Current Treatment Options and Emerging Strategies for Fibroid Management

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Citation

Abstract

Although hysterectomy remains the definitive treatment for symptomatic uterine fibroids, other options are needed for women who wish to preserve fertility or otherwise avoid surgery. Newer procedures such as laparoscopic myomectomy, myolysis/cryomyolysis, MRI-guided focused ultrasound surgery fulfill the needs of some women, but may cause morbidity and recurrence. Studies support the safety and effectiveness of uterine artery embolization (UAE) and laparoscopic uterine artery occlusion (LUAO), which are less invasive procedures that seek to treat fibroids by producing permanent uterine ischemia. However, these procedures might affect fertility, and LUAO poses some technical challenges. Doppler-guided Uterine Artery Occlusion is a promising investigational, minimally invasive procedure that targets the same putative mechanism of action of UAE and LUAO but causes temporary uterine ischemia. Results from future studies, with more patients and longer follow-up, should help us match the needs of each patient and their clinical presentation to the most appropriate treatment.

INTRODUCTION

Although most uterine fibroids (leiomyomas) are asymptomatic and remain undiagnosed, these common benign tumors may cause significant gynecologic morbidity, particularly in premenopausal women. [1] Uterine fibroids may lead to abdominal pain, menorrhagia and metrorrhagia that may be associated with dysmenorrhea, reduced fertility, and increased risk for preterm labor and delivery and for cesarean delivery. [2,3]

Estimates of the incidence of uterine fibroids vary widely both in the United States and Europe because of under-diagnosis and differences in diagnostic methods, classification, and study populations. [2] Among US women, rates of uterine fibroid diagnosis per 1,000 person-years range from 12.8 for all races, 12.5 for white women, and 37.9 for black women regardless of diagnostic method (ie, clinical examination, ultrasound, or surgical) to 1.9, 1.5, and 3.8, respectively, for hysterectomy-confirmed cases. [1] In one large US study (N = 910) in women, the leiomyoma status of a random sample of women aged 35 to 49 years from the Washington, DC, area was determined. [4] The results demonstrated an overall prevalence of 54%; of these, 27% were white and 66% were black. [4] Ultrasonographic screening in premenopausal women found that 51% of those with no previous diagnosis had evidence of uterine leiomyomas, with a greater than 80% cumulative incidence by age 50 years in black women and 70% in white women. [5] In terms of clinical prevalence, many authors report that uterine fibroids occur in 20% to 40% of premenopausal women, but studies of their prevalence in young asymptomatic women range from as low as 3.3% to as high as 77%. [3]

According to a 1994 to 1999 US surveillance investigation, uterine fibroids accounted for 73% of all hysterectomies including 68% of hysterectomies among black women, 33% among white women, and 45% among women of other ethnicities. [6] The overall rate of hysterectomy attributed to uterine fibroids increased from 1.8 per 1,000 woman-years during 1988 to 1993 to 2.1 per 1,000 woman-years during 1994 to 1999, possibly because of an increased availability of ultrasound in obstetrician–gynecologist clinics for diagnosis. [6,7] In the UK, approximately 30% of the 42,500 annual hysterectomies are performed for fibroids. [8]

Not surprisingly, managing and treating uterine fibroids poses a significant economic burden. Flynn and colleagues [9] have estimated more than 2 billion dollars in annual total direct costs (including patient care, ambulatory surgery, outpatient clinic, and diagnostic testing) for the treatment of uterine fibroids in the United States, with more than 1.5 billion dollars attributed to inpatient care associated with

hysterectomy. Others have estimated a $4,624 average annual excess cost for each woman diagnosed with uterine fibroids, including the costs of more clinic visits, diagnostic tests, procedures, disability claims, and work loss in the United States. [10] In this study, total costs for the women with uterine fibroids were 2.6 times higher than for matched controls. In addition to medical costs associated with the presence of symptomatic uterine fibroids, there are costs that are more difficult to measure, such as work loss associated with heavy bleeding, which has been estimated to be $1,692 annually per woman. [11]

Clearly, symptomatic uterine fibroids place a significant burden to individuals and society in terms of morbidity, medical resource utilization, and economic costs. Recent advances in the development of minimally-invasive fibroid treatments may improve fibroid management by positively impacting patient care and reducing costs. However, a number of efficacy endpoints are used to determine the effectiveness of uterine fibroid treatment, such as reduction of fibroid size, reduction of bleeding, and quality of life (QOL) questionnaires (fibroid-related or generic), [12] and not all studies consistently report the same efficacy endpoint. Therefore, it is difficult to compare the effectiveness of the various treatment options available. The purpose of this article is to examine current and novel approaches for the management of fibroids, focusing particularly on innovative techniques for occluding the uterine artery, such as uterine artery embolization (UAE), laparoscopic uterine artery occlusion (LUAO), and Doppler-guided Uterine Artery Occlusion (D-UAO; Table 1).

