomy.
It seems clear from high-quality trials that pregnancy rates are higher after myomectomy when compared with women undergoing no or placebo procedures.\textsuperscript{20,21}

The mechanisms whereby submucous leiomyomas impact fertility are at the present time unclear. However, the Yale group has also produced high-quality evidence that such lesions may impart a global molecular impact that results in inhibition of the receptivity of the endometrium to implantation as determined by the presence of transcription factors such as HOXA-10 and -11. There seems to be a “field effect” that includes TGF-β-mediated reduction in the levels of endometrial HOXA-10 and -11 expression, both over the myoma, and remotely in the endometrium overlying apparently normal myometrium. Based on available evidence, this change is not seen in the endometrium of women with intramural or subserosal myomas.\textsuperscript{17,22}

Whereas study of the impact of submucous leiomyomas on early pregnancy performance is difficult because of the multiplicity of factors potentially impacting early pregnancy loss, it seems likely that such lesions are associated with an increased risk of early pregnancy failure. In the metaanalysis of Pritts et al.,\textsuperscript{20} there were significantly higher spontaneous abortion rates in women with submucous leiomyomas (two studies, relative risk 1.68, 95% confidence interval 1.37–2.05, \textit{P} = .022), a difference that seemed to be addressed by resectoscopic myomectomy.

The mechanisms by which submucous fibroids impair pregnancy outcomes remain unknown. Some investigators have reported that histologic examination of the endometrium overlying myomas\textsuperscript{23,24} and opposite the fibroid\textsuperscript{24} show glandular atrophy. Such a finding may be a histologically related manifestation of the biochemical impact of the submucous leiomyoma described by Rackow et al.\textsuperscript{22} reflecting a mechanism whereby implantation and nourishment of the developing embryo is impaired.

The Pritts et al.\textsuperscript{20} metaanalysis suggested that intramural myomas may have a role in the genesis of infertility or in in vitro fertilization success, but currently available evidence did not support the performance of myomectomy to improve fertility outcomes.\textsuperscript{20} To date, studies have not been categorized by FIGO myoma type, leaving the possibility that there is a difference between outcomes and interventions associated with type 3 lesions and those that do not abut the endometrium (type 4 and greater).

\textbf{Other Symptoms}

If leiomyomas grow to the point of distorting surrounding structures they may cause a number of other symptoms that include pressure, urinary incontinence, and, less commonly, impact on bowel function.\textsuperscript{25} Pain is another symptom frequently attributed to leiomyomas, and, for various reasons, sexual function may be adversely impacted. All of these symptoms can, and usually are caused by a plethora of other issues, a circumstance, given the prevalence of leiomyomas, that creates an opportunity for misdiagnosis of cause and effect. However, it is apparent that when leiomyomas achieve a threshold volume, bulk-related symptoms can substantially impact the quality of life for the woman. Unfortunately, there are few data evaluating the prevalence of these symptoms.

For years the author has told residents that when pain and leiomyomas coexist, pain is likely from another source, which some have called Munro’s Rule. However, this rule was unencumbered by any evidence beyond the clinical experience of its author, and some studies seemed to suggest that leiomyomas and pain were related. However, such studies were hampered by an incomplete evaluation for other causes of pelvic pain, by evaluation based on ultrasound alone, and apparently not
adequately considering other gynecologic and nongynecologic causes of pelvic pain. Fortunately, attention is being paid in the literature to the putative relationship between leiomyomas and pain by analyzing for comorbid conditions. A retrospective case control study of women undergoing hysterectomy for leiomyomas demonstrated that those with concomitant adenomyosis were more than three times more likely to have pelvic pain including dysmenorrhea, dyspareunia, and noncyclic pain. Another retrospective study demonstrated that of 131 patients who underwent laparoscopic myomectomy or hysterectomy, 113 had concomitant endometriosis, and those women who had both endometriosis and leiomyomas were more likely to have pain than those with leiomyomas alone. These data suggest that Munro’s Rule may have some legs and that when faced with a patient with leiomyomas and chronic pelvic pain, the clinician should be wary of ascribing the cause of the symptoms to the leiomyomas.

**DIAGNOSING AND CHARACTERIZING LEIOMYOMAS**

Because uterine leiomyomas are highly prevalent and frequently asymptomatic, it is important to both obtain a detailed and structured history and undertake a careful evaluation of the uterus before concluding that leiomyomas are contributing to the clinical problem. Just because there are symptoms and leiomyomas, the two are not necessarily related in a cause-effect fashion.

The diagnosis of leiomyomas is generally accomplished with one or a combination of hysteroscopy and radiologic techniques that may include transvaginal sonography (TVS), saline infusion sonography (SIS), and magnetic resonance imaging (MRI). The goal is to identify and characterize the lesions, distinguish leiomyomas from adenomyomas, and identify those that are submucous in location. Lesions should be characterized as to the extent of myometrial penetration and the relationship to the uterine serosa because transcervical resection is not considered appropriate when the leiomyoma is close to or in contact with the serosal layer.

*Leiomyomas Impacting the Endometrial Cavity*

Given the notion that only submucous leiomyomas contribute to infertility, early pregnancy loss, and heavy uterine bleeding (AUB-Lsm), accurate determination of the relationship of myomas to the endometrial cavity is essential for patient counseling and treatment planning. Blind instrumentation has been demonstrated to be inadequate for precise depiction of the structure of the endometrial cavity when compared with any of a number of imaging techniques, including those that are ultrasound-based, and direct inspection with hysteroscopy.

