Evidences in Uterine Artery Embolization: A Radiologist’s Primer

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Abstract
Uterine artery embolization is an established minimally invasive therapy for symptomatic fibroids. It has also been used for other diseases of the uterus, including adenomyosis, uterine arteriovenous malformation, ectopic pregnancy, abnormal invasive placenta, and postpartum hemorrhage. In this review, we provide an updated and comprehensive review of uterine artery embolization based on the evidence published. We review the indications, the role of MRI, technical aspects, and complications of the procedure. The issues with a future pregnancy, risk of infertility, and fetal radiation are discussed as well.

Keywords
- uterine artery embolization
- fibroids
- arteriovenous malformation
- pseudoaneurysm
- perinatal period
- ectopic pregnancy

Introduction
Diseases related to the uterus, such as uterine fibroids, adenomyosis, and pregnancy-related uterine and placental diseases constitute a major part of morbidity in women. Many of these patients eventually undergo invasive surgical therapy when medical management fails. Minimally invasive therapies such as uterine artery embolization (UAE) are safe and effective for many of these conditions. However, there are concerns regarding appropriate indications, future infertility risk, and radiation injury with UAE. The published literature is heterogenous and often confusing. We attempt to provide an updated and comprehensive evidence-based review regarding indications, the role of imaging, technical aspects, complications, radiation and infertility concerns of uterine artery embolization in various uterine pathologies.

UAE for Fibroids
Uterine fibroids are the most common benign pelvic tumors in women with a prevalence ranging from 4.5 to 68% depending on study population.1 Around 25 to 50% of these patients are symptomatic with bleeding or pelvic pain. Around 30% of these patients resort to invasive surgical therapies including myomectomy or hysterectomy.1 The number of UAE procedures for fibroids is increasing and various societies have suggested guidelines with subtle differences (Table 1). While the Society of Interventional Radiology (SIR) guidelines of 2014 recommended UAE for all symptomatic fibroids, the Royal College of Gynecology (RCOG) endorses primary myomectomy as the first line option in patients who wish for future pregnancy, with UAE reserved for surgically unfit patients.2 The Cardiovascular Interventional Radiology Society of Europe (CIRSE) standards of practice...
The recent FEMME trial that evaluated the cost utility of myomectomy versus UAE showed UAE to be associated with higher costs (difference of 645 pounds) in 4 year horizon. These results point out that the short-term results of UAE are good, while the long-term results of myomectomy are better, as UAE may require frequent reinterventions.

**Investigations**

A trans-abdominal ultrasound is recommended for preoperative workup. However, pre-procedure MRI can help in predicting the treatment response of UAE. Fibroids are usually hypointense on T2-weighted images. However,
moderate degrees of T2 hyperintensity can be seen in hypercellular fibroids, whereas marked hyperintensity suggests degeneration. Duvnjak et al had shown that higher ratio (>2.6) of T2 hyperintensity of fibroids compared with adjacent myometrium was associated with increased volume reduction of more than 50% of the fibroid. Fibroids with T1 hyperintensity respond poorly due to hemorrhagic necrosis or fat within. The fibroid location can also affect the response, with submucosal fibroids having higher volume reduction compared with intramural or subserosal fibroids due to predominant supply from the uterine radial arteries. Kalina et al showed that fibroids with enhancement which is more than the myometrium on gadolinium-enhanced MRI show more significant volume reduction (61.3% vs. 47.6%) than hypo-enhancing fibroids. MRI also helps predict ovarian artery supply to fibroids. Normally, the ovarian arteries are very small and the visualization of ovarian arteries on pelvic MRA indicates substantial contribution from them resulting in incomplete embolization if overlooked. MRI is superior to ultrasound as it allows tissue characterization of uterine fibroids and helps distinguish them from malignant tumors such as low-grade leiomyosarcoma. Diffusion-weighted MRI and T1 perfusion techniques help differentiate malignant tumors with a sensitivity of 94%, and this distinction is vital as these tumors are treated by definitive surgery.

**Pre-procedure Antibiotics**

The possible site of infection after UAE is either from the arterial access site or ascending infection from the vagina by *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococcus*, and *Escherichia coli*. SIR recommends prophylactic intravenous cefazolin (1–2 g) 1 hour before procedure with the addition of 100 mg of doxycycline, twice daily for 1 week in cases of associated hydrosalpinx. Though Assaf et al found no change in the rate of infectious complications between individuals with and without post-procedure antibiotics (1.8% vs. 1.3%), RCOG endorses a combination of cephalosporin and metronidazole, quinolones or amoxicillin post-procedure. However, the choice of antibiotic depends on local hospital guidelines.

