Review

Embolization of uterine arteries with PVA for treatment of uterine fibroids

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Abstract

The desire for minimally invasive techniques in a very common entity in gynecology, the symptomatic fibroids, prompted the medical community to propose UAE as an alternative to surgical and hormonal treatment. It was Ravina et al in 1995 who firstly proposed this technique for uterine fibroids management.

The aim of the present study is to examine the safety and the efficacy of using uterine artery embolization with PVA for the treatment of uterine fibroids compared to the conventional methods. Detailed research was conducted via the PubMed database using the keywords: “uterine”, “fibroids”, “embolization”, “with”, “PVA”.

Further extend research need to be done in order to clarify the safety and the efficacy of this therapeutic technique, focusing on the reproductive potential, the adverse effects and the recurrence after the procedure.

***Keywords**: “uterine”, “fibroids”, “embolization”, “with”, “PVA”.*

Introduction

Uterine fibroids or lyomyomas are the most common benign tumors of women in the reproductive age, that occur in about 40% of women by the age of 35 years old (1). Their frequency is three times bigger during the preclimacteric period. They are estrogen-responsive neoplasms composed of uterine smooth muscle cells and fibrous connective tissue (2). There is a wide range for the dimensions of the tumor from 1mm to 20cm or more. Their prevalence is difficult to estimate (3). They constitute a major health issue and lead a vast majority of women to undergo a hysterectomy (1). While the vast majority of fibroids are asymptomatic, some of them may cause irritating symptoms at rates of 10 to 40%. These symptoms include pelvic pressure and pain, leg and back pain, heavy and prolonged bleeding during menstruation (menorrhagia) or between period cycles (intermenstrual bleeding), abdominal bloating, urinary frequency or incontinence, constipation and reproductive dysfunction (2). Although fibroids are mainly beyond danger, the cost for annual health care for women with fibroids is excessively higher the one for women without uterine fibroids, excluding the missed workdays.

The diagnosis of uterine fibroids is settled by the ultrasound that is made on a regular basis after the palpation of enlarged uterus. The MRI may also be useful in the diagnosis of fibroids. In fact, MRI provides a higher resolution of the fibroids and thus, better mapping of the fibroids.

There are numerous types of treatment. The conservative ones depend both on the

size and the number of fibroids, on the age and the willing of the woman for reproduction and finally, on the intensity of the symptoms and the discomfortness. The purpose of this kind of management is to eliminate the graveness of bleeding and decrease the volume of the tumors. Such procedures are also applied before surgery for hysterectomy and myomectomy.

Another approach for the treatment of uterine fibroids was applied in Paris in 1992 when Ravina et al. were the first to use embolization of the uterine arteries for this purpose. The results of the study were published in 1995 (2). Their approach was relied to the observation of symptom amelioration among women who had undergone embolization so as to reduce intraoperative bleeding before myomectomy.

Materials and Methods

Detailed research was conducted through the published bibliography via PubMed and Scopus database using the following keywords: “uterine”, “fibroids”, “embolization”, “with”, “PVA”. Data were extracted utilizing a common data elicitation form, using the aforementioned keywords. The study was made with respect to the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources guidelines. Specifically, as regards the PRISMA, the records that were initially identified through PubMed search were 55 and through Scopus search 7. Additional 4 articles were identified from similar articles and 1 article through the review of references. The full text articles assessed for eligibility were 44 and the records excluded articles, title and abstract non relevant were 23. There was 1 duplicate article. From the articles assessed for eligibility, 2 of them were in French and 1 was written in German so they were excluded. From the articles assessed for eligibility 8 of them were not relevant and they were excluded. Finally, 32 references fulfilled the above-mentioned criteria and used in the present work.

Results

Several multicenter and institutional studies have confirmed the effectiveness of uterine arteries embolization for treating uterine fibroids for more than a decade.

