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REVIEW

Treatment of fibroids via uterine artery occlusion (uterine artery embolization and Doppler-guided uterine artery occlusion): potential role in today's armamentarium

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Abstract Uterine fibroids, the most common benign tumors of the female reproductive system, are the most common indication for hysterectomy. However, this procedure is not the ideal treatment for many women including those who desire to preserve their fertility or simply do not want to undergo surgery. New technologies and surgical innovation provide treatments that are less associated with morbidity such as uterine artery embolization, magnetic resonance imaging-guided focused ultrasound, and laparoscopic uterine artery occlusion. This manuscript will discuss the putative mechanism of action and clinical application of uterine artery occlusion using Doppler-guided Uterine Artery Occlusion, a new investigational treatment modality for uterine fibroids.

Keywords Uterine fibroids · Treatment · Transvaginal uterine artery occlusion

Abbreviations

UAE	Uterine artery embolization
LUAO	Laparoscopic uterine artery occlusion
D-UAO	Doppler-guided uterine artery occlusion
LNG-IUD	Levonorgestrel-releasing intrauterine device
GnRH	Gonadotropin-releasing hormone
PBLAC	Pictorial blood loss assessment chart
US FDA	United States Food and Drug Administration
UFS-QOL	Uterine fibroid symptoms quality of life scale
SF	Short-form
MRgFUS	MRI-guided focused ultrasound surgery
FIBROID	Fibroid registry for outcomes data
UAO	Uterine artery occlusion
EMMY	EMbolization versus hysterectoMY

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Introduction

Leiomyomata uteri, or uterine fibroids, are the most common benign tumor of the female reproductive system [1–3]. The incidence of uterine fibroids varies with ethnicity and increases with age during the reproductive years, with an estimated cumulative incidence of >80% for Black women and almost 70% for White women by age 50, respectively [4]. The economic burden associated with uterine fibroids is significant; average annual health care costs in the United States are 3.2 times higher for a woman with uterine fibroids compared with a woman without fibroids [5].

The pathophysiology of uterine fibroids is not fully elucidated. Uterine fibroids are monoclonal, and distinct karyotypes are seen in multiple uterine fibroids from the same woman, suggesting independent growth [6]. In addition, hormones such as estrogen and progesterone, and growth factors such as insulin-like growth factor-1 [7] and transforming growth factor β [8, 9], are thought to stimulate uterine fibroid growth. Obesity may increase the risk of developing uterine fibroids [10], whereas parity appears to decrease the risk [11].

Conventional treatments for uterine fibroids include surgical procedures such as hysterectomy and myomectomy, which may be associated with significant morbidity in rare cases. However, the treatment of uterine fibroids has undergone recent technological advances that have facilitated the development of less invasive gynecologic procedures, such as uterine artery embolization (UAE), laparoscopic uterine

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artery occlusion (LUAO), and Doppler-Guided uterine artery occlusion (D-UAO). As compared to traditional surgical procedures, the advantages of less invasive procedures include less blood loss, less tissue trauma, less adhesion formation, less pain, shorter hospitalization times, and shorter recovery times for women [12, 13]. Understanding the putative mechanisms of action for these uterine fibroid treatments may provide insights into the pathophysiology of uterine fibroids and serve to optimize treatment selection. This review provides an overview of available treatment options, highlighting D-UAO and its proposed mechanism of action. D-UAO is a new, minimally invasive procedure currently in development for the treatment of uterine fibroids.

Current treatment options for uterine fibroids

When uterine fibroids are asymptomatic or when a woman is close to menopause, the conventional course of action is to monitor fibroid growth for the evolution of symptoms along with serial biannual examinations and ultrasound [14, 15]. For other women, treatment decisions are based on patient age, desire to maintain fertility, desire for uterine preservation, desire to avoid major surgery, symptom severity, uterine fibroid size, and rate of uterine fibroid growth.

Medical treatment options

Hormonal therapies such as oral contraceptives, the levonorgestrel-releasing intrauterine device (LNG-IUD), gonadotropin-releasing hormone (GnRH) agonists and antagonists (i.e., leuprolide acetate), androgens (i.e., danazol), progestins, progesterone receptor agonists (i.e., mifepristone), and selective progesterone receptor modulators (i.e., asoprisnil) have been used to manage uterine fibroids. Although oral contraceptives, progestins, and danazol may improve symptoms of uterine fibroids, there is little evidence to demonstrate their effective reduction of myomas [6].