**Vascular Access**

The access artery can be unilateral common femoral artery (CFA), bilateral CFA, or radial artery. Compared with unilateral approach, bilateral femoral access is associated with shorter procedure times (54.9 vs. 62.9 minutes, *p* = 0.026), shorter fluoroscopic times (12.8 vs. 16.6 minutes, *p* = 0.046) and reduced radiation to ovaries (25% less in bilateral access group). Except for minor groin pain at the puncture site, there was no significant increase in access site complications in the bilateral access group. Radial access is also used, as it has fewer complications rate compared with femoral access. Left radial artery is usually preferred due to fewer manipulations needed in the arch of aorta, thus minimizing the risk of cerebral embolism and reducing the distance from the access site to the uterine artery (5-10 cm less compared with right side). Longer length (125 cm) catheters are preferred in the radial route. An RCT by Evgeny et al comparing trans-radial vs. transfemoral access for UAE in 153 patients showed that trans-radial access was associated with shorter procedure times (32.2 ± 7.9 vs. 39.2 ± 9.7 minutes, *p* < 0.001), uterine artery catheterization time (12.3 ± 5.7 vs 19.0 ± 6.0 minutes, *p* < 0.001) and radiation dose (0.28 ± 0.14 mSv vs. 0.5 ± 0.2, *p* < 0.001) compared with transfemoral access.

**Embolization Materials for Fibroid Embolization**

Particulate materials are preferred for fibroid embolization. Various embolic materials include nonspherical polyvinyl alcohol particles (PVA, Cook Medical, Bloomington, IL and Contour, Boston Scientific, Natick, MA), spherical tris-acrylic gelatin microspheres (Embospheres, Merit Medical inc., USA), and Polyzene F-coated hydrogel microspheres (Embozene, Varian Medical Systems, Pala Alto, CA, USA). Nonspherical PVA particles have an irregular shape and tend to occlude in the peri-fibroid vascular plexus leading to moderate perivascular inflammatory change and partial recanalization (90% at 6 months). Spherical PVA particles are associated with less tumor infarction compared with nonspherical PVA particles. Embospheres are compressible, allow easy passage through the microcatheter and cause less aggregate formation within the catheter or in this vasculature. This property enables deeper penetration into the distal vasculature, resulting in occlusion of more distal arteries. Inflammation with embosphere is less intense compared with nonspherical PVA. A meta-analysis by Das et al showed no superiority of the available embolic materials for UAE.
The choice of the size of particles is also important due to the presence of utero-ovarian anastomosis that measures ~350 µm in size. Small PVA particles with a size less than 350 µm though have better penetration into distal vessels, causing more intense ischemic necrosis of fibroids and therapeutic response but have a higher chance of non-target embolization through utero-ovarian anastomosis (Fig. 2). PVA particles of 500 to 750 microns result in more proximal occlusion, but with less non-targeted embolization. In a study comparing 350 to 500 micron and 500 to 700 micron, there was no difference in outcomes at 6 months though smaller PVA was associated with higher post-procedure pain. A detailed description of various embolization materials used in UAE is given in Table 2.

### Table 2: Embolization agents in UAE, advantages and disadvantages and specific use

<table>
<thead>
<tr>
<th>Agent</th>
<th>Property</th>
<th>Advantage</th>
<th>Disadvantages</th>
<th>Specific use</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA particle</td>
<td>Non-spherical (500-700)</td>
<td>• Irregular particles • Causes arteriolar occlusion</td>
<td>• Permanent agent • Less ovarian failure due to larger size</td>
<td>• Proximal occlusion • Catheter clumping Fibroids</td>
</tr>
<tr>
<td>PVA particle</td>
<td>Non-spherical (350-500)</td>
<td>• Irregular particles • Causes arteriolar occlusion</td>
<td>• Better distal embolization in</td>
<td>• More chances of passing through utero-ovarian anastomosis • More pain</td>
</tr>
<tr>
<td>Embospheres</td>
<td></td>
<td>• Spherical particles • Uniform size</td>
<td>• Less catheter block • Better and uniform penetration • Lesser pain</td>
<td>• Higher cost Fibroids</td>
</tr>
<tr>
<td>NBCA</td>
<td></td>
<td>• Liquid permanent embolic</td>
<td>• Can permeate distally in case difficult emergency cannulation</td>
<td>• Uterine ischemia Refractory PPH, distal pseudoaneurysm</td>
</tr>
<tr>
<td>Gelfoam</td>
<td></td>
<td>• Temporary agent</td>
<td>• Concentration can be adjusted for proximal or distal embolization • No risk for permanent ischemia</td>
<td>• Temporary agent Post-partum hemorrhage</td>
</tr>
<tr>
<td>Vascular Coils</td>
<td></td>
<td>• Permanent agents, proximal artery occlusion</td>
<td></td>
<td>Inability to prevent flow through collaterals</td>
</tr>
</tbody>
</table>