Figure 1

Table 1: Non-pharmacologic Approaches for the Treatment of Symptomatic Uterine Fibroids

Approach	Specialist	Advantages	Disadvantages
Hysterectomy	Gynecologic surgeon	Definitive therapy	Loss of fertility; hospitalization; long recovery time; cost
Myomectomy	Gynecologic surgeon	Preservation of fertility	Recurrence; hemorrhage
Myolysis	Gynecologic surgeon	Outpatient, effective	Risk of adhesions; fertility not advised; less effective for large, multiple fibroids
MRI-guided percutaneous myolysis	Interventional radiologist	Outpatient	Requirement for MRI limits procedure access
MRgFUS	Interventional radiologist	Outpatient, rapid resolution of fibroid symptoms, short recovery time, low incidence of complications, minimal pain	Lack of long-term data; requirement for MRI limits procedure access; effect on fertility and pregnancy unclear (not advised for women who wish to preserve fertility); cost
UAE	Interventional radiologist	No blood loss, nonsurgical, effective, treats all fibroids	Pain; inpatient stay; effect on fertility and ovarian reserve requires further investigation
LUAO	Advanced gynecologic endoscopist, surgeon with advanced laparoscopy skills	Outpatient, treats all fibroids, effective, uterine and cervical preservation	Invasiveness; requirement for advanced laparoscopic skills; limited data; unknown effect on fertility and ovarian reserve
D-UAO	Gynecologic surgeon	Outpatient, uterine and cervical preservation, little pain, normal menstruation restored quickly, minimally invasive	Limited data

MRI, magnetic resonance imaging; MRgFUS, MRI-guided focused ultrasound surgery; UAE, uterine artery embolization; LUAO, laparoscopic uterine artery occlusion; D-UAO, Doppler-guided Uterine Artery Occlusion.

PHARMACOLOGIC TREATMENT OPTIONS

Oral contraceptives and progestins have been used to control uterine bleeding, but there is little evidence demonstrating their effectiveness in reducing the size of uterine fibroids. [13] Pharmacologic options that have some evidence of efficacy in the management of symptomatic uterine fibroids include the progesterone receptor antagonist mifepristone, the selective progesterone receptor modulator (SPRM) asoprisnil, and gonadotropin-releasing hormone (GnRH) agonists/antagonists. Small scale randomized studies showed that low-dose mifepristone reduced amenorrhea, improved anemia, and reduced uterine size, without causing endometrial hyperplasia. [14,15,16] A randomized placebo-controlled trial in women with evidence of uterine fibroids indicated that 24 weeks of treatment with the GnRH agonist leuprolide acetate depot was safe and caused significant, albeit temporary, reductions in uterine size and fibroid-related presenting symptoms, most prominently menorrhagia, but also bloating, pelvic pressure, and urinary frequency. [17] Long-term use of GnRH agonists is associated with loss of mineral bone. To prevent osteoporosis, estrogen/progestogen add-back therapy is used; however, the combination is not considered to be cost effective. Small

studies using GnRH antagonists demonstrated rapid reduction in fibroid size, which may be explained by the lack of a flare-up of gonadotropin secretion. Treatment of leiomyoma with GnRH antagonists, by daily injections or by depot injections, resulted in shrinkage of the leiomyoma by 30% to 50% within 4 to 8 weeks. [18,19] Gonadotropin-releasing hormone analogs may have applications in reducing the size of uterine fibroids particularly to facilitate myomectomy or relieve compression of neighboring organs. [20]

Asoprisnil is the first SPRM to reach advanced clinical trials. The exact mechanism by which asoprisnil reduces uterine fibroid volume remains to be elucidated, but appears to involve a reduction in uterine blood flow, [21] possibly by cell-type specific inhibition of growth factor expression and activity in leiomyoma cells. [22] In a recently reported randomized, placebo-controlled trial in women with uterine fibroids, 12 weeks of asoprisnil treatment appeared to be well tolerated and significantly reduced fibroid volume, bloating, and pelvic pressure. [23] The most common adverse events associated with asoprisnil treatment were headache, abdominal pain, asthenia, pharyngitis, nausea, infection, enlarged abdomen, sinusitis, and flu syndrome. A few patients also developed asymptomatic ovarian cysts. In addition, the use of asoprisnil was associated with unique morphological changes and decreased levels of cell proliferation in fibroids. [24] Results of additional studies are forthcoming.

HYSTERECTOMY

As discussed above, uterine fibroids are the most common diagnosis associated with hysterectomy, which is performed approximately 600,000 times each year in the United States and 42,500 times each year in the United Kingdom. [7,8] Hysterectomy is the definitive treatment for women with symptomatic uterine fibroids because it removes all the fibroids without posing a risk of recurrence. This surgical procedure is usually associated with a high level of patient satisfaction. Beyond the obvious loss of fertility, other disadvantages of hysterectomy include the fact that it is a major surgery that requires prolonged recovery time and carries a risk of complications such as hemorrhage, bowel or bladder injury, infection, pain, or even death. Hysterectomy rates may be declining in favor of other less invasive procedures according to an analysis of data collected from 1997 to 2003 regarding patient members of Kaiser Permanente Northern California who had undergone hysterectomy, myomectomy, or UAE. [25] More definitive

studies in different populations are needed to determine whether this is a widespread phenomenon.

