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# AAGL Practice Report: Practice Guidelines for the Diagnosis and Management of Submucous Leiomyomas

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**ABSTRACT** Submucous leiomyomas or myomas are commonly encountered by gynecologists and specialists in reproductive endocrinology and infertility with patients presenting with 1 or a combination of symptoms that include heavy menstrual bleeding, infertility, and recurrent pregnancy loss. There exists a variety of interventions that include those performed under hysteroscopic, laparoscopic and laparotomic direction; an evolving spectrum of image guided procedures, and an expanding number of pharmaceutical agents, each of which has value for the appropriately selected and counseled patient. Identification of the ideal approach requires the clinician to be intimately familiar with a given patient's history, including her desires with respect to fertility, as well as an appropriately detailed evaluation of the uterus with any one or a combination of a number of imaging techniques, including hysteroscopy. This guideline has been developed following a systematic review of the evidence, to provide guidance to the clinician caring for such patients, and to assist the clinical investigator in determining potential areas of research. Where high level evidence was lacking, but where a majority of opinion or consensus could be reached, the guideline development committee provided consensus recommendations as well. Journal of Minimally Invasive Gynecology (2012) 19, 152–171 © 2012 AAGL. All rights reserved.

*Keywords:* Fibroid; Leiomyoma; Myoma; Submucous; Submucosal; Infertility; Pregnancy loss; Abortion; Menorrhagia; Abnormal uterine bleeding; Heavy menstrual bleeding; Myomectomy; Hysteroscopy; Uterine artery embolization

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English-language articles from MEDLINE CINAHL, Current Contents EMBASE, and the Cochrane Database of systematic reviews, published by December 31, 2010, were searched by use of the key words or combinations of the key words "myoma, leiomyoma, myoma, submucous, submucosal, infertility, pregnancy loss, abortion, menorrhagia, abnormal uterine bleeding, myomectomy, hysteroscopy, resection, vaporization, and metrorrhagia" for all articles related to submucous myomas. The quality of evidence was rated with the criteria described in the Report of the Canadian Task Force on the Periodic Health Examination (Fig. 1) [1].

Uterine leiomyomas are tumors of the myometrium that have a prevalence as high as 70% to 80% at age 50 [2] but that seems to vary with a number of factors including age, race, and, possibly geographic location. Prevalence in symptom-free women has been reported to be as low as 7.8% in Scandinavian women aged 33 to 40 [3], whereas in the United States it is almost 40% in white patients and more than 60% in women of African ancestry in the same age group [2]. Leiomyomas are listed as the diagnosis for about 39% of the approximately 600 000 hysterectomies performed each year in the United States [4]. These benign tumors, also called *myomas,* are usually asymptomatic, but they have been associated with a number of clinical issues including abnormal uterine bleeding (AUB) especially heavy menstrual bleeding (HMB), infertility, recurrent pregnancy loss, and complaints related to the impact of the enlarged uterus on adjacent structures in the pelvis, which are often referred to as "bulk" symptoms. Unfortunately,

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E-mail: Tourale@aagl.org.

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**Fig. 1**

Classification of evidence and recommendations.

The MEDLINE database, the Cochrane Library, and PubMed were used to conduct a literature search to locate relevant articles. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. When reliable research was not available, expert opinions from gynecologists were used.

Studies were reviewed and evaluated for quality according to a modified method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.
II Evidence obtained from non-randomized clinical evaluation
- II-1 Evidence obtained from well-designed, controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research center.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:
Level A—Recommendations are based on good and consistent scientific evidence.
Level B—Recommendations are based on limited or inconsistent scientific evidence.
Level C—Recommendations are based primarily on consensus and expert opinion.

and despite the prevalence and clinical impact of these lesions, there is a dearth of high-quality research available to guide the clinician in the treatment of patients with these tumors.

It is generally perceived that the symptoms of HMB, infertility, and recurrent pregnancy loss largely occur as a result of lesions that distort the endometrial cavity that are therefore adjacent to the endometrium and consequently referred to as *submucous leiomyomas*. Whereas the development of hysteroscopically-directed surgical techniques provides the opportunity to remove such myomas transcervically in a minimally invasive fashion, it is clear that this approach is not appropriate for all patients, making evaluation and selection extremely important features of clinical care. Selected individuals with submucous myomas may be appropriate for a range of medical interventions, as well as a spectrum of hysteroscopic, laparoscopic, or laparotomically directed (those performed via laparotomy) procedures. Consequently, this guideline is designed to provide a context for the management of women with submucous leiomyomas with a particular focus on resectoscopic myomectomy.

## Histogenesis/Pathogenesis

Leiomyoma and myoma are synonymous terms describing monoclonal tumors arising from the muscular layer of the uterus. Anatomically, the human uterus comprises 3 basic layers, the endometrium, the myometrium, and the visceral peritoneum or serosa. On the basis of their relationship to the uterine wall at the time of diagnosis, myomas are referred to as submucous, intramural, or subserosal. On the basis of their topography, histochemistry, and response to gonadal steroids, it is more than likely that submucous myomas originate in the junctional zone (JZ) of the myometrium.

**Table 1**

ESGE: Classification of submucous myomas

| |
|---|
| Type 0 |
| Entirely within endometrial cavity |
| No myometrial extension (pedunculated) |
| Type I |
| <50% myometrial extension (sessile) |
| <90-degree angle of myoma surface to uterine wall |
| Type II |
| ≥50% myometrial extension (sessile) |
| ≥90-degree angle of myoma surface to uterine wall |

Modified from Wamsteker et al. *Obstet Gynecol.* 1993;82:736–740.

It has been observed that JZ thickness changes throughout the menstrual cycle in conjunction with endometrial thickness, and JZ myocytes show cyclic changes in estrogen and progesterone receptors mimicking those of menstruation. Furthermore, the expression of estrogen and progesterone receptors is significantly higher in submucous myomas compared with subserosal myomas [5]. In addition, submucous myomas have significantly fewer karyotype aberrations than outer myometrial myomas, regardless their size, which may be important in retarding their growth and their cellular response to gonadal steroids [6,7].

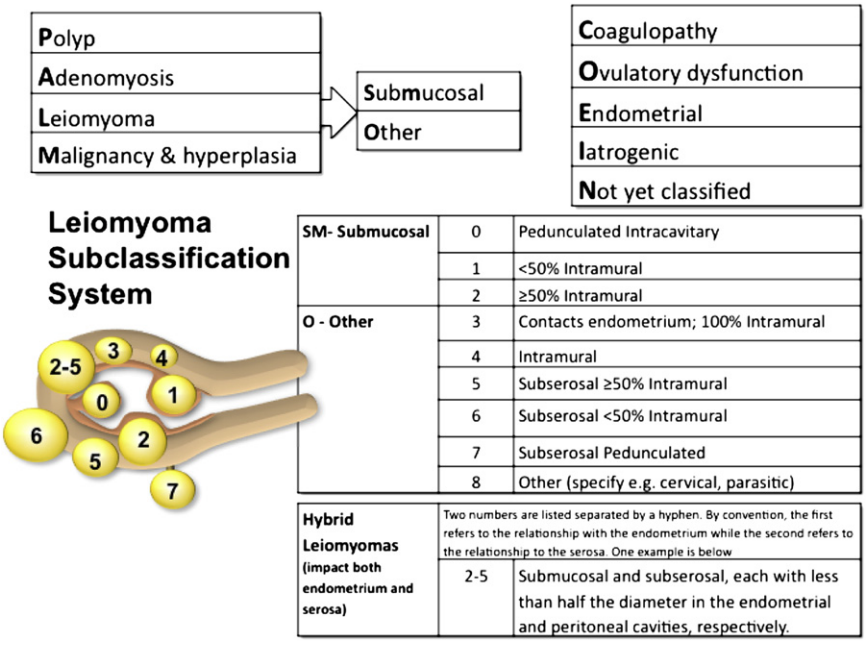
## Classification of Submucous Leiomyomas

Categorization or classification of submucous leiomyomas can be useful when considering therapeutic options, including the surgical approach. The most widely used system categorizes the leiomyomas into three subtypes according to the proportion of the lesion's diameter that is within the myometrium, usually as determined by saline infusion sonography (SIS) or hysteroscopy (Table 1) [8]. The FIGO (International Federation of Gynecology and Obstetrics) system for classification of causes of AUB in reproductive-aged women uses the same system for categorization of submucous leiomyomas but adds a number of other categories, including type 3 lesions that abut the endometrium without distorting the endometrial cavity (Fig. 2) [9]. In addition, this system allows categorization of the relationship of the leiomyoma outer boundary with the uterine serosa, a relationship that is important when evaluating women for resectoscopic surgery. Thus, a European Society of Gynecological Endoscopy (ESGE) type 2 leiomyoma that reaches the serosa is considered to be a type 2-5 lesion and therefore is not a candidate for resectoscopic surgery.

