Clinical aspects of uterine artery embolization
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INTRODUCTION
Uterine fibroids are the most common benign tumors in the female genital tract and consist of a proliferation of smooth muscle cells with an extracellular matrix of collagen. Growth of fibroids is influenced by estrogen, progesterone, and a variety of growth factors (1, 2). After menopause, fibroids tend to regress. Fibroids may be located in an intramural, submucosal or subserosal position and they may be pedunculated on a thin stalk.

Incidence of uterine fibroids

Although the true incidence of fibroids is unknown due to the high prevalence of asymptomatic patients, it is generally reported as 20% to 40% in women of reproductive age (3, 4). Black women have three times more often fibroids than white women (5). Most fibroids are asymptomatic, but a substantial proportion of women with fibroids have significant and sometimes disabling symptoms such as heavy menstrual bleeding, pelvic pain and pressure, dyspareunia, and urinary frequency and urgency. Presence of fibroids can reduce the possibility of pregnancy in women attempting conception (6). Symptoms are often of sufficient severity to necessitate surgical intervention; fibroids are the most common indication for hysterectomy. In the United States about 300,000 hysterectomies are performed to remove fibroids each year. In The Netherlands, this figure is estimated to be 5000-8000 hysterectomies per year.

Treatment

Since uterine fibroids are benign, treatment is only indicated if symptoms are severe. Medical treatment may consist of analgesics or hormonal therapy. Nonsteroidal anti-inflammatory drugs (NSAIIDs) are often effective for the relief of pain and diminish uterine bleeding. Hormonal therapy may include oral contraceptive pills, levonorgestrel containing IUD’s and gonadotropin-releasing hormone analogs. However, long-term benefits of hormonal therapy are questionable (7, 8). In addition, many patients have an aversion against hormonal therapy or do not tolerate it well. For patients requiring interventional treatment options include hysterectomy, myomectomy and uterine artery embolization. Selection of treatment modality depends on many factors such as patient’s age, severity of symptoms, comorbidity, wish to future conceive and number, size and location of the fibroids (7, 8). Choice of treatment should be tailored to the
specific needs of the individual patient. Hysterectomy is by nature the definitive treatment for fibroids. However, it is a major operation, with an overall complication rate of about 20% (9,10). In addition, hysterectomy may have a negative psychosocial effect by reduced sexual interest, arousal and orgasm, as well as a negative impact on mood and impaired body image (11). Myomectomy with preservation of the uterus can be performed only in patients with fibroids of a certain number, size, and location. Another disadvantage of myomectomy is the substantial risk of fibroid recurrence and the frequent requirement for further surgery (12,13). Therefore, myomectomy is performed less frequently than hysterectomy in The Netherlands.

A relatively new option, uterine artery embolization (UAE), is now available for patients who do not wish to undergo surgery and intervention is considered indicated. UAE was a well-known tool in the treatment of post partum hemorrhage. In 1995 Merland was the first to perform a pre-operative UAE in order to reduce the blood loss during a planned hysterectomy by his colleague the gynecologist Ravina (14). However, it was discovered that after UAE the infarcted fibroids shrank with clinical improvement of patient’s symptoms obviating the need for hysterectomy. In the years to follow UAE developed into a successful tool in the management of uterine fibroids and is nowadays an accepted alternative for surgery. Since UAE is a percutaneous procedure it has two advantages over surgery. It is less invasive (and therefore the recovery time and hospital stay are shorter) and the uterus is preserved, which is not only important for women who wish to conceive (15).

There is some evidence that patients with larger single fibroids and larger uterine fibroid burden may have less improvement and less satisfaction with the results of UAE (16,17). In addition, some fibroids are considered less-than-ideal candidates for embolization such as broad-ligament fibroids, cervical fibroids, small-stalked pedunculated fibroids, and intracavitary fibroids. However, this perception of relative contra-indications is based on clinical experience only without evidence from systematic studies to substantiate these assumptions. The only contra-indications to UAE are pregnancy, suspected pelvic cancer and active pelvic infection. UAE is the therapy of choice in patients who are poor surgical candidates such as obese women or women with previous pelvic surgery.
Arterial supply to the uterus

Most fibroids receive their blood supply from the uterine arteries (Fig. 1). Occasionally the ovarian arteries are additionally involved in uterine blood supply. Anastomoses between the left and right uterine arteries and between the uterine and ovarian arteries are sometimes present. Fibroids are typically surrounded by a dense arterial perifibroid plexus, while the center of the fibroid is hypovascular (18). UAE is aimed to occlude the vessels of the perifibroid plexus inducing ischemic infarction of the fibroid. The devascularized fibroids shrink in several months resulting in relief of symptoms. Pathological studies of uteruses after embolization typically show hyaline necrosis or coagulative necrosis of the tumor mass (19). In general, a successfully treated fibroid will be permanently devascularized. Incompletely infarcted fibroids may grow again and new fibroids may develop over time.

Figure 1. Arterial supply to the uterus and fibroids
MR imaging is used to evaluate the size, location and number of fibroids, both at baseline and at follow-up (Fig. 2).

**Uterine Artery Embolization**

Uterine artery embolization is performed in an angiography suite in the department of Radiology. Via a femoral approach, a catheter is positioned into the uterine artery under fluoroscopic imaging. An arteriogram is obtained to visualize the anatomy of the arterial plexus supplying the fibroids (Fig. 3).

Embolization is then performed by injection of an embolic agent in order to block the vessels of the perifibroid plexus. The embolization is flow directed to the vessels supplying the fibroid. Since the arteries of the perifibroid plexus are much larger than the arteries supplying the myometrium, these vessels are preferentially occluded inducing ischemia of the fibroids only with sparing of the normal myometrium. Embolization is terminated when the vessels of the perifibroid plexus are occluded with sluggish flow in the uterine artery. Then, the procedure is repeated in the contralateral uterine artery (Fig. 4).

