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Review Article

Unmet Therapeutic Needs for Uterine Myomas

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ABSTRACT Uterine myomas may develop in many women, but only become clinically significant in about one third of the affected population. Although uterine myomas are most often benign, they are associated with debilitating symptoms and commonly result in hysterectomy. Current treatments for uterine myomas include pharmacologic therapies, delivery of focused energy, alteration of uterine vascular supply, or surgical procedures. Factors such as the woman's desire for future pregnancy, the importance of uterine preservation, symptom severity, and tumor characteristics direct the choice of therapeutic approach. The ideal treatment will have the following characteristics: easy to perform, minimally invasive, cost effective, preserves fertility, preserves the uterus, efficacious, acceptable tolerability and durability, and low incidence of myoma recurrence. Journal of Minimally Invasive Gynecology (2009) 16, 11–21 © 2009 AAGL. All rights reserved.

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The most common tumors in reproductive-aged women are uterine myomas, also called ''leiomyomas'' or ''fibroids.'' Although myomas are malignant only in approximately 0.5% of reported cases [1,2], they are the major cause for hysterectomy in the United States [3,4]. Uterine myomas are often associated with debilitating symptoms that can cause loss of work and increase individual and societal medical expenses [5]. These debilitating symptoms include menorrhagia, anemia, pelvic pressure and/or pain, abdominal distention, urinary frequency, constipation, and rare occurrences of pregnancy loss or infertility [6,7]. Based on insurance data from 1999 to 2003 in the United States, the estimated annual cost to a woman with symptomatic myomas is $4624/woman, $771 of which is the result of lost work [8]. Moreover, the estimated total myoma treatment cost for the year 2000 in the United States was $2.1 billion, $1.7 billion of which was attributed to the expense of hysterectomies [9].

Although the causes of uterine myomas are unclear, tumor growth is thought to be stimulated by estrogen, progesterone, and growth factors such as insulin-like growth factor and transforming growth factor-β [10–13]. Myomas appear after menarche [14] and decline after menopause [15,16]. Based on these observations, the increased hormone levels associated with pregnancy should promote tumor growth. However, the risk of myomas is reported to be 20% to 50% lower among women who have given birth compared with nulliparous women, and the risk appears to decrease with increasing parity [16–19]; this inverse association between parity and the presence of myomas appears to be caused by the increased clotting and resultant transient ischemia that occurs with childbirth [20]. Race may be a risk factor for uterine myoma development. Based on an epidemiologic study of 1364 women [21], an estimate of the overall incidence of uterine myomas in white women by age 35 years is nearly 40% and by age 50 years approaches 70%; in comparison, for black women, these figures are approximately 60% and 80%, respectively. As reviewed [22], the risk factors for uterine myomas are largely based on 9 formal epidemiologic studies. Among these studies, menopause and parity were commonly associated with a reduced risk for myoma development [22]. However, these studies have conflicting results for additional risk factors such as obesity, oral contraceptive use, and cigarette smoking [22]. It is unclear whether methodological differences can account for these inconsistencies. These unresolved questions will have to be addressed in future studies.

Currently, therapies are intended to reduce or eliminate myoma symptoms by reducing the size of tumors, reducing the amount of bleeding, or by removing the uterus or myomas. The therapeutic approach is influenced by the patients'

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symptom severity, tumor characteristics, and uterine preservation wishes. Diagnosed but asymptomatic patients often monitor their own progression, whereas symptomatic patients have several options. The subsequent sections are an overview of current therapies accompanied by their strengths and shortcomings, and a therapeutic advance on the horizon.

Pharmacologic Therapies for Uterine Myomas

Current pharmacologic therapies include gonadotropin-releasing hormone (GnRH) agonists/antagonists, oral contraceptives, progestins, and mifepristone. Although hormonal therapies are advantageous because they are noninvasive, myomas often reoccur after therapy has ceased. In addition, adverse events can be associated with these therapies, and their long-term efficacy is either undesirable, or, in the case of mifepristone, unknown. Oral contraceptives and progestins are used to manage symptoms such as bleeding [23,24], and can, therefore, be particularly useful in symptomatic women who have small myomas.

Gonadotropin-releasing hormone is a hormone that stimulates the synthesis and secretion of gonadotropins and several other hormones [25]. When GnRH is administered continuously, a brief flare-up or increase in gonadotropin release occurs that is followed by GnRH receptor down-regulation. This down-regulation causes a hypogonadotropic state. Similarly, GnRH antagonists block GnRH receptors to induce a hypogonadotropic state [11]. However, GnRH antagonists lack the flare-up and the subsequent therapeutic effects of GnRH antagonists occur within several weeks compared with several months associated with GnRH agonists [26–29].