There is a role for transvaginal ultrasound as a screening tool. In nonpregnant women with AUB, TVS showing an absence of myomas adjacent to or deflecting the endometrial echocomplex (EEC) is usually associated with a hysteroscopic examination negative for submucous leiomyomas. However, there is high-quality evidence from a Cochrane systematic review that demonstrates TVS to be still inferior to either SIS or hysteroscopy for the distinguishing intramural from submucous leiomyomas. SIS is also known as sonohysterography or contrast sonography and is performed using vaginal ultrasound in conjunction with the transcervical instillation of a sonolucent substance such as saline, an approach that is comparable to hysteroscopy in its sensitivity for the diagnosis of intracavitary polyps and submucous myomas. Consequently, when ultrasound demonstrates myomas that exist suspiciously close to the EEC or when the EEC is deflected or difficult to evaluate, additional evaluation with saline infusion sonography or hysteroscopy should be considered.
Hysteroscopy is generally considered to be the gold standard of evaluation of the endometrial cavity for the presence of type 0 to 2 leiomyomas as well as other characteristics such as diameter and location (anterior, posterior, fundal, cornual, and so forth). Diagnostic hysteroscopy can usually be performed in an office environment, but unfortunately, at least in North America, relatively few clinicians seem comfortable with this approach, with most performing the procedure in a ambulatory surgery center or traditional operating room. A patient with a tortuous or stenotic cervix may be difficult to examine with office hysteroscopy, but most examinations can be performed successfully and comfortably with adequate and sufficient local anesthesia.\(^{35}\)

MRI is another modality that has been shown to be accurate in the evaluation of the endometrial cavity in women with AUB. It is apparent that MRI is superior to either ultrasound or hysteroscopy at characterizing the relationship with the myometrium, including the serosa.\(^{36}\) MRI has particular value in selected patients when neither SIS nor hysteroscopy are feasible because of virginal status or for women who have other issues with passing a device through the vagina.

**Leiomyomas and the Myometrium**

The myometrium is assessed to determine the extent of submucous myoma (type 0–2) involvement, to characterize types 3 to 6 leiomyomas, and to distinguish between leiomyomas and adenomyomas. Two-dimensional (2-D) TVS is generally useful for the evaluation of myomas in the myometrium, although variations in echogenicity can in some instances reduce the sensitivity of the examination. In addition, such 2-D imaging can be challenging when the mass comprising myoma and myometrium is large, because it is difficult to adequately image and track the various lesions identified. In such instances, three-dimensional (3-D) sonography may provide additional value.

Adenomyosis is a disorder characterized by endometrium or endometrial-like tissue within the myometrium. Although typically diffuse in nature, in some instances the disorder may be focal with lesions that have sonographic characteristics superficially similar to leiomyomas. In appropriately trained hands and with contemporary equipment, TVS is quite sensitive for the diagnosis of diffuse adenomyosis, and it approaches MRI in sensitivity.\(^{37}\) However, there is less evidence evaluating the ability of TVS to distinguish focal adenomyosis (an adenomyoma) from leiomyomas, where MRI may be superior.\(^{37}\) Color flow Doppler ultrasound helps to distinguish focal adenomyosis from leiomyomas because myometrial vessels course around the lesion, whereas in adenomyosis the vessels pass through the lesion retaining their vertical orientation to the endometrial cavity.\(^{38}\)

MRI has been demonstrated sensitive in the evaluation of the myometrium for leiomyomas and is also effective at distinguishing them from adenomyomas.\(^{39}\) MRI also seems superior to TVS, SIS, and hysteroscopy for measuring the myometrial extent of submucous leiomyomas.\(^{36}\)

**EXPECTANT MANAGEMENT OF LEIOMYOMAS**

The process of watchful waiting is an option for most women with leiomyomas; however, counseling is difficult, in part because of variability in the natural course of any group or collection of tumors. The Fibroid Growth Study followed 262 leiomyomas in 72 women using sequential MRI scans over a period of 12 months. The median growth rate was 9%, but serially measured volume varied from an 89% reduction to a 138% increase.\(^{40}\) Tumors in the same women grew at different rates, and whereas growth rates in black women and white women were similar under the age of 35, for
women 35 and older the growth rate was much lower in white women. The growth rates for SM myomas were similar to those in other locations in the uterus. This information may be of value, for example, for the woman in the late reproductive years who has acceptable control of symptoms. She may choose to wait for menopause rather than undergo surgical therapy for her SM leiomyomas. Expectant management is more difficult for young women with, for example, intramural myomas (type 3 or 4), who are not currently in a position to try to conceive but who realize that their lesions may create symptoms and/or incrementally greater uterine damage with the passage of time.

**MEDICAL MANAGEMENT OF LEIOMYOMAS**

The use of medical therapy has expanded due to new information about the factors that affect myoma growth, the availability of new therapeutic agents, and a more reasoned understanding of the relationship of leiomyomas to symptoms. However, it is unlikely that these agents will have much of a role for women with infertility and AUB-Lsm because reduction (not elimination) of the structural distortion of the cavity is unlikely to result in improved fertility or pregnancy performance.

**Gonadotropin-Releasing Hormone Agonists**

The administration of gonadotropin-releasing hormone agonists (GnRH-a) results in amenorrhea secondary to the creation of a hypoestrogenic and hypoprogestogenic state. For women with leiomyoma-related symptoms, these agents may be used strategically in a number of ways that range from short-term courses in preparation for surgery to longer term use that may even preempt the need for operative intervention. GnRH-a administration results in a reduction of both leiomyoma and total uterine volume by a mean of about 50% by 12 weeks. This outcome is temporary, however, because the volume of both the uterus and myoma return to baseline levels within a few months following the cessation of therapy. Although the use of GnRH-a is associated with the side effects of hypoestrogenemia, including vasomotor symptoms and vaginal atrophy, the only concerning adverse outcome is osteopenia if therapy is prolonged for more than 6 months. This reduction in bone density can be mitigated with the use of so-called add-back therapy with an estrogen, selected types of progestins, or estrogen-progestin combination therapy.

Short-term use (2–3 months) of GnRH-a, in conjunction with iron supplementation, provides an opportunity for the woman with AUB and associated anemia to reconstitute her circulating hemoglobin levels without resorting to either blood transfusion or emergency surgery. By ameliorating fatigue, the woman has the opportunity to select long-term medical or surgical therapy in a less stressed environment. For women who have decided on an operative intervention, GnRH-a–induced amenorrhea is a way to defer surgery to a more convenient time.