Fig. 2: Anatomy of uterine artery. (A), (B) diagrammatic and angiographic image of internal iliac artery which divides into anterior and posterior branch. From the posterior division (yellow arrow) superior gluteal artery, iliolumbar and lateral sacral arises caliber. From the anterior division, inferior gluteal artery (green arrow) is a large branch coursing outside the pelvis. Other branches from anterior division include obturator artery which passes through obturator foramen and have a distal fork like configuration (blue arrowhead), Internal pudendal artery (yellow arrowhead) which passes through greater sciatic foramen reentering the pelvis through lesser sciatic foramen providing vascular supply to pelvic organs. Uterine artery (white arrow) arising from inferior gluteal artery has a ‘U’ shaped course with descending (orange arrow), transverse (white arrow) and ascending course (blue arrowhead) as shown in image (C). Cervicovaginal arteries (black arrow) arise from the transverse part of uterine artery and need to be spared while embolization to prevent vaginal ischemia.
Pain Management
Significant pain after fibroid embolization is due to ischemia of the uterus releasing lactate and adenosine that stimulate chemosensitive receptors. The pain is usually severe and cramping in nature and is most severe in the initial 2 to 3 hours, and stabilizes by 8 to 12 hours. It can also be seen as part of post embolization syndrome, which may present with fever and fatigue, commonly on the third post-procedure day. Various pain management strategies are described, including NSAIDs and opioids, patient-controlled analgesia, nerve block, and intrauterine artery injection of analgesics. A systematic review showed that the combination of NSAIDs, acetaminophen and intrauterine injection of lignocaine had better control of pain compared with NSAIDS only. Intraarterial use of lignocaine (20–200 mg) into uterine arteries after embolization helps in the reduction of post-procedure pain for 7 hours (half-life of lignocaine 90–120 minutes) with reduced requirement of narcotic dose. Superior hypogastric nerve block (SNBH) effectively reduces procedural pain and decreases the need for opioid analgesic. It is done by instilling 3 mL of 0.5% ropivacaine (75–100 mg) or 15–20 mL of 0.5% bupivacaine at the level below the abdominal aortic bifurcation (L5 level) and the anesthetic effect usually lasts for 8 to 12 hours. The injection can be done fluoroscopically after locating the aortic bifurcation by a catheter or angiogram. Post-procedure, patient-controlled analgesia (PCA) for 24 hours followed by naproxen 500 mg BD or ibuprofen 800 mg three times a day next seven days is effective in reducing post embolization syndrome. Opioids including fentanyl, morphine, hydromorphone, hydrocodone, and oxycodone can also be considered in cases of severe pain.

Fertility and Ovarian Reserve Function Post-uterine Fibroid Embolization
A significant concern related to uterine fibroid embolization is future fertility. The cause of infertility includes (1) reduced blood supply to uterine endometrium, (2) residual distortion of uterine cavity by any embolized involuting fibroid having a submucosal extension, thereby resulting in abnormal placentation and miscarriage, and (3) a decrease in ovarian function due to nontarget ovarian embolization through utero-ovarian anastomosis. The risk of ovarian failure after the UAE is high in women more than 45 years of age. A systematic review by Karsen et al showed that the pregnancy rate was lesser in patients undergoing UAE (50% vs. 78%) with a higher miscarriage rate compared with myomectomy (60% vs. 20%). A RCT by Mara et al showed that myomectomy had a superior reproductive outcome than UAE within 2 years of treatment with higher pregnancy rate (78% vs. 50% p < 0.05) and lower abortion rate (23% vs. 64%, p < 0.05). A systematic review by Sandberg et al suggested that if a patient is a surgical candidate and concerned about future pregnancy, myomectomy should be the first choice. UAE may be considered in fibroids, that are surgically challenging to treat in sub-fertility patients. The diminution of ovarian reserve leading to infertility after UAE is controversial. Razavi et al classified the utero-ovarian anastomosis (UOA) into three types and described a high change ovarian failure after UAE in type Ib, and type III UOA and in patients with age more than 45 years. Sheikh et al described the use of coils and 700 to 900 μm PVA particles to occlude the UAO in type 1b and type III to reduce ovarian failure. However, a systematic review by Tare et al that compared case–control and three cohort studies, showed that ovarian reserve as measured by the level of anti-mullerian hormone (AMH) and follicular stimulating hormone (FSH) was not affected by UAE. However, majority of the population included in their study were less than 40 years. In the EMMY study, which analyzed a homogenous population, the level of FSH used as a measure of the ovarian reserve was seen to increase after embolization more in women over 45 years of age. In summary, the ovaries of younger age exhibit greater recovery after ischemic damage suggesting that the infertility is more likely to be due to uterine and endometrial causes than ovarian in younger age, compared with those of age > 45 years.

