

Uterine Fibroid Embolization: A Review for Endovascular Trainees

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Abstract: We review uterine fibroid embolization (UFE), detailing the procedure, appropriate patient selection, and review evidence supporting the use of UFE as an alternative to more invasive surgical management of uterine fibroids. We provide a brief overview of leiomyomas (fibroids), including relevant anatomy, accepted therapy for leiomyoma-related symptoms and UFE's current role in the treatment of fibroids. Finally, we propose a multidisciplinary model in which we discuss the three general leiomyoma treatment modalities: pharmacological, surgical or non-surgical procedural and detail the endovascular specialist role, with special attention towards our primary audience of the endovascular trainee.

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Key words: Uterine fibroid embolization, UFE, UAE, embolization therapy, leiomyoma, endovascular trainee

Introduction

Fibroids, also known as leiomyomas, are the most common benign tumor in women of reproductive age, and the most common pelvic tumor overall in women.^{1,2} They arise from smooth muscle cells and fibroblasts in the myometrium, and have a very small risk for malignant transformation. Classified based on location, they can be found in the submucosal, intramural, sub-serosal, and cervical regions of the uterus. Being estrogen dependent, their size and thus, symptoms can vary with the menstrual cycle, with largest size noted during the follicular phase, when high levels of estrogen are present. Leiomyomas are more prevalent in women with long histories of unopposed estrogen in instances of low parity, early menarche, delayed menopause, and obesity. Evidence shows a positive relationship between the prevalence of fibroids and alcoholic consumption, but a relationship with smoking and fibroids remains inconclusive.³ When symptomatic, fibroids often present with abnormally heavy menstrual bleeding and/or bulk-related symptoms due to mass effect (bloating, constipation, urinary frequency, lower extremity edema) depending which direction the tumor grows.⁴

Interdisciplinary Consideration to Fibroid Treatment

An interdisciplinary approach is key to effectively managing patients with symptomatic fibroids. Uterine fibroid embolization (UFE) or Uterine Artery Embolization (UAE) is a minimally-invasive procedure introduced in 1995 for the treatment of symptomatic uterine fibroids. Alongside gynecologists, a team base approach is vital to the patients' treatment plan and the practice referral pattern. We pose the importance of identifying subsets

of patients who would benefit from UFE, pharmacologic, or surgical intervention.

Medical management of symptomatic fibroids consists of pain medication, OCPs, progestin-releasing IUD, GnRH agonists, and selective progestin receptor modulators.⁵ All of the hormonal options are aimed at decreasing the anabolic effects of estrogen at the myometrium. By modulating the hypothalamic-pituitary axis by overstimulating GnRH, the agents create a hypoestrogenic state. While for some this is a great option, patient compliance is an issue given the side effect profile experienced of menopausal symptoms, such as hot flashes, sleep disturbances, vaginal dryness, and decreased bone density.

When symptoms persist with medical management, the patient may be evaluated for UFE or surgery. Hysterectomy and myomectomy remain the most common interventions offered to patients with symptomatic uterine fibroids resistant to medical therapy. Apart from a focused discussion on fertility (as we will highlight) between the provider and patient, the current considerations between whether a patient should undergo surgery or UFE comes with tradeoffs between less complications, fewer days hospitalized (typically <1 day), and quicker recovery for UFE vs traditional definitive surgical treatment. Below we discuss some of the benefits UFE pose compared to surgery.

When considering the patient undergoing treatment for symptomatic fibroids who wishes to retain the option of becoming pregnant in the future, careful consideration and discussion is paramount. Excluding the option of hysterectomy for this group, comparisons can be made of UFE to myomectomy—which has been the historical surgical choice for fertility preserving fibroid treatment.

Fertility rates following myomectomy have been found to be at 53.6–55.9%,^{6,7} whereas fertility rates following UFE have not been as effectively quantified. A recent 2020 literature review published in the *British Journal of Radiology* by Ludwig, et al, found an approximated gross pregnancy rate post-UFE to be 38.3%.⁶ This number, however, included patients up to the age of 45 and disregarded critical factors such as efforts to conceive and past surgical or medical history.