There may be a lasting impact of GnRH-a therapy on women with AUB and leiomyomas. A study on women who had completed 6 months of GnRH-a, randomized to either placebo or medroxyprogesterone acetate, found that a majority (about 55%) of each group experienced an improvement in their bleeding for months following discontinuation of agonist. This evidence suggests that GnRH-a may have prolonged therapeutic benefit in such women, making the use of intermittent courses a potential nonsurgical strategy for women in the late reproductive years. Unfortunately, the studies were not designed to truly determine the causes of the bleeding in that there was no attempt to identify the location of the leiomyomas. Consequently, many of these women without submucous lesions may have had, for example, AUB-O
(ovulatory disorder) because it is suspected that type 3 to 8 lesions do not cause abnormal bleeding.

Using GnRH-a to reduce uterine volume may facilitate the performance of minimally invasive hysterectomy in selected patients. Stovall and colleagues found that 80% of women scheduled for hysterectomy with uteri greater than 14 weeks in estimated volume at baseline were able to undergo vaginal hysterectomy if GnRH-a was administered for the 3 months immediately prior to surgery. Such an approach may also have merit in facilitating laparoscopic hysterectomy and even laparoscopic supracervical hysterectomy, the latter by reducing the time for laparoscopically-directed morcellation, although there have been no clinical trials evaluating this hypothesis. There also exist data that show reduced blood loss associated with abdominal myomectomy; however, the absence of a difference in the incidence of blood transfusions makes the use of GnRH-a in this setting of questionable value.

The evidence is mixed evaluating the preoperative use of GnRH-a for reduction of the duration and risks of resectoscopic removal of submucous leiomyomas. Early studies suggested that systemic intravasation of the uterine distention media was less, surgical time was reduced, and the procedures were easier to perform. However, in a nonrandomized but controlled trial comparing resectoscopic myomectomy with and without preoperative treatment for 2 months with GnRH-a, the operating time was significantly longer in the GnRH-a group: 57.6 min versus 40 minutes. This outcome was suggested by the investigators to be secondary to GnRH-a–related contracted uterus and cervical stenosis. In two recently published RCTs, operating time was either unchanged or significantly reduced in the GnRH-a–treated population. Notably, systemic absorption of distention media was significantly reduced in the study that reported reduced operating times. Review of these articles demonstrates that there were substantial differences in study design: one randomized women with type 1 and 2 myomas, whereas the other excluded type 2 lesions, limiting the study population to patients with only types 0 and 1 leiomyomas. Neither study showed a reduction in the incidence of incomplete excision or the need for further procedures, although one of the trials may have been inadequately powered to make such a conclusion.

Surgery may be unsuitable for some women for a number of reasons such as existing comorbidity or because there have been multiple previous pelvic surgical procedures, which substantially elevate the risk of surgery. Some women may simply prefer medical therapy. In such instances, long-term GnRH-a may be attractive, particularly for those who are near the time of menopause. In such instances decisions should be made regarding the use of add-back therapy with estrogen or estrogen-progestin compounds.

**Progestins**

There is no currently available evidence regarding the use of systemic progestins for women with AUB-Lo (AUB in the presence of leiomyomas that do not distort the endometrial cavity), but there is evidence that the levonorgestrel releasing intrauterine system LNG-IUS may be effective in selected patients. A prospective but nonrandomized clinical trial included women with AUB-Lo with a sonographically-determined uterine volume less than 380 mL but at least one type II submucous leiomyoma 5 cm or less and no type 0 or type 1 lesions greater than 3 cm. The reduction in menstrual blood loss at 3, 6, and 12 months postinsertion reached 90%, comparable with that of a group of women treated in the same center using a thermal balloon, and expulsion rates were about 5%.
Another group evaluated the impact of the LNG-IUS on women with leiomyomas without determining the relationship of those myomas to the endometrial cavity. The study showed high efficacy but, given the absence of endometrial cavity evaluation, it is likely that the study included many with abnormal uterine bleeding secondary to endometrial causes.56

Further study is required, but it would seem that LNG-IUS is a reasonable option for women with modestly enlarged uteri and at least selected type 2 leiomyomas. However, for very enlarged cavities, the clinical impression remains that therapeutic efficacy is less and spontaneous expulsion more common.

**Antiprogestins**

The important if not critical role of progesterone in the growth and development of leiomyomas has been described in this article.57–59 The selective progesterone receptor modulator (SPRM) mifepristone, 5 mg per day, has been shown to dramatically reduce or even eliminate the symptom of AUB while reducing the volume of leiomyomas by about 50%, with few side effects.10,60,61 In earlier studies using higher doses of mifepristone, endometrial hyperplasia was occasionally seen, but this adverse outcome seems uncommon, if not rare, at the 5 mg dose. Larger scale clinical trials will be necessary to further elucidate the cost-effectiveness of this approach. It is anticipated that within the next few years there will be additional SPRMs that have similar impact on leiomyomas and bleeding symptoms.

**Aromatase Inhibitors**

Aromatase inhibitors inhibit the physiological conversion of androgens to estrogens in the ovary and in peripheral tissues and thereby have the potential to impact leiomyoma growth. Indeed, there exists high-quality evidence showing that aromatase inhibitors reduce myoma volume by a mean of about 50%.62,63 A RCT from Iran showed that the aromatase inhibitor letrozole was superior to GnRH-a in reducing myoma volume without vasomotor symptoms.64 That these agents have undergone large-scale long-term clinical trials as adjuvant therapy for women diagnosed with breast cancer makes them interesting options for selected patients. Larger scale trials of these agents and their utility in the treatment of abnormal uterine bleeding associated with leiomyomas (AUB-L) and bulk symptoms are anticipated.

**PROCEDURAL AND SURGICAL INTERVENTIONS**

**Myomectomy**

In 1845, Atlee65 first reported removal of leiomyomas via laparotomy, traditionally called abdominal myomectomy. The principles of contemporary abdominal myomectomy were established by Bonney,56 with his publication of 20 years of experience and amplified by his 1946 report of 806 cases. The low morbidity and mortality were remarkable, with only 2 deaths in the last 400 cases (overall mortality of 1.1%).

Like many surgical procedures that were introduced in the 19th and 20th centuries, abdominal myomectomy had not been subjected to rigorous clinical evaluation comparing it with expectant, medical, and other surgical approaches to the various manifestations of uterine leiomyomata. Fortunately there remains controversy regarding its value; there are gradually accumulating data regarding the utility of myomectomy, especially for the treatment of infertility.