Surgical treatment options

Hysterectomy (definitive treatment)

Hysterectomy remains the standard, definitive treatment for uterine fibroids [1–3]. Advantages of total or subtotal hysterectomy include the treatment of all fibroids, the elimination of recurrence, and a substantially improved quality of life [16]. Whether performed by the vaginal, abdominal, or laparoscopic route, hysterectomy is associated with permanent loss of fertility, significant physical, emotional, and economic recovery, and complications including bleeding, bowel and urinary tract injury, infection, and rarely death. Since the introduction of several non-hysterectomy alternatives such as endometrial ablation, rates of hysterectomy for the treatment of uterine fibroids are decreasing (2.13 per 1,000 women in 1997 vs. 1.91 per 1,000 women in 2003; $P < 0.0001$) [17].

Myomectomy

For women who desire to preserve their fertility, surgical removal of one or more fibroids can be accomplished by myomectomy performed via laparotomy, laparoscopy, or hysteroscopy [6]. Nevertheless, myomectomy is not a definitive treatment, and fibroid recurrence has been reported in 16.7% to 22.3% of women and is more likely with multiple fibroids [18, 19]. Myomectomy is associated with complications including hemorrhage, postoperative adhesion formation to adjacent viscera and adnexa, the need for subsequent cesarean section, uterine rupture during subsequent pregnancy, and the potential to undergo repeat myomectomy (or in most cases hysterectomy) for symptomatic fibroid recurrence [6].

Myolysis/cryomyolysis

Myolysis, another conservative surgical option for symptomatic uterine fibroids, uses focused energy to truncate vascular perfusion to fibroids resulting in coagulation necrosis [20]. Historically, the Nd:YAG laser was first used to perform myolysis [21]; this technique was later modified by the employment of a 5-cm bipolar needle with a bipolar current of 50–75 watts [22, 23]. More recently, the freezing of fibroids, called cryomyolysis, has been used laparoscopically with supercooled probes to cause sclerohyaline degeneration of fibroids [24]. Real-time ultrasound is typically used to gauge the extent of treatment during treatment with this modality. Although thermomyolysis and cryomyolysis have shown promising reductions in fibroid volume and fibroid-related symptoms [25, 26], no large randomized, controlled studies have assessed the long-term efficacy of either of these techniques. Whereas myolysis preserves the uterus and is associated with minimal blood loss, delayed thermal necrosis is adhesiogenic and the inability to critically gauge the extent of treatment can risk under-treatment of fibroids or over-treatment damaging the surrounding myometrium [24]. Furthermore, myolysis is suboptimal treatment for large or multiple fibroids and not appropriate for women who desire to maintain fertility because of its potential for uterine rupture from myometrial weakening [27].

Nonsurgical treatment options

MRI-guided focused ultrasound surgery (MRgFUS)

MRgFUS is a US FDA-approved procedure for premenopausal women with symptomatic fibroids who do not desire to maintain fertility [28]. It is a noninvasive treatment performed by interventional radiologists under mild sedation in an outpatient setting. This procedure uses a focused ultrasound beam to generate thermal energy, which destroys fibroid tissue in a localized area through coagulative necrosis [29]. The MRI-guided technology enables the visualization of patient anatomy, maps the volume of fibroid tissue to be treated, and if required, adjusts the temperature in the tissue targeted for treatment.

MRgFUS has demonstrated efficacy in reducing fibroid volume and fibroid-related symptom severity [30, 31]. A study of premenopausal women with symptomatic uterine leiomyoma reported a mean reduction in fibroid volume of 13.5 and 9.4% at 6 ($n = 109$) and 12 months follow-up ($n = 82$), respectively [30]. In addition, 70.6 and 51.2% of women demonstrated a ten-point reduction in the symptom severity scale using the UFS-QOL instrument at 6 and 12 months, respectively. However, 28% of women sought alternative surgical therapy for their uterine fibroids at 12 months following MRgFUS [31].