MYOMECTOMY

Myomectomy via laparotomy, hysteroscopy, or laparoscopy is the surgical option of choice for the removal of uterine fibroids in symptomatic women who wish to preserve their fertility or otherwise desire to keep their uterus. [13] However, these procedures should only be performed by surgeons with advanced training. Compared with myomectomy via laparotomy, laparoscopic myomectomy is associated with shorter hospital stays and quicker recovery time. [13] Key considerations for determining whether to proceed via laparotomy or laparoscopy are the number, location, and size of fibroids, as well as surgical considerations such as pelvic pathology and contraindications against laparoscopy, such as cardiovascular or pulmonary dysfunction. [13]

Myomectomy via both laparoscopy and laparotomy carries a significant risk of recurrence, possibly necessitating hysterectomy. Most studies reported 20% to 30% recurrence rates, but there is wide variability depending on factors such as study design, recurrence definitions, diagnostic methodology, length of observation, and patient selection. [13] For example, a study that used transvaginal ultrasonography to monitor fibroid recurrence in 149 patients who underwent myomectomy by laparotomy reported a 62% rate of fibroid recurrence and 9% rate of major surgery in 5 years with a lower risk of recurrence in women with solitary myomectomy and smaller preoperative uterine size. [26] In a case series study, Doridot and colleagues [27] reported fibroid recurrence in 45 (22.9%) of 196 women who underwent a laparoscopic myomectomy; the cumulative recurrence risk was 12.7% at 2 years and 16.7% at 5 years. These authors noted that the presence of more than 1 fibroid and nulliparity were risk factors for recurrence. Other potential complications of myomectomy include blood loss, infection, development of adhesions, and uterine rupture at a subsequent pregnancy.

Laparoscopic myomectomy poses a risk of necessitating conversion to laparotomy because of technical difficulties. Dubuisson and colleagues [28] observed 4 preoperative factors that were independent risk factors for conversion: size of largest fibroid 50 mm or more by abdominal and transvaginal ultrasonography, preoperative treatment with GnRH agonists, and intramural or anterior location of the main myoma.

MYOLYSIS AND CRYOMYOLYSIS

Myolysis, which uses laser energy or bipolar electrodes to cause coagulation necrosis in fibroids by damaging proteins and blood vessels, was originally developed as an alternative to myomectomy for women who wished to preserve their fertility. [29] Myolysis has shown some efficacy in reducing fibroid size in some patients, [30] but is associated with a risk of bowel adhesions and coagulation of the myometrium. [29] Donnez and colleagues [29] recommend that myolysis be used primarily for large, intramural, symptomatic fibroids that might be too difficult or time consuming for endoscopic myomectomy. Results from a non-randomized study suggest that, compared with endometrial ablation alone (n = 52), the combination of myolysis and endometrial ablation (n = 88) might reduce the need for subsequent surgery, including hysterectomy, in women with symptomatic fibroids and bleeding. [31] Besides the use of laser or laparoscopic bipolar needles, probes can also be placed by magnetic resonance imaging (MRI)-guided percutaneous procedures. [32]

Cryomyolysis, a refinement of the myolysis technique, entails the laparoscopic or hysteroscopic placement of a cryoprobe into the center of a fibroid and freezing to –100 C to –120 C to cause myoma coagulation. [33] Case series studies from 2 groups in Italy have shown that laparoscopic cryomyolysis appears to be effective in causing fibroid shrinkage (25% reduction) and symptom relief in most patients, at least up to 12 months following the procedure. [34,35]

MRI-GUIDED FOCUSED ULTRASOUND SURGERY

Magnetic resonance imaging–guided focused ultrasound surgery (MRgFUS) is a procedure approved in 2004 by the US Food and Drug Administration for the treatment of pre- or perimenopausal women with symptomatic uterine fibroids who desire to keep their uterus and have completed child bearing. Magnetic resonance imaging–guided focused ultrasound surgery combines focused high-intensity ultrasound waves to heat and destroy fibroid tissue, by induction of coagulative necrosis, and MRI to visualize anatomy, map the target fibroid tissue, and monitor the tissue temperature during treatment. [36] Although the end result of this procedure is similar to myolysis and cryomyolysis, MRgFUS has the added benefit of MRI visualization of treatment effectiveness. Magnetic resonance imaging–guided focused ultrasound surgery treats 1 fibroid at a time, and it cannot be used to treat fibroids close to sensitive organs, such as the bowel or bladder, or those

behind scar tissue. Also, the duration of the sonication portion of the procedure should be limited to 3 hours because prolonged immobilization may lead to increased risk of deep venous thrombosis or pulmonary embolism. [36]

The safety and efficacy of MRgFUS has been studied in single-arm prospective studies in women with clinically significant uterine fibroids. Stewart and colleagues [37] reported that among 55 enrolled patients, 76% were able to successfully complete the full treatment sessions in an outpatient setting with a small increase in pain and discomfort (as self-reported on a 4-point scale) and no major complications. In a subgroup of women who also underwent preplanned hysterectomy, pathologic examination of the uterus showed a 3-fold increase in volume of histologically confirmed necrosis compared with treatment volume (P <0.005); this finding coincides with the hypothesized mechanism of action, which is that with injury to a single cell, mediators of apoptosis are generated and can spread through gap junctions to extend the area of tissue destruction. Results from the pivotal study of a single treatment with MRgFUS (N = 109) showed that 71% of treated patients reached the targeted symptom reduction levels (defined as a 10-point reduction in symptom severity score (SSS; 100-point scale) of the Uterine Fibroid QOL Instrument) at 6 months post-procedure and 51% at 12 months. [38] Mean decreases in SSS were 39% at 6 months and 36% at 12 months. [38] The most frequent adverse events associated with this outpatient procedure were abdominal pain, other pain, nausea/vomiting, and positional back pain. [36] Results from a prospective study in 35 symptomatic women scheduled to undergo hysterectomy showed that 1 and 6 months after MRgFUS, 61% of patients reported a significant or partial improvement of symptoms; 6 patients underwent hysterectomy during the follow-up period. [39] In this study, the uterine fibroid volume decreased 12% at 1 month and 15% at 6 months.