![Figure 2. MR before and after UAE.](image-url)
Figure 3. Pre UAE angiogram.

Figure 4. Post UAE angiogram.
After the procedure, most patients have moderate to intense pelvic pain that requires treatment with intravenous narcotics and NSAIDs. Patients also may have malaise, fatigue, and myalgias for several days. About a third of patients develop a mild fever. Most patients return to normal activities within 2-3 weeks after the procedure. Many patients will have light vaginal bleeding, spotting, or a brownish vaginal discharge for several days. Menstrual bleeding, pelvic pain, pressure, and urinary symptoms are usually reduced by the second or third menstrual cycle (20,21).

**Adverse effects of UAE**

The most common combination of symptoms during recovery is the so-called post embolization syndrome (PES) consisting of pelvic pain, mild fever, and general malaise. The syndrome can usually be managed with analgesics and antipyretic agents. Although prophylactic antibiotics are routinely administered before embolization, infection occasionally occurs. It is important to distinguish PES from infection, which is a less common but potentially serious complication (22,23). No deaths have been reported in any of the large clinical studies (20,24,25). Vaginal expulsion of a fibroid or of fibroid tissue occurs in 2-8% of women after UAE, and in some cases surgical extraction may be necessary. Transient or permanent amenorrhea as a result of partial non-targeted embolization of the ovaries occurs sporadically, especially in women of perimenopausal age. Other non-targeted embolic complications have been very rare and include ischemic damage to the bladder, vagina or vulva (26,27).

**Clinical results of UAE**

Since the introduction of UAE in the 90’s of the last century, a number of large observational studies have been performed (20,24,28,29). These studies have shown that heavy menstrual bleeding, pelvic pain, pressure, and urinary symptoms improve in the vast majority of patients.

The EMMY Trial (Uterine Artery Embolization versus Hysterectomy for Uterine Fibroids) was a multicenter, randomized trial in which embolization was compared with hysterectomy in 177 patients in The Netherlands (15,30). After embolization, patients
recovered more rapidly with shorter hospital stay than after hysterectomy. Improvements in health related quality of life was substantial and similar after both therapies. However, a quarter of patients who were embolized had recurrent symptoms that subsequently necessitated hysterectomy. The REST Trial (Randomized Trial of Embolization versus Surgical Treatment for Fibroids) was a multicenter study of 157 patients who were randomly assigned to surgery (hysterectomy or myomectomy) or embolization (31). Health related quality of life after both treatments was similar, although after surgery a greater reduction in symptoms was reported. After a median follow-up of 32 months, a fifth of embolized patients were additionally treated for the same or recurrent symptoms. Another long-term follow-up study also showed that by 5 years after treatment, a fifth of patients who were embolized required repeated intervention (32). Altogether, these studies show that in patients with uterine fibroids symptom relief and health related quality of life is similar after UAE and surgery. However, a fifth to a quarter of patients treated with UAE need additional treatment during follow-up.

American and European guidelines

The American College of Obstetricians and Gynecologists concludes, based on level A evidence that UAE is a safe and effective option for appropriately selected women who wish to retain their uteri. The College also recommends caution when considering embolization in women who desire to retain their ability to conceive, because age-related amenorrhea can occur in a small minority of patients and because there is a possibility of abnormal placentation (33). The Society of Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe state that UAE is indicated for the presence of uterine fibroids that are causing significant lifestyle-altering symptoms, specifically mass effect on the bladder or intestines, and/or dysfunctional uterine bleeding that is prolonged, associated with severe dysmenorrhea, or is causing severe anemia (34).
Aim of this thesis

In the previous section we explained current general concepts of UAE. Although UAE is now widely accepted as a treatment modality for women with symptomatic fibroids, based on the published randomized clinical trials, many technical and clinical issues still are not fully clarified. The aim of this thesis is to address some of these pending issues.

A technical consideration in UAE is the endpoint of embolization. A complete occlusion of the uterine arteries as an endpoint might be needed for adequate infarction of the fibroids but this technique is prone to the occurrence of ischemic complications by inadvertent occlusion of normal arteries to the uterine stroma, ovaries and vagina. On the other hand, a more limited embolization endpoint leaving the ascending segment of the uterine artery open to prevent ischemic damage to normal structures, might result in insufficient infarction of the fibroids. The technique of this limited embolization and the clinical results will be investigated.

Another technical consideration is the embolic agent that is used. While in earlier studies mostly polyvinyl alcohol particles were used, these particles caused catheter blockage in a substantial proportion of procedures. The newer gelatin microspheres were introduced for easier handling without blockage of the catheter. We will evaluate the clinical and imaging results of patients treated with a new type of gelatin microspheres.

Although UAE provides good clinical results on the short-term, the results on the long-term are not firmly established. We will assess the mid- and long-term clinical and imaging results of large cohorts of women treated with UAE.

Although UAE is suitable for most patients with fibroids, there are several factors that are considered contra-indications by some but disputed by others that have never been evaluated. We will assess results of UAE in patients with pedunculated fibroids, in patients with an IUD in situ and in patients with a large fibroid burden.
In summary, this thesis tries to find answers on the following questions:

1. Does limited uterine artery embolization provide sufficient clinical results?
2. Do the new gelatin microspheres as embolic agent offer comparable clinical results than with conventional particles?
3. Are the good short-term clinical results of UAE sustained on the mid- and long-term?
4. Should the presence of pedunculated fibroids be considered a contra-indication for UAE?
5. Should an IUD be removed prior to embolization?
6. Should we refrain from UAE in patients with a large fibroid burden?
References