The ESGE and the expanded FIGO classification systems are relatively simple and provide a framework for both

**Fig. 2**

FIGO classification of submucous leiomyomas. Reproduced, with permission granted by FIGO, from: Munro et al 2001 [9].




research and clinical medicine, leaving investigators and clinicians to add, as deemed appropriate, other variables such as size, number, and location of the leiomyomas in the uterine wall. Many of these limitations have been incorporated into another classification system that has been designed to take into account 4 criteria: the penetration of the myoma into the myometrium (same as ESGE/FIGO system for submucous lesions), the proportion of the local endometrial surface area occupied by the base of the myoma, the largest diameter of the myomas, and, finally, the topography of the tumor, which is defined as its location in the upper, middle, or lower third of the corpus and its orientation–transverse orientation (anterior-posterior or lateral; Table 2) [10]. These authors present evidence that the more detailed classification is better than the ESGE system at predicting perioperative outcomes such as the likelihood of completing a hysteroscopic myoma resection and the amount of fluid deficit experienced during the procedure. However, this system was not analyzed with respect to its ability to predict other important outcomes such as successful treatment of HMB or subsequent fertility, outcomes that have been reported with the ESGE system. In a study of 108 women, fertility rates after treatment at a mean of 41 months were 49%, 36%, and 33% in type 0, 1, and 2 lesions, respectively [11]. These investigators also presented data on operating time, intraprocedure distending media absorption, requirements for additional procedures, and bleeding outcomes by use of objective criteria that showed an ability of the ESGE system to provide prognostic information with respect to the ability to completely resect the myomas.

It seems clear that a classification system for leiomyomas that allows categorization of submucous lesions is useful from both a clinical and research perspective, because it should facilitate patient selection and counseling and the pooling of like data among both basic science and clinical investigators. At this time, there are insufficient data to suggest which system(s) provide the best combination of clinician acceptance and clinical and research utility. A

**Table 2**

Presurgical classification of SM myomas

| Points | Penetration of myometrium | | Largest myoma diameter | | Extension of myoma base to endometrial cavity surface | | Location along uterine wall (third) | | Lateral wall (+1) |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | | <2 cm | | <1/3 | | Lower | | |
| 1 | <50% | | 2 to 5 cm | | <1/3 to 2/3 | | Middle | | |
| 2 | >50% | | >5 cm | | >2/3 | | Upper | | |
| Total score | _____ | + | _____ | + | _____ | + | _____ | + | _____ |

Modified from Lasmar et al. *J Minim Invasive Gynecol.* 2005;12:308–311.

potentially useful compromise, at least for the present, would be to use the ESGE/FIGO systems in the clinical environment, recognizing that features of the Lasmar system may be useful to consider in selected clinical situations and in the context of basic science and clinical research.

## Clinical Considerations

### *Significance of Submucous Leiomyomas*

Submucous myomas have been implicated in women with AUB, infertility, and adverse pregnancy outcomes including multiple pregnancy losses. In the reproductive years, the symptom of chronic AUB has been defined as an abnormality in the frequency, cycle regularity, duration, and volume of bleeding from the uterine corpus, as defined by the patient, that is present for most of the previous 6 months [9,12].

### *Submucous Leiomyomas and Malignancy*

Although uterine leiomyomas are extremely common in women, malignancy in a myoma is rare. The incidence of uterine sarcoma in women undergoing hysterectomy for presumed uterine leiomyomas is 0.23% to 0.49%, although in women in the sixth decade it may rise above 1% of hysterectomy specimens [13,14], and for resectoscopic surgery it has been reported in 0.13% of cases [15,16]. There are no data specific to submucous leiomyomas. Nevertheless, considering the prevalence of myomas, the specter of potential malignancy should only rarely be a factor in treatment decisions for premenopausal women.

### *Submucous Leiomyomas and Chronic Abnormal Uterine Bleeding*

It is widely perceived that the most clinically significant bleeding manifestation of submucous myomas is the symptom of HMB, which refers only to the subset of patients with AUB who complain of excessive volume or duration of bleeding. Although such patients typically appear to continue to have ovulation by virtue of the preservation of a cyclically predictable onset of flow every 22 to 35 days, irregular onset may also be present suggesting the coexisting presence of a disorder of ovulation (FIGO AUB-O). Although it is the general perception that only those leiomyomas involving the endometrial cavity are contributing causes of AUB and especially HMB, this is difficult to prove, in part because there are many other potential causes of AUB that may coexist with leiomyomas.

There is little evidence describing the role of submucous leiomyomas in the genesis of acute uterine bleeding, which, on the basis of the FIGO system, is bleeding to the extent that urgent or emergent intervention is required [9]. However, there is some evidence supporting the relationship of submucous leiomyomas to chronic AUB, particularly the symptom of HMB.

Overall, the prevalence of submucous myomas identified in a systematic review of 11 studies in women with AUB was 23.4% [17]. When stratified by menopausal status, submucous myomas were found in 23.4% of premenopausal women (6 studies) [17] and 4.5% of postmenopausal women with AUB (1 study) [18]. In another large, single-site, retrospective study of hysteroscopic findings in 4054 women experiencing AUB, and from of all age groups, submucous leiomyomas were found in 7.5% [19]. Although these studies fall short of proving that submucous myomas cause AUB, they suggest that there may be a relationship.

Evidence for a causal role of leiomyomas in the genesis of HMB is perhaps more convincingly found in studies evaluating the impact of submucous myomectomy. Although the apparently successful role of myomectomy can be confounded if it is combined with other interventions such as endometrial ablation [20,21], those studies where the procedure was limited to myomectomy are more reflective of the impact of the leiomyomas on bleeding outcomes [11,22,23]. In these studies, the long-term "success" rates of 62% [23] to 90.3% were reported, with the latter series of 285 patients undergoing hysteroscopic myomectomy reporting results at 5 years with "success" defined as a "surgery-free" interval [22].

The mechanisms whereby submucous leiomyomas cause or contribute to AUB, including HMB, are unclear. It seems likely that in most instances the mechanical or molecular mechanisms involved in endometrial hemostasis are disturbed, but, to date, unfortunately there are no available studies that have adequately investigated these hypotheses. In a minority of cases, the perimyoma vasculature is likely the source of the bleeding. Clearly, more research should be focused on this important topic.

### *Effects of Submucous Leiomyomas on Fertility*

In general, uterine myomas are found in 5% to 10% of women with infertility and in 1.0% to 2.4% of women with infertility myomas are the only abnormal findings [24–26]. A 2009 systematic review of the evidence reported on the effects of myomas on infertility and of myomectomy in improving outcomes [27]. Of 347 studies initially evaluated, 23 were included in the data analysis, and only 4 provided pertinent data on the effects of submucous myomas on fertility by use of either SIS or hysteroscopy to define the location of the lesions [28–31]. The authors concluded that women with submucous myomas, compared with infertile women without such myomas, demonstrated a significantly lower clinical pregnancy rate (4 studies), implantation rate (2 studies), and ongoing pregnancy/live birth rate (2 studies) [27].

Further evidence regarding the impact of submucous myomas on fertility can be found in studies evaluating the impact of myomectomy. It seems clear from high-quality studies that pregnancy rates are higher after myomectomy than no or "placebo" procedures [27,32]. The impact of myomectomy on fertility outcomes is discussed later in this guideline.

The mechanisms whereby submucous leiomyomas impact fertility are, at the present time, unclear. However, there is evidence that such lesions may contribute to a global

molecular impact that inhibits the "receptivity" of the endometrium to implantation as determined by the presence of the transcription factors HOXA-10 and -11. Investigators have demonstrated that there is a reduction in the levels of endometrial HOXA-10 and -11 expression, both over the myoma, and remotely in the endometrium overlying normal myometrium that is not seen in the endometrium of women with intramural or subserosal myomas [33].

### *Effects of Submucous Leiomyomas on Pregnancy Loss*

It is difficult to study the impact of submucous leiomyomas on early pregnancy performance; however, it is likely that they are associated with an increased risk of early pregnancy failure. In the metaanalysis of Pritts et al [27], there were significantly higher spontaneous abortion rates in women with submucous myomas (2 studies, RR 1.68, 95% CI 1.37–2.05, p =.022), a difference that seemed to vanish after resectoscopic myomectomy. In this systematic review, no difference was seen in the rate of preterm delivery. Another systematic review could only identify 2 small studies that reported 53% and 43% spontaneous abortion rates in a total of 30 patients [34].

The mechanisms whereby submucous myomas impair pregnancy outcomes are unknown. Histologically, the endometrium overlying submucous myomas [35,36] and opposite the myoma [36] shows glandular atrophy, which may impair implantation and nourishment of the developing embryo.