In the latter part of the 20th century, the advent of operative endoscopy changed the spectrum of surgical options for the woman with symptomatic leiomyomas. The introduction of hysteroscopically-directed management of submucous myomas
offered an option with dramatically reduced surgical morbidity.\textsuperscript{67} Laparoscopic myomectomy also offered an approach with potentially lower surgical morbidity than the laparotomic approach.\textsuperscript{68,69}

With the increased ability to perform myomectomy with minimally invasive approaches comes another question: When should myomectomy be offered or performed? Indications for myomectomy by any approach are currently being reevaluated as cost containment incentives, medical therapy, consumer pressure, and academic introspection combine to reinforce the long known fact that most myomas are asymptomatic and do not require treatment. Even in the face of symptoms, as previously discussed, it is prudent not to assume that patient complaints are caused by the myoma felt on examination or imaged on ultrasound.

\textbf{Preoperative preparation and evaluation}

Preparation for myomectomy is undertaken in view of the need of the patient to understand the procedure, considering the expectant, medical, and other surgical options. The patient should have a clear understanding of potential complications as well as the expected and possible degree of postoperative disability. The potential for unanticipated hysterectomy should be reviewed. All of this information should be documented in the clinical notes and the informed consent document.

Most would find it prudent to preoperatively confirm tubal patency (if the procedure is designed to preserve or improve fertility) and to obtain as much information as possible regarding the location and extent of the myomas using one or a combination of hysterosalpingogram, SIS, hysteroscopy, and MRI. Such information may help in the selection of incision sites and perhaps in determining the route of access. If there is clinical suspicion that the masses in the uterus represent adenomyosis, MRI imaging may be appropriate because in such instances, conservative surgery is unlikely to improve reproductive performance. Ancillary investigations should be performed as appropriate; however, a hemoglobin or hematocrit is essential. In addition, because of the potential for blood loss, the patient should be provided the opportunity for collection and storage of autologous blood, provided her hemoglobin levels and the time available before surgery permit.

The preoperative use of suppressive medical therapy with GnRH-a, as discussed previously, may be particularly important for those women who have AUB and associated anemia because creation of amenorrhea can be expected to facilitate the restoration of hemoglobin levels, provided sufficient amounts of iron are administered over an adequate amount of time.\textsuperscript{45}

There is controversy regarding the impact of prelaparotomic myomectomy GnRH-a use on the ability of the surgeon to detect small myomas intraoperatively and on the subsequent risk of recurrence. One RCT suggested that surgeons were more likely to miss myomas when the patient was treated with GnRH-a, whereas another showed no such relationship.\textsuperscript{70,71} A Cochrane systematic review of RCTs concluded that, in addition to improving both pre- and postoperative hemoglobin levels, preoperative GnRH-a also reduced both operating time and the rate of vertical skin incisions.\textsuperscript{72}

\textbf{Procedures}

\textbf{Resectoscopic (hysteroscopic) myomectomy}. Resection and vaporization are resectoscopic techniques used to remove leiomyomata, with limitations related to the size, number, and location of the tumors, especially in the cornual region, and to the proportion of the tumor that is in the myometrium. In addition, the goals of the patient with respect to fertility are important, because optimal retention or enhancement of fertility may require complete excision of the myoma with maximum preservation of
endometrial and myometrial integrity. Resectoscopic myomectomy is more likely to result in improved bleeding symptoms (> 90%) than successful treatment of infertility (53%–70%).73–75

Preoperative imaging is important, not only to select appropriate patients for resectoscopic surgery, but also to plan the technical approach itself. Lesions that are totally within the endometrial cavity (type 0 and superficial type 1) and that are appropriately sized (generally ≤ 5 cm diameter) can generally be vaporized and/or excised with relative ease. However, for those lesions that penetrate into the myometrium to a substantial degree (deep type 1 and type 2 tumors), careful planning and substantial skill with the resectoscope are important requisites. The margin between the uterine serosa and the deepest extent of the myomas should be measured,76 and if it is less than 5 to 8 mm, the author suggests that intraoperative ultrasound and/or laparoscopy may be necessary to prevent injury to extrauterine structures such as bowel.

In most instances resectoscopic myomectomy is performed in a standard operating room under appropriate anesthesia. The patient is positioned in the dorsal lithotomy position, the cervix dilated, and the resectoscope positioned with a suitable electrode and attached to an electrosurgical generator. The author typically uses a combination of dissection, vaporization, and removal of the residual leiomyoma with a Corson forceps. Resection of deep submucous myomas is more often associated with systemic absorption of substantial amounts of distending fluid, a feature that should be made clear to patients, because in such instances the procedure may have to be aborted and completed at a later time.74,77

Laparotomic myomectomy. Laparotomic myomectomy may be performed if there are many leiomyomas, if they are very large, or if they involve adjacent structures in a way not suitable for the safe conduct of laparoscopic technique. At laparotomy, there exist a number of approaches that may reduce blood loss, including preoperative GnRH-a, mechanical vascular tourniquets, myometrial injection of vasoactive substances, and careful dissection technique. Vascular tourniquets are applied after creating windows in the broad ligaments that allow straps (usually urethral catheters or Penrose drains) to be placed around the uterine isthmus, occluding the blood supply from the uterine arteries. The vessels in the infundibulopelvic ligaments can be occluded bilaterally with vascular clamps, thereby obstructing the blood supply from the ovarian arteries, but in practice the author rarely takes this step.78,79 The vasoactive substance of choice is dilute vasopressin, 20 units in 60 to 100 cc of normal saline, injected around the myomas, taking care to avoid intravascular infusion.80

Avoidance of posterior incisions may be important because they have been associated with a greater incidence of postoperative adhesions,81 and it is prudent to apply microsurgical techniques including meticulous hemostasis, careful tissue handling, and the use of fine caliber suture on peritoneal surfaces. There is some information supporting the use of adhesion barriers over myomectomy incisions.82,83 Unfortunately, no data exist evaluating the impact of adhesion barriers on fertility.