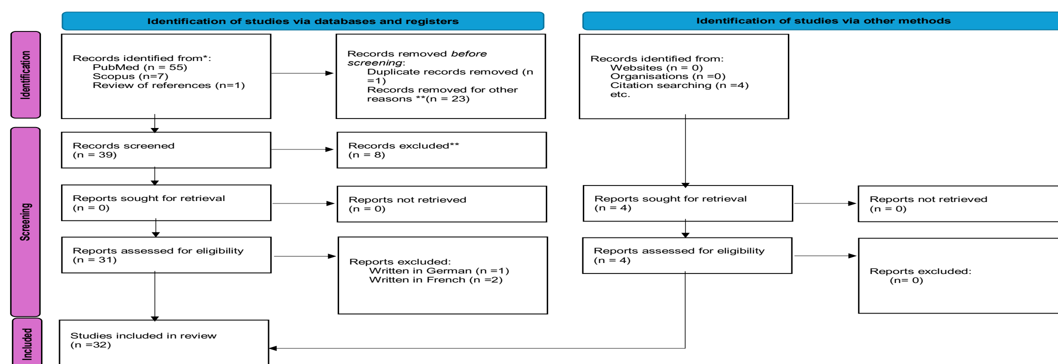

Figure 1. PRISMA 2020 flow diagram for new systematic reviews

Menorrhagia and bulk-related symptoms were diminished in a great percentage (approximately 90% and 85% respectively), were unnecessary in few cases. The vast majority indicated a significant shrinkage in the volume of the largest fibroid and of the uterus (approximately 50-60% and 40-50% respectively). Additionally, significant ameliorations were reported for dysmenorrhea, urinary frequency, abnormal uterine bleeding. Even though UAE provided a great relief of the symptoms caused by the fibroids, there are various adverse effects. Specifically, several studies reported transient (10%) or permanent amenorrhea (<45 years old: 3%, >45 years old: 5%), postprocedure endometrial or uterine infection requiring emergent hysterectomy (2%) and finally nontarget embolization (1%)(1).

Discussion

Fibroids are categorized based on their affinity with the uterus as intramural, submucosal and subserosal. The last two (submucosal and subserosal) can be described as pedunculated or exophytic. Exophytic fibroids have a wide-based attachment to the uterus, while Pedunculated ones are attached to the uterus by a stem which is narrower than 50% of the diameter of the lyomyoma. Although, all types of the fibroids are capable of provoking menstrual disturbances and symptoms, submucosal fibroids are more likely to cause abnormal uterine bleeding whereas subserosal ones are more commonly associated with bulk-related symptoms.

History of uterine artery embolization (UAE) for fibroids symptoms management. The first uterine embolization was successfully carried out in Paris in 1974 by neuroradiologist Jean-Jacques Merland to heal intractable menorrhagia in a woman with uterine fibroids who was extremely debilitated. Dr. Merland in concert with gynecologist Dr. Jacques Ravina a few years later, started performing UAE prior to myomectomies in order to diminish bleeding during surgery and reduce transfusion requirements. It was in 1993 when Dr. Merland and Dr. Ravina commenced a multicenter trial observing the effectiveness and safety of UAE as a minimally invasive management for symptomatic myomas. In 1995 the first results from using polyvinyl alcohol (PVA) particles were published in Lancet. The results indicated that in the majority of the patients there was a recession of symptoms and thus initiated a universal interest in UAE as an alternative option for uterine fibroids management. In 1997 Goodwin in United States also highlighted an average 60-65% reduction in dominant myoma size, 3 months after an UAE performance. However, Goodwin also reported one case of a patient developing endometritis and pyometra, requiring hysterectomy. Over times, numerous studies followed looking at the security and the efficacy of UAE as a viable substitute treatment of uterine fibroids (2).

Technique. The purpose of this minimal invasive technique is to decrease uterine fibroids by selectively embolizing bilateral uterine arteries. Although it is possibly to exist minor differences between UAE techniques depending on the various interventional radiologists and among organizations.

Before the procedure patients are submitted to a pelvic magnetic resonance imaging (MRI) in order to give a precise measurement of the largest fibroid and the uterine volumes and the precise anatomy of each woman (4).

A local anesthesia is applied so as to

enable vessel puncture. UAE is performed by an interventional radiologist. A 5-F catheter (Cordis) supported on a Roadrunner 0.035 hydrophilic guide wire (Cook) is inserted into the internal iliac artery and a coaxial 2.3-F microcatheter is advanced into the uterine artery (5,6). Embolization is carried out under fluoroscopic control, until the arched branches and branches emanating from the uterine artery's primary stem vanished and vascular stasis was noted. The procedure is performed with the catheter tip positioned beyond the cervicovaginal branch by using embolic agents such as polyvinyl alcohol (PVA) particles (Bearing; Merit Medical) (7,8). PVA particles are mixed 1:1 with a 60ml solution of normal saline and contrast agent (9). One to two vials of 355-500μm PVA are being injected initially into each uterine artery and the amount augments to 500-700μm in that case that the endpoint is not attained. This endpoint tallies to an angiographic picture of a patient horizontal segment without flow in the ascending chunk of the uterine artery (10). Embolization continues until the cessation of blood flow in the ascending uterine artery for 10 heart beats is completed.

The first 24h after the UAE all participants are under intravenous administration of analgesia. A day after the procedure an MRI is conducted in order to quantify the volume shrinkage of the uterus and of the largest fibroid (11).