## Diagnosis of Submucous Leiomyomas

The diagnosis of submucous leiomyomas is generally accomplished with one or a combination of hysteroscopy and radiological techniques that may include ultrasonography, (typically transvaginal ultrasonography [TVUS]), SIS, and magnetic resonance imaging (MRI). The goal is to determine a number of factors including distinguishing leiomyomas from adenomyosis and confirmation of submucous location, as well the number, size, location, and the extent of myometrial penetration of each identified submucous myoma. Of particular importance is the relationship of the submucous myoma to the uterine serosa, because transcervical resection is not considered appropriate when the leiomyoma is close to, or in contact with, the serosal layer because of an increased risk of perforation and serious injury.

Evaluation of the value and accuracy of imaging techniques for submucous leiomyomas is a challenge, because ideally, evaluation of sensitivity and specificity requires comparison with hysterectomy and appropriate pathological evaluation. Hysterosalpingography, a contrast radiologic evaluation, is frequently used in infertility investigation to evaluate tubal patency. However, hysterosalpingography is suboptimal for the evaluation of the endometrial cavity because available evidence suggests that, although it is relatively sensitive for intrauterine abnormalities (81.2%–98%), there is a high incidence of false-positive findings with a limited specificity of 15% to 80.4% [37–39]. Consequently, a normal hysterosalpingogram does not provide confidence that the endometrial cavity is normal.

There is high-quality evidence from a Cochrane systematic review that demonstrates SIS and hysteroscopy to be equivalent for the diagnosis of submucous leiomyomas, with both superior to TVUS [40]. A double-blinded study demonstrated that although TVUS and MRI are roughly equivalent in diagnosing the presence of leiomyomas, determination of other features such as location, and proportion of the tumors in the endometrial cavity, is best accomplished with MRI [41]. The same group also compared standard TVUS, SIS, MRI, and hysteroscopy with subsequent hysterectomy for the detection of intracavitary lesions and found that MRI, SIS, and hysteroscopy were equally effective and were superior to TVUS, but that MRI was superior to the other techniques in evaluating the relationship of submucous leiomyomas to the myometrium [42]. It should be noted that, unlike MRI, TVUS is very operator dependent, a factor that must be considered when evaluating comparisons of technique [43].

It is useful to distinguish adenomyosis from leiomyomas, because therapeutic approaches are very different, including surgery, for which there is no defined role in adenomyotic lesions. In a study comparing TVUS and MRI for the diagnosis of adenomyosis, with hysterectomy and histopathologic evaluation, the referent technique, MRI, was shown to be more sensitive but equally specific [44].

Understanding the location and type of leiomyomas is best appreciated when the clinician takes the steps necessary to view the images her or himself. This is particularly important when surgery is being contemplated or planned, because both the appropriateness and the approach to the surgical procedure are frequently highly dependent on high-quality and accurately-interpreted imaging.

## Nonresectoscopic Therapy

There exist a number of approaches to the management of leiomyomas that do not involve removal of the lesions themselves.

### *Prevention*

There is some evidence that the development or growth of leiomyomas can be altered by medical interventions, although no identified studies have been specifically limited to submucous leiomyomas, At least 4 retrospective studies reported that oral contraceptives reduced myoma risk by approximately 30% [45–48]. One of these studies compared 843 women with myomas to 1557 controls and found that current users of oral contraceptives had an OR for myomas of 0.3 (95% CI 0.2 to 0.6). After 7 years of use, the OR was 0.5 (95% CI 0.3–0.9) [47].

There is also some evidence that intrauterine progestins may have value in preventing the development of leiomyomas. A multicenter, prospective study reported on 2226 American women (18 to 38 years old) randomized to either

the levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena; Bayer Healthcare, Wayne, NJ) (n = 3416 women-years) or the copper-containing Cu-T-380A (n = 3975 women-years) [49]. Among the users of Cu-T-380A, the incidence of myomas increased significantly with time, and with age at insertion. Although no women required surgery either for myomas or for an enlarged uterus in the LNG-IUS group, 5 in the Cu-T-380A cohort had myomectomy, and 1 had a hysterectomy. Another prospective study demonstrated that over 3 years, the total uterine volume in women with leiomyomas reduced, and although the reduction in leiomyoma volume did not reach significance, what may be as important is that they did not grow [50]. The potential impact of progestins on leiomyoma development has been evaluated in a study on depot medroxyprogesterone acetate that showed, at 5 years, a reduction in the risk of leiomyoma development, and, short of that, leiomyoma volume [51]. Although these data fail to prove that near-continuous or continuous systemic or local progestin therapy reduces the risk of leiomyomas, it should provide some comfort for those with a strong family history or known preclinical lesions.

### *Expectant Treatment*

The process of "watchful waiting" or expectant management is an option for some with submucous leiomyomas; however, it is difficult to counsel women, in part because of variability in the natural course of any specific submucous myoma. Indeed, in 1 longitudinal study of myoma growth as measured by ultrasonography, 21% of the tumors regressed compared with baseline, with the vast majority of these submucous in location [52]. In another prospective study with sequential SIS, myomas grew an average of 1.2 cm per 2.5 years, but greater variation in growth rates was noted [53]. In the Myoma Growth Study, 262 leiomyomas in 72 women were monitored with sequential MRI scanning over a period of 12 months. The median growth rate was 9%, but there was a wide range, from 89% shrinkage to a 138% increase in volume [54]. Notably, tumors in the same women grew at different rates, and although the growth rates in black and white women were similar under the age of 35, for those 35 and older, the growth rate in white women was much lower. The growth rates for submucous myomas was similar to that in other locations in the uterus [55]. This information may be of value, for example, for the woman in the late reproductive years who has acceptable control of symptoms. She may chose to wait for menopause rather than undergo surgical therapy for her submucous leiomyomas.

### *Medical Therapy for AUB Associated with Leiomyomas*

There are a number of circumstances where symptoms caused by, or associated with, uterine leiomyomas may respond to medical therapy. Such interventions may be designed to treat AUB, reduce the volume of the leiomyomas, or both. However, there is neither rationale nor evidence for the use of medical therapy for the management of infertility or recurrent pregnancy loss in women with submucous leiomyomas.

There is evidence that a number of medical interventions may be effective for HMB in at least some patients with submucous leiomyomas, although the evidence, in many instances, is difficult to find because of characteristics of the design of many of the studies. For example, although the LNG-IUS has been shown in 1 prospective study to significantly reduce HMB in women with type 2 leiomyomas [56], in other studies the location of the leiomyomas was either not specified [50], or, as was the case with one systematic review, submucous myomas were typically excluded [57]. A similar circumstance exists with tranexamic acid where a recent randomized clinical trial that showed reduction in HMB in women with leiomyomas did not specify the location of the lesions [58]. As a result, the utility of these and other medical interventions for HMB associated with SM leiomyomas will remain unclear pending the design and implementation of studies that distinguish between abnormal bleeding associated with submucous myomas and myomas that do not involve the endometrial cavity.

A number of medical interventions have been shown effective in temporarily reducing the size of leiomyomas including GnRH agonists (GnRHa), selective progesterone receptor modulators, and aromatase inhibitors, each of which reduces uterine and leiomyoma volume a mean of approximately 30% to 45% after 3 months of administration [59–62]. Whereas only GnRHa are approved for this approach in the United States, aromatase inhibitors may be at least equally effective and without the bleeding often seen in the second week after initiation of GnRHa therapy [62]. All of these agents typically result in amenorrhea, which provides an opportunity, in selected patients at least, to restore both the hemoglobin level and iron stores allowing for planning of a more enduring therapeutic approach [63]. However, there may be a place for sustained therapy with one of these agents, particularly in those near to menopause or for women with comorbidities that might significantly increase the risk of surgical intervention [64,65]. Studies specifically designed to evaluate these approaches in women with submucous leiomyomas are lacking. Discussion of the role for GnRHa for preparation of the uterus for resectoscopic myomectomy is found below.

### *Uterine Artery Embolization and Occlusion*

Occlusion of the uterine arteries and, consequently, the predominant blood supply to the uterus, was introduced in the middle 1990s as a technique for treating symptoms related to leiomyomas and one that could, for some, replace the need for traditional surgical intervention. Vascular occlusion is usually accomplished by the interventional radiological technique of uterine artery embolization (UAE), but has also been described as uterine artery occlusion (UAO) performed laparoscopically [66] or transvaginally [67,68].

The techniques involved with UAE and UAO are beyond the scope of this document.

There exists a substantial body of evidence suggesting that UAE is effective for the treatment of bulk symptoms or HMB associated with uterine leiomyomas [69]. However, the role of UAE in the management of women with submucous myomas is controversial. The MYOMA registry multivariate analysis of predictors of improvement on symptom scores and quality of life (QoL) outcomes at 3 years after UAE indicated that submucous myoma location was associated with improved symptom and QoL score outcomes [70]. However, several studies have suggested that submucous myomas may confer a higher risk of intervention for post UAE infection, although diagnosis is difficult, and it is difficult to determine whether the most important variable is myoma size or location [71–74]. Patients with submucous myomas and AUB have been reported to have a higher rate of failure and subsequent reoperation rate than patients treated for UAE for non-bleeding-related symptoms [75].

