

UPDATE ON THE CONSERVATIVE TREATMENT OF UTERINE FIBROIDS - UTERINE ARTERY EMBOLIZATION (UAE), PROTOCOL, EMBOLIGENIC MATERIALS

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Abstract: Uterine leiomyoma is the most common benign genital tumour, consisting of analogous elements of the uterine muscle. The predominance of the structural elements outlines the myomatous or fibrous appearance.(1) Uterine leiomyoma is a major public health problem in women of reproductive age. Uterine fibroids may be present in percentages of 15-20% in women of childbearing age and in 30-40% percentages in women over 30 years of age.(2,3) Newer figures reveal a percentage higher than 50% regarding the frequency of uterine fibroids diagnosed on ultrasound in premenopausal women without symptomatology.(4) Microscopic research has found the presence of uterine fibroids in up to 77% of the uterus that have been operated. Usually, most are asymptomatic. Embolization of the uterine artery is a safe and effective mini-invasive method that provides permanent infarction of the tumour tissue without its subsequent relapse followed by a significant improvement in symptomatology with rapid socio-professional reintegration. An alternative to classical surgery is the of the Uterine Artery Embolization (UAE), a technique with an efficiency of over 85% in terms of dominant symptoms: pain and haemorrhage.(5,6) It is not yet known whether the fertility of the woman is affected later. However, medium-term studies appear to indicate a favourable outcome.(6,7,8) It is a primary or adjunctive therapy to surgery.Following conservative surgery or by embolization of uterine arteries, the quality of life of women is fully preserved, with normal genital functions, hormonal and biological balance being fully preserved

An alternative to classical surgery is UAE, a technique with an efficiency of over 85% regarding the dominant symptoms: pain and hemorrhage.(5,6) Reduction in leiomyoma volume occurs in 39-69% of cases. The concept of therapeutic vascular embolization dates from 1904, when Dawbain described the preoperative injection of paraffin into the external carotid artery in patients with malignant tumours in the head or neck region. The method was first used in France in 1991. The catheter is inserted into the femoral or brachial artery and is placed under radiological control. Small particles of polyvinyl alcohol are injected, followed by a sponge of gelatin in the vessels that irrigate the leiomyoma. Both uterine arteries are usually embolized. It is not yet known whether the woman's fertility will be affected later.(9) Embolization is generally cheaper than abdominal myomectomy, although the process itself is somewhat more expensive, but hospitalization is shorter.(10)

I. Definition

Embolization of the uterine artery is a safe and effective mini-invasive method that provides permanent infarction of the tumour tissue without its subsequent relapse, followed by a significant improvement in symptomatology with rapid socio-professional reintegration.

II. History

The concept of therapeutic vascular embolization dates back to 1904, when Dawbain (11) described the preoperative injection of paraffin into the external carotid artery in patients with malignant tumours in the head or neck region.

In obstetrics and gynecology, the earliest communications on the use of uterine embolization (1976)

involved the treatment of bleeding in malignant disorders.(12,13,14). Subsequently, this procedure was used in postpartum hemorrhages, after gynecological interventions, in ectopic pregnancy and gestational trophoblastic disease, arteriovenous malformations, etc., the success rate ranging from 86% to 100%.(15)

Embolization of the Uterine Artery (UAE) in the treatment of uterine fibroids was used among the first by Ravina in 1991 (7), with the aim to reduce intraoperative bleeding during hysterectomy or myomectomy. Surprisingly, in some situations where this embolization was performed days-weeks before surgery, the patients reported a significant improvement in symptomatology, and on ultrasound, it was found a reduction in the size of the fibroids, which even led to the cancellation of the scheduled surgery, and of course, to amplifying research efforts on embolization of the uterine artery as a direct method for uterine fibroid treatment. Thus, if in 1998 there were reported about 800 interventions worldwide, in October 2000, the Interventional Radiology Society reported the existence of a number of 10,500 cases already, using the uterine artery embolization technique for the treatment of leiomyomas (16), and in November 2002, 25,000 to 30,000 total interventions of this kind were performed across the globe.

III. Surgical technique

Arteriography is an invasive method involving arterial puncture and the introduction of a catheter up to the vascular segment to be investigated, followed by injection of the contrast medium.(17)

Creating a vascular access port

Achieving a vascular access port involves performing

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an arterial puncture by the Seldinger method and mounting a vascular access sheath.(18) The most common area of the vascular approach is the inguinal area (figure no. 1). This area allows, relatively easy, arterial access by puncturing the femoral artery. Other alternative arterial access ways are, in order of frequency of use (19), the brachial, radial, axillary ones.