The proposed advantages to treatment with MRgFUS include rapid resolution of uterine fibroid symptoms, short recovery time, low incidence of complications, and no exposure to ionizing radiation. It is a non-invasive outpatient radiology procedure that is performed by an interventional radiologist, does not necessitate admission, and causes minimal pain. However, MRgFUS treats only one fibroid at a time and cannot be used to treat uterine fibroids in close proximity to sensitive organs, such as the bowel and bladder [29]. Potential complications include minor skin burns and non-targeted sonication of the uterine serosa and sciatic nerve. There are no long-term data on the effects of using this method, and 21% of women who undergo this procedure require another surgical procedure within 12 months [31, 32]. Because a specific MRI system is required, access to the procedure is limited. Last, MRgFUS is not advised for women who desire children because postprocedural pregnancy outcomes have not been determined.

Fibroid treatment via uterine artery embolization and occlusion

Uterine artery embolization (UAE)

Many available procedures to treat uterine fibroids are limited by their ability to treat only one fibroid at a time. Subsequently, new procedures have been developed to globally treat uterine fibroids. UAE is a technique initially performed to manage postpartum hemorrhage [33]; however, in 1995, Ravina et al. demonstrated that UAE used prior to myomectomy reduced uterine fibroid volume and menorrhagia [34]. Since approximately 94% of the blood flow to uterine fibroids is delivered by the uterine arteries [35], permanent disruption of the blood perfusion to the uterine fibroids through bilateral embolization would be an effective treatment option; UAE has become a widely accepted global treatment of uterine fibroids.

UAE, which is generally performed by an interventional radiologist using general anesthesia or with the patient under conscious sedation, involves the injection of polyvinyl alcohol particles or trisacryl gelatin microspheres until uterine vessel occlusion via embolization occurs. Once occlusion has occurred, it is believed that prolonged transient uterine ischemia occurs, the myometrium clots, and the myometrium becomes hypoxic. The myometrium is reperfused by collateral arteries, and the uterine clots are lysed. Uterine fibroids are unable to lyse clots, and therefore undergo infarction and ischemic necrosis [36].

Several studies have reported significant short-term and long-term improvements in fibroid size, fibroid-related symptoms, and quality of life following UAE [37–39]. Using the Fibroid Registry for Outcomes Data (FIBROID), which contains prospective data on more than 3,000 women who have undergone UAE [40], a study reported that at 6 ($n = 1,797$) and 12 months ($n = 1,701$), 85.5 and 86.8% of women, respectively, achieved a ten-point improvement in symptom severity score measured by the UFS-QOL. At 12 months, 82% of women reported that they would recommend UAE to a family member or friend, thereby indicating patient satisfaction [41].

UAE is commonly associated with a number of adverse events, including pelvic pain, infection, postembolization syndrome, menstrual dysfunction, hematomas at the puncture site, allergic reactions to the radiographic dye, and incomplete uterine artery occlusion (UAO) [42, 43]. Furthermore, other possible complications include embolization of the ovarian artery that may result in permanent amenorrhea or premature menopause, transcervical myoma passage, uterine necrosis, postprocedure uterine failure resulting in need for subsequent hysterectomy, and in rare instances, death from sepsis or pulmonary embolism [42, 43]. Results from the EMbolization versus hysterectoMY (EMMY) trial, which compared outcomes in women who had undergone UAE ($n = 88$) with women who had undergone hysterectomy ($n = 89$), reported that at 2 years' follow-up, 23.5% of women in the UAE group had undergone a hysterectomy [44].

When compared to myomectomy, UAE provides better control of fibroid-related bleeding and pain and good relief