Morbidity at laparotomic myomectomy was recently reviewed in 128 patients operated on by 46 surgeons with varying amounts of training; a likely measure of procedure effectiveness, because it reports results from surgery performed by a spectrum of surgeons.84 The average uterine size was consistent with 14 weeks gestation, and the average estimated blood loss was 342 cc. Five had blood loss in excess of 1 L, the transfusion rate was 20%, and 1 patient required intraoperative hysterectomy. Postoperative complications included wound infection (1), deep venous thrombosis (1), and postoperative fever.
Laparoscopic myomectomy. Laparoscopically-directed myomectomy is in some ways controversial, but it has been demonstrated to be effective in a number of observational studies, and with selected patients and expert surgeons was associated with shorter hospitalization, faster recovery, fewer adhesions, and reduced blood loss. However, the spectrum of myoma size and location, the difficulty with morcellation and removal, and the technical requirements for manipulation of needles and suture with which to close the uterine incisions make the procedure difficult to perform. Nevertheless, retrospective comparative studies and available RCTs suggest that in selected patients, fertility outcome is about 50% to 60% with both the laparoscopic and laparotomic approaches. Another outcome important to women undergoing myomectomy is pregnancy outcome. Currently available evidence suggests that patients selected for laparoscopic myomectomy and operated on by skilled surgeons will have similar pregnancy outcomes compared with those who have laparotomic myomectomy.

A review of the advantages, limitations, and concerns regarding laparoscopic myomectomy may be useful. The principal potential advantage compared with the laparotomic approach is the reduction of both direct and indirect costs. The small abdominal incisions generally reduce the need for analgesia, allow nearly immediate mobilization and alimentation, and facilitate earlier hospital discharge, frequently on the same day of surgery. In addition, the lack of a significant abdominal incision allows a faster return to economic productivity, thereby reducing the indirect cost of care.

Theoretically, the reduced need for packs and manual retraction would minimize tissue trauma and subsequent adhesions. On the other hand, multiple myomas cannot usually be removed through the same incision, and the surgeon loses the ability to palpate uterine tissue to detect smaller myomas. It is also more difficult to apply laparoscopic technique to myomas in problem areas such as those adjacent to the uterine arteries or the cornua, thereby preserving tubal patency. As is the case with any laparoscopic procedure, there are geometric limitations posed by the location of the instrument ports. In some instances it may be more difficult to reapproximate myometrial and serosal tissue, a feature that may enhance the development of adhesions and which may increase the risk of uterine rupture should pregnancy occur. Morcellation of the excised tumors is now facilitated by the development of efficient endomechanical morcellators. All of these factors conspire to increase operating time, frequently offsetting the reduction in postoperative direct costs intrinsically associated with laparoscopic surgery.

Minilaparotomy (with or without laparoscopic assistance). Frequently, laparoscopically-directed technique is not feasible or appropriate for a component of the procedure such as dissection near the cornua. In such instances, a relatively small suprapubic incision can be enlarged sufficiently to complete that portion of the dissection or other component of the procedure, often with externalization of the myoma and/or uterus. This approach can also be used primarily without laparoscopic assistance.

From a short-term perspective, myomectomy by minilaparotomy or laparoscopic myomectomy with minilaparotomy have similar short-term outcomes including time to discharge, postoperative pain, and return to normal activity, when each is compared with the standard laparotomic approach. Consequently, for clinicians who are not experienced or skilled with laparoscopic myomectomy, minilaparotomy-based approaches may provide patients with many of the benefits of minimal access surgery.
**Vaginal myomectomy.** There are a number of instances in which removal of a leiomyoma can be performed vaginally. The most obvious situation is when a submucous myoma prolapses through the cervical canal so that it can be removed simply by transecting or avulsing the stalk. This removal is typically accomplished by grasping the myoma with a tenaculum or ring forceps and twisting it until the lesion becomes detached. Clinically significant bleeding rarely occurs. In many instances the procedure can be performed in the office or procedure room with no or local anesthesia or in some instances with systemically administered anxiolysis or anesthesia. There may be value to performing postprocedure transvaginal ultrasound or hysteroscopy to evaluate for the presence of additional lesions in the endometrial cavity.

For submucous leiomyomas that have not prolapsed through the cervical canal, vaginal myomectomy has also been described following dilation of the cervix with laminaria, which are natural (elm) or synthetic rods that osmotically absorb existing fluid and slowly dilate the canal. Small myomas can be removed intact, whereas morcellation can be used to facilitate the removal of larger lesions.

Another approach is vaginal hysterotomy, a technique that the author uses, in which incisions are made in the cervix to facilitate removal, a procedure that is hidden in a report published by Goldrath more than 20 years ago. This approach can be used for leiomyomas that are present in the lower uterine segment and extend to the cervical canal, a location that is extremely challenging to access resectoscopically. To facilitate the procedure, the urinary bladder is dissected from the cervix in a fashion similar to that used for vaginal hysterectomy. Then, anterior and/or posterior longitudinal incisions are made in the cervix and extended as high as necessary to allow access to the myoma and dissection from the uterus. The incisions are closed with full-thickness continuous delayed absorbable suture. The author usually performs a second-look hysteroscopic procedure 3 to 4 weeks later to dissect free adhesions that may occlude the canal. Although successful for bleeding, the impact of this approach on fertility has not been evaluated, so patients must be cautioned in this regard.

**Uterine Artery Embolization or Occlusion**

Uterine artery embolization (UAE) is the use of interventional radiographic technique to occlude both uterine arteries with polyvinyl alcohol microspheres positioned by a catheter passed through the right femoral artery. The procedure is generally performed under conscious sedation over a time that typically ranges from 30 to 90 minutes. Immediate postprocedure pain is generally substantial, requiring institutional admission at least overnight, typically with a requirement for narcotic analgesia. In some instances this pain is experienced in conjunction with fever, nausea, and vomiting—a constellation of symptoms that has been termed postembolization syndrome. Complications are relatively infrequent but include, in addition to postembolization syndrome, misembolization of tissues that include the ovary, ureter, and other structures; infection that has been associated with severe sepsis; and, rarely, death. Randomized trials with short-term outcomes do demonstrate that UAE likely has lower morbidity than hysterectomy, but patients should expect the side effects mentioned earlier and a readmission rate of 5% to 10%.