In young women, GnRH agonists are typically used as a preoperative therapy to reduce myoma size. In perimenopausal women, GnRH agonists are used to reduce myoma bulk before the onset of menopause, when myomas normally decline [11]. As reviewed [11], several studies with GnRH agonists have reported decreased uterine volume, myoma volume, and blood loss. These reductions were often coupled by relief of pelvic pressure, urinary frequency, nocturia, and constipation [11]. However, GnRH agonists are a temporary treatment because myomas quickly return to their original size after therapy is discontinued [30].

Decreased bone mineral density is a common adverse event that can occur if GnRH agonist treatment is used for more than 6 months [31]. GnRH agonist treatment can cause 6% loss in trabecular bone, not all of which is reversible after therapy is discontinued [11,31]. Hot flashes occur in most (80%–100%) women who receive GnRH agonists; other effects may include vaginal dryness, irregular bleeding, headaches, depression, hair loss, and musculoskeletal stiffness [11].

To minimize bone loss associated with prolonged GnRH agonist therapy, hormonal replacement therapy, such as oral estrogen, progesterone, tibolone, and raloxifene, may be coadministered with GnRH agonists. Tibolone and raloxifene were used by postmenopausal women to prevent osteoporosis [11,32]. Estrogen and progesterone can also be added back to prevent bone loss [31]. In a trial of premenopausal women, the efficacy of a GnRH agonist and tibolone was compared with that of a GnRH agonist and placebo. Uterine shrinkage was not inhibited and patients had preserved bone density [33]. In a similar trial, the efficacy of a GnRH agonist plus raloxifene was studied for 6 months in women (N = 57) with symptomatic uterine myomas. Significant decreases in uterine and myoma size and myoma-related symptoms were observed (all $p < .05$); no significant changes in bone mineral density were reported [32]. Gonadotropin-releasing hormone agonists are considered to be viable short-term therapies; these therapies are not routinely recommended for long-term use based on their adverse event profile and the risks associated with long-term decreases in estrogen and progesterone levels. Moreover, myoma regrowth occurs after therapy is discontinued.

Reductions of uterine and myoma size occur more quickly with GnRH antagonists because they lack the flare-up associated with GnRH agonists. These agents are commonly used as a preoperative therapy in young women and before the onset of menopause in perimenopausal women. Cetrorelix (Solvay Pharmaceuticals, Marietta, GA), a GnRH antagonist, was studied in 18 premenopausal women with uterine myomas [27]. By ultrasound examinations, cetrorelix treatment reduced the mean uterine volume by 45% in 16 women after 3 months of treatment, but was not efficacious in 2 women. Myomectomy was performed in 12 women and hysterectomy was necessary in 3 women. One woman maintained the uterine volume decrease for 2 years after cetrorelix treatment. However, this woman was 45 years old at the beginning of the study, so she may have become menopausal during this 2-year period. Common adverse events associated with this therapy were caused by estrogen deprivation; all women experienced hot flashes and became amenorrheic. However, within 1 month of treatment cessation, normal menses resumed for all women who did not undergo hysterectomy. These findings are similar to those of GnRH agonists and indicate that GnRH antagonists should be considered a short-term therapy.

Mifepristone (Danco Laboratories, LLC, New York, NY), an antiprogestin, may be another pharmacologic option for women with myomas because the initial trials of mifepristone (5–50 mg/day) reported reductions in myoma size and symptoms [34–36]. A randomized, double-blind, placebo-controlled trial studied the efficacy of a daily 5-mg dose of mifepristone for 6 months in 42 women with symptomatic myomas [37]. In this trial, mifepristone treatment was associated with a significant reduction in uterine volume, blood loss, and increased mean hemoglobin levels (all $p < .001$). Women given mifepristone had significant decreases in symptom severity and increases in quality-of-life (QOL) measures using the Uterine Fibroid Symptom-QOL

questionnaire ($p < .05$). In addition, the incidence or severity of adverse events was not statistically different between the treatment groups. However, higher rates of cystic glandular dilatation of the endometrium were noted in the mifepristone-treated group. Additional adverse events were reported in a trial comparing 2 doses of mifepristone (5 and 10 mg/day) [34]. These included hot flashes, headache, nausea, vomiting, mood swings, diarrhea, decreased libido, weakness, and fatigue. Also, simple endometrial hyperplasia occurred in 28% of treated women, and hepatic enzymes were elevated in 8% of the women. Because clinical studies were limited to 6 months, the long-term efficacy and tolerability of mifepristone is currently unknown.