of bulk-related symptoms [45], significantly shorter time to return to normal activity, fewer missed work days, lower incidence of adverse events, and higher health-related quality of life compared with myomectomy (all $P = 0.05$) [46]. UAE was associated with less blood loss and had shorter mean hospitalization times compared with hysterectomy (all $P < 0.01$); however, both procedures provide similar quality of life and symptom improvement and have similar major complication rates [47]. Although successful full-term pregnancies following UAE have been reported [48, 49], the effect of UAE on future pregnancy is uncertain and further investigation is needed to evaluate preservation of fertility and the long-term effects on uterine integrity [50]. Although pregnancy outcomes after UAE are limited in number, data are emerging. In the large retrospective study of women treated with UAE ($N = 1,200$), Walker and McDowell reported that 56 women became pregnant, but only 33 pregnancies were successful [48]. There were 17 miscarriages, 3 terminations, 2 stillbirths, and 1 ectopic pregnancy. Twenty-four pregnancies occurred in 21 women of a 555-patient study [51]. The pregnancies resulted in 18 live births, 4 miscarriages, and 2 elective terminations. Although based on a small population, higher incidences of abnormal placentation, placenta accreta, and placenta membranacea were reported in these women than previously published. Last, two comparison studies of pregnancy outcomes have been conducted after UAE or laparoscopic myomectomy [52, 53]. A statistically higher risk of preterm delivery ($P = 0.008$) and malpresentation ($P = 0.046$) was reported with pregnancy after UAE compared to laparoscopic myomectomy [52]. In addition, Holub et al. reported a significantly higher miscarriage rate ($P < 0.05$) among women after UAE [53].

Laparoscopic UAO (LUAO)

Due to the increased risk of complications associated with UAE, a less invasive laparoscopic procedure for the occlusion of uterine arteries has been developed for the global treatment of uterine fibroids. During the LUAO procedure, a lateral retroperitoneal approach is used and vascular clips or bipolar coagulation occludes the uterine arteries [54]. Once occlusion has occurred, similar to UAE, it is believed that a prolonged period of transient uterine ischemia occurs, during which the myometrium clots and becomes hypoxic. Reperfusion of the myometrium occurs by the collateral arteries, and the uterine clots are lysed. The inability of uterine fibroids to lyse the clots causes them to infarct and undergo ischemic necrosis [36].

Several studies have demonstrated the efficacy of LUAO to reduce fibroid volume and improve fibroid-related symptoms. In 68 women, more than 12 months following LUAO, the average reduction in dominant fibroid volume was 57.8%, and the percentage of women reporting improvement in symptoms was 93.2%; the postoperative complication rate was 7.3% [55]. LUAO is technically feasible when performed by an expert with advanced laparoscopic skills, as evidenced by the short average operating time of 35 min, clinic discharge within 20 h, and lack of perioperative complications in a small pilot study ($N = 8$) [54]. A prospective study ($N = 114$) reported a 9% ($n = 10$) recurrence rate at median follow up of 23.6 months and a 7.1% ($n = 8$) complication rate, and five women required subsequent hysterectomy or myomectomy. Febrile morbidity was the most common complication experienced by 3.5% ($n = 4$) of women; one woman experienced endometrial stromal sarcoma [56]. Further studies are needed to provide long-term results and comparative data to determine if this procedure is appropriate for women who desire to maintain fertility [29].

Compared to uterine artery embolization (UAE), LUAO has a number of putative advantages including the ability to complete the procedure in an outpatient setting, the obviation of ovarian vessel micro-embolization associated with the development of premature menopause, and comparable efficacy in a small number of women. Comparative disadvantages include the need for advanced laparoscopic skills, the risks associated with general anesthesia, the limitation of data to a small number of women, and the unpredictable effects on future fertility.

Doppler-guided uterine artery occlusion (D-UAO)

Although UAE is effective in treating uterine fibroids, Dickner et al. suggested that temporarily occluding the uterine arteries may be just as effective in the treatment of uterine fibroids [57]. The D-UAO procedure, which is a transvaginal, minimally invasive, 6-h outpatient procedure in the United States and day surgery in the European Union, can be performed by a gynecologic surgeon. It utilizes a device containing a vascular clamp, a Doppler receiver, and Doppler ultrasound crystals to perform bilateral occlusion of the uterine arteries. The use of Doppler technology allows for the audible identification of both uterine arteries and confirmation of complete occlusion through loss of audible signals characteristic of pulsatile uterine artery flow [58–60]. It has been hypothesized that similar to the mechanism of action of UAE, D-UAO also causes the myometrium to clot; myometrial clots are subsequently lysed. The uterus is reperfused following clamp removal; however, uterine fibroids remain clotted and infarct due to their inability to perform fibrinolysis [36]. Although the biological mechanism that prevents fibrinolysis by fibroids is unknown, several factors may contribute. The concentration of tissue plasminogen activator, an enzyme that enables fibrinolysis, is higher in the myometrium than in myomas [61]. Fibroids also have a decreased

vascular density compared to other uterine tissues that limits blood supply to fibroids [62].