Figure no. 1. Schematic representation of a vascular access port

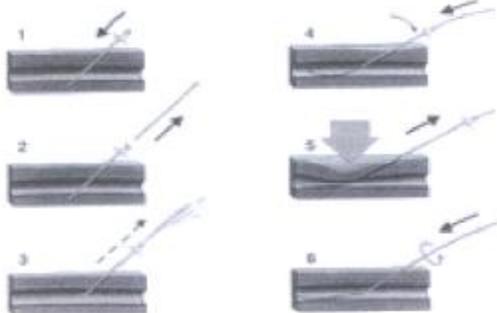
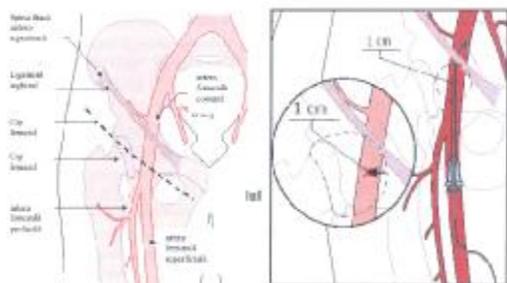


Figure no. 2. Femoral approach



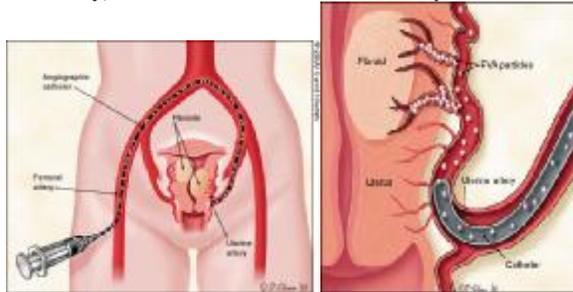
In the case puncturing the right femoral artery is not possible (lack of pulse or multiple punctures at the same level), contralateral approach is attempted.(20) If it does not succeed in this place as well, other puncture sites may be at the level of the brachial artery or radial artery (very rare and not recommended is at the level of axillary artery). The access path: commonly, bilateral femoral “cross-over”. The second type of approach is the brachial one, which presents a number of advantages: unilateral approach, the patient is not immobilized in the bed (possible ambulatory intervention), reduces the time of intervention, eliminates the difficulties related to a high aortic bifurcation; disadvantages: it requires 125 cm catheters; more difficult arterial puncture.

In Romania, the bilateral femoral approach with double crossing over is used, which reduces the intervention time and thus, the accumulated radiation dose.

Introducing and positioning the catheter, selectively, in the interested vascular territory

Angiographic catheters are essentially some flexible plastic tubes with an inner lumen and the end of which (the distal, intravascular extremity) has different shapes designed to facilitate the selective arterial approach in a certain vascular territory. Using the arterial sheath provided with a valve that prevents the blood from flowing, the catheter is inserted. Under fluoroscopic guidance, this one advances to the targeted vascular area (figure no. 3). By rotating the catheter, due to its preforming curve, and by helping us with a guide (coaxially inserted through the lumen of the catheter) selective or supraseductive catheterization of certain vessels (21) is performed.

Figure no. 3. Introducing and positioning the catheter, selectively, in the interested vascular territory



An infrarenal aortography is performed using contrast medium, in our case Iopamiro 300, for the detection of pelvic vascularisation and the leiomyoma. Through crossing over, the catheter is passing the bifurcation of the aorta in the other common iliac, the internal iliac, and from this one into the uterine artery, where it either advances distally as close as possible to the arteries irrigating the fibroma, either it is positioned proximally (in this case, the method is called free flow embolization), and fine particles of Tachocomb of 1 mm, PVA (polyvinylalcohol) of 150-300 μ or 300-500 μ or 5 mm gel platelets are injected.

IV. Emboligenic materials

The most commonly used materials for uterine embolization are PVA (polyvinyl alcohol) particles, embospheres and Gelaspon / Tachocomb fragments. Depending on the indication and the anatomical structure to be embolized, embolic materials should be carefully selected.