FIBROID TREATMENT VIA UTERINE ARTERY OCCLUSION OR EMBOLIZATION

UTERINE ARTERY EMBOLIZATION

Originally developed to manage postpartum hemorrhage, [40] UAE was later shown to reduce uterine fibroid volume and menorrhagia. [41] Performed by an interventional radiologist, UAE involves placement of a 4- or 5-French catheter into the uterine arteries via a transcutaneous femoral approach (performed under conscious sedation) and injection of trisacryl gelatin microspheres or polyvinyl alcohol particles into these arteries to cause occlusion. [33] Uterine artery

embolization, which usually requires an overnight stay, normally causes a period of ischemic pain lasting 2 to 3 hours, followed by a plateau of pain, and then a gradual decrease in pain over the next 2 to 3 days. [33]

As with other procedures reviewed in this article, most of the data on UAE safety and efficacy were derived from case series rather than randomized controlled trials (RCTs). An analysis of data from 400 consecutive patients found a low rate of short-term complications, with no deaths and no major disabling injuries in women who underwent UAE at 2 institutions in Washington, DC. [42] In a study of 50 women who were asked to complete a baseline assessment and health-related QOL questionnaire, patients reported significant improvements in QOL measures and fibroid specific symptoms 3 and 6 months post-UAE. [43] Results from the voluntary, multicenter, prospective Fibroid Registry for Outcomes Data (FIBROID) showed that among 3,160 enrolled patients, 0.66% experienced a major in-hospital complication, 4.8% had a major post-discharge event within 30 days of the procedure, 2.4% had inadequate pain relief (the most common adverse event that required additional hospital treatment), and 1% required additional surgical intervention within 30 days after UAE. [44,45] A year after UAE, follow-up data from 1,701 patients showed that the mean symptom score improved from 58.6 to 18.23 (P <0.001), but 5.3% of patients had no symptom improvement, 2.9% had a hysterectomy, and 7.3% (primarily women 45 years or older) had amenorrhea due to embolization. [46] One limitation of this study is that the 1-year data were not available for 20% of patients, which might have skewed the results if these dropouts had experienced more unfavorable outcomes than the rest of the study population.

The Dutch Uterine Artery Embolization in the Treatment of Symptomatic Uterine Fibroid Tumors (EMMY) trial compared UAE (n = 88) with hysterectomy (n = 88) for the treatment of menorrhagia caused by uterine fibroids. [47] The primary endpoint of this RCT was whether at least 75% of patients treated with UAE would avoid subsequent hysterectomy. Recently updated results showed that 2 years post-treatment, 23.5% of patients in the UAE group had undergone a hysterectomy and that there were no significant differences in improvement compared with baseline in terms of pain and bulk-related complaints. [48]

An important concern with UAE is its possible impact on menstruation and ovarian function. Chrisman and colleagues [49] reported that regular menses resumed in 56 (85%) of 66 patients (who had regular periods before the procedure) after an average of 3.5 weeks. Nine of 10 patients who failed to resume regular menstruation had laboratory results consistent with ovarian failure; also, these 9 patients were older than 45 years of age. The authors reported no difference in presenting symptoms, amount of occluding material used, or fibroid size between patients who did or did not resume regular menstruation.

Current data indicate that UAE controls menorrhagia in 85% to 95% of patients and bulk-related symptoms in 70% to 90% of patients, with a low rate of symptom recurrence. [50] In the absence of much comparative data and data with long follow-up, UAE does appear to have a lower risk of complications, shorter duration of hospitalization, and faster recovery compared with surgical alternatives such as hysterectomy and myomectomy. [50] However, the potential risk of loss of ovarian function associated with UAE is a serious consideration in women who desire to retain fertility. [51]

LAPAROSCOPIC UTERINE ARTERY OCCLUSION

Laparoscopic uterine artery occlusion uses a laparoscopic lateral retroperitoneal approach to achieve uterine artery occlusion. Unlike with UAE, patients undergoing LUAO are placed under general anesthesia, and artery occlusion is performed using ultrasonically activated sheets, clips, or electrosurgery. [52,53] Early indication of the short-term safety and efficacy of this procedure was reported by Lichtinger and colleagues [52] in a study of 8 patients who underwent LUAO for the treatment of fibroids associated with abnormal uterine bleeding, pelvic pain or pressure, or anemia. All patients in this study were discharged within 20 hours of the procedure, and all 5 patients who had abnormal bleeding at baseline reported a satisfactory decrease without developing amenorrhea. Seven of 8 patients had complete disappearance of the pain or pressure they had experienced before the procedure, with the remaining patient experiencing significant relief of these symptoms. These authors cautioned that LUAO should be performed only by surgeons with advanced skills in laparoscopy.