A preliminary study ($N = 10$) demonstrated that a paracervical vascular clamp inserted transvaginally folds the vaginal tissue around the uterine arteries, interrupting blood supply, without injury to the ureters, vagina, or cervix [58]. Several case reports have demonstrated the efficacy of D-UAO in reducing uterine volume, menorrhagia, and other fibroid-related symptoms. In one report, a 43-year-old woman with fibroid-related menorrhagia achieved a 70% reduction in severity of menorrhagia, a 44% reduction in uterine volume, and decreases of 71, 84, 99, and 100% in four measured fibroids. In addition, no pain medications were required after hospital discharge the day after the procedure and postprocedure examination found no ureter damage from the clamp [59]. Similarly, at three months following D-UAO, another 43-year-old woman with fibroid-related menorrhagia, dysmenorrhea, and pelvic pressure and pain achieved reduced bleeding, a 77.2% reduction in dominant fibroid volume, and a 48.9% reduction in uterine volume. No sign of injury to vaginal skin was detected at clamp removal or one- and three-month follow up [60].

A prospective study of 40 women with symptomatic fibroids further examined the efficacy and safety of D-UAO [63]. As determined by MRI, the average reduction in dominant fibroid and uterine size six months after the procedure was 30–35 and 20%, respectively. Women with menorrhagia experienced a 35–40% reduction in menstrual blood loss that was associated with an average 35% reduction in Ruta Menorrhagia scores. There were no reports of amenorrhea, and overall, minimal adverse events were reported. However, five women experienced a total of six hydronephrosis events; the condition spontaneously resolved in three women and the remaining three events were experienced by two women. The condition was alleviated in one of these women, after unilateral ureteral stenting. The second woman experienced hydronephrosis that spontaneously resolved, but then experienced contralateral hydronephrosis that was treated with unilateral stenting followed by endoureterotomy. Subsequently, the procedure was modified to prevent further cases of hydronephrosis. The modifications include bladder filling prior to the procedure in order to move the ureters away from the uterine arteries, proper clamp size selection, and clarification in the instructions for use.

Comparison of mechanism of action in D-UAO versus UAE

With UAE, uterine arteries are permanently occluded, and uterine fibroids undergo necrosis due to abrupt uterine ischemia. With D-UAO, both the ascending and descending branches of the uterine arteries are compressed; therefore, insufficient blood flow is supplied to the uterus, a clot forms, and the myometrium becomes hypoxic. After approximately 6 h, the clot lyses, and blood flow is slowly restored to the uterus through collateral arteries. Since clot lysis does not occur in the blood vessels within the fibroids, the tumors are destroyed. The time course of myometrial ischemia can be monitored via pH. As clots form in the myometrium and hypoxia occurs, the metabolism shifts from an oxidative pathway to anaerobic glycolysis, resulting in an accumulation in lactic acid and corresponding drop in uterine pH. Once the uterus becomes reperfused, the pH returns to baseline values [64]. The entire process takes approximately six hours (Fig. 1).

It has also been hypothesized that uterine fibroid death following UAO may be due to apoptosis rather than necrosis, as seen with UAE. Park and colleagues have reported differences in the pathology of uterine fibroids following UAO and UAE [65]. Necrosis (uncontrolled cell death) was detected in the uterine fibroids treated with UAE, while some apoptosis (controlled "physiologic" cell death) was detected in women who underwent UAO, suggesting that, during UAE, the abrupt transition to a state of ischemia causes necrosis, while during UAO, a more controlled, gradual induction of ischemia takes place, allowing for controlled cell death or apoptosis. This difference is noteworthy because the abruptness of ischemia is known to be correlated with the severity of pain experienced by the patient [65]. In addition, following D-UAO, the uterus more quickly returns to normal compared with UAE, which suggests less long-term damage occurs and reduces the chance that fertility is lost [65]. Thus, postprocedural pain associated with UAE may be explained by higher levels of necrosis. However, additional research is warranted to test these hypotheses.

