Uterine Artery Occlusion in Patient with Fibroids, Infertility, and Symptoms, Clinical Studies

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13.1 Introduction

Traditional operative treatments for symptomatic fibroids are laparotomy with hysterectomy or myomectomy, involving considerable morbidity (Guarnaccia and Rein 2001; Dicker et al. 1982). Myomectomy involves the shelling out of fibroids from the myometrium, and in the case of submucosal fibroids these can be removed surgically via hysteroscopic procedures (Fernandez et al. 2001). Although morbidity is reduced with endoscopic surgery, this technique is not widely available and has limitations.

13.1.1 New Treatment Options

A number of minimally invasive treatments options are now available for the treatment of symptomatic fibroids. Surgical treatments with endoscopic technique include hysterectomy, myomectomy, and myolysis (Dubuisson et al. 1997). Multiple fibroids pose a significant problem for treatment. When myomectomy or myolysis is performed and all clinically identified fibroids are removed or "killed," in approximately half of the patients fibroids are seen at a later time (Nezhat et al. 1998). Medical therapy like ulipristal acetate was noninferior to once-monthly leuprolide acetate in controlling uterine bleeding and was significantly less likely to cause hot flashes, and treatment with ulipristal acetate for 13 weeks effectively controlled excessive

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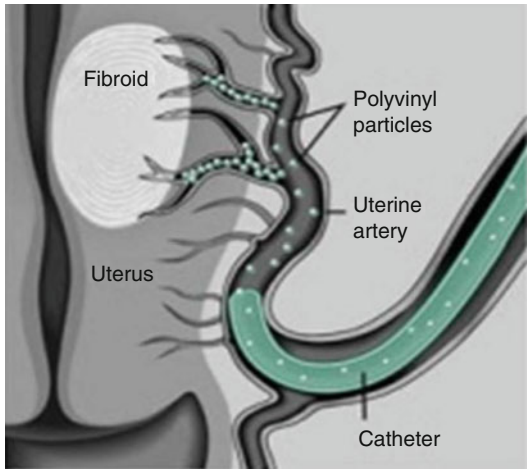

Fig. 13.1 Embolization of the fibroids

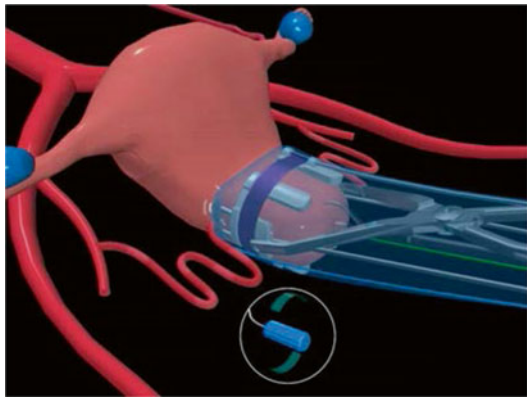

Fig. 13.2 Temporary clamping of the uterus

bleeding due to uterine fibroids and reduced the size of the fibroids before surgery (Donnez et al. 2012). However, medical therapy of fibroids will not be discussed further in this chapter.

Nonsurgical treatments include medical therapy and treatments interfering with the blood supply to the uterus or the fibroids, uterine artery embolization performed by interventional radiologist, or laparoscopic uterine artery occlusion by the gynecologist. Even simpler treatment is the nonincision temporary uterine clamp, placed in the side fornices in the vagina directed with Doppler ultrasound.

The continued therapy goal for symptomatic fibroids must take into consideration the needs and desires of the patients, i.e., length of hospital stay, time to return to work, adverse events, and childbearing plans. Hysterectomy continues to be costly in billions of dollars spent annually, as well as in the more fundamental terms of morbidity and mortality when compared with the less invasive alternatives (Goldfarb 2000) (Figs. 13.1 and 13.2).