Adverse effects. Despite the fact that uterine arteries embolization is a safe, highly efficient and well-tolerated procedure, it is normally associated with side effects occurrence. There is a symptomatologic chain defined as “postembolization syndrome” that is observed in 15-50% of patients and is usually terminated within less than a week (12). The most common collateral effect is crampy pelvic pain, which normally arises about 20 minutes after the embolization of the second uterine artery (ischemia) (13). The pain is usually constant with a variant intensity. The first hours immediately after the embolization the pain is usually severe, but it decreases after 6-8 hours. However sometimes the pain persists in some cases with variable intensity and frequency for 4-5 days. Intravenous analgesia (NSAIDS, opioid) is required the first 6-8 hours after the procedure. Thereafter, the pain can be managed with oral anti-inflammatory and analgesic drugs. Most of the times, pain is accompanied by fever in the terms of inflammatory reaction (cytokine release), because of tissue ischemia. There is a slight percentage (about 20%) when the temperature exceeds 38 °C and has a variable periodicity. Moreover, the first hours after the embolization, there is commonly nausea and vomiting partly as a consequence of the administration of opiates.

Additionally, another adverse effect may be the development of acute endometritis with purulent contents (11), despite the administration of prophylactic antibiotics, in consequence of postembolization ischemia or infraction (13). Further, some other extremely rare collateral effects are the Escherichia coli infection leading to hysterectomy, the development of tubo-ovarian abscess (14) and finally the infection of the fibroid itself resulting in perforation of the fundal myometrium.

Another side effect concerning the embolic agent is the fact that after being injected, irregularly shaped PVA particles have a tendency to clump together, increasing the effective size of PVA relative to its real size. This could result in an embolic blockage that occurs closer than planned (15).

In addition, one could mention as disadvantages of the method of the uterine arteries embolization for fibroid management the utilization of radiations

during the procedure and the permanently implanted material (PVA). Furthermore, there is a slight risk of uterine or ovarian malignancy in patients who would have otherwise had a hysterectomy.

The majority of patients who undergoes uterine arteries embolization is able to be discharged within 24-36 hours with a prescription of per os analgesic therapy for a short period. They are generally able to resume normal activities of their everyday life within 8-10 days after the embolization (16).

Finally, it is reported that in some cases there are calcifications post the uterine arteries embolization peripherally. The peripheral calcifications that are usually observed on the US after 6 months of the procedure, are contributed of the peripheral deposition of the injected PVA particles, occluding small arteries rather than arterioles (17).

Conventional methods vs UAE. Surgical or hysteroscopic myomectomy or even hysterectomy is considered to be the first line conventional methods for uterine fibroids management. However, there is evidence indicating that these methods are linked to high blood loss, extend operating time, discomfort, postoperative morbidity and long hospitalization. Furthermore, 20%-50% of women who have myomectomy will eventually need further surgery to treat fibroids, usually hysterectomy (18).

It has been demonstrated that by using hormonal therapy of pregestational compounds or gonadotropin-releasing hormone agonists may significantly ameliorate symptoms and diminish the size of fibroid tumors, but that within a short period of time (few months) of stopping treatment, leiomyomata quickly grow back at their initial size. These drugs are currently used as a temporizing strategy in perimenopausal women or as a way to reduce fibroids size and vascularity prior to surgery because the drawback of longer-term therapy include osteoporosis, menopausal symptoms and amenorrhea to women who desire pregnancy.

The use of uterine arteries embolization for treating fibroids constitutes an alternative minimally invasive method for women suffering from bulk symptoms (19). It has been demonstrated by several studies that the therapeutic efficiency of percutaneous embolization in diminishing treated fibroid size (estimated approximately from 50% to 60%) and ameliorating of menstrual dysfunctions and all those symptoms related to myomas, with success rates from 85% to 95% in the short and medium term (16). With an average volumetric reduction of 57.7% (range 10%-90%) for the uterus at 24 months and 76.1% (range 17%-100%) for the dominant myoma, the vast majority of treated patients have indicated a progressive size reduction of fibroids and, to a lesser extent, of the uterus itself. However, reinvention was necessary longtermly (within five years approximately) for some patients (20,21,22).

In comparison to myomectomy and hysterectomy, uterine artery embolization for uterine fibroid management is usually less invasive, maintains the uterus and necessitates less hospitalization and rehabilitation time (3 and 44 days respectively or laparotomic myomectomy and 4-6 and 60 days respectively for hysterectomy). Moreover, it is important to mention that the embolization provides the ability to treat all the fibroids of the uterus in one only session.

Overall, UAE is a method with a very high success rate that exceeds 80%.

Indications. UAE is absolutely contraindicated in cases of pregnancy, active infection and presumed ovarian or uterine malignancy. Coagulopathy, immunocompromise and prior pelvic radiotherapy are relative contraindications

for a woman to undergo UAE (23). Embolization might be the best treatment option for women with symptomatic fibroids who are not candidates for surgical procedures or who even are unwilling to undergo a surgical procedure based on ethics, such as the reluctance to receive blood transfusion (18).