The best available evidence regarding the incidence of spontaneous expulsion of myomas 3 months or more after UAE suggests that it may occur in about 2.5% of cases [71]. It is difficult to find well-designed studies evaluating this risk in women with submucous myomas, in part because of inconsistent preprocedure imaging. The best available study followed 40 patients with submucous leiomyomas prospectively and found a spontaneous expulsion rate of 50% [76]. Another prospective study found that about a third of the "dominant" submucous leiomyomas became intracavitary (type 0) leiomyomas, whereas 20% of the type 0 lesions were not seen at follow-up MRI, suggesting spontaneous expulsion [77].

There have also been reports of a persistent vaginal discharge that may follow UAE in women with submucous myomas that may be related to tumor infarction and communication with the endometrial cavity through the endometrium [78].

Finally, it appears that pregnancies in patients after UAE have an increased rate of spontaneous abortion than a matched population [79] a factor that makes the procedure of questionable value in women with leiomyoma-associated infertility or the desire for pregnancy in the future.

The evidence would suggest that UAE be used judiciously in women with submucous leiomyomas, where the procedure should be used with some caution. This may be especially true for women with infertility or the desire for future pregnancy. Those women with bleeding or bulk symptoms associated with submucous leiomyomas may have symptomatic improvement with UAE, but can be counseled that they may have a greater risk of periprocedural or delayed complications such as infection, chronic vaginal discharge, and spontaneous passage of an infarcted leiomyoma.

## Energy-Based Leiomyoma Ablation

Leiomyomas may be destroyed with the targeted application of energy. In the medical literature are reports of leiomyoma ablation or "myolysis" with radiofrequency electricity [80–83], laser energy [84], cryotherapy [85,86], microwaves [87], and focused ultrasonography [88–90]. At the present time, the only device approved by the Food and Drug Administration is magnetic resonance guided–focused ultrasound (MRg-FUS).

The role of MRg-FUS in the treatment of submucous myomas in women with AUB, and especially HMB, has not been established, and, as is the case with UAE, it is unlikely that there is any value in the treatment of submucous myoma–related infertility or recurrent pregnancy loss. One study reported on 109 women with myomas treated at 7 sites. Of the myomas treated, 22% were submucous, 57% were intramural, and 21% were subserosal. At 6 months, the mean reduction in myoma volume was 13.5%, and 79.3% of women reported significant improvement in their myoma symptoms. However, no subgroup analysis of symptom outcome by myoma location was reported [91]. As a result, the role for MRg-FUS in the management of submucous leiomyomas remains unclear. Given the available alternatives, treatment of submucous leiomyomas with MRg-FUS should likely be limited to properly designed clinical trials.

## Endometrial Ablation

For women who are no longer interested in fertility and who suffer from AUB associated with submucous leiomyomas, endometrial ablation (EA) may have a role in highly selected patients. Ablation may be performed by hysteroscopically-guided technique or, in limited instances, with one of the available EA devices.

After the introduction of nonresectoscopic EA devices designed to treat HMB, concomitant treatment of submucous myomas has been reported with a thermal balloon [92], a radiofrequency mesh electrode [93], hysteroscopically guided free fluid [94–97], and microwave energy [98,99]. In the randomized controlled trials (RCTs) mandated by the Food and Drug Administration designed for regulatory approval of these EA devices, none, except the microwave device (MEA; Microsulis Medical Ltd., Edinburgh, Scotland), included patients who had uterine cavity distortion from submucous myomas. The microwave device was approved for treating AUB in patients with submucous myomas with a diameter of 3 cm or less that did not impede the ability of the microwave probe to reach the entire endometrium. In this trial, the success rate at 1 year in the evaluable patients with myomas (90.3%) was similar to that of patients without leiomyomas, which, in turn, was similar to that for the group treated with resectoscopic EA [98].

The results of a RCT comparing thermal balloon EA (Thermachoice; Ethicon Women's Health and Urology, Sommerville, NJ) versus rollerball EA also demonstrated equal efficacy in a population of women with HMB who had selected type 2 submucous leiomyomas $\leq$3 cm in diameter. Furthermore, there were more complications in the hysteroscopically-treated group [92]. A retrospective

comparison of the Hydrothermablation system (Boston Scientific, Natick, MA) found the success rate to be lower in those with, rather than without, submucous leiomyomas, but the overall success rate was high, with only 11 of 95 (11.5%) undergoing hysterectomy at a median follow-up time of 31 months [97]. Finally, in a single-armed, 1-year study of the Novasure radiofrequency ablation system (Hologic Inc., Bedford, MA) in patients with type 1 or 2 myomas, 95% of the 65 patients were successfully treated [93].

In summary, when women with HMB who are not interested in future fertility and have selected type 2 and perhaps type 1 submucous myomas, generally $\leq$3 cm or less in diameter, EA appears to confer a high degree of success, at least in the short term. At the present time, there is inadequate evidence to suggest that 1 device or technique, such as resectoscopic ablation, is clearly more efficacious than another. Discussion of the combination of EA and hysteroscopic myomectomy is found later in this document.

## Myomectomy (Nonhysteroscopic)

In some instances, the abdominal approach may be desirable or necessary for the treatment of submucous leiomyomas. One such example occurs when submucous leiomyomas are not appropriate for resectoscopic surgery because they extend to the uterine serosa (eg, type 2-5, or 2-6 lesions); or where an abdominal approach is necessary for other reasons such as the requirement to remove other intramural (types 3 and 4) or large subserosal lesions (types 5, 6, or 7). Preservation of endometrial surface area is also a consideration for women who are infertile, or who wish to retain fertility, as, in some instances, and particularly with multiple type 2 myomas, resectoscopic myomectomy might result in removal or destruction of a significant proportion of the endometrial surface. At this time, there is no guidance provided in the literature regarding the proportion of the endometrial cavity involved with submucous myomas that should trigger a decision to proceed abdominally. As a result, and at this time, the role of this variable will have to be determined by the clinician/surgeon.

The abdominal approach selected should be determined after considering a number of factors including the size, number and location of the myomas, the presence or absence of coexisting pathology such as adhesions, and the training, skill, and experience of the surgeon. Where possible, a minimally invasive approach such as laparoscopic myomectomy should be selected, but it is essential that the surgeon have the skills not only to remove the myomas safely, but to repair the myometrial defect in a fashion similar to that when laparotomic myomectomy is performed [100]. Some surgeons may choose to facilitate the laparoscopic process using microprocessor assisted ("robotic") techniques that preserve the advantages of the minimally invasive approach [101,102]. It is apparent from a number of case series that abdominal morcellation of leiomyomas confers some risk of the development of "parasitic" myomas developing from fragments left in the peritoneal cavity [103–105]. Although uncommon, the actual incidence or this adverse event is unknown but probably underestimated. Regardless, these reports provide support for the notion of a meticulous approach for the removal of myoma fragments at the time of laparoscopic or even laparotomic myomectomy.

In some cases, vaginal myomectomy may be appropriate. The most obvious circumstance exists when pedunculated submucous myomas prolapse through the cervix. In such instances the lesion can be removed with appropriate instrumentation, usually a combination of twisting and transection. It is not clear whether ligation of the stump is necessary to maintain hemostasis. If performed in the operating room setting, it may be appropriate to evaluate the endometrial cavity hysteroscopically to determine if there are other similar lesions. When the leiomyoma is within the cervical canal or traverses the isthmus into the lower uterine segment, resectoscopic technique may be difficult. In the circumstance of a type 0 or selected type 1 lesions vaginal myomectomy following dilation and extraction may be appropriate but care must be exercised when faced with deeper type 1 tumors. In some instances, the formation of one or more longitudinal incisions in the cervix has been described to facilitate removal [106].

## Hysteroscopically Directed Myomectomy

### *General Considerations*

Indications for submucous myomectomy include AUB, typically HMB, infertility, and recurrent pregnancy loss. The route of myomectomy depends on a number of factors including the desire for future fertility, the size, number, and location of the submucous leiomyomas, and, particularly with type 2 lesions, the relationship of the deepest aspect of the myoma(s) to the uterine serosa. The presence of other, coexisting pelvic disease may influence the choice of route, as might the training, experience, surgical expertise and bias of the surgeon, and the availability of appropriate equipment. Where possible, transcervical or hysteroscopic myomectomy is preferred because of its efficacy, and the reduction in surgical morbidity afforded by the absence of abdominal incisions. Historically, by far the most common hysteroscopic technique has been transcervical resectoscopic myomectomy (TCRM) with a modified urologic resectoscope, first reported in 1976 [107]. However, there now exists a growing number of other hysteroscopic techniques for dissection, vaporization, or morcellation and excision of submucous myomas. In general, submucous myomas (types 0, 1, and 2) up to 4 to 5 cm diameter can be removed under hysteroscopic direction by experienced surgeons, whereas larger and multiple myomas are best removed abdominally. Type 2 myomas are more likely to require a multistaged procedure than types 0 and 1 [8,10,11,22].