Asoprisnil (TAP Pharmaceuticals, Lake Forest, IL), a selective modulator of the progesterone receptor, was also effective in decreasing myoma size and suppressing blood loss. A randomized, double-blind, placebo-controlled, 12-week trial was conducted to evaluate the efficacy and tolerability of asoprisnil (5, 10, and 25 mg/day) in 129 women with uterine myomas [38]. Asoprisnil showed significant, dose-dependent suppression of uterine bleeding (5 mg/day, $p \leq .01$; and 10 and 25 mg/day, $p \leq .001$). In addition, the rates of amenorrhea for the 5-, 10-, and 25-mg doses were 16%, 36%, and 70%, respectively, whereas no women developed amenorrhea in the placebo group.

At 4 and 8 weeks, the 25-mg/day dose of asoprisnil was associated with significant reductions in myoma volume, compared with placebo, from baseline values (both $p \leq .05$). The 10- and 25-mg/day doses of asoprisnil were associated with significantly less bloating, and the 25-mg/day dose was associated with significantly less pelvic pressure at week 12 (all $p \leq .01$) [38]. Adverse events associated with asoprisnil treatment included bloating, flatulence, breast pain, hot flashes, and night sweats. In addition, 9 patients developed 4- to 7-cm asymptomatic ovarian cysts while receiving asoprisnil treatment. This trial was followed by a double-blind study of 33 women who were randomized to receive asoprisnil (10 or 25 mg) or placebo for an average of 95 days before hysterectomy [39]. Samples of the endometrium, myometrium, and myoma tissue were assessed morphologically after hysterectomy was performed. Asoprisnil treatment was associated with novel morphologic changes and decreased levels of cell proliferation in myoma tissue. Collectively, these studies indicate asoprisnil may be a therapeutic alternative, but long-term studies are needed. Currently, phase III trials are in progress.

Hysterectomy

Hysterectomy is the definitive treatment for uterine myomas because the procedure eliminates existing myomas and the potential for further myoma growth [40–42]. In a study of 314 women, greater than 90% patient satisfaction was reported for hysterectomy. However, within 3 years after the procedure, 48% of women regretted the loss of fertility and 33% had concerns regarding their femininity [43]. In addition, an associated surgical morbidity and mortality exists with this procedure [44], which includes blood loss, adhesions, tissue granulation, infection, postoperative pain, incontinence, constipation, sexual dysfunction, depression, and damage to the vagina, bladder, ureters, and rectum [44–48]. Complication rates and recovery appear to improve with a laparoscopic approach (Table 1) [49]. Except for recovery, there appears to be no advantage to supracervical hysterectomy versus total hysterectomy [50]. Other disadvantages to this procedure include surgical cost (~$7707) [51] and loss of wages during recovery.

Myomectomy

Selective removal of the myomas, called ''myomectomy,'' is an alternative that preserves the uterus and fertility. Myomectomy may be performed by multiple techniques: laparotomy, mini-laparotomy, laparoscopy, laparoscopy-assisted mini-laparotomy, robot-assisted laparoscopy, hysteroscopy, or vaginal [52]. The estimated procedural costs for myomectomy range from about $4000 to $9000, depending on the exact method used [53,54].

Laparoscopic procedures were associated with a lower risk of adhesions compared with an open laparotomy approach [55]. Indeed, in a study of 32 patients comparing the frequency of adhesion formation for laparoscopic versus open myomectomy, a study [56] found that the laparoscopic approach resulted in significantly fewer and less severe adhesions. It was also suggested that intraoperative bleeding may be reduced with the use of the laparoscopic route [57]. In addition, the laparoscopic route was associated with a number of other advantages. For instance, a study of myomectomy outcomes reported that in comparison with laparotomy, laparoscopy was associated with decreased febrile morbidity, a lower decrease in hemoglobin levels, fewer blood transfusions, and a shorter postoperative hospital stay [58]. Also, in this study, no significant differences between laparotomy and laparoscopic myomectomy were reported for rates of pregnancy (55.9% vs 53.6%), abortion (12.1% vs 20%), preterm delivery (7.4% vs 5%), or cesarean section (77.8% vs 65%) [58]. Several other studies show excellent pregnancy rates postmyomectomy as reported (Table 2) [59]. After 1 year, myoma recurrence was similar among both treatment groups; myomas

Table 1
Laparoscopic hysterectomy versus open abdominal hysterectomy

Lower intraoperative blood loss (WMD, 45.3 mL; 95% CI, 17.9–72.7)
Smaller decrease in hemoglobin level (WMD, 0.55 g/L; 95% CI, 0.28–0.82)
Shorter hospital stay (WMD, 2 days; 95% CI, 1.9–2.2)
Speedier return to normal activities (WMD, 13.6 days; 95% CI, 11.8–15.4)
Fewer wound or abdominal wall infections (OR, 0.32; 95% CI, 0.12–0.85)
Fewer unspecified infections or febrile episodes (OR, 0.65; 95% CI, 0.49–0.87)
Longer operating time (WMD, 10.6 min; 95% CI, 7.4–13.8)
More urinary tract (bladder or ureter) injuries (OR, 2.61; 95% CI, 1.22–5.60)

WMD = weighted mean difference.