In addition, it is believed that the mechanism of fibroid death and myometrial survival following prolonged ischemia evolves from the biology of myometrial clotting

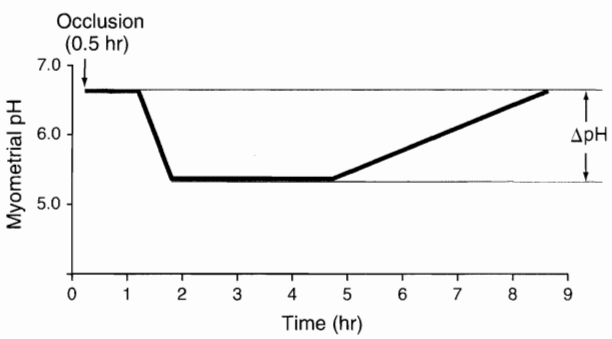

Fig. 1 The proposed mechanism of action of D-UAO. Occlusion of uterine arteries results in a sharp decline in myometrial pH due to clot formation. Following clot lysis (after approximately 6 h), the pH returns to the normal level

Table 1 Comparison of UAE and D-UAO Procedures [29, 67]

Characteristic	UAE	D-UAO
Uterine preservation	Possible	Yes
Global treatment	Yes	Yes
Preservation of fertility	Mixed obstetric outcomes, so not appropriate for women who desire fertility	Maintains uterine function; however, pregnancy outcomes unknown
Minimally invasive	Yes, inpatient radiology procedure	Yes, outpatient procedure
Mechanism of action	Prolonged uterine ischemia	Transient uterine ischemia; myometrial pH changes and redirection of blood flow
Effect on ovaries	Potential to cause ovarian failure	No effect on ovarian blood flow (no reports of amenorrhea)
Postprocedure pain	Associated with significant pain that generally requires hospital readmission	Low incidence of postprocedure pain
Requirement for specialized training	Yes, must be performed by interventional radiologist	No, can be performed by a gynecologic surgeon
Reintervention rate	20–29% of women require additional surgery within 5 years	Unknown reintervention rate
Risks associated with procedure	Misembolization, ovarian failure, uterine necrosis and sepsis, passage of submucous myomata, permanent amenorrhea or premature menopause, postembolization syndrome, allergic reactions to radiographic dye, and mortality	Lower urinary tract infections, back pain, suprapubic pressure and urgency, dysmenorrhea, and hydronephrosis

UAE uterine artery embolization; *D-UAO* Doppler-guided uterine artery occlusion

following childbirth [66]. Clotting and lytic factors increase during pregnancy. Uterine contractions that occur during and after childbirth slow blood flow to the myometrium. Reduced blood flow, the increased presence of clotting and lytic factors, and torn placental blood vessels cause myometrial clotting. Fibrinolytic enzymes lyse myometrial clots, but not placental vessel clots; therefore, the myometrium is reperfused, but the placental tissue is not. Ischemia results in placental tissue death, but not myometrial death. Thus, fibroid death that occurs by D-UAO may be similar to placental death that occurs following postpartum clotting of uteroplacental arteries [66].

Advantages of D-UAO

Overall, there are several putative advantages of D-UAO over current treatment options for uterine fibroids. As compared to UAE, D-UAO may be associated with fewer complications, less pain, and normal menstruation restored following the procedure (Table 1) [57–60, 67]. Compared with other treatment options, which require a referral to a radiologist, D-UAO is minimally invasive, is based on conventional gynecologic surgery techniques, and therefore, can be performed by a gynecologic surgeon providing continuity of gynecologic care [36].

Conclusion

Ultimately, the choice of treatment for uterine fibroids should be a carefully balanced decision after all reasonable surgical and non-surgical options are reviewed in the context of known efficacy and relative risk. Whereas some women may opt to undergo myomectomy, myolysis, or some type of hysterectomy, others will choose the treatment perceived to be the least invasive that will preserve uterine function and have the shortest hospitalization and recovery time, with the least amount of pain. D-UAO is a nonhormonal and minimally invasive approach to fibroid management that may maintain uterine integrity. This promising new treatment is currently in multicenter, randomized prospective clinical trials, and data are forthcoming.

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