Particles (22)-useful for distal embolization (small arteries and arteries)

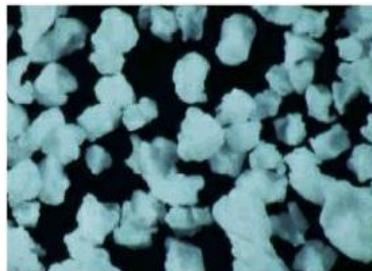
- sponge (Gelfoam) 60- gelatine that makes temporary occlusion about 8 hours
- microfibrillar collagen - temporary agent
- polyvinyl alcohol (PVA) - permanent agent

PVA (Trufill, Ivalon etc.) (figure no. 4)– the most commonly used even since 1970

- is a non-biodegradable synthetic material; it induces acute inflammation, angioneerosis, thrombosis and fibrosis of the vessel into which it is injected; it is non-radiopaque, safe, biocompatible (no allergic reactions have been reported),
- non-resorbable (25-30 years) - permanent embolization

Disadvantages of using PVA: uneven sizes of particles, thus presenting a migration risk, aggregation possibility - catheter plugging, multiple particles are needed to close a vessel; it produces a moderate inflammatory reaction in the embolized vessels, potential recanalization risk during months in the case of proximal aggregation of large particles.

Figure no.4. PVA



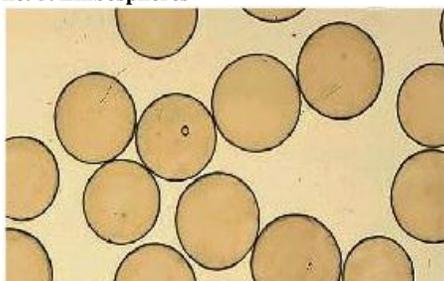
The ethylcellulose particles may also contain a cytotoxic agent (cisplatinum) with prolonged release. This also causes arterial obstruction with tissue necrosis and local chemotherapy.

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Embospheres (23) (figure no. 5) are more expensive and therefore less used; they do not aggregate.

- small particles of 150-300 μ predominantly embolize distally affecting a wider territory, which causes the increase in post-embolization syndrome manifestations with increased pain as a result of necrosis and extended ischaemia as well as increased risk of occlusion of the ovarian artery;(24)
- the large particles of 500-700 μ embolize proximally and consequently, the post-embolization syndrome will appear much diminished, the risk of recanalization will increase and the infection risk will decrease;
- fewer particles than PVA are used - erroneous embolization risk is reduced
- disadvantages –non-resorbable and more expensive than PVA.(25)

Figure no. 5. Embospheres



Tachocomb, Gelaspon (figure no. 6) - collagen films covered with fibrinogen, purified thrombin and aprotinin, from which fragments of different sizes are cut off. Very small particles can also be broken off in suspension;

- mimic the first and last stage of the coagulation cascade;
- they have the advantage of being cheap, easy to aggregate – cover the large vessels, but they are difficult to handle;

In addition, they are “temporary agents” - they resorb in 1-2 weeks, but due to the important inflammatory reaction, permanent occlusion of the small vessels is achieved, while the blood flow in the large vessels is resumed.(26) They can also be used to ease the embolization, intra-arterial injection of vasodilators, papaverine and nitroglycerin.(24)

Repeating angiography a few weeks after embolization showed: resumption of blood flow in the uterine artery after PVA and Embosphere, lack of flow after Gelaspon.

Figure no. 6. Gelaspon



Embolization technique

After studying the vascular anatomy of the uterus and choosing the embolization material, embolization starts. The uterine artery is supraseductively catheterized. If, due to manipulation of the angiography guide and catheter, spasms occur in the catheterized vessels, one should wait for a few minutes, and if spasms are not relieved, vasodilators (nitroglycerin, verapamil etc.) will be administered.

The embolization material mixed with the contrast medium (for visualization) is injected until the reflux occurs behind the catheter. A control injection is performed in which the area served by the catheterized vascular branch should not be visualized (figures no. 7,8). The final infrarenal aortogram (27) reveals the quasi-total obstruction of the blood flow in the fibrous node and the antegradefilling of the ovarian artery in up to 4% of the cases. The technique is then repeated for the uterine artery on the opposite side. In some cases, pain in the tumour formation (due to devascularisation) can occur, which can be treated by administering antialgic medication.

Figure no. 7. Embolization of bilateral uterine arteries (right, left) before and after embolization

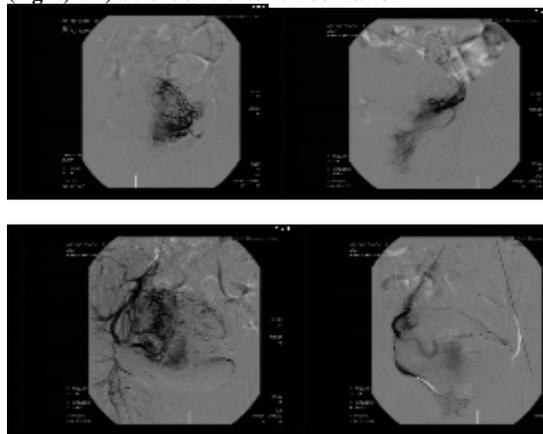
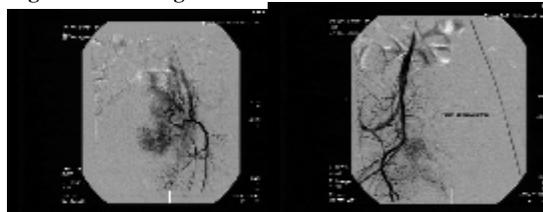