Adapted from Cochrane Database of Systemic Reviews 2006, Issue 1, Art No.: CD003677, with permission from Wiley [49].

Table 2
Pregnancy outcomes after laparoscopic myomectomy (patients attempting pregnancy)

Study	Number Pregnant	Pregnancy Rate	SAB	Live Birth Rate	C/S Rate	Uterine Rupture
RCT's	30 L/S	54%	20%	77%	65%	0
Seracchioli, 2000	33 abd	56%	12%	88%	78%	0
Case Control	44 L/S	42%	7%	93%		0
Bulletti, 1999	12 No Tx	11%	45%	55%		0
	27 Unexpl	25%	7%	93%		0
Case Series						
Ribeiro, 1999	18	64%	12%	78%	57%	0
Landi, 2003	72		17%	79%	46%	0
Campo, 1999	13	54%	15%	85%	45%	0
Malzoni, 2003	21	55%	15%	81%	57%	0
Seracchioli, 2003	9	39%	22%	78%		0
DiGregorio, 2002	65	44%	11%	86%	92%	0
Dubuisson, 2000	100	53%	31%	69%	42%	1 surgical site
Seinera, 1997, 2000	64		12%	86%	80%	0
Stringer, 1997, 2001	7		28%	72%	57%	0
Rossetti, 2001	21	66%	22%	78%	71%	0
Dessolle, 2001	44	41%	14%	82%	32%	0
Darai, 1997	17	39%	23%	58%	33%	0
Nezhat, 1999	42		20%	75%	78%	0
Dubuisson, 1996	7	33%	0%	100%	57%	0
Miller, 1996	30	71%	13%	87%		0
Campo, 2003	22	61%	14%	86%	40%	0
Total L/S (n)	626					1

SAB, spontaneous abortion; C/S, cesarian section; RCT, randomized controlled trial; L/S, laparoscopic myomectomy; abd, abdominal myomectomy; Tx, treatment; Unexpl, unexplained infertility.

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reappeared in 12 of 66 women who underwent laparoscopy and in 12 of 65 women who underwent laparotomy. Three women underwent a second myomectomy, and 1 woman was treated by hysterectomy in the laparotomy group, but none had a follow-up operation in the laparoscopy group. Reported predictive factors for myoma recurrence after myomectomy by laparotomy or laparoscopy include nulliparity and the number of myomas [23,52,60]. Disadvantages of myomectomy include surgical morbidity and mortality, a high risk of adhesion formation (lower if performed laparoscopically), and a risk of uterine disruption during pregnancy [23,61].

Hysteroscopic myomectomy is a well-established treatment option for patients with submucous myomas, which are often associated with menorrhagia, repeated pregnancy loss, or infertility [42,62,63]. In an analysis of 122 patients treated by hysteroscopic myomectomy for submucous myomas, 71.4% were satisfied with the results of the surgery; 16 patients required additional surgical procedures for myomas, and 6 patients eventually had a hysterectomy [64]. In another study of 108 women with submucous pedunculated (n = 54), sessile (n = 30), or intramural (n = 24) myomas who underwent hysteroscopic myomectomy, the overall 3-year cumulative recurrence rate of myomas was 34% [65]. The 3-year cumulative probability of conception in women with pedunculated, sessile, or intramural myomas was 49%, 36%, and 33%, respectively [65]. Hysteroscopic myomectomy showed reproductive benefits in women who are infertile. An analysis of fertility outcomes in women with diagnosed infertility and submucous myomas reported a cumulative pregnancy rate of 55.3% after hysteroscopic myomectomy [66].

Endometrial ablation, the targeted destruction of the uterine lining [67], is another option for management of excessive bleeding associated with submucous myomas. It is often performed concomitantly with hysteroscopic myomectomy, but it can be used as a monotherapy in some women whose submucous myomas are primarily intramural or small intracavity [68]. A study compared the outcomes of 177 patients with submucous myomas who underwent hysteroscopic myomectomy with (n = 73) or without (n = 104) concomitant endometrial ablation [69]. In this study, bleeding was controlled in 96% of patients who underwent endometrial ablation, compared with 81% of patients who did not undergo endometrial ablation (p = .003). Endometrial ablation is associated with loss of fertility, so it is only appropriate for women who do not intend to have future children [42].

Complications associated with hysteroscopic myomectomy and hysteroscopic techniques for endometrial ablation include the potential for uterine perforation, injuries to adjacent structures, and fluid overload [62,70]. In rare cases, excessive fluid absorption can cause pulmonary edema or fatal hyponatremia [70]. Hysteroscopic myomectomy is an advanced surgical procedure; in complex cases it is associated with significantly higher rates of complications than other hysteroscopic procedures [62].