In a 2005 prospective multicenter trial out of Ontario by Pron et al, the pregnancy outcomes of 555 patients treated for symptomatic fibroids with UFE were analyzed.⁸ While the authors note their study was not designed to evaluate the rate of fertility (as the denominator of women attempting to achieve pregnancy was not optimally defined) the study did show reasonably good pregnancy outcomes. Twenty four pregnancies were conceived, only four spontaneous abortions, four preterm deliveries, a 50% rate of vaginal delivery, and abnormal fetal growth in four of the births. In 2007, A randomized prospective trial by Mara et al, compared UFE with myomectomy and analyzed outcomes and implications of future fertility.⁹ Perinatal outcomes including mean birth weight, mean completed gestational weeks, preterm delivery, cesarean section, postpartum hemorrhage, perinatal hypoxia, preeclampsia, and intrauterine growth restriction were similar in both groups. Study limitations were small sample size and unequal number in each group attempting to conceive (40 in myomectomy and 26 in UFE group). The rates of spontaneous abortion and pregnancy were 64% and 50%, respectively, after UFE (both higher compared to many other observational and retrospective studies), and 23% and 78%, respectively, after myomectomy. The differences in outcome for these two parameters were of statistical significance ($p < 0.05$). The relative risk of infertility after UFE compared to myomectomy in this study was 2.22 (95% CI 1.11, 4.44).

Many patients in existing studies and case reports have variable factors that confound direct analysis or comparison which include, advancing maternal age, uterine wall compromise, previous spontaneous abortions, prior uterine surgeries, variable technique and skill of endovascular specialist performing UFE, unknown desire to conceive and carry a fetus to term. Additionally, the most well-controlled studies often have small population sizes which make it difficult to gain meaningful clinical information from them.

What has been demonstrated is that pregnancy is attainable for women following UFE and many pregnancies will proceed uneventfully to successful delivery. However, as discussed above, the exact fertility rate following UFE remains uncertain, and there is evidence correlating to higher rates of preterm delivery and spontaneous abortions when compared to myomectomy. Providers must take into account both aspects of the current published data and have an open and honest discussion with our patients to balance the benefits and risks of UFE in the scope of fertility. Additional randomized, controlled research into fertility and pregnancy following UFE would be of great benefit.

Uterine Fibroid Embolization: Assessing Outcomes

The populations of patients most likely to benefit from UFE are patients that will respond well to pharmacological or surgical intervention. The 2005 EMMY Trail—a multi-center randomized controlled trial (RCT) enrolling 177 patients found that UFE when compared with hysterectomy had a similarly low major complication rate (4.9 vs 2.7 $p = 0.68$) with a significant reduction in length of hospital stay (mean [SD]: 2.5 [2.7] vs 5.1 [1.3] days, $p < 0.001$).¹⁰ Additionally, the 2007 REST trial, another multi-center RCT, enrolling 157 patients with a 2:1 ratio of randomly assigned to either UFE or Surgery (hysterectomy or myomectomy), found no significant difference in primary outcome, quality of life after 1 year post procedure measured by health survey (SF-36 score), as well as a statistically significant reduction in hospital stay in UAE group vs surgical group (1 day vs 5 days; $p < 0.001$).¹¹ These two studies were instrumental in showing the viability of UAE as an alternative to traditional interventions.

Multiple studies, including Fonseca et al's meta-analysis of ten randomized controlled trials, demonstrated that when compared with surgical methods of treating symptomatic fibroids, UAE has a lower risk of major complications.¹² Patients who had UAE also were found to have significantly shorter median duration of hospitalization while a minority of patients who received UAE required reintervention in larger numbers compared to surgical methods.^{12,13,14}

Contraindications

Absolute contraindications to UFE include pregnancy, suspected leiomyosarcoma or endometrial, cervical or ovarian malignancy. Understanding that preoperative embolization of these malignancies can be indicated when it is prior to surgical resection, the use of embolization as a sole therapy for a suspected malignancy is not indicated.

Relative contraindications include coagulopathy or requirement for continual anti-coagulation, renal insufficiency, prior severe allergic reaction to iodinated contrast.

Pre-Procedural Planning

In addition to a detailed history and physical exam and patient counseling, pre-procedure evaluation consists of a contrast-enhanced MRI to assess fibroid number, size, and location, and vascularity. Prior assessment of the patient's uterine blood supply can also be useful, as there have been five distinct internal iliac artery branching patterns that have been described in the literature.^{4,15,16}

The most common origin of the uterine artery (UA) is described as the first branch of the anterior division of the internal iliac artery (IIA). The internal iliac artery classically bifurcates into anterior and posterior segments (77%), with variations including trifurcation (14%), four or more stems (3%) or one stem (4%). The arterial supply to the uterus is primarily via the UA,

a tortuous and classically “U” shaped vessel with descending, transverse and ascending segments. It commonly (51%) arises as the first or second branch of the anterior division of the internal iliac artery. However, it may also arise as the first branch of the internal iliac artery (6%) or rarely originate directly from the abdominal aorta.^{4,15,16}

The uterine artery is typically tortuous in patients with fibroids,^{17,18} and we can use the characteristic appearance to help identify it on imaging. This is also true when ovarian supply is noted. Arterial mapping also helps identify collateral flow to the uterus, most commonly from the ovarian artery.^{17,18} Since untreated collaterals can be the culprit of insufficient tumor infarction after uterine artery embolization, it is helpful to identify this anomaly pre-procedurally, can increase the overall intra-procedural and fluoroscopy time, thus increasing the risk for prolonged radiation, infections, and complications.