There is evidence that UAE is an effective long-term solution for most women who select it. In a relatively large study of 200 patients, HMB was substantially reduced in 87% of patients at 3 months and 90% at 12 months of follow-up. In this same group of patients, the total uterine volume reduced by 27% and 38% at 3 and 12 months, respectively. By 5 years, 73% had continued symptom control with 13.7%...
and 4.4% undergoing hysterectomy and myomectomy respectively. Another US registry that includes more than 2100 women has reported high degrees of satisfaction with the procedure and 3-year postprocedure hysterectomy and myomectomy rates of 9.8% and 2.8%, respectively. Perhaps the most extensive review of UAE has been published in 2004 by the Royal College of Obstetricians and Gynaecologists in the United Kingdom. In this analysis, 32 articles representing 25 series of cases reported mean uterine volume and dominant fibroid volume reduced 26% to 50% and 40% to 75%, respectively, at 6 months following the procedure and marked improvement in bleeding experienced by 60% to 90% of those treated. Finally, the Cochrane review of the three RCTs concluded that UAE offers an option to hysterectomy and, in some instances, myomectomy; UAE is associated with reduced institutional stay and faster return to normal activities; and overall satisfaction was equal to that of hysterectomy. However, unscheduled visits related to pain, fever, and discharge were more common.

The issue of fertility following UAE is still under investigation. It is clear that conception and successful term delivery can occur following UAE, but what is not clear is the incidence of infertility and of myoma-related pregnancy complications. The literature is mixed regarding the impact of UAE on fertility and subsequent pregnancy; it is possible that the impact is minimal in this population that already has an increased incidence of infertility. However, there may be unknown or unexpected adverse events such as the excess of intraperitoneal adhesions associated with UAE, described in a case control study from McGill University.

In summary, bilateral UAE seems to offer an option to women with AUB-L that may provide long-term resolution of symptoms without the need for traditional surgical interventions. The role of this procedure in women who wish to conceive is unclear and requires further study. Clearly, myomectomy is the more traditional approach and for those with intracavitary lesions is the most appropriate procedure especially for those with infertility or wish to preserve fertility.

Localized uterine artery occlusion (UAO) using laparoscopically-directed techniques has also been described. The uterine vessels are occluded with electrodesiccation or clips without the need for embolization. A number of series have been published with results similar to those available for UAE. Two prospective comparative trials have demonstrated that clinical results may be similar and that patients undergoing UAE seem to experience much less pain than patients who are treated with embolization. In a double-blind RCT from the author’s institution, procedure-related outcomes of localized UAO using coils deposited in the uterine arteries by a fluoroscopically-guided catheter were superior to traditional UAE with microspheres. The UAO patients had little procedure-related pain and could be discharged home the same day. Longer term studies are needed, however, to evaluate the comparative clinical outcomes of the two techniques.

**Hysterectomy**

As noted in the introduction, of the approximately 600,000 hysterectomies performed each year in the United States, a large proportion are performed for leiomyomas of the uterus. The technical aspects of hysterectomy are discussed elsewhere in this issue.

It is clear that if total hysterectomy is to be performed and if it can be accomplished vaginally, vaginal hysterectomy is the preferred route from the perspective of cost, morbidity, and cosmetic result. The problem arises when vaginal hysterectomy is not feasible or is beyond the skill set of the operating surgeon. In such circumstances and with the advent of electromechanical laparoscopic morcellators and vaginal...
morcellating techniques, laparoscopic total and supracervical hysterectomy may be the only practical alternative to total abdominal hysterectomy for management of uteri with very large leiomyoma volume. Appropriate selection of patients excludes those without known or suspected preinvasive or invasive cervical and endometrial neoplasia.

**Investigative Surgical Approaches**

**Leiomyoma ablation or myolysis**

Techniques designed to destroy rather than remove leiomyomas have been termed myolysis or myoma ablation. Several such techniques are under development using liquid nitrogen for hypothermic ablation, laser or radiofrequency electricity, and, more recently, focused ultrasound energy, directed and monitored by ultrasound or MRI for hyperthermic ablation. These approaches have shown some promise, but well-designed clinical trials are necessary not only to determine their efficacy but, even if efficacious, to compare them with other techniques for clinically relevant outcomes.

**Hypothermic leiomyoma ablation.** The first publication of hypothermic treatment of leiomyomas was from the Yale group in New Haven, Connecticut, in 1996. The technique, sometimes called cryomyolysis, uses probes cooled either by liquid nitrogen or by differential gas exchange, as described by Joule-Thompson. The probe is passed into a leiomyoma and then activated, resulting in a reduction of local temperature to less than −90°C, creating an ice ball, the size and shape reflecting features of the probe and the duration of application. Lethal tissue damage occurs at −20°C, but at the edge of the ice ball the tissue temperature is approximately 0°C and consequently is not destructive to the tissue. A potential advantage of this technique over hyperthermic approaches is the ability to predict the limits of treated tissue by simultaneously imaging the ice ball with ultrasound.

The extent of tissue necrosis may be secondary to the degree of vascular damage. When tissue cools, the damaged vascular endothelium detaches from the internal surface of the vessel, a process that contributes to the development of edema and local activation of platelets. The resulting thrombosis then occludes the local circulation, thereby enhancing both local ischemia and tissue necrosis. The result is a graded response as histopathologic examination shows complete necrosis in the central aspects of the target area and tissue sparing in the periphery of the previously frozen tissue. The relative uniformity of cell death in the zones that reach −20°C or lower suggests that the principal clinical impact of cryomyolysis is one that is secondary to the vascular impact on tissue. There is also evidence that leiomyomata may be more sensitive to freezing than normal myometrial tissue, whereas the effects of laser or radiofrequency electrical energy are similar in myoma and adjacent healthy myometrium. If this evidence is accurate, hypothermic ablation techniques may have a degree of tissue specificity and could aid the clinician in preserving neighboring myometrium.