Myolysis and Cryomyolysis

Myolysis and cryomyolysis, the destruction of myomas by focused energy, should be considered for women who do not desire fertility. These procedures are generally performed during laparoscopy and, similar to myomectomy, are applied to myomas 1 at a time. A pilot study of 20 premenopausal women compared the effectiveness of cryomyolysis and hysterectomy [71]. Cryomyolysis effectively reduced myoma size, resolved bleeding, and abolished or reduced pain. Also, 1 year after the procedure, 75% of patients were strongly satisfied with cryomyolysis compared with 57.1% of patients satisfied with hysterectomy. The primary advantages of myolysis include uterine preservation and minimal blood loss, and it is an outpatient surgical procedure. However, concerns of adhesion formation, destruction of the normal myometrium, and inadequate determination of treatment depth are associated with this technique [71,72]. Myolysis and cryomyolysis are not optimal for women with large or multiple myomas [73]. These techniques are not advisable for women who desire pregnancy in the future because risk exists of uterine rupture, abnormal placenta development, and reduced reproductive capacity from adhesion formation [72,74]. Finally, multiple variations of myolysis techniques make comparative assessments difficult, and randomized studies need to be completed to determine the long-term efficacy and tolerability.

Uterine Artery Embolization

A noninvasive treatment that preserves the uterus is uterine artery embolization (UAE), also called ''uterine fibroid embolization.'' This procedure, which costs an estimated $5698 on average [51], globally treats the uterus and is performed by an interventional radiologist. Because uterine arteries deliver approximately 94% of the blood supply to uterine myomas, disrupting blood flow through these arteries significantly diminishes blood supply to uterine myomas [75]. Based on this idea, the UAE procedure was developed to reduce myomas by occluding blood flow in the uterine arteries. The UAE procedure involves an injection of trisacryl gelatin microspheres, polyvinyl alcohol particles, or gelatin sponge into the uterine arteries for occlusion. After the injection and subsequent occlusion, it is thought that prolonged uterine ischemia occurs, the myometrium clots, and it becomes hypoxic. The uterine clots are lysed after the myometrium is perfused by collateral arteries. Because uterine myomas are unable to lyse clots, infarction and ischemic necrosis occurs [76].

The clinical efficacy of UAE was studied extensively. This is primarily because of the Fibroid Registry for Outcomes Data (FIBROID), a database of information from more than 3000 women undergoing UAE from 72 sites [77]. Follow-up data from 1797 patients at 6 months and 1701 patients at 12 months revealed that UAE provided improvements in myoma-related symptoms and QOL [78]. At 12 months, 82% of patients indicated they would recommend UAE to family members or friends. In addition, 5.47% of patients had no improvement in symptoms, 5.0% had no improvement in QOL, and 2.9% had subsequent hysterectomy. Data from the FIBROID database indicated that major complications occurred only in 0.66% of 3041 UAE-treated patients. Within the first 30 days after UAE, the complication rate in 2729 patients was 4.8%, and the most common adverse event was inadequate pain relief that resulted in hospitalization in 2.4% of the patients. In addition, during the same period of time, 31 (1.1%) patients required additional surgery to treat their myomas, which included 3 hysterectomies [79]. Thus far, no published data exist on fertility after UAE within the FIBROID database [78,79].

The outcomes of women who underwent UAE (n = 81) or hysterectomy (n = 75) were compared in the Embolization Hysterectomy randomized controlled trial. The UAE was successfully performed in 72 (88.9%) of the 81 women who accepted UAE treatment. Technical failures caused unilateral uterine embolization in 5 (6.2%) women, and the procedure was unable to be performed in 4 (4.9%) women; these 4 women subsequently underwent hysterectomy. No significant differences occurred in the rate of major complications in the first 6 weeks. However, the rate of minor complications was higher for UAE, but the length of hospital stay was lower compared with hysterectomy [80]. Follow-up data after 2 years revealed that both groups had similar rates of moderate pain improvement (UAE, 84.9%; hysterectomy, 78.0%) and moderate bulk-related improvements (UAE, 66.2%; hysterectomy, 69.2%). Although hemoglobin levels significantly increased in both groups, the mean increase in the hysterectomy group was significantly higher (2.03 vs 1.37 g/dL, respectively; p =.037). At 24 months, 23.5% of women in the UAE group had undergone a hysterectomy. This included the 4 (4.9%) women who were unable to be treated with UAE and had subsequent hysterectomies. For the remaining cases, hysterectomies were performed in 14 women for the persistence or relapse of menorrhagia and in 1 woman for an increase in pain/bulk symptoms. The overall success rate of UAE (76.5%) was lower in this study compared with the earlier uncontrolled studies (98.5%–95.5%) [81]. In addition, the recurrence of myoma-related symptoms was high, and a 20% to 29% chance of myoma-related symptoms occurred within 5 years of UAE [82]. Also, treatment failure was associated with subserous, submucosal, and pedunculated myomas and myomas larger than 8 cm [83].