One of the greatest concerns to the hysteroscopic surgeon is the risk of perforation. An abdominal approach, be it laparotomic, laparoscopic, or "robotic," is also most

appropriate when the submucous myoma is a type 1-5 or 2-5 traversing the myometrium and reaching the uterine serosa. In such circumstances, resectoscopic myomectomy may be neither feasible nor safe.

### *Patient Selection*

*Abnormal Uterine Bleeding*

After TCRM alone, long-term cohort studies have indicated that patient satisfaction is in the range of 70% to 80%, with 14% to 16% of women requiring additional surgery [21,108,109]. However, achievement of a high rate of success requires careful patient selection and consideration of a number of factors including the number of submucous myomas and their location, size, and type, including their relationship to the uterine serosa.

When evaluating the suitability of patients for TCRM, it is important to consider the myoma type, the risk of incomplete excision, and the patient's tolerance for more than 1 procedure. The long-term results of TCRM for AUB were evaluated in 285 women followed up for a median of 42 months [22]. The authors found that type 2 myomas could be eventually resected but required a larger number of repeat procedures than the more superficial types 0 and 1 myomas, which almost invariably were completed with a single operation, findings also reported by others [8,10,11]. In an analysis of factors that might help predict the need for further surgery, the authors identified 2 subgroups of patients. Those women with a normal uterine size and not more than 2 submucous myomas identified at hysteroscopy were projected to have a risk of needing more surgery within 5 years of 9.7%, whereas those with an enlarged uterus and 3 or more submucous myomas had a risk of further surgery that was greater than 35% at 5 years.

The use of concomitant EA at the time of TCRM has been suggested as a method for improving the chance of success in treating HMB for women who do not desire future fertility. A retrospective comparison of outcomes of women undergoing TCRM only with those of women undergoing combined TCRM and endometrial ablation showed a higher success rate when ablation was added to the procedure [110]. In women in whom the myoma was completely resected, bleeding was controlled in 96.7% of those having concurrent EA compared with 84.4% in women not undergoing ablation. When the myoma was not completely resected, 92.3% of women achieved control after concurrent ablation in contrast to 70.4% if ablation was not done. Another retrospective comparison of hysteroscopic myomectomy alone versus hysteroscopic myomectomy and EA demonstrated a greater reduction in the requirement for menstrual pads in those who had concomitant endometrial ablation [20]. A case control study comparing TCRM and EA to EA alone reported a repeat surgery rate of 34.6% in the TCRM group and 39.6% in the EA only group at a mean of 6.5 years after surgery [111]. No RCTs were found comparing these 2 techniques.

Other factors may increase the risk of subsequent surgery. For example, adenomyosis was the most common finding in women eventually requiring a hysterectomy in the study discussed previously [110]. The anticipated time to menopause should be considered in the decision-making process. Hysteroscopically directed treatment of a large uterus with multiple myomas may be less likely to provide long-term relief to a young woman than a woman in the late reproductive years who may reach menopause without the requirement for major surgical intervention. Although this seems an obvious conclusion, no data were identified that specifically addressed this question.

*Infertility*

In a systematic review of leiomyomas and fertility, Pritts et al [27] concluded, "it is agreed that [submucous] myomas lower fertility rates and their removal enhances the rates of conception and live births" [27]. However, there is some evidence that although fertility rates are increased, they may not be returned to "normal" and that the differences may be, in part, based on features of the leiomyomas at baseline. In an Italian study of 108 women that used the ESGE classification system, fertility rates at a mean of 41 months after the procedure were 49%, 36%, and 33% in type 0, 1, and 2 myomas, respectively [11]. A recently published RCT compared TCRM with no treatment in 215 women with primary infertility who were demonstrated to have submucous myomas on the basis of ultrasound scanning results. Women were randomized to TCRM or diagnostic hysteroscopy with biopsy only. During the follow-up period, 63% of the treated group conceived as compared with 28% of the untreated group. Fertility rates increased after TCRM for type 0 and type 1 myomas, but no significant difference was noted between the groups for type II myomas [32].

Although these data provide some evidence that should assist surgeons with counseling of patients, a number of questions remain unanswered. For example, the impact of resection on fertility based on the area of the remaining endometrium is unclear. It could be hypothesized that, if resection leaves relatively little remaining endometrium, fertility would be compromised and that in such cases—which might include large or multiple submucous myomas, and particularly those that are type 2—myomectomy should be accomplished by a transabdominal route. Clearly future investigation should consider these important issues.

*Recurrent Pregnancy Loss*

The relationship of submucous myomectomy to the problem of recurrent pregnancy loss is less clear because there is less evidence and a high background natural risk of first-trimester loss. The available evidence is suggestive of benefit, because, in the systematic review by Pritts et al [27], the post-submucous myomectomy relative risk of spontaneous pregnancy was 0.77 (1 study) when compared with control subjects with myomas in situ (no myomectomy), and RR 1.24 (2 studies) when compared with infertile women with

no myomas. Clearly more data are required, but this evidence suggests that, at least in selected patients, submucous myomectomy may reduce the risk of spontaneous abortion.

### *Technical Approach to Transcervical Surgery for Leiomyomas*

#### *Preprocedural Preparation: Suppressive Medical Therapy before TCRM*

Potential uses of medical therapy before the performance of TCRM include reduction of leiomyoma volume, creation of amenorrhea to facilitate restoration of hemoglobin and iron stores, and facilitation of the procedure including improved visualization and reduced systemic absorption of distending media. The most investigated such agents are GnRH agonists. Whereas high-quality data exist demonstrating the efficacy of these agents in facilitating the treatment of anemia before the procedure [112], the data regarding the impact on other outcomes is more mixed. Administration of GnRHa 2 months before hysteroscopic myomectomy resulted in 35% reduction of the endometrial cavity area [113], an outcome that the authors concluded allowed complete resection of larger myomas in one setting. However, this was a single-armed study with no comparison group, thereby limiting the validity of these conclusions.

Studies evaluating the impact of GnRHa on surgical time have met with mixed results. In a non-RCT comparing hysteroscopic myomectomy with and without preoperative treatment for 2 months with GnRHa, the operating time was significantly longer in the GnRHa group, 57.6 minutes versus 40 minutes [114], an outcome suggested by the authors to be secondary to GnRHa-related contracted uterus and cervical stenosis. However, in 2 RCTs, operating time was either unchanged [115] or significantly reduced [116] in the GnRHa-treated population. Notably, systemic absorption of distention media was significantly reduced in the study that reported reduced operating times [116]. Review of these articles demonstrates that there were substantial differences in study design; one randomized women with type 1 and 2 myomas [115] whereas the other excluded type 2 lesions, limiting the study population to patients with only types 0 and 1 leiomyomas [116]. Neither study showed a reduction in the incidence of incomplete excision or the need for further procedures, although the first study [105] may have had inadequate power to make such a conclusion.

Consequently, for TCRM, the utility of GnRHa in reducing operative time, systemic absorption of media or the chance of repeat surgery remains unclear. However, there is still a potential role for these agents in creating amenorrhea to facilitate reestablishment of normal hemoglobin levels, especially before surgery.

#### *Cervical Preparation before TCRM*

Forceful dilation of the cervix is widely perceived to increase the risk of cervical tears and uterine perforation discussed later in this guideline. The risks are greater in postmenopausal women, for those without previous vaginal delivery, and for women with previous surgery for cervical neoplasia. In such circumstances, ripening of the cervix may be beneficial with laminaria tents, preoperative prostaglandins, and intraoperative intracervical injection of dilute vasopressin.

LAMINARIA. Laminaria "tents" are narrow natural or synthetic rods designed to gradually dilate the cervix over a period of hours by radial, osmosis-induced expansion. There have been a number of clinical trials evaluating this technique in pregnancy, usually in preparation for first- or second-trimester termination [117]. However, there were only 2 comparative trials, or even reported series, identified in the literature search in nonpregnant women [118,119]. Both of these trials compared laminaria with misoprostol, with one reporting equivalent efficacy, but with laminaria "insertion difficulty" identified in 36.1% of the cases, and patients finding the approach unacceptable in 23.6% [118]. This compared with no "insertion difficulty" with misoprostol and only 2.8% of the patients finding the procedure unacceptable. The other trial had somewhat different conclusions describing both fewer side effects and a reduced requirement for surgical dilation (from 70% o 28%) with laminaria [119].

Reported techniques usually involve placing a small laminaria "tent" through the internal cervical os 1 day before surgery. Although there are no available data, a number of logical, consensus-based recommendations may be made. A paracervical block with a long-acting agent such as bupivacaine may decrease discomfort during and after the insertion of laminaria. Uterine cramps may be decreased/avoided by the use of preoperative nonsteroidal antiinflammatory drugs or opioids. Clearly, more clinical trials would be beneficial in determining the place for laminaria in the priming of the cervix for hysteroscopic procedures.