Figure no. 8. Images before and after embolization



The irradiation dose corresponds to 15 minutes of fluoroscopy, the total dose being of 150-225 mSU, and the ovarian one of 22-50 mSU.

V. Postprocedure care

The patient requires maximum 3 days of hospitalization with symptomatic treatment, NSAIDs, antiemetics, antibiotics. In 10% to 40% of cases, the so-called post-embolization syndrome is described, characterized by: - presence of pelviabdominal pain with a bimodal distribution at 6-12 hours caused by uterine ischaemia and 3-5 days after the intervention; headaches, nausea, vomiting, subfebrilities, leukocytosis. If the fever does not cede within 24-36 hours, hysteroscopy and curettage are required.(28)

VI. Selection of patients for embolization. Indications:

A. Ideal candidate (28,29)

1. Young patients with multiple fibroids who want to have children (for whom hysterectomy is not an alternative)

- allows the simultaneous therapy of all fibroids
- preserves the reproductive function of the uterus

2. Symptomatic uterine fibroids

- refusal of hysterectomy
- the refusal of blood transfusion
- refusal / contraindication of general anesthesia

3. Patients nearing menopause

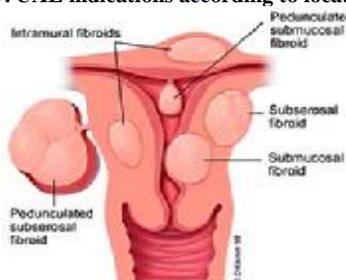
- far less aggressive intervention than hysterectomy

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- cheaper compared to hormone therapy.

B.UAE indications by size, number and location of fibroids

Figure no. 9. UAE indications according to location



- **Irrespective of the size**
 - large embolized fibroids require more careful follow-up to avoid any possible overinfection of necrotic structures
 - embolization + segmental myomectomy for very large fibroids
- **Number**
 - by embolization, all existing fibroids are simultaneously devascularized, even those of small size, undetected by imaging methods
- **Localisation** (figure no. 9)
 - the most indicated are intramural or submucosal well-vascularized fibroids
 - subserosal, pedunculated fibroids are not considered ideal for embolization (30,31,32). Embolization + segmental myomectomy are recommended.

VII. Embolization protocol applied in the SUUB Clinic in the framework of the selection and post-procedure evaluation of patients who have benefited from conservative mini-invasive treatment of uterine fibroids - embolization of uterine artery.

A. Pre-interventional criteria	
1. Menstrual status data	<ul style="list-style-type: none"> - post menopause - amenorrhea - bleeding between menstruations - the duration of the menstrual cycle - regularity of the menstrual cycle
2. Reproductive status data	<ul style="list-style-type: none"> - number of pregnancies - number of abortions (spontaneous, induced) - the number of extrauterine pregnancies - the number of pregnancies completed before 37 weeks of gestation - number of births by caesarean section - post-partum hemorrhages - sexually active patient - it is important to have data on the contraceptive methods used, - patient in the menopause (whether or not she uses hormone replacement therapy), - patient with suspected infertility – the following information is important: if she has been / is undergoing infertility treatment; if there were 3 or more consecutive spontaneous abortions plans for a future pregnancy
3. Other associated gynecological pathology	<ul style="list-style-type: none"> - endometriosis - pelvic inflammatory disease - adenomyosis - others
4. Present symptomatology	<ul style="list-style-type: none"> - menorrhagia - metrorrhagia - intermenstrual or menstrual pelvic pain