One study [84] analyzed the frequency and severity of UAE complications in 400 women who underwent UAE. This analysis showed that 10.5% of women experienced adverse events. The most common events were allergic reaction or rash (2.5%), myoma passage (2.5%), recurrent or prolonged pain (1.25%), and urinary tract infection (1.0%). Additional studies found that most women had severe pelvic pain within the first 24 to 72 hours after UAE [76]. Also, postembolization syndrome, which consists of pain, nausea, vomiting, fever, leukocytosis, and malaise, can occur in the

first month after the procedure [85]. Serious reported complications include uterine infection, necrosis of the bowel, sepsis, and death [83,86].

One concern with the UAE procedure is the potential for ovarian failure, which may be the result of embolization of the ovarian blood supply. To study this concern, an observational trial was conducted in 66 premenopausal women who underwent UAE for uterine myoma treatment [87]. Patients were considered to have ovarian failure if they were amenorrheic, had clinical symptoms of menopause, and had elevated levels of follicle-stimulating hormone (>20 IU/L). Based on these criteria, 9 (14%) of 66 women had ovarian failure within 24 to 76 weeks after the UAE procedure. A second trial investigated ovarian reserve function in 177 premenopausal women who underwent UAE or hysterectomy for symptomatic myomas by comparing the levels of hormonal indicators of premature ovarian failure [88]. Based on these measures, this trial showed that both UAE and hysterectomy affected ovarian reserve function. Uterine artery embolization is not recommended by the American College of Obstetricians and Gynecologists for women who desire future fertility because of the potential for ovarian failure [89]; however, the National Institute for Health and Clinical Excellence (NICE) Guidelines on Heavy Menstrual Bleeding from the United Kingdom informs women that UAE or myomectomy will potentially allow them to retain their fertility [90]. In addition, reports exist of successful pregnancies after UAE. For example, a study of 1200 women who underwent UAE reported 56 completed pregnancies, and 33 (58.9%) had successful outcomes [91]. In this study, 17 miscarriages, 3 terminations, 2 still births, and 1 ectopic pregnancy occurred. Pregnancy after UAE may be associated with a higher incidence of abnormal placentation. One study [92] noted this in 3 of 18 pregnancies that occurred in women who had previously undergone UAE. All 3 women were nulliparous; 2 women experienced complete placenta previa, and the third had placenta membranacea with accreta. Although it is unclear whether or not these complications were directly related to the UAE procedure, the authors recommended close monitoring of placental status during a pregnancy after UAE.

Laparoscopic Uterine Artery Occlusion

An alternative to embolizing uterine arteries is laparoscopic uterine artery occlusion (LUAO). Because it is a relatively new surgical procedure and requires advanced laparoscopic skills, limited clinical safety and efficacy data exist. In a study of 68 women treated with LUAO, the reported symptomatic improvement was 93.2% for patients ranging 3 to 36 months posttreatment. At 12 months, the average reduction in uterine and dominant myoma volume was 39.1% and 57.8%, respectively [93]. The frequency of complications and recurrence of myomas was determined in 114 women after LUAO. The median follow-up time was 23.6 months; 7.1% of women experienced complications, and 9% had recurrent myomas. Two women required hysterectomy/myomectomy as a result of myoma necrosis [94]. This procedure is limited by myoma location and associated risk of surgical morbidity/mortality, although these risks are reportedly low [94]. Advantages of LUAO are that it preserves the uterus and is an outpatient procedure. However, long-term clinical data are needed, and the appropriateness of LUAO is unclear for women who desire fertility [82].

Magnetic Resonance Imaging–guided Focused Ultrasound Surgery

A noninvasive procedure, magnetic resonance imaging–guided focused ultrasound surgery (MRgFUS), is approved by the US Food and Drug Administration for the treatment of uterine myomas in premenopausal women who do not desire fertility [82]. This procedure is performed by an interventional radiologist who uses a focused, high-frequency, high-energy ultrasound beam to thermally coagulate tissue. A magnetic resonance imaging–based thermal mapping system facilitates volume and temperature measurements of the treated tissue. Thus, the extent of treatment can be followed in real time [95,96]. Total treatment time for MRgFUS is approximately 2 to 4 hours because prolonged immobilization may lead to an increase of deep vein thrombosis or pulmonary embolism [97,98]. During the procedure, only 1 myoma is treated at a time sequentially, and MRgFUS cannot be used to treat myomas located near sensitive organs, such as the bowel or bladder or those behind scar tissue [82]. Its use in 55 premenopausal women with symptomatic myomas led to myoma necrosis [99]. Three days after the procedure, 25% of women reported discomfort, whereas only 10% of the women reported taking pain drugs after treatment. Two patients reported first-degree skin burns, and 1 patient reported bleeding caused by the thermal procedure.