PROSTAGLANDINS (MISOPROSTOL). High-quality evidence from RCTs suggests that misoprostol, a synthetic prostaglandin $E_1$ analogue (200–400 μg) taken orally or vaginally, 12 to 24 hours before surgery, facilitates cervical dilation and minimizes traumatic complications in premenopausal women [120–127]. There is evidence from 1 RCT involving postmenopausal women that vaginal estradiol, 25 μg/d, for 2 weeks, followed by vaginal misoprostol (1000 μg) the evening before the procedure, resulted in a significantly more "ripe" cervix than was the case for misoprostol alone [128]. As discussed above, vaginal misoprostol has been compared with laminaria tents where 2 RCTs arrived at somewhat conflicting results with respect to both efficacy and side effects [118,119].

INTRACERVICAL VASOPRESSIN. Vasopressin is a neurohypophyseal hormone that initiates contractions of smooth muscle and blood vessels in the uterus and elsewhere. A well-designed RCT evaluated injection of 10 mL (20 mL total) of a dilute solution of vasopressin solution (4 U in saline solution 80 mL) at 3:00 and 9:00 of the cervix at the time of hysteroscopy. These investigators showed that

vasopressin was associated with a significantly reduced force for dilation but no difference in the incidence of cervical trauma [129]. However, only 1 randomized trial of vasopressin for this purpose has been reported.

PROPHYLACTIC ANTIBIOTICS. The overall risk of infection in hysteroscopic procedures is low, ranging from 0.01 to 1.42% [130,131], with the risk of endometritis following resectoscopic myomectomy of 0.51% [131]. The role for prophylactic antibiotics has not been established, either in hysteroscopy in general, or in submucous myomectomy in specific but, given the low risk of infection following hysteroscopic procedures in general, it is unlikely that they would be of benefit. Possible exceptions might include resectoscopic surgery in women with a past history of pelvic inflammatory disease, [132] an approach supported by the American College of Obstetricians and Gynecologists [133].

### *Instrumentation*

Effective performance of hysteroscopic myomectomy requires both appropriate instrumentation and the knowledge and skill to use it safely. Although small myomas can be removed with conventional hysteroscopic instruments such as scissors or hysteroscopic grasping forceps, larger lesions require a system designed to morcellate or vaporize the tumors. In addition, because hysteroscopic myomectomy requires the establishment of a distended uterus, with attendant risks of systemic media absorption, systems designed to accurately measure input and output should be available, so that systemic absorption can be accurately quantified in real time. The setting for hysteroscopic myomectomy—office, surgical center, or operating room—depends on a number of factors including the requirement for anesthesia and the availability of the required equipment.

#### *Hysteroscopic Systems*

Small-diameter bipolar electrodes or laser fibers can be passed through the instrument channel of most standard hysteroscope sheaths 5 mm or greater in diameter. In some instances, dissection of smaller submucous myomas can be accomplished with such energy sources.

The most commonly employed system for removal of submucous myomas is the urologic resectoscope, slightly modified for gynecology. Uterine resectoscopic surgery is generally performed in the context of an operating room using local anesthetics, with or without conscious sedation, or with regional or general anesthesia. All modern resectoscopes are of a continuous flow design, allowing constant turnover of distending media that facilitates visualization by rinsing out blood and debris. Traditional resectoscopes are designed for monopolar electrodes and require nonconductive distension media to allow completion of the electrical circuit. Bipolar resectoscopes require the use of conductive media, such as normal saline [134–137]. For optimum safety and effectiveness, the surgeon should have a detailed understanding of the design and assembly, and, where necessary, troubleshooting strategies for the system in use. Although beyond the scope of this document, it is incumbent on the surgeon to have a clear understanding of the principles of radiofrequency electrosurgery including, but not limited to the differences between waveforms, and factors that impact the current or power density created by the various electrodes.

More recently, mechanical hysteroscopic resection systems have been developed based upon the orthopedic shaver, that include a hollow cylindrical blade with a side aperture that is used to morcellate the myoma sequentially. These systems generally have integrated suction removal systems to remove tissue fragments that have been created by the blade [138]. Such systems may be used with saline distension media and do not require electrical current.

### *Myomectomy Techniques*

There are 3 basic methods for removing leiomyomas under hysteroscopic direction—morcellation, cutting with an electrosurgical loop, and vaporization. When performing radiofrequency-based hysteroscopic myomectomy on women who wish to preserve fertility, every effort should be made to minimize thermal damage to the tissue adjacent to the incision. Care must be taken to ensure the loop does not touch adjacent endometrium. The depth of thermal injury in tissue is proportional to a number of factors including the voltage of the output and the exposure time [139]. If the power setting is too low for the surface area of the electrode that is used, the electrode will drag in the tissue, thereby increasing the time of exposure and thus the depth of thermal injury. Whether myomectomy with mechanical devices is associated with an improved outcome with respect to fertility or pregnancy outcomes has not been evaluated.

There exist a limited number of published cohort studies that use a 5Fr bipolar electrode to treat submucous myomas in an outpatient clinic setting, generally with morcellation and extraction of the fragments [140,141]. The study with the largest sample size reported the excision of 123 submucous myomas 0.5 to 2.0 cm in diameter, of which 74 (60%) were removed in a single session, whereas the remaining 49 (40%) required a second procedure, generally when the submucous myomas had a diameter greater than 1 cm [141]. Despite the absence of anesthesia, 99 (80%) women tolerated the procedure well, whereas 20 (16%) and 4 (3%) of the remainder experienced some or moderate discomfort, respectively. The authors reported no complications.

The most commonly employed approaches use the resectoscope, a radiofrequency electrosurgical generator, and either a loop or a bulk-vaporizing electrode. Loop electrosurgical resection is performed with the electrode activated with low voltage (“cutting”) current to allow the repetitive creation of “strips” of myoma, with periodic interruptions of the procedure to allow removal of the tissue fragments. These “chips” of tissue can be removed one at a time manually with the cutting loop without current. Alternatively, the

chips can be left in place until they obstruct visualization of the uterine cavity for later removal with graspers or suction.

Bulk electrosurgical vaporization is performed with a large surface-area electrode activated with low voltage current to vaporize relatively large volumes of tissue. Ideally such vaporization results in no tissue fragments, with the tumor gradually reduced in volume until it is feasible to extract the residual mass with grasping forceps [142]. Compared with loop resection, vaporization with these electrodes has been shown, in randomized trials of EA, to result in significantly less systemic absorption of distension media [143], likely because of a greater degree of adjacent thermal injury [144]. Available but lower quality evidence suggests that this advantage may be seen in hysteroscopic myomectomy as well [145]. The large surface area of these electrodes creates the need for higher generator output to establish the power density necessary to efficiently vaporize tissue. If set too high, the power settings increase the current delivered through the electrodes, including the dispersive electrode, a circumstance that may increase the risk of dispersive pad skin burns [146]. It is likely that this risk is largely reduced with generators that measure tissue impedance, a circumstance that allows for a lower power setting on the generator. Although it is the perception that vaporization should reduce operating time because of a reduced need to interrupt the procedure to remove tissue fragments, there are no available data to support this hypothesis.

Mechanical resection of leiomyomas has been reported in a limited fashion. A single pilot RCT included both leiomyomas and polyps and concluded that the mechanical device was more efficient than the radiofrequency resectoscope [147].

The removal of type-0 and most type-1 lesions is generally straightforward, but for deep type 1 and type 2 lesions that extend close to the serosa, within a few millimeters, there may be a role for the concomitant performance of laparoscopy, not necessarily because it reduces the chance of perforation, but because it allows for the creation of a safe buffer of gas around the uterus should perforation occur. Alternatively, intraoperative transabdominal ultrasonography can be performed when performing dissection of leiomyomas that are believed to be close to the uterine serosa [148]. The fluid contrast in the endometrial cavity may allow the surgeon to determine the amount of myometrium between the electrode and the uterine serosa. Unfortunately, there are few published data describing this technique or of the results when it is performed.

### *Complications of Hysteroscopic Myomectomy*

#### *Traumatic*

Perforation of the uterus can occur with dilators, mechanical grasping tools, or the hysteroscopic/resectoscopic system. If perforation occurs with mechanical instruments, and no bowel injury is suspected, the patient can be observed expectantly. Laparoscopy should be reserved for those circumstances where bowel injury is suspected, where there appears to be a large defect, or in the presence of heavy bleeding. If perforation occurs with an activated electrode, one has to assume that there has been a bowel injury until proven otherwise, and laparoscopy or laparotomy is recommended [149,150]. As discussed previously in this guideline, the risk of cervical laceration and uterine perforation is reduced with the preoperative use of laminaria or misoprostol. Although the force required for cervical dilation appears to be reduced with the intraoperative use of dilute intracervical vasopressin, there are far fewer available data to determine if the risk of cervical laceration or uterine perforation is reduced.