In its present but experimental form, the technique is performed laparoscopically, usually under general anesthesia, with the telescope inserted through the umbilicus, or higher in the event of a large uterus. After exposure of the cervix with a speculum or retractors, a uterine manipulator is positioned and used to stabilize and manipulate the uterus, thereby optimally positioning the myomas for insertion of the probe (cryoprobe). The surgeon also positions additional ports, as required, for the instrument access necessary to perform the procedure. The location and number are determined at the time of the procedure based on the size and location of the myomas to be treated. An incision in the uterus, over the leiomyoma, is made with a monopolar...
electrosurgical hook or blade to create a passageway that is 4 to 5 mm wide and about 1 cm deep or less from the estimated inferior surface of the myoma. For myomas 4 cm or less in diameter a single central incision is adequate, whereas for larger diameter lesions multiple incisions will be required. The cryoprobe is then passed through the appropriate ancillary port and inserted into the myoma via the previously created tunnel. For larger myomas it is thought useful to reduce the blood supply from both the serosa and the endometrial vessels. Consequently, there exists a strategy of freezing the myoma superficially and then deeply using additional incisions, the number determined by the myoma volume.\textsuperscript{121–124}

There are a number of studies evaluating this technique. In most instances both myoma volume and related symptoms, including HMB, are reduced by approximately 50% at 6 months and even more at 12 months following therapy.\textsuperscript{121,123–125} These data are encouraging in that they suggest that hypothermic ablation is potentially a minimally invasive, safe, and feasible procedure in selected patients, There remain a number of questions including the effect of hypothermic ablation on fertility and future pregnancy, although a recent small series of 9 patients demonstrated that such patients may remain fertile and have essentially normal pregnancy outcomes.\textsuperscript{126}

It is clear that these studies are insufficient to demonstrate long-term outcomes and that further studies with larger sample size and longer follow-up are needed to confirm the preliminary data. As a result, hypothermic ablation or cryomyolysis should still be considered an experimental procedure.

**Hyperthermic leiomyoma ablation by laser and radiofrequency electrical energy.** In the early 1990s coagulation of leiomyomas was reported under laparoscopic guidance using either laser (neodymium-doped yttrium aluminium garnet [Nd:YAG] or infrared) energy\textsuperscript{127–129} or a bipolar radiofrequency (RF) electrical probe.\textsuperscript{130,131} The energy from these different kinds of electromagnetic waveforms is converted first to mechanical energy, oscillating intracellular protein, then to the elevation of intracellular temperature that causes coagulative necrosis and resulting devascularization within the treated tissue. The volume of necrosis created is dependent on the amount of electromagnetic energy delivered to the tissue. There remain challenges related to predicting or monitoring the local distribution of this energy in tissue, although probes/electrodes with thermal couples that measure local temperature have some promise.

Hyperthermic myoma ablation is an investigational procedure that has been described via laparoscopy, hysteroscopy, and under ultrasound direction. When the procedure is performed laparoscopically, the laser fiber, monopolar or bipolar electrode is passed through the instrument channel of an operating laparoscope or ancillary cannulas and used to pierce the myoma and advance into its core. An attempt is made to coagulate the entire myoma by repeated insertions at multiple concentric sites. A few investigators have described the use of hysteroscopically-directed application of laser energy to ablate myomas or the portions of type 1 or 2 myomas that remain in the myometrium. The Nd:YAG fiber is guided through the instrument channel of an operating hysteroscope and positioned in the intramural myoma.\textsuperscript{129} Unfortunately, positioning such a fiber without being able to view the uterine serosal surface is a concern. As a result, there is also some work under way evaluating the potential role of ultrasound-directed positioning of RF electrodes for the purpose of electrosurgical leiomyoma ablation, but no data are yet available.\textsuperscript{132}

There are some outcome data available for laparoscopic hyperthermic myoma ablation. Typically there is a decrease in myoma volume within 6 months of up to 50% of the original size.\textsuperscript{128–131} There is also evidence of reduction in the volume of HMB.
but in the study with the largest sample size, it is unclear how much of this reduction is related to concomitant hysteroscopically-directed treatment. Postablation pregnancy is a lingering concern because a number of investigators have reported adverse outcomes such as rupture of the uterus.133,134

**Hyperthermic leiomyoma ablation by focused ultrasound energy.** The potential for treatment of uterine leiomyomas using high-intensity focused ultrasound (HIFU) was first described in a multicenter feasibility study in 2003.135 Focusing ultrasound energy essentially with a parabolic mirror for the ablation of tissue is a noninvasive technique first described in 1927 and then again in 1942.136 The technique was slow to develop because of limitations in the control of the process of coagulative necrosis. With improvements in real-time imaging including ultrasound and MRI have come the potential for use of HIFU as a viable therapeutic instrument. Magnetic resonance-guided focused ultrasound surgery (MRgFUS) has now been evaluated in a number of tissues including breast,137 brain,138 and prostate gland.139 Under development is the use of ultrasound for the direction of focused ultrasound energy.132,140

The treatment of uterine leiomyomas is performed in a specially designed suite with the patient positioned on a procedure table overlying the ultrasound generator. This system functions to create an array of pulsed high-intensity ultrasound beams that are focused on the target tissue, directed by MRI or possibly ultrasound imaging. One such array generates a volume of tissue ablation in the range of 6 mm by 25 mm using 2-D measurements. The device is then refocused to an adjacent target and the process repeated until the desired volume of tissue ablation is reached. Tumor necrosis is also dependent on the time of exposure. With MRI, the degree of tumor necrosis can to a degree be estimated, allowing the ability to thermally map the region of the target tissue to a prespecified temperature as measured by the proton resonance frequency shift.141,142 However, preliminary studies comparing MRI-based treatment volume with the volume of nonperfused or necrotic tissue based on postprocedure hysterectomy and histologic examination reveal that the volume of myoma or myometrial necrosis is three-fold higher than that predicted by MRI.143

For uterine leiomyomas, the currently available data are almost totally derived from MRgFUS techniques. The patient is treated in an MRI suite where she is placed in the prone position with the abdomen resting over the treatment device. Conscious sedation is generally administered with a variable combination of narcotics and anxiolytics. The focused ultrasound unit is a spherically curved radiator contained within a sealed water bath. MRI is performed to ensure that bladder and bowel are not in the path of the ultrasound beams, and if so, manipulation or repositioning of the patient is done in an attempt to remedy the situation. Treatment, called *sonication*, is performed in a systematic fashion with typical treatment times to date being about 2 hours and time in the suite about 3 hours. Patients are discharged home about 1 hour following the end of the procedure.