A subsequent study with MRgFUS was conducted in 109 women who reported a mean reduction of 13.5% and 9.4% in myoma volume after 6 months and 12 months, respectively [82]. In addition, a 10-point improvement on the symptom severity scale of the Uterine Fibroid Symptom-QOL questionnaire was reported by 70.6% of women at 6 months and 51.2% of women at 12 months. This represented a clinically significant improvement based on a previous report of the mean Uterine Fibroid Symptom-QOL scores of women with or without symptomatic myomas [100]. However, 28% of women sought alternative treatment by 12 months after the MRgFUS procedure [98]. The short recovery time, low incidence of complications, and lack of exposure to ionizing radiation are advantages associated with the MRgFUS procedure. Although it is not currently recommended for women who desire to retain fertility, a clinical trial is currently underway to determine the potential fertility- and pregnancy-related complications associated with MRgFUS [101]. Complications associated with the procedure include minor skin burns, nausea, and nontarget sonication of the uterine serosa and sciatic nerve. Additional drawbacks of this

Table 3
Overview of current myoma therapies

Approach	Appropriate population	Advantages	Disadvantages	Potential issues for fertility/future pregnancy
GnRH agonists	Preoperative therapy in young or premenopausal women	Nonsurgical	Temporary treatment, myoma regrowth on cessation, and adverse events	None
GnRH agonists + estrogen/progestin	Preoperative therapy for young or premenopausal women	Nonsurgical	Temporary treatment and myoma regrowth on cessation	None
GnRH antagonists	Preoperative therapy for young or premenopausal women	Nonsurgical	Temporary treatment and myoma regrowth on cessation	None
Hormonal therapies	May be appropriate for broad use in women with myomas	Nonsurgical	Limited long-term data, adverse events	UNK
Hysterectomy	Women who require removal of uterus, who are close to menopause, or who do not desire fertility	Definitive therapy	Loss of fertility, surgical morbidity and/or mortality, costly procedure	Complete loss of fertility
Myomectomy	Women with visible and/or palpable myomas	Preserves fertility	Recurrence of myomas, surgical morbidity	Potential uterine rupture during pregnancy
Myolysis/cryomyolysis	Women who do not desire fertility with several, small myomas	Preserves uterus, outpatient surgery	Risk of adhesions, less effective for large and multiple myomas, undertreatment or overtreatment, fertility not advised	Reduced reproductive capacity because of adhesion formation, potential uterine rupture during pregnancy, abnormal placenta development
UAE	Women who have small myomas (<8 cm), but are not subserous, submucosal, or pedunculated	Treats uterus globally, no blood loss, and nonsurgical	Pain, possible postembolization syndrome, possibility of severe complications, fertility requires further investigation, performed by an interventional radiologist	Potential ovarian failure, abnormal placenta development
LUAO	Women with small or large myomas, subserosal myomas	Effective in skilled hands	Requires technical skill, dependent on myoma location, recurrence of myomas, fertility is unclear, insufficient long-term data	UNK
MRgFUS	Women with small myomas (<8 cm)	Incisionless, bloodless, and fast return to work	Fertility is unclear, recurrence of myomas is unclear, costly procedure, insufficient long-term data, performed by an interventional radiologist	Data pending

GnRH = gonadotropin-releasing hormone; LUAO = laparoscopic uterine artery occlusion; MRgFUS = magnetic resonance imaging–guided focused ultrasound surgery; UAE = uterine artery embolization; UNK = unknown.

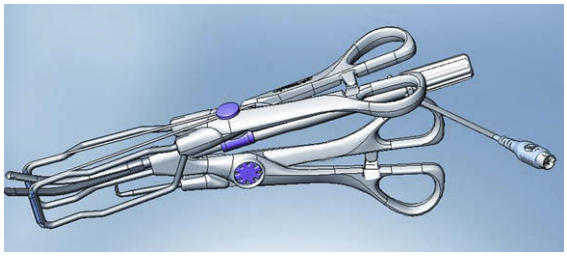

Fig. 1. Uterine artery clamp used for Doppler-guided Uterine Artery Occlusion.

procedure are access to the required equipment and expense (>$10 000). Also, insurance often will not cover this procedure [102].