#### *Excessive Fluid Absorption*

Excess absorption of non-crystalloid distension media can cause serious fluid and electrolyte imbalance, pulmonary and cerebral edema, cardiac failure, and death [151–154]. Although complications associated with excess fluid absorption are relatively uncommonly encountered in urologic resectoscopic surgery in males, premenopausal women undergoing resectoscopic surgery in the uterus may be at greater risk because of the inhibitory impact of female gonadal steroids (most likely estrogen) on the sodium/potassium ATP'ase pump [155]. Detailed guidelines for fluid management will be published by the AAGL (in preparation at time of press), and so the content provided below serves only as a summary.

The goals of fluid management include the following: (1) prevention of excess absorption; (2) early recognition of excess absorption; and (3) choosing the distending medium least likely to cause complications in the event of excess absorption.

Fluid distending media can be infused either by gravity or by pump systems, each of which generate intrauterine pressure that contributes to the volume of systemic absorption. Such absorption has been shown to increase when the intrauterine pressure exceeds the mean arterial pressure. This pressure is typically 90 to 132 cm (36 to 52 inches) of water [156] and can be achieved by placing the container of fluid at these heights or by pump mechanisms that monitor pressure. Consequently, the intrauterine pressure should be maintained at the lowest pressure that allows good visualization for performance of the hysteroscopic myomectomy.

Intracervical injection of agents that cause uterine contraction, such as vasopressin [129,157] and the prostaglandin F2$\alpha$ agonist carboprost, [158] have also been shown to decrease fluid absorption.

Early recognition of excess absorption is based on careful monitoring of intake and output in a fashion that is regularly reported to the surgeon. The use of electronic measuring devices is encouraged, as manual calculation of intake and output is subject to error, and containers of fluid are often overfilled by about 2.5% to 5%, leading to erroneous calculations [159]. Typically, 1000 mL is suggested as the maximum allowable amount of absorption, but the size of the patient, her medical status, and the medium chosen all

greatly influence the amount that is acceptable. Regardless of these parameters, the AAGL Practice Guideline on hysteroscopic distention media (currently in development) will suggest that 2500 mL is the maximum allowable systemic absorption in a hysteroscopic procedure, but that in some circumstances, such as individuals of small stature, or those compromised by comorbidities such as heart failure, such volumes of hypotonic fluid would not be tolerable.

The selection of distending media influences the potential consequences of excess fluid absorption. Monopolar instruments require non-conductive distending media that include 1.5% glycine, 3% sorbitol and 5% mannitol solutions. Although excess absorption of these agents can cause hypotonic (glycine, sorbitol) or isotonic (mannitol) hyponatremia, it is the hypo-osmolar-associated cerebral edema that has been associated with the most severe complications including death [160]. Five percent mannitol is isotonic, and although excess absorption can cause hyponatremia, there appears to be a reduced incidence of hypoosmolality, and, consequently, reduced frequency of cerebral edema [161]. Because it is an osmotic diuretic, mannitol may cause a rapid elimination of free water, which likely assists in the correction of associated hyponatremia.

If mechanical or bipolar instruments are being utilized then it is possible to use electrolyte containing solutions, such as normal saline, to distend the uterus. Such distension media are associated with fewer unfavorable changes in serum sodium and osmolality than the electrolyte free media used with monopolar instruments [134–137]. Their use, however, does not eliminate the need to prevent excess absorption or to closely monitor fluid balance, as overload can cause pulmonary edema and has even caused death [162].

*Bleeding*

Heavy bleeding from the endometrial cavity is uncommon after hysteroscopic surgery in general. Intracervical injection of a prostaglandin F2$\alpha$ analog (Carboprost, Hemabate; Upjohn, Kalamazoo, MI) causes uterine contraction and may provide some control of such bleeding [158]. Persistent or heavy bleeding can also be treated by the placement of a Foley catheter/balloon into the endometrial cavity, inflating it with sufficient saline until the bleeding stops. The balloon may be deflated after 1 hour and removed if bleeding has subsided. Another option for controlling bleeding is uterine artery embolization with interventional radiologic techniques. Finally packing the uterus with vasopressin-soaked gauze has been described for the management of severe cases [150], but the potential risks of systemic intravasation of vasopressin make this an approach of last resort.

*Thermal Burns*

Thermal injury caused by the use of radiofrequency electricity may be related to the active electrode, the dispersive electrode, or may be caused by current diversion, the latter a circumstance unique to monopolar resectoscopes. Active electrode trauma can occur as a result of unintentional activation while the electrode is resting on the abdominal wall or when it is near the vulva, vagina, or cervix. Such circumstances can be prevented by careful management of the activation pedals, and by delaying attachment of the electrosurgical cables to the resectoscope until the surgeon is ready to place it in the endometrial cavity. More sinister burns occur when the uterus is perforated by an active electrode causing injury to surrounding structures, most commonly the bowel or vessels. At least 2 deaths are known from injuries to major pelvic vessels during resectoscopic surgery and unrecognized uterine perforation. Avoiding activation of an electrode when it is being advanced largely prevents this type of injury. As discussed in the section on perforation, when perforation of the uterus is known or suspected to occur as a result of an activated electrode, abdominal exploration is mandatory.

Dispersive electrode burns are now relatively uncommon with the advent of isolated circuit electrosurgical systems, and the generalized availability of electrode impedance monitoring systems in contemporary electrosurgical generators. Monitoring of the electrical impedance allows the system to detect either the absence or the partial detachment of a dispersive electrode and give the signal to prevent electrode activation. Absent such a system, the dispersive electrode can be partially detached to the point that the power density rises to a level sufficient to cause thermal injury to the underlying skin. Although it is always important to ensure that there is good contact between the dispersive electrode and the skin, it is especially important in circumstances where dispersive electrode monitoring is not available.

Another circumstance that could contribute to dispersive electrode injury is the use of bulk vaporization electrodes that require relatively high power settings to generate sufficient current density to create the desired electrosurgical effect. Even with an appropriately attached electrode, thermal injury has been described. The role of the design of the electrosurgical generator is not clear, but it is apparent that those without active electrode impedance monitoring require higher power settings to achieve the desired effect. Consequently, it is important to apply this technique with the lowest power setting necessary to vaporize the tissue, and, where possible, to use electrosurgical generators with active electrode impedance monitoring.

It has been known for some time that electrical burns can occur in association with the use of the monopolar resectoscope. Such injuries result from stray radiofrequency current reaching and being focused on unintended tissue including the vulva, vagina and cervix [158–160,163–165]. The basic mechanism seems to involve current that is directly or capacitively coupled to the resectoscope's external sheath where it normally flows to the surrounding cervix. If the external sheath retains enough contact with the cervix, the current may be dispersed (defocused) and no injury results. However, if the sheath is not in good contact with the cervix or in the presence of a short and/or scarred cervical

canal, the current may flow from the sheath to whatever tissue it is in contact with, such as the vagina or vulva, potentially causing a burn if a high enough current density is attained [166]. As a result, the surgeon should ensure that the cervix isn't excessively dilated relative to the diameter of the resectoscope and that the external sheath is maintained in the cervical canal whenever the electrode is activated.

There may be other factors that influence the risk of current diversion and thermal injury to the vagina and vulva. Although it is not clear whether all or most of the energy must be transferred to the external sheath for these burns to occur, it is apparent that there are circumstances where a larger proportion of the generator's output is transferred to the external sheath, a potential contributor to these risks. Damage to the insulation can cause 100% of the energy to be transferred to the sheath if the electrode is not in contact with tissue, a circumstance referred to as "open activation." Such "short circuits" frequently cause radiofrequency "leakage" that manifests with interference on the video monitor or stimulation of nerves or skeletal muscle to cause, for example, jerking movements of the legs. If any of these circumstances is noted, the integrity of the electrical circuit, including the electrode insulation, should be immediately checked. Open activation should be avoided by ensuring that the electrosurgical unit should be activated only when the electrode is in contact with tissue. Finally, because coupling, and even electrode insulation damage is also related to voltage, the higher voltage inherent in dampened and modulated waveform (coagulating) current probably increases risk, and appropriate caution should be applied when using this waveform. For submucous myomectomy, there are few requirements for the use of such high-voltage outputs.

*Adhesions*

Intrauterine adhesions can occur after hysteroscopic myomectomy to the point that they adversely impact fertility. Much of the available data comes from a single retrospective study. When second-look hysteroscopy was performed after 1 to 3 months on 153 women who underwent TCRM, 2 (1.5%) of 132 with single myomectomy had intrauterine adhesions [167]. Nine women who had myomas on opposing surfaces of the endometrium had an intrauterine device placed at the end of the procedure in an attempt to reduce adhesion formation. Seven (78%) were noted to have adhesions on follow-up hysteroscopy. An additional 7 women with opposing myomas had office hysteroscopy 1 to 2 weeks after the resection, all of who had adhesions, which were easily divided with the tip of the hysteroscope. At their follow-up hysteroscopy, the endometrial cavity remained free of adhesions.