UFE Technique and Complications

Using ultrasound-guided Seldinger technique with a micro-puncture access kit, trans-femoral artery (TFA) or trans-radial artery (TRA) access is obtained. There are no statistically significant differences in clinical outcomes or procedure time between UAE with TRA or TFA access, though more patients with TRA access were discharged on the day of the procedure in comparison to patients accessed by the TFA.^{15,16} TRA allows the patient to ambulate immediately post-procedurally, which greatly adds to patient comfort and is our preferred access point.

If femoral approach is desired, typically a cobra, Rosch inferior mesenteric or RUC catheter + 0.035 torqueable wire, such as a guidewire (Terumo, Japan), is chosen to catheterize the common iliac artery. If radial access is obtained, a 125 MPA catheter can be used to easily catheterize the hypogastric arteries from above.

As the wire and catheters are advanced to the pelvis, serial angiograms are obtained to aid localization with standard visceral contrast injection rates. A power injector is helpful in forming the proximal arterial map. When nearing the hypogastric artery, the image intensifier is then set to the contralateral oblique to provide the best visualization of the UA origin. After selecting the UA, hand runs are preferred angiogram of choice.

A microcatheter and microwire, such as the Progreat microcatheter (Terumo, Japan) and .016 Fathom Steerable Guidewire (Boston Scientific, MA) are advanced into the uterine artery. Caution is required in this integral step as distal catheterization may cause vasospasm in many patients, which can preclude embolization. This phenomenon can also be noted after treatment initialization, leading to a false end point, with vasodilatation occurring shortly after catheter removal. Close attention to the super selective angiogram at this point is necessary. Apart from identifying tumor blush, all opacified vessels must be studied closely to avoid non-target embolization, with the most common being cervicovaginal branches originating from the horizontal portion of the artery. Once the UA has been selected and collaterals accounted for, UFE can commence.

The most commonly used embolic agents are nonspheri-

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Acrylamide PVA hydrogel microspheres (a-PVAM)-utilizes the properties of PVA as well as calibrated particles. A randomized double blind non inferiority trial published in CVIR demonstrated non-inferiority of outcomes of patients undergoing UFE with a-PVAM compared to TAGM embolic material.²¹ Spherical PVA has been shown to be inferior in fibroid infarction and should not be used for UFE.²²

cal polyvinyl alcohol (ns-PVA) particles and tris-acryl gelatin microspheres (TAGMs) (eg, Embosphere microspheres; Merit Medical, UT).^{19,20} The former are long studied particles which are irregularly shaped and heterogenous in calibration embolic material which do not completely occlude the vessel lumen and rely on thrombus formation to complete vessel occlusion. The later (TAGM) are calibrated microspheres made from microporous cross-linked acrylic beads embedded with gelatin. These microspheres are sized to have a diameter necessary for complete occlusion of arterial lumen.

A systemic review and meta-analysis by Das et al, which encompassed five randomized control trials (n=295) and five non-RCTs (n=617), found there was no evidence of superiority between four of the embolic agents reviewed (TAGM, ns-PVA, a-PVAM, Polyzene F).²⁰ However, a sub-analysis between TAGMs and spherical PVA microspheres that found TAGMs demonstrated a greater percentage of fibroid devascularization than spherical PVA (TAGM vs sPVA 30 vs 19 assessing 100% devascularization and 14 vs 23 assessing <99 % devascularization, p=0.049).²⁰

Embolic material is injected slowly and in small aliquots using the flow in the uterine vessel to carry the embolic material to the fibroid arterial supply. The embolic agent is administered with a goal of “near stasis” or slow flow noted on angiogram. It is at this point where the most frequent patient complaint and the well known adverse effect of pain following UFE can be addressed. Recent studies describe the use and efficacy of pain control via intra-arterial lidocaine injection.^{24,27} Most commonly lidocaine can be mixed with the embolic material or given just after embolization is preformed. We discuss this topic further under the subtitle post procedural management below. Attention is then turned to the contralateral UA and UFE is preformed in a similar manner. If femoral access was preformed, contralateral access may be obtained.