Doppler-guided Uterine Artery Occlusion: A New Option for Myoma Treatment

An overview of the currently available myoma treatments described above is presented in Table 3. The limitations of these options suggest that an unmet therapeutic need still exists. Doppler-guided Uterine Artery Occlusion (D-UAO) is a new myoma treatment for which studies in the United States, Canada, Mexico, and Europe are currently being conducted. Doppler-guided Uterine Artery Occlusion (UAO) is an outpatient treatment in the United States that can be performed by a gynecologic surgeon. This minimally invasive procedure occludes the uterine arteries with a vascular clamp that is inserted into the vagina (Fig. 1). Doppler crystals are positioned in the tips of this device to audibly identify pulsatile blood flow. Thus, the location and occlusion of uterine arteries can be determined and followed during the procedure. Doppler-guided UAO was used for transvaginal uterine identification in 109 healthy premenopausal women [103]. In this study, the Doppler-guided approach successfully identified the location and depth of the uterine arteries in 108 women. A subsequent study in 10 women with symptomatic myomas showed that after the successful location of uterine arteries, the disruption of uterine artery blood flow could be achieved by placing the paracervical vascular clamp transvaginally [104]. Arterial closure was confirmed by the absence of the characteristic sound of pulsatile artery flow. Similar to UAE, this treatment is based on the principle of depriving myomas of blood supply to cause tissue death [20,105]. It was hypothesized that the myometrium develops blood clots on D-UAO clamp application and, when the clamp is removed 6 hours later, the clot undergoes fibrinolysis and uterine reperfusion occurs. Uterine myomas, however, cannot lyse clots and are permanently deprived of their blood supply [76]. Therefore, the vessels that supply the myomas remain clotted because of poor collateral circulatory support, and subsequently the myomas infarct [76]. The biological mechanism that prevents fibrinolysis in myomas is unclear but may be the result of higher levels of the enzyme, tissue plasminogen activator, that facilitates fibrinolysis, in the myometrium than in myomas [106]. The decreased vascular density in myomas, compared with other uterine tissues, may also be a contributing factor [107]. The uterus is treated globally; further, the use of D-UAO is contraindicated in pedunculated or submucous myomas.

The D-UAO procedure requires anesthesia (epidural anesthesia, paracervical block plus patient-controlled analgesia, or intravenous sedation plus patient-controlled analgesia), primarily to prevent the patient from accidentally dislodging the clamp. Although no reports of associated deep vein thrombosis exist, measures to prevent deep vein thrombosis are necessary because the clamp must be in place for 6 hours (data on file). For this purpose, pneumatic compression boots should be used instead of anticoagulants that could interfere with D-UAO's proposed mechanism of action.

Case report results suggest that D-UAO is effective in reducing uterine volume and myoma-associated bleeding. In a case report of a 43-year-old woman with menorrhagia, dysmenorrhea, and pelvic pain, uterine and dominant myoma volume had decreased (48.9% and 77.2%, respectively) 3 months after D-UAO [108]. A second case report showed that a 43-year-old woman with multiple myomas had a 70% reduction in menorrhagia symptoms 6 months after the D-UAO procedure [109]. Eight months after treatment, clinical examination confirmed a 44% decrease in uterine volume and a 71% to 99% reduction in myoma volume.

Forty women with symptomatic myomas were examined in a pilot study of the efficacy and safety of D-UAO [110]. Follow-up magnetic resonance imaging at 6 months showed an average 30% to 35% reduction in dominant myoma volume, with a 20% average reduction in uterine size. A 30% to 40% reduction in menstrual blood loss was experienced by women with menorrhagia, which was also associated with a 35% average reduction in Ruta Menorrhagia scores. Overall, cases of amenorrhea were not reported, and adverse events were minimal. Five women experienced a total of 6 hydronephrosis events. The hydronephrosis spontaneously resolved in 3 of the women; unilateral stenting was used to alleviate the hydronephrosis in 1 case, whereas in the other, spontaneous resolution of hydronephrosis was followed by contralateral hydronephrosis that was treated with endoureterotomy after unilateral stenting. This led to the implementation of a mitigation strategy to prevent further cases of hydronephrosis. The modifications included bladder filling before the procedure to move the ureters away from the uterine arteries and proper clamp size selection and orientation of the clamp on application. Because this mitigation strategy was established, no further cases of hydronephrosis were reported (data on file). Although D-UAO appears to maintain uterine function, its effect on fertility was not yet studied. Clinical trials are now in progress to provide long-term data on efficacy and tolerability.

Conclusions

Numerous treatment options are available to women with symptomatic uterine myomas. Many new procedures are

minimally invasive and have short recovery times, short hospitalization stays, and minimal pain and scarring, and are administered by a gynecologic surgeon. Treatment should be individualized to a woman's specific needs and clinical symptoms.

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