13.2 Uterus Circulation

Uterus has a very rich blood supply through two extrinsic arterial systems, the uterine and ovarian arteries. Intrinsic uterine arteries consist of ascending uterine, arcuate, radial, and peripheral arteries implicating free flow through the uterus. Fibroids receive their blood supply from the intrinsic arteries, primary from branches of arcuate arteries, and the vessels are located in the pseudocapsule around the fibroids. The ipsilateral uterine and ovarian arteries are connected by communicating branches. In addition to its primary (uterine artery) and secondary (ovarian artery) extrinsic blood supply, the uterus enjoys a vast network of lesser known arterial collaterals (Burbank and Hutchins 2000). If the blood supply from the right or left uterine artery is occluded, blood from the left or right artery will supply the myometrium by communications through arcuate arteries. Finally, if both uterine arteries are occluded, blood flow to the myometrium will develop from the ovarian arteries through communicating arteries. In addition to the primary and secondary blood flow, the uterus has a vast network of collateral arterial communication from the aorta external iliac and femoral artery branch (Chait et al. 1968) (Fig. 13.3).

Diagram showing the extrinsic arteries of the left side of the uterus, including the aorta and the renal and ovarian arteries arising from the abdominal aorta, the uterine artery arising from the internal iliac artery, and the utero-ovarian communicating artery. Symmetrical arteries are present on the right but are not shown.

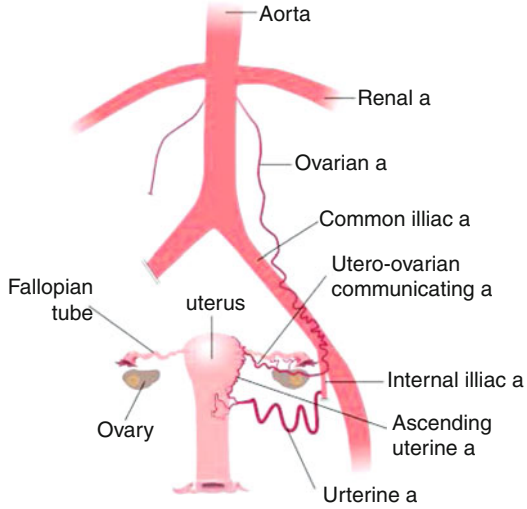

Fig. 13.3 Blood supply to uterus

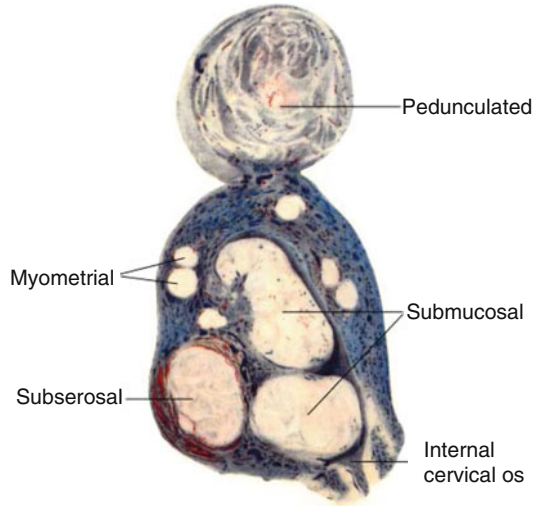

Fig. 13.4 Different types of fibroids and degeneration

13.3 Fibroid Life Cycle

Fibroid degeneration is the physiological way of terminating further growth of fibroids. Fibroids are particularly susceptible to degeneration because their rapid growths need increased blood supply. Fibroids have unsubstantiated connection to the uterine blood supply and as a consequence they frequently outgrow their blood supply, and consequently two thirds of the fibroids show degeneration (Huang et al. 1996). Larger fibroids are more frequently associated with degenerative changes compared to the smaller ones (Cramer et al. 1996). The different types of degenerative changes are hyaline or myxoid degeneration (75 %), calcification (10 %), cystic degeneration (10 %), fatty degeneration, and red degeneration during pregnancy (Fig. 13.4).

13.4 Implication of Uterine Ischemia

When the uterine circulation is interrupted, unperfused myometrium quickly becomes hypoxic which will create pain. During ischemia, myometrial energy is derived anaerobically from the breakdown of glycogen through the glycolytic pathway (Laudanski 1985). After the uterine arteries are occluded, most blood stops flowing in myometrial arteries and veins, and the uterus becomes ischemic. It is postulated that myomas are killed by the same process that kills trophoblasts – transient uterine ischemia (Burbank 2004).