Additional data with LUAO are available from case series and a small randomized trial. For example, a Czech study of LUAO in 68 consecutively enrolled women reported that with a median follow-up of 14.5 months, 93.2% of patients had improvement in menorrhagia or dysmenorrhea, and there was a 57.8% average reduction in volume of the dominant fibroid. [53] The mean time in surgery was 30.8

minutes (range 15-20 min), with a mean blood loss of 14.7 mL, 2.4-day mean hospital stay, and a 7.3% rate of postoperative complications. A larger retrospective analysis from the same Czech group reported that 8 (7.1%) of 114 women who underwent LUAO had complications, none had intraoperative complications or permanent injuries, and 10 (9.0%) of patients had fibroid recurrence. [54] At median follow-up at 23.6 months, the recurrence-free survival interval rate (ie, with no clinical failure, no recurrence) was 88.3%.

An analysis of data from a Norwegian randomized controlled trial in 58 premenopausal women with symptomatic uterine fibroid showed that fewer patients treated with UAE compared with LUAO complained of heavy bleeding (4% vs 21%, P = 0.044) 6 months post-procedure. [55] However, the postoperative use of ketobemidone, an opioid analgesic, was higher after UAE compared with LUAO (46 mg vs 12 mg, P <0.001), suggesting that LUAO caused less postoperative pain. A brief report from a prospective cohort study comparing LUAO with UAE raised concerns about increased risk for preterm birth and cesarean delivery with both procedures and higher rates of spontaneous abortion following UAE than LUAO (43.7% vs. 15%). [56] Data from prospective trials with larger numbers of patients and longer follow-up are necessary to determine whether there are truly any differences in the safety and effectiveness of these procedures.

DOPPLER-GUIDED UTERINE ARTERY OCCLUSION

The positive experience with UAE and LUAO raises the question of whether temporarily occluding the uterine arteries may be just as effective as permanent occlusion or embolization in the treatment of uterine fibroids. To this end, Dickner and colleagues [57] demonstrated that a Doppler-guided nonincisional transvaginal approach could be used to successfully identify uterine arteries in 108 of 109 healthy premenopausal women despite wide variability in the position and depth of these arteries. These findings were the basis for the development of a uterine device (D-UAO) composed of a cervical tenaculum incorporating a guiding monorail and a paracervical vascular clamp with integrated Doppler ultrasound crystals, connected to a battery-powered ultrasound transceiver to generate an audible Doppler signal.

Lichtinger and colleagues [58] studied D-UAO in 10 symptomatic women with intramurally located uterine fibroids (>3 cm in average diameter by ultrasound) and found that it could be used to safely and effectively occlude the uterine arteries. After the uterine arteries were located with the audible Doppler signal, the paracervical vascular clamp was placed transvaginally and bilateral occlusion was achieved by folding the vaginal tissue around the uterine arteries to interrupt blood flow. In this pilot study, the investigators reported a 26-minute average time of clamp closure (range, 10-59 min), which resulted in the uterus remaining blanched throughout this period in all patients. Also in all patients, after the clamp was opened, the Doppler signal from the clamp returned immediately and the uterus regained a pink tonality. In addition, the ureters were never obstructed, and there was no evidence of injury in the vagina or cervix after clamp removal.

Case reports provide the initial evidence of the efficacy of D-UAO in reducing uterine volume, menorrhagia, and other fibroid-related symptoms. [59,60] Also, according to a preliminary report from a prospective study in 40 women, 6 months after D-UAO the dominant fibroid size was reduced 30% to 35%, and uterine size was reduced by an average of 20%. [61] In addition, patients with menorrhagia had a 35% to 40% reduction in menstrual blood that was associated with an average 35% reduction in Ruta Menorrhagia scores. Patients experienced few adverse events, with no reports of amenorrhea. Because 5 women experienced 6 hydronephrosis events (which spontaneously resolved in 3 patients and were effectively treated in the other 2), the procedure was successfully modified by filling the bladder to move the ureters away from the uterine arteries prior to the D-UAO, restricting excessive device movement while searching for uterine artery signal, and limiting the use of the larger clamp size to cervices larger than 4.5 cm. Since this mitigation strategy was implemented, no new cases of hydronephrosis have been reported (data on file).

Doppler-guided Uterine Artery Occlusion is performed under anesthesia (in the form of epidural, paracervical block plus patient-controlled analgesia, or IV sedation plus patient-controlled analgesia) to prevent patient movement and potential dislodgement of the device. Deep venous thrombosis prophylaxis with pneumatic compression boots is used because the D-UAO device must stay in place for 6 hours. Anticoagulants are not recommended because they might interfere with the putative mechanism of action of this procedure. Additional clinical studies of D-UAO are ongoing.