UAE in Adenomyosis
Adenomyosis is commonly seen in the fourth to fifth decade presenting as dysmenorrhea, menorrhagia, or abdominal pain. The management is by medical therapy with hysterectomy reserved for refractory cases. UAE is emerging as a potential alternative. Liang et al showed a success rate of 88% in controlling bleeding with a pain score reduction from 7.45 to 1.32 (p < 0.001). The short term (6-month) success rate described by Kim et al amounts to 82 to 83%, while Popovic et al showed a long-term (5-year) success

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**Table 3 Utero-ovarian anastomosis and significance**

<table>
<thead>
<tr>
<th>Type</th>
<th>Morphology</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Ovarian artery connects to uterine mural artery and then supplies fibroid. Flow in tubal arteries is toward the uterus on selective uterine angiogram</td>
<td>Chances of failure of UAE high</td>
</tr>
<tr>
<td>Ib</td>
<td>Same as type Ia. Reflux of contrast into an ovarian artery is seen during pre-embolization angiogram followed by washout of contrast washout toward the uterus</td>
<td>Ovarian failure risk</td>
</tr>
<tr>
<td>II</td>
<td>The ovarian artery directly supplies fibroid apart from uterine artery</td>
<td>Chances of residual fibroid</td>
</tr>
<tr>
<td>III</td>
<td>Ovary is supplied by uterine artery with flow in the tuboovarian segment is toward the ovary</td>
<td>Ovarian failure risk</td>
</tr>
</tbody>
</table>
UAE in Arteriovenous Uterine Malformations

Uterine AVMs (Fig. 4) are of two types: congenital or acquired. Congenital AVM occurs due to a defect in embryological differentiation leading to abnormal arteriovenous communications. Even though these are present since childhood, they are commonly noticed during the reproductive period and are frequently associated with multiple feeders from other pelvic arteries in addition to uterine artery. Acquired AVMs involve fistulous communication between uterine artery branches and venous plexuses in the myometrium. These are more common and seen in conditions with prior uterine interventions, uterine surgery, and in gestational trophoblastic disease and infection. Ultrasound is the initial imaging test and shows multiple cystic structures in uterine myometrium on grayscale, and high turbulent flow on color flow imaging. Doppler parameters can help in guiding treatment. Timmerman et al and Lee et al in their studies showed AVMs with high PSV (≥ 83 cm/s) required embolization whereas lesions with a PSV of less than 39 cm/s required only conservative medical management. For women who wish to preserve uterus, expectant management and UAE are the main methods of treatment. Hysterectomy is considered in individuals who do not wish to have future pregnancies or in whom UAE has failed. A systematic review by Yoon et al reported that the primary success rate of UAE in acquired AVM was 61%, whereas, in cases of repeated embolization, it was 91%. Recent studies by Delplanque and Zhu et al showed that the success rate of UAE was 71% to 87% in acquired AVMs. Sophie et al, in 22 patients, showed reasonable fertility rates post UAE (6/7, 85.7%) compared with expectant management (2/5, 33.3%), with no miscarriages and ectopic pregnancy. Pei et al showed similar results in 62 acquired AVMs treated with UAE where 10 patients became pregnant and resulted in the delivery of a healthy live baby. Young age and lack of uterine distortion by fibroid are the probable reasons for successful pregnancy. The choice of embolizing material is variable and in cases of ovarian artery supply, temporary occlusion by gelfoam is sufficient as the main goal is to prevent bleeding.