A Fonseca et al metanalysis found UFE had a major complication rate of 4.4% (7 studies, n=795) with complications including on-target embolization and post-embolization syndrome (PES), and very rare reports of transvaginal fibroid sloughing and infection.¹² PES is thought to be caused by cell death leading to the release of tissue breakdown products, inflammatory mediators, and vasoactive substances from the tumor and adjacent normal tissues. PES classically presents as self-limited pain, nausea, vomiting, and fever. Preliminary evidence suggests that there may be an associated leukocytosis in approximately 20% of patients with PES within the first 24 hours.²⁵

Post-procedure Management

The post-procedural management of UAE is largely based on the patient adherence to medication/recovery instructions once discharged. Postprocedural care includes hydration, nonsteroidal anti-inflammatories, IV Acetaminophen, antiemetics, and narcotics²⁶ to combat the most common symptoms seen such as nausea, pain, and mild inflammation of the lower abdomen/pelvis. Our post-procedural pain regimen is noted in the side box. In our experience using this post-op regimen, we have rarely had to admit a patient for pain control.

Multi-modal pain control continues to be an evolving area of investigation including noninvasive measurements (PCA, adding ketamine to pain control regimen, scheduled IV Ketorolac) and invasive methods of pain control intra-arterial administration of lidocaine, hypogastric nerve block).^{23,24,26-28} As previously mentioned, a 2017 randomized control clinical trial (Noel-Lamy et al) showed intra-procedural intra-arterial injection of lidocaine demonstrated significant decrease in pain four hours post-procedure as compared to control.²⁷ In this study patients undergoing UFE were randomized into three arms: group A received 10 mL of 1% lidocaine mixed with embolic material, group B received the same amount of lidocaine after embolization and group C received no lidocaine and was deemed the control group. Pain scores were assessed at 4, 7, and 24 hours post procedure with significant difference in group A and B (lidocaine group) compared to control. Further, in hospital-narcotic use was calculated and found to be significantly lower in groups A and B compared to control (8.5 mg and 11.1 mg vs 17.4 mg, $p=0.03$).

This study was followed up in February 2020, where a prospective randomized trial resulted in a reduced amount of post-procedural pain in the early hours and reduced opioid usage in the first 24 hours following UFE.²⁴ In this study, intra-arterial lidocaine (1 % of 10 mL) was administered to bilateral uterine arteries after embolization in one group compared to another group undergoing UFE with the same material (microsphere) without any post embolization lidocaine injection. A visual analog pain scale was administered to patients at 2,4,7, 10, and 24 hours post procedure. There was a significant reduction in VAS score in the lidocaine group at 2 hours, while there was no difference in the following VAS pain scores. Morphine use was recorded in both groups for 24 hours following UFE, the lidocaine group used significantly less (11.2 mg vs 20.2 , $p=0.03$) morphine for pain control.

A 2019 systematic review by Saibudeen et al found no statistical difference between opioids \pm NSAIDs \pm acetaminophen (4.84, SD = 1.56); opioids \pm NSAIDs \pm acetaminophen + nerve block (4.7, SD = 1.37) opioids \pm NSAIDs \pm acetaminophen + intrauterine artery drug administration (4.09, SD = 0.60); and opioids \pm NSAIDs \pm acetaminophen + other (5.30, SD = 1.13).²³ Further discussion within this review noted that only three clinical trials were found which studied the benefit of adding steroids, ketamine, or alpha-2-receptor blockers to the opioid protocol. These did not reveal any statistical significance in pain score; however, due to small number of studied patients, no conclu-

sions were reached. Similarly, due to the overall heterogeneity of literature, further trials focusing on hospitalization time and well-defined and recognized pain scores are required to further evaluate pain control post-UFE.²³

Patients are typically seen for a post-discharge follow up at 3 months post-procedure with a follow-up MRI to document the amount of fibroid infarction, and again at 6 months. Patients are counseled about the signs and symptoms of complications such as non-response to NSAIDs, fever, or foul-smelling vaginal discharge.²⁹ Decisions regarding reintervention are made based upon symptoms (eg. good response in terms of volume reduction but unchanged heavy menstrual bleeding might result in reintervention, whereas the opposite situation might not) and degree of viable fibroid tissue on follow-up MRI, but is rare in our experience.

Conclusion

UFE remains on the forefront of therapeutic options for symptomatic leiomyomas. The American College of Radiology 2017 appropriateness criteria, labeled management of uterine leiomyomas with UFE as "usually appropriate" in regards to all variant populations addressed by the expert panel.³⁰ The American College of Obstetricians and Gynecology (ACOG) states that "based on good and consistent scientific evidence (level A)... and long- and short-term outcomes, uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri".³¹ Indeed, UFE is a well-known and effective therapeutic tool recognized by the interventional radiology and medical communities as a collective. By advocating for patient safety and experience, we can be confident in the service we provide to resolve menorrhagia and bulk-related symptoms in minimally invasive manner with UFE. ■

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