PROPOSED MECHANISM OF ACTION OF UTERINE ARTERY OCCLUSION AND EMBOLIZATION

Burbank and Hutchins [62] proposed that uterine fibroids could be treated through the creation of transient uterine ischemia produced surgically in the case of LUAO and embolically in the case of UAE. The rationale for this hypothesis, which provides the putative mechanism of action for these procedures, is based on the fact that the uterus and, by default, uterine fibroids are mainly supplied with blood from branches of the uterine arteries. When these arteries are bilaterally occluded by surgery or injection of embolic particles, uterine blood flow is almost completely stopped, leading to blood clotting within the intrinsic arteries of the uterus and in the fibroids. The myometrial cells withstand this transient ischemia, and after approximately 6 hours, the clotted blood in the intrinsic uterine arteries lyses, reperfusing the uterus with the aid of blood flow from collateral arteries. However, fibroids are unable to lyse the clotted blood, causing eventual infarction and necrosis that results in reduced uterine volume and fibroid size. [62,63] The mechanism of action of D-UAO is thought to function in a similar way. In this case, clamp application stops uterine artery blood flow, triggering the sequence of blood clotting, uterine ischemia, and fibroid infarction and necrosis. This mechanism of fibroid death and myometrial survival following prolonged ischemia appears to use the same biological processes that cause placental death after postpartum clotting of uteroplacental arteries. [64] Some experimental evidence in support of this mechanism of action comes from monitoring of uterine pH (as a proxy for hypoxia and lactic acidosis) before, during, and 24 hours after outpatient LUAO, which showed a time course of pH drop and rise in the myometrium that appears to be consistent with the transient ischemia hypothesis. [63]

CONCLUSIONS

Options for the treatment of symptomatic patients with uterine fibroids have increased, particularly with the introduction of less invasive surgical procedures. Although hysterectomy remains the definitive treatment, laparoscopic myomectomy, myolysis and cryomyolysis, and MRgFUS are choices that might fulfill the needs of some women who wish to preserve their uterus or otherwise avoid major surgery. These new surgical procedures offer patients shorter hospital stays and recovery times as well as less pain and scarring, but they also pose risks such as recurrence and loss of fertility. Several studies support the safety and effectiveness of UAE and LUAO, 2 minimally invasive procedures that treat fibroids via uterine artery occlusion or embolization, which produces uterine ischemia that subsequently causes fibroid infarction and necrosis. However, these procedures might affect fertility, and LUAO poses significant technical challenges. Doppler-guided Uterine Artery Occlusion is a promising new procedure currently in clinical trials in the United States and Europe that is based on the same putative mechanism of action as UAE and LUAO, without harming uterine function, at least according to initial studies. Randomized studies and prospective studies with larger numbers of patients and longer follow-up are needed to fully evaluate the safety and efficacy of all these interventions. Results from future studies should help us match the specific needs of each patient and their clinical presentation to the most appropriate treatment optoni

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References

1. Schwartz SM, Marshall LM, Baird DD. Epidemiologic contributions to understanding the etiology of uterine leiomyomata. Environ Health Perspect. 2000;108(suppl 5):821-7.
2. Payson M, Leppert P, Segars J. Epidemiology of myomas. Obstet Gynecol Clin North Am. 2006;33(1):1-11.
3. Ryan GL, Syrop CH, Van Voorhis BJ. Role, epidemiology, and natural history of benign uterine mass lesions. Clin Obstet Gynecol. 2005;48(2):312-24.
4. Wegienka G, Day Baird D, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MC, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol. 2003;101(3):431-7.
5. Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003;188(1):100-7.
6. Keshavarz H, Hillis SD, Kieke BA, Marchbanks PA. Hysterectomy surveillance --- United States, 1994--1999. MMWR CDC Surveill Summ. 2002;51(SS05):1-8.
7. Lepine LA, Hillis SD, Marchbanks PA, Koonin LM, Morrow B, Kieke BA, et al. Hysterectomy surveillance-- United States, 1980-1993. MMWR CDC Surveill Summ. 1997;46(4):1-15.
8. Edwards RD, Moss JG, Lumsden MA, Wu O, Murray LS, Twaddle S, et al. Uterine-artery embolization versus surgery for symptomatic uterine fibroids. N Engl J Med. 2007;356(4):360-70.
9. Flynn M, Jamison M, Datta S, Myers E. Health care resource use for uterine fibroid tumors in the United States. Am J Obstet Gynecol. 2006;195(4):955-64.
10. Hartmann KE, Birnbaum H, Ben-Hamadi R, Wu EQ, Farrell MH, Spalding J, et al. Annual costs associated with diagnosis of uterine leiomyomata. Obstet Gynecol.

2006;108(4):930-7.

11. Cote I, Jacobs P, Cumming D. Work loss associated with increased menstrual loss in the United States. Obstet Gynecol. 2002;100(4):683-7.

12. Spies JB, Coyne K, Guaou GN, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002;99(2):290-300.

13. Frishman GN, Jurema MW. Myomas and myomectomy. J Minim Invasive Gynecol. 2005;12(5):443-56.

14. Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. Obstet Gynecol. 2003;101(2):243-50.

15. Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. J Minim Invasive Gynecol. 2005;12(3):227-33.

16. Fiscella K, Eisinger SH, Meldrum S, Feng C, Fisher SG, Guzick DS. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstet Gynecol. 2006;108(6):1381-7.