UAE in Antenatal Bleeding

There is increasing use of UAE in controlling antepartum bleed in ectopic pregnancy and invasive placenta. Scar ectopics (Fig. 5) require early termination in the first trimester. Various treatment options include systemic methotrexate, hysteroscopic resection, dilatation and curettage. Timor et al showed bleeding rate (due to the slow action of the drug, which results in growth of embryo and placental...
tissue) with methotrexate was 62%, thus requiring further treatment. Hysteroscopic removal or dilation and curettage (D & C) in cervical scar ectopic results in profuse life-threatening bleeding due to lack of normal myometrium in cervix. UAE has shown to reduce preoperative bleeding in cases of surgical evacuation. Systematic review by Pektas et al showed 82% of cases treated initially with UAE alone require further treatment by curettage or methotrexate. Though the exact time interval between the UAE and evacuation of products is not clearly defined, it is better to do the evacuation as early as possible after UAE, because delaying evacuation results in recruitment and development of uterine collaterals.

Abnormal invasive placenta (Fig. 6) includes placenta accreta, increta, and percreta. Planned delivery by cesarean section is performed at 34 to 36 weeks of gestation. Endovascular interventions help in preserving the uterus and decreasing intraoperative bleeding. Endovascular interventions include prophylactic balloon occlusion (PBO) and uterine artery embolization. In PBO compliant balloons are placed underfluoroscopy guidance and are inflated after the delivery of the baby and clamping of the umbilical cord. Balloon occlusion can be performed either proximally at the infrarenal abdominal aorta, bilateral common iliac arteries, or distally at the internal iliac or uterine arteries. Proximal occlusion in the aorta is quick to perform with less radiation exposure to the fetus and it also reduces bleeding from collaterals compared with distal occlusion. Uterine artery embolization can be considered after balloon occlusion if there is persistent bleeding. In a systematic review, Shahin et al compared proximal versus distal balloon occlusion and reported that proximal balloon occlusion of the abdominal aorta resulted in better control of blood loss (mean difference-1.391 mL, \( p < 0.001 \)), lower hysterectomy rates, and less fetal radiation dose. Wu et al showed average fetal radiation dose in aortic balloon occlusion was 5.1 ± 3 mGy in 230 patients, whereas the radiation dose with internal iliac balloon occlusion was 21 to 61 mGy. The average radiation dose absorbed by the skin for 10 to 35 minutes of fluoroscopy was ~450 to 1600 mGy, and the dose absorbed by ovaries was 7 to 378 mGy, which is far less compared with the recommended dose limits.

**UAE in Postpartum Bleed**

Postpartum hemorrhage (PPH) is an important cause of morbidity and mortality worldwide with more than 1 lakh death per annum. It is defined as blood loss of more than 1000 mL of blood associated with features of volume loss such as hypotension and tachycardia. It can be primary, which occurs within the first 24 hours due to uterine atony,
trauma to the genital tract, retained placental tissues or coagulopathic disorders or secondary (occurring 24 hours to 12 weeks) due to retained placental tissue, infection, coagulopathy, uterine artery pseudoaneurysm (Fig. 7) or AVM. The latest FIGO guidelines recommend UAE for refractory PPH uncontrolled by medical and nonsurgical methods, provided there is availability of skilled personnel. UAE can be considered when conservative management fails. It is preferable to perform angiography after 30 minutes of administration of uterotonics, as these drugs cause vasospasm, obscuring the total extent of the problem. During angiography, contrast extravasation is seen in 21 to 52% of cases, and the most common source of bleeding is from distal branches of the uterine artery, or vaginal arteries. Absorbable gel foam as embolizing material is preferred as it stops bleeding and allows recanalization within 2 to 4 weeks, thereby preventing ischemia. Liquid embolics such as N-butyl cyanoacrylate are used only when the total permanent occlusion of the vessel is required in recurrent or refractory PPH or in large pseudoaneurysms. In cases where the bleeding site is not identified, empirical embolization of bilateral uterine arteries or anterior division of the internal iliac artery can be attempted. Systematic review by Zhang et al showed that UAE was successful in controlling bleeding in 90.5% of cases with 91 to 100% of independent predictors for clinical failure.

**Conclusion**

In conclusion, uterine artery embolization is a safe, effective, and minimally invasive technique in treating various uterine pathologies such as fibroids, adenomyosis, and uterine vascular malformations. It can help reduce bleeding and preserve the uterus in abnormal invasive placenta and scar ectopic pregnancy. Proper patient selection and consideration of appropriate technical aspects can achieve better success rate.

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None.

**Conflict of Interest**

None declared.

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