More research needs to be done to clarify whether myoma's location, size and blood flow characteristics are significant predictors of the embolization's outcome.

It has been demonstrated that patients who underwent previously a myomectomy are more likely to have a successful result after UAE. This leads to the assumption that a combination of myomectomy and embolization may be more efficacious (10).

Impact on reproductive potential. The vast majority of the women that undergo uterine artery embolization is aged between 30 and 40 years. This raises the question if there is an impact on the reproductive potential of the patients. A crucial aspect in such context is radiation exposure during the embolization, taking into consideration that ovaries are among the most radiosensitive organs. The dose of the radiation exposure varies and depends on the fluoroscopy duration, the experience of the operator and the amount of the sequences performed. According to the data from the International Commission on Radiological Protection, the ovarian exposure dose related to possible infertility is 2.5-6 Gy. The optimal angiographic equipment with the use of pulsed fluoroscopy, accompanied by a highly experienced operator result in an average fluoroscopy time about 10.9 min and dose of ovarian exposure to 9.5 cGy (24). It is therefore very unlikely that infertility may be caused directly by radiation dose exposure of patients during the procedure.

The vast majority of women that underwent uterine embolization for fibroid treatment, maintain a normal menstrual cycle. It is indicated in multiple studies that spontaneous pregnancies successfully arise after the procedure. However, in over than 5% of cases developed amenorrhea (temporary or permanent) accompanied by further ovarian failure signs. Amenorrhea may occur when part of the embolic material reaches the blood supply through anastomoses from the uterine artery to the ovaries (25). Even though, the majority of the women in these cases are older than 45 years (26), there have also been reported episodic cases of ovarian failure in younger women (27). The dominant etiopathogenetic hypothesis is the one of a secondary ovarian hypoperfusion to nontarget embolization through collateral uterine ovarian cycle or a flow inversion in ovarian arteries after uterine arteries bilateral obstruction.

There has not been found a difference in FSH levels after the procedure. Two case-control studies (prospective and long-term studies) have confirmed by using a combined evaluation of a) ultrasound (ovarian volume and follicular number) and b) clinical (FSH and estradiol plasma level on the 3rd day of menstrual cycle) of ovarian functionality that the embolization does not affect the ovarian reserve in women under the age of 40 and does not accelerate the menopause in older women.

Post-procedure amenorrhea may arise because of a massive ischemic injury at endometrial level, which can provoke atrophy or formation of secondary intrauterine symphysis due to chronic inflammation processes related to tissue necrosis.

There are reports in the literature that suggest an increased miscarriage risk (27-60%), premature birth (over 28%), fetal malposition (17%), caesarian section (over 50%), low birth weight (7%), abnormalities in implantation and placentation processes such as placenta previa and placenta accreta

(7%) (28), an increased risk of postpartum hemorrhage (13-20%) and finally spontaneous abortion (30.4%) (29) after uterine embolization, compared to general population tendency. It is believed that generally pregnancy after uterine arteries embolization appears to be safe, with low morbidity. Although, myomectomy remains the first option for patients with fibroids that intend to have a pregnancy.

Factors that may affect the outcome. There are various factors that may influence the outcome of a uterine artery embolization for treating fibroids. Specifically, the location of myomas lead to a different response to the procedure. Submucosal leiomyomas are more likely to subsist a great change in volume, that correlates with better clinical result (30). Pedunculated subserosal fibroids are less likely to undergo a volume reduction. Further, the location of the individual leiomyomas influences the success of infarction. Pedunculated serosal leiomyomas are less probable to subsist infarction than transmural leiomyomas (31). Lastly, the age of the patients, the baseline uterine size and finally the size of the fibroids don't seem to affect the success of the procedure (32). However, further research needs to be done in order to clarify the impact of such factors.

Conclusions

Eliminating symptoms, significantly diminishing the fibroid size, preventing future myoma recurrence and maintain fertility are the goals of the optimal treatment for uterine fibroids. UAE seems to be a great alternative to traditional surgical or hormonal therapy, not only because of its safety and tolerability, but also due to its generally high efficacy in long term. This therapeutic method provides significant socioeconomical benefits if compared to surgical treatments, especially concerning hospitalization and convalescence period, offering a faster recovery and return of the patient to daily activities.

Nonetheless, further studies are required to assess the technique's reproducibility and the outcomes accomplished on the framework of women's healthcare. Though, the number of pregnancies without complications is augmenting and both spontaneous and secondary with assisted reproductive techniques are reported to women who underwent uterine arteries embolization. Finally, UAE is giving a new unexplored yet horizon in the field of medicine as this method could be used in the treatment of other pelvic entities such as hyper vascular pelvic masses of different types, including abdominal pregnancy, cervical pregnancy and arteriovenous malformations.

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