The first published clinical study was a seven-center multinational multiinstitutional trial that described a series of 109 patients treated with the ExAblate 2000 system (InSightec, Haifa, Israel).144 The mean fibroid volume of these patients, depending on the number of myomas, was 294 to 346 cm³, whereas the mean treatment volume was only 32 to 36 cm³, or about 10% to 11% of the total. There were relatively few treatment-related serious outcomes, but only 79.3% of the patients were available for follow-up at 6 months. The mean fibroid volume reduction was 13.5% ± 32 and, using the multidimensional Uterine Fibroid Symptoms and Quality of Life Questionnaire (UFS-QOL), there was a mean 27.3-point reduction in the score compared with baseline.
In a subsequent study and one that resulted in US Food and Drug Administration approval of the ExAblate 2000 device for use in the United States, 109 of 176 women enrolled were treated in seven sites in the United States, Europe, and Israel. In this trial the mean uterine volume was 595.0 ± 362.5 cm³, the mean myoma volume was 284.7 ± 225.4 cm³, and the mean treated myoma volume as estimated by MRI was 25.6 ± 18.4 cm³. Several mild skin burns resulted, and 1 patient had a sciatic nerve injury that had resolved by the 12-month evaluation. The mean reduction in UFS-QOL was 23.8, and at 12 months with only 82 of the original cohort available for evaluation, 51.2% of the women reached the targeted reduction of at least 10 points.

More recently and in a well-designed comparative trial, the preprocedural use of GnRH-a has been shown to potentiate the effect of focused ultrasound energy as measured by intraprocedural MRI. In a subsequent reported clinical series evaluating 49 women and followed for 12 months, UFS-QOL reductions of 45% were seen at 12 months, and 83% achieved at least a 10-point reduction in the scale. The reduction in targeted myoma volume was 37% at 12 months in the patients available for evaluation.

The clinical results associated with MRgFUS are promising, but both myoma reduction and the measured relief of symptoms seem disproportionate to the amount of myoma treated. The feasibility study previously discussed demonstrated that the volume of tumor necrosis exceeded the treated volume by a factor of three. More recently a retrospective comparison was published comparing predicted volume of treated tissue, treatment volume based on MRI-determined temperature elevation, and MRI-determined volume of post treatment nonperfused tissue. In this comparison, and only in larger areas of sonication, the volume of nonperfused tissue was double that of the treated volume based on MRI-measured tissue temperature. The investigators suggest that this larger area of necrotic tissue was caused by vascular occlusion and “downstream” ischemia, but the possibility exists that MRI is not as accurate as thought for the determination of treated tissue in these lesions.

Despite the apparent promise of leiomyoma ablation, there are still no published trials comparing any of the three procedures with experimental or established approaches such as UAE or occlusion, medical therapy, myomectomy, or hysterectomy. Indeed, some patients who have symptoms related to type 2 myomas may be candidates for endometrial ablation by any of a number of techniques. Furthermore, although the impact of myoma ablation on fertility and pregnancy is unknown, the few adverse outcomes reported following hyperthermic ablation with MRgFUS must be reason for concern. It is also clear that a number of patient characteristics including myoma size, location, and the presence of adhesions or abdominal scarring may to a greater or lesser extent impact or even preclude some patients from undergoing myoma ablation.

MRI- or ultrasound-guided FUS are the only techniques that have to date delivered energy to tissue without direct contact by the energy source with the treated tissue. Consequently, this approach offers the potential for incisionless surgery, at least for the selected patients who would qualify for therapy. However, the issue of prediction of the treatment volume must remain an area for concern given the structures that surround the uterus and the possibility for injury.

Despite all of the aforementioned reservations, these seem to be promising techniques to reduce the invasiveness of traditional surgery. The procedures should be subjected to appropriately designed clinical trials that can better define their role in the management of the myriad clinical circumstances associated with uterine leiomyomas.
For the present, the techniques must still be considered experimental and should be performed in a structured environment by well-experienced groups with patients carefully selected and counseled considering all available options. Careful observation and reporting of all results, both positive and negative, will help to define the role that myoma ablation has in the management of symptoms, including AUB, related to uterine leiomyomas.

SUMMARY

Leiomyomas are such common tumors of the uterus that at least two-thirds of women will have at least one by the age of 50. Despite this high incidence, we know relatively little about their cause, growth and development, and contribution to the genesis of reproductive disorders. The prevalence of lesions puts women with associated but unrelated symptoms at risk for unnecessary and/or unsuccessful interventions, especially if they have not been carefully evaluated and counseled. Indeed, because the majority of leiomyomas do not cause symptoms, when a woman presents with AUB, infertility, pelvic pain, or vague abdominal complaints, it is possible if not likely that the cause of the problem exists elsewhere. The other overwhelming impression that can be gleaned is this: when leiomyomas are the cause of the symptoms, particularly in women desiring to preserve fertility, the tumors have already and frequently induced irreparable harm, a circumstance that cries out for a strategy of early detection and interventions designed to minimize morbidity.

Fortunately, because of the efforts of a few, we are just beginning to understand the potential molecular mechanisms by which leiomyomas may contribute to reproductive tract symptoms such as AUB, infertility, and pregnancy loss, work that may contribute to the development of more specific medical therapeutic techniques and strategies. The use of increasingly precise and accessible imaging for diagnosis, combined with the application of customized intrauterine drug-releasing systems or minimally invasive and highly accurate targeted ablative technologies that minimize collateral damage, may provide women the opportunity to avoid the mutilating, painful, expensive, and frequently unsuccessful surgical interventions of today that are applied to end-stage disease.

For the present, clinicians should evaluate any woman with reproductive tract symptoms and leiomyomas carefully and with skepticism, ensuring that they have done all that is necessary to determine if the lesion or lesions are related to the problem. If leiomyomas are the suspected or known cause, clinicians must also be prepared to offer or otherwise provide access to the complete spectrum of care that the patient deserves, regardless of the limitations of the clinician’s training, experience, or institutional environment. Such an approach will limit the number of unnecessary and ineffective interventions and, it is hoped, minimize morbidity while optimizing quality of life for affected women.

REFERENCES