Although the numbers are small, and given that the risks of office hysteroscopy are low, a liberal approach to early "second-look" seems reasonable. If, on preoperative assessment, it can be anticipated that a large proportion of the cavity will be denuded of endometrium after resection, an abdominal approach (laparotomy, laparoscopy, or "robotic") to myomectomy should be considered.

## Recommendations

### *The Following Recommendations and Conclusions are Based on Good and Consistent Scientific Evidence (Level A)*

1. Submucous leiomyomas contribute to infertility, and although their removal improves pregnancy rates, the fertility rate remains lower than is the case for women with normal uteri.
2. In women under the age of 50, the incidence of sarcoma in submucous myomas is extremely low. Clinical decisions in such women should be made with the understanding that submucous lesions are very rarely malignant.
3. Hysteroscopy, infusion sonohysterography (saline solution, gel) and MRI are all highly sensitive and specific for the diagnosis of submucous leiomyomas.
4. Hysterosalpingography is less sensitive for diagnosing submucous myomas than hysteroscopy, infusion sonohysterography, and MRI, and is much less specific.
5. Transvaginal ultrasound is less sensitive and less specific for diagnosing submucous myomas than hysteroscopy and infusion sonohysterography.
6. Magnetic resonance imaging is superior to other imaging and endoscopic techniques in characterizing the relationship of submucous leiomyomas to the myometrium and uterine serosa.
7. Endometrial ablation can be an effective therapy for selected women with type 2 leiomyomas and HMB who do not wish to become pregnant in the future.
8. Cervical preparation techniques can reduce the requirement for dilation, and, likely, the incidence of uterine trauma associated with hysteroscopic surgery, including hysteroscopic myomectomy for submucous myomas. This can be accomplished before surgery with laminaria or prostaglandins or during surgery with intracervical injection of a low dose of dilute vasopressin solution.
9. The preoperative use of GnRHa facilitates the process of treating anemia in women planning surgery for submucous myomas.

### *The Following Recommendations and Conclusions are Based on Limited or Inconsistent Scientific Evidence (Level B)*

1. Submucous myomas increase the incidence of abnormal uterine bleeding, most commonly HMB, but the mechanisms by which the bleeding increases are unclear.
2. Submucous myomas increase the risk of recurrent early pregnancy loss.
3. The LNG-IUS appears to reduce the incidence of submucous leiomyomas.
4. If fertility enhancement is not a goal, women with asymptomatic submucous myomas can be watched expectantly.

5. Hormonal treatment with progestin-containing agents such as combination oral contraceptives, LNG-IUS, or depot medroxyprogesterone acetate may successfully treat AUB and reduce the growth rate of submucous leiomyomas.
6. The impact of leiomyoma ablation techniques on submucous leiomyomas and the overlying and nearby endometrium has not been established.
7. The role for GnRHa administered for the purpose of reducing operating time, the amount of systemic absorption of distention media, and the risk of incomplete resection of submucous myomas has not been established.
8. For women desiring future fertility, or who are currently infertile, an abdominal approach to submucous myomectomy should be considered when there are 3 or more submucous myomas or in other circumstances where hysteroscopic myomectomy might be anticipated to damage a large portion of the endometrial surface.
9. Hysteroscopic myomectomy with the removal of the entire myoma is effective for the relief of HMB.
10. If hysteroscopic myomectomy is performed for AUB, and future fertility is not an issue, concomitant endometrial ablation may reduce the risk of subsequent uterine surgery.
11. Postoperative bleeding can be managed either with intracervical prostaglandin $F2_{\alpha}$ (carboprost) or with tamponade by use of an inflated balloon catheter.
12. Distention media complications can be minimized with strict monitoring of fluid deficit, preferably with weighted monitoring systems and the adherence to institutionally predetermined fluid loss guidelines.
13. The risk of monopolar current diversion resulting in lower genital tract burns may be reduced by maintaining contact of the external sheath with the cervix, avoiding activation of the electrosurgical unit when the electrode is not in contact with tissue, ensuring the sustained integrity of the electrode insulation, and minimizing the use of high-voltage ("coagulation") current when performing hysteroscopic submucous myomectomy.
14. Postmyomectomy intrauterine synechiae are more common after multiple submucous myomectomies. In such circumstances, and when fertility is an issue, second-look hysteroscopy and appropriate adhesiolysis should be considered.

### *The Following Recommendations and Conclusions are Based Primarily on Consensus and Expert Opinion (Level C)*

1. The direct source of abnormal uterine bleeding in women with submucous myomas is usually the endometrium itself, a circumstance that allows for the selection of medical therapies aimed at the endometrium or for endometrial destruction, provided fertility is not an issue.
2. Women with submucous myomas and abnormal uterine bleeding who are in the late reproductive years may be considered for suppressive therapy with GnRH agonist, or other medical therapies, which may be used continuously or continued intermittently until menopause.
3. With currently available evidence, embolic and ablative therapies are not appropriate for women with submucous myomas who have current infertility or who wish to conceive in the future. These techniques include UAE and occlusion, as well as leiomyoma ablation with radiofrequency electricity, cryotherapy, and MRg-FUS.
4. When planning the appropriate surgical approach, the surgeon should personally evaluate the images from any uterine imaging studies.
5. If hysteroscopic myomectomy is to be performed with a monopolar or bipolar resectoscope or any other surgical device, the surgeon should be familiar both with the device and the related fundamentals of electrosurgery or other energy source.
6. When performing radiofrequency electrosurgical procedures with monopolar instruments, it is mandatory to use electrolyte-free fluid distension media such as 5% mannitol, 5% glycine, or 3% sorbitol. Provided the use of careful fluid monitoring and adherence to protocols designed to terminate procedures if unacceptable thresholds are met, there is no currently available evidence to suggest that one hysteroscopic fluid distention medium is safer than the other. However, 5% mannitol is isosmolar and is an osomotic diuretic, features that make it theoretically safer than other electrolyte-free options for uterine distention.
7. Provided adequate training, available equipment, and appropriate analgesia or anesthesia, small submucous myomas can be removed in the office setting.
8. There may be a role for concomitant laparoscopy or ultrasound when hysteroscopic myomectomy is performed on deep type 2 submucous myomas.
9. Intrauterine adhesions can be minimized if opposing tissue is not resected during a single surgery.
10. Second-look hysteroscopy may be effective for postoperative intrauterine adhesions and thereby could reduce the long-term risk of adhesion formation.

### *Recommendations for Future Research*

1. Characterize the type of leiomyomas according to the new FIGO subclassification system for submucous leiomyomas and, in particular, to conduct research distinguishing between type 2, 3, and 4 leiomyomas.
2. Further evaluate the role of submucous leiomyomas in the genesis of AUB. Such studies could determine the histologic and molecular characteristics of the endometrium of women with submucous leiomyomas and HMB and compare them with those of women with normal menstrual bleeding and no myomas, women with

HMB and no myomas, and women with HMB and myomas that are not submucous.
3. Understanding of the histogenesis and molecular profile of submucous myomas may help develop medical or ischemia-inducing therapies for prevention or treatment of submucous myomas.
4. Evaluate the impact of submucous leiomyoma size and number on parameters such as HMB, infertility, and pregnancy loss.
5. Clinical trials evaluating the impact of medical therapies on women with HMB and submucous leiomyomas are needed. Such agents could include combination oral contraceptives, tranexamic acid, and progestins such as the LNG-IUS or danazol on the duration and volume of HMB.
6. Evaluate the impact of selective progesterone receptor modulators and aromatase inhibitors on heavy menstrual bleeding associated with submucous leiomyomas.
7. Prospective evaluation of the impact of uterine artery embolization or occlusion on submucous leiomyomas is necessary.
8. Prospectively evaluate of the impact of selective leiomyoma ablation on submucous myomas, the molecular profile of the adjacent endometrium and the related symptoms of abnormal uterine bleeding or infertility.
9. Long-term studies on the impact of various endometrial ablation techniques on the symptom of HMB in women with submucous leiomyomas should be performed.
10. Comparative evaluation of the efficacy and effectiveness of different methods for preparation of the cervix for resectoscopic surgery should be initiated.
11. Comparative evaluation of clinically relevant outcomes comparing resectoscopic myomectomy with loop and bulk vaporizing electrodes is important.
12. Rigorous evaluation of the role for simultaneous ultrasound and/or laparoscopy on the safety and efficacy of resectoscopic myomectomy for type 2 leiomyomas has great merit.
13. Identification of the impact of myomectomy on the molecular characteristics of the endometrium and myometrium at baseline is a basic study necessity.
14. Further evaluation of the role of anti-adhesion agents after hysteroscopic myomectomy is of clinical importance.

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