17. Friedman AJ, Hoffman DI, Comite F, Browneller RW, Miller JD, for the Leuprolide Study Group. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. Obstet Gynecol. 1991;77(5):720-5.

18. Gonzalez-Barcena D, Alvarez RB, Ochoa EP, Cornejo IC, Comaru-Schally AM, Schally AV, et al. Treatment of uterine leiomyomas with luteinizing hormone-releasing hormone antagonist Cetrorelix. Hum Reprod. 1997;12(9):2028-35.

19. Felberbaum RE, Ludwig M, Diedrich K. Medical treatment of uterine fibroids with the LHRH antagonist: Cetrorelix [in French]. Contracept Fertil Sex. 1999;27(10):701-9.

20. Chillik C, Acosta A. The role of LHRH agonists and antagonists. Reprod Biomed Online. 2001;2(2):120-8.

21. Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev. 2005;26(3):423-38.

22. Wang J, Ohara N, Wang Z, Chen W, Morikawa A, Sasaki H, et al. A novel selective progesterone receptor modulator asoprisnil (J867) down-regulates the expression of EGF, IGF-I, TGFbeta3 and their receptors in cultured uterine leiomyoma cells. Hum Reprod. 2006;21(7):1869-77.

23. Chwalisz K, Larsen L, Mattia-Goldberg C, Edmonds A, Elger W, Winkel CA. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. Fertil Steril. 2007;87(6):1399-412.

24. Williams AR, Critchley HO, Osei J, Ingamells S, Cameron IT, Han C, et al. The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata. Hum Reprod. 2007;22(6):1696-704.

25. Jacobson GF, Shaber RE, Armstrong MA, Hung YY. Changes in rates of hysterectomy and uterine conserving procedures for treatment of uterine leiomyoma. Am J Obstet Gynecol. 2007;196(6):601.e1-601.e6.

26. Hanafi M. Predictors of leiomyoma recurrence after myomectomy. Obstet Gynecol. 2005;105(4):877-81.

27. Doridot V, Dubuisson JB, Chapron C, Fauconnier A, Babaki-Fard K. Recurrence of leiomyomata after laparoscopic myomectomy. J Am Assoc Gynecol Laparosc.

28. Dubuisson JB, Fauconnier A, Fourchotte V, Babaki-Fard K, Coste J, Chapron C. Laparoscopic myomectomy: predicting the risk of conversion to an open procedure. Hum Reprod. 2001;16(8):1726-31.

29. Donnez J, Squifflet J, Polet R, Nisolle M. Laparoscopic myolysis. Hum Reprod Update. 2000;6(6):609-13.

30. Phillips DR, Nathanson HG, Milim SJ, Haselkorn JS. Laparoscopic leiomyoma coagulation. J Am Assoc Gynecol Laparosc. 1996;3(4 suppl):S39.

31. Goldfarb HA. Combining myoma coagulation with endometrial ablation/resection reduces subsequent surgery rates. JSLS. 1999;3(4):253-60.

32. Hindley JT, Law PA, Hickey M, Smith SC, Lamping DL, Gedroyc WM, et al. Clinical outcomes following percutaneous magnetic resonance image guided laser ablation of symptomatic uterine fibroids. Hum Reprod. 2002;17(10):2737-41.

33. Sharp HT. Assessment of new technology in the treatment of idiopathic menorrhagia and uterine leiomyomata. Obstet Gynecol. 2006;108(4):990-1003.

34. Ciavattini A, Tsiroglou D, Piccioni M, Lugnani F, Litta P, Feliciotti F, et al. Laparoscopic cryomyolysis: an alternative to myomectomy in women with symptomatic fibroids. Surg Endosc. 2004;18(12):1785-8.

35. Zupi E, Marconi D, Sbracia M, Exacoustos C, Piredda A, Sorrenti G, et al. Directed laparoscopic cryomyolysis for symptomatic leiomyomata: one-year follow up. J Minim Invasive Gynecol. 2005;12(4):343-6.

36. ExAblate. InSightec® ExAblate® 2000 System Magnetic Resonance guided Focused Ultrasound Surgery [prescribing information]. 2004.

37. Stewart EA, Gedroyc WM, Tempany CM, Quade BJ, Inbar Y, Ehrenstein T, et al. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. Am J Obstet Gynecol. 2003;189(1):48-54.

38. Stewart EA, Rabinovici J, Tempany CM, Inbar Y, Regan L, Gostout B, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006;85(1):22-9.

39. Rabinovici J, Inbar Y, Revel A, Zalel Y, Gomori JM, Itzchak Y, et al. Clinical improvement and shrinkage of uterine fibroids after thermal ablation by magnetic resonance-guided focused ultrasound surgery. Ultrasound Obstet Gynecol. 2007;30(5):771-7.

40. Oliver JA, Jr., Lance JS. Selective embolization to control massive hemorrhage following pelvic surgery. Am J Obstet Gynecol. 1979;135(3):431-2.

41. Ravina JH, Herbreteau D, Ciraru-Vigneron N, Bouret JM, Houdart E, Aymard A, et al. Arterial embolisation to treat uterine myomata. Lancet. 1995;346(8976):671-2.