	<ul style="list-style-type: none"> - urinary frequency - lumbar pain - pain that irradiates the pelvic limb - infertility - dyspareunia
5. Previous treatments for the current symptomology	a. medical treatment b. surgical treatment: <ul style="list-style-type: none"> - myomectomy - hysteroscopy - dilation and curettage of the uterus - endometrial ablation - previous embolization
6. Past medical history	
7. Investigations required before the intervention	a. laboratory-CBC <ul style="list-style-type: none"> -FSH -LH -17-beta estradiol b. imaging investigations - must provide data on fibroma: <ul style="list-style-type: none"> - the dimensions of the uterus - the sagittal axis <ul style="list-style-type: none"> - AP - transverse - volume - about fibroma - the number of fibromatous nodules <ul style="list-style-type: none"> - localization - morphology - sizes - association or not with adenomyosis
B. Uterine embolization intervention	
1. Medication	<ul style="list-style-type: none"> ▪ prophylactic treatment with antibiotics pre- and post-intervention is instituted ▪ treatment of pain before and after the intervention: Acetaminophen, NSAIDs, sedation, others.
2. Embolization technique	<ul style="list-style-type: none"> ▪ the arterial access line may be unilateral or bilateral, at the femoral or brachial level ▪ embolized uterine artery - right or left ▪ end-point- complete occlusion of the uterine artery <ul style="list-style-type: none"> - embolization limited to a certain level of the uterine artery - other embolized arteries <ul style="list-style-type: none"> ▪ embolic agents - spherical <ul style="list-style-type: none"> - non-spherical PVA - gelaspon
3. Post-embolization clinical status	Patients' clinical status is followed-up for any possible side effects, such as: <ul style="list-style-type: none"> • hematoma at the puncture site; • reactions to the contrast agents; • symptomatic embolizations in other areas; • thromboembolic events; • pains that require hospitalization over 48 hours; • urinary retention; • fever over 37.6 °C, requiring hospitalization over 48 hours; • nausea, vomiting that require hospitalization over 48 hours; • recurrent pain; • urinary infections; • bleeding; • other complications.
C. First check-up- one month after embolization	
The following are to be noticed:	
1. time of recovery 2. initiation of a drug therapy: - progesterone contraceptives <ul style="list-style-type: none"> - GnRH agonists - NSAIDs - hemostatic treatment, others 	
3. establishing the therapeutic strategy in case of reintervention.	

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D. Second check-up- 3 months after embolization	
1. Menstrual status	<ul style="list-style-type: none"> • amenorrhea - symptoms that suggest menopause - biologically confirmed menopause • bleeding outside the menstrual cycle • the duration and regularity of the menstrual cycle
2. Symptoms (their improvement or worsening will be assessed)	<ul style="list-style-type: none"> • menorrhagia; • metrorrhagia; • intermenstrual or menstrual pelvic pain; • frequency of urination; • constipation; • lumbar pain; • lower limbs pain;
3. Imaging investigations - which assess the uterine size, number of fibromatous nodules, their location and morphology.	<ul style="list-style-type: none"> • MRI with and without contrast; • Transabdominal ultrasound; • Transvaginal ultrasound

CONCLUSIONS

Embolization of uterine arteries is a safe and effective method of therapy of uterine fibroids. The method allows the preservation of intact internal genital organs and even fertility, thus avoiding the possible complications (physical, mental, need for a transfusion) of hysterectomy.

In cases where surgery is contraindicated or refused by the patient, embolization of the uterine arteries, alone, is an effective method of therapy of uterine leiomyomas, with very good results reported in the literature and highlighted in this study.

Embolization of the uterine arteries is a conservative method of resolving uterine fibromatosis; it can be used as primary therapy or as adjunctive therapy to the surgical procedure.

Embolization of uterine arteries is a safe and effective method of therapy of uterine fibroids. The method allows for the preservation of internal genital organs and even fertility, thus avoiding the possible (physical, mental) complications of hysterectomy. Although so far, it has not been indicated to women who want a pregnancy, the statistics indicate a majority among the nulliparous.

The contraindications are primarily angiographic and the presence of neoplasia, and there are no clear indications to make us opt for the embolization of uterine arteries; secondly, we mention as contraindication, the advanced age, uncontrolled hypertension (BP > 180mmHg), treatment with anticoagulants (AP < 50%), severe renal impairment, severe hepatic failure, decompensated heart failure, undiagnosed fever, multiple myeloma, active pelvic infection, etc.

Complications occur with low frequency, insignificant morbidity and mortality.

The main advantages of uterine artery embolization therapy are: it does not involve blood loss, no transfusions are required during surgery, surgery does not require general anesthesia, there is no surgical risk. Rapid post-intervention recovery, menopausal induction - less frequently compared to the treatment with Gn-RH agonists. All leiomyomas are treated simultaneously, very low recurrence, virtually null and reduced hospitalization versus surgical methods (1-2 days).

Conventional, laparoscopic conservative surgical methods along with uterine artery embolization are not concurrent, mutually exclusive, each having well-established

indications and contraindications.

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