42. Spies JB, Spector A, Roth AR, Baker CM, Mauro L, Murphy-Skrynarz K. Complications after uterine artery embolization for leiomyomas. Obstet Gynecol. 2002;100(5 Pt 1):873-80.

43. Spies JB, Warren EH, Mathias SD, Walsh SM, Roth AR, Pentecost MJ. Uterine fibroid embolization: measurement of health-related quality of life before and after therapy. J Vasc Interv Radiol. 1999;10(10):1293-303.

44. Myers ER, Goodwin S, Landow W, Mauro M, Peterson E, Pron G, et al. Prospective data collection of a new procedure by a specialty society: the FIBROID registry. Obstet Gynecol. 2005;106(1):44-51.

45. Worthington-Kirsch R, Spies JB, Myers ER, Mulgund J, Mauro M, Pron G, et al. The Fibroid Registry for outcomes data (FIBROID) for uterine embolization: short-term outcomes. Obstet Gynecol. 2005;106(1):52-9.

2001;8(4):495-500.

46. Spies JB, Myers ER, Worthington-Kirsch R, Mulgund J, Goodwin S, Mauro M. The FIBROID Registry: symptom and quality-of-life status 1 year after therapy. Obstet Gynecol. 2005;106(6):1309-18.

47. Hehenkamp WJ, Volkers NA, Donderwinkel PF, de BS, Birnie E, Ankum WM, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. Am J Obstet Gynecol. 2005;193(5):1618-29.

48. Volkers NA, Hehenkamp WJ, Birnie E, Ankum WM, Reekers JA. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2007;196(6):519.e1-519.e11.

49. Chrisman HB, Saker MB, Ryu RK, Nemcek AA, Jr., Gerbie MV, Milad MP, et al. The impact of uterine fibroid embolization on resumption of menses and ovarian function. J Vasc Interv Radiol. 2000;11(6):699-703.

50. Worthington-Kirsch RL. Uterine artery embolization for fibroid disease is not experimental. Cardiovasc Intervent Radiol. 2005;28(2):148-9.

51. American College of Obstetricians and Gynecologists. Uterine artery embolization. ACOG Committee Opinion No. 293. Obstet Gynecol. 2004;103:403-4.

52. Lichtinger M, Hallson L, Calvo P, Adeboyejo G. Laparoscopic uterine artery occlusion for symptomatic leiomyomas. J Am Assoc Gynecol Laparosc. 2002;9(2):191-8.

53. Holub Z, Jabor A, Lukac J, Kliment L, Urbanek S. Midterm follow-up study of laparoscopic dissection of uterine vessels for surgical treatment of symptomatic fibroids. Surg Endosc. 2004;18(9):1349-53.

54. Holub Z, Eim J, Jabor A, Hendl A, Lukac J, Kliment L. Complications and myoma recurrence after laparoscopic uterine artery occlusion for symptomatic myomas. J Obstet Gynaecol Res. 2006;32(1):55-62.

55. Hald K, Klow NE, Qvigstad E, Istre O. Laparoscopic occlusion compared with embolization of uterine vessels: a randomized controlled trial. Obstet Gynecol. 2007;109(1):20-7.

56. Holub Z, Mara M, Eim J. Laparoscopic uterine artery occlusion versus uterine fibroid embolization. Int J Gynaecol Obstet. 2007;96(1):44-5.

57. Dickner SK, Cooper JM, Diaz D. A nonincisional, Doppler-guided transvaginal approach to uterine artery identification and control of uterine perfusion. J Am Assoc Gynecol Laparosc. 2004;11(1):55-8.

58. Lichtinger M, Herbert S, Memmolo A. Temporary, transvaginal occlusion of the uterine arteries: a feasibility and safety study. J Minim Invasive Gynecol. 2005;12(1):40-2.

59. Vilos GA, Vilos EC, Romano W, Abu-Rafea B. Temporary uterine artery occlusion for treatment of menorrhagia and uterine fibroids using an incisionless Doppler-guided transvaginal clamp: case report. Hum Reprod. 2006;21(1):269-71.

60. Istre O, Hald K, Qvigstad E. Multiple myomas treated with a temporary, noninvasive, Doppler-directed, transvaginal uterine artery clamp. J Am Assoc Gynecol Laparosc. 2004;11(2):273-6.

61. Vilos GA, Lichtinger M. Transvaginal Doppler-guided uterine artery occlusion for the management of leiomyomata uteri: initial pilot study results. J Minim Invasive Gynecol. 2007;14(6):S104. Abstract 286.

62. Burbank F, Hutchins FL, Jr. Uterine artery occlusion by embolization or surgery for the treatment of fibroids: a unifying hypothesis-transient uterine ischemia. J Am Assoc Gynecol Laparosc. 2000;7(suppl 4):S1-S49.

63. Lichtinger M, Burbank F, Hallson L, Herbert S, Uyeno J, Jones M. The time course of myometrial ischemia and reperfusion after laparoscopic uterine artery occlusion-theoretical implications. J Am Assoc Gynecol Laparosc. 2003;10(4):553-66.

64. Burbank F. Childbirth and myoma treatment by uterine artery occlusion: do they share a common biology? J Am Assoc Gynecol Laparosc. 2004;11(2):138-52.

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