Over time, stagnant blood in these arteries and veins clots. Then, tiny collateral arteries in the broad ligament including communicating arteries from the ovarian arteries open and cause clots within myometrium to lyse and the uterus to reperfuse. Fibroids, however, do not survive this period of ischemia (Lichtinger et al. 2003). This is a unique organ response to clot formation and ischemia. After the uterine arteries are bilaterally occluded, either by uterine artery embolization or by laparoscopic obstruction, women with fibroids experience symptomatic relief after some time.

13.5 Practical Aspects of Procedure: Uterine Artery Occlusion

In 1964, Bateman reported the successful treatment of menorrhagia in four patients with fibroids and three with functional uterine bleeding

(Bateman 1964). This was the first published article that demonstrates that uterine artery occlusion by ligation, division, or excision is an effective treatment for menorrhagia associated with fibroids and in patients without pathology.

Laparoscopic bipolar coagulation of uterine arteries and anastomotic sites of uterine arteries with ovarian arteries represents another modality of avoiding hysterectomy in some women (Liu 2000; Liu et al. 2001). This procedure was first described in 2000 in three women with symptomatic fibroids who required conventional surgical treatment. Uterine size and dominant fibroid size were assessed by ultrasonography before and after surgery. Both uterine arteries, as well as anastomosis zone of uterine arteries with ovarian arteries, were occluded in all three women. Surgery was uneventful, and patients were hospitalized for only 2 days. All women experienced improvement in symptoms with no complications. Postoperative ultrasound showed progressive reduction in size of the dominant fibroid (Liu 2000).

In another study 46 premenopausal women, age 43 (34–51) years with symptomatic uterine fibroids, undergoing radiologic embolization ($n=24$) or laparoscopic closure of the uterine arteries ($n=22$) (Hald et al. 2004, 2007; Istre et al. 2004). The laparoscopic technique reduced picture blood assessment score after 6 months by 50 % in both groups. Uterus volume was also reduced by 35–40 % in both groups. Postoperative pain and use of pain relief differed significantly, as patients required more pain medication after embolization: ketobemidon 38 mg compared with 16 mg in the laparoscopic group (P = 0.008). In conclusion, we found that laparoscopic occlusion of uterine vessels is a promising new method for treating fibroid-related symptoms, with less postoperative pain than embolization and comparable effects on symptoms.

Women with fibroid(s) unsuitable for laparoscopic myomectomy (LM) were treated with uterine artery embolization (UAE) or laparoscopic uterine artery occlusion (LUAO). Before the procedure, patients treated with UAE ($n=100$) had a dominant fibroid greater in size (68 vs. 48 mm) and a mean age lower (33.1 vs. 34.9 years) than surgically treated patients ($n=100$). After 6 months, mean shrinkage of fibroid volume was 53 % after UAE and 39 % after LUAO ($p=0.063$); 82 % of women after UAE, but only 23 % after LUAO, had complete myoma infarction ($p=0.001$). Women treated with UAE had more complications (31 vs. 11 cases, $p=0.006$) and greater incidence of hysteroscopically verified intrauterine necrosis (31 vs. 3 %, $p=0.001$). Both groups were comparable in markers of ovarian functions and number of nonelective reinterventions. The groups did not differ in pregnancy (69 % after UAE vs. 67 % after LUAO), delivery (50 vs. 46 %), or abortion (34 vs. 33 %) rates. The mean birth weight of neonates was greater (3,270 vs. 2,768 g, $p=0.013$) and the incidence of intrauterine growth restriction lower (13 vs. 38 %, $p=0.046$) in post-UAE patients.

Both methods are effective in the treatment of women with future reproductive plans and fibroids not suitable for LM. UAE is more effective in causing complete ischemia of fibroids, but it is associated with greater risk of intrauterine necrosis. Both methods are an effective treatment for PPH and fibroids. Pregnancy is possible after UAE. Recurrent PPH is a serious and frequent complication. Synechia is also a potential complication. Desire of childbearing should be considered when choosing embolization or surgery and, in case of embolization, the choice of material used (Berkane and Moutafoff-Borie 2010a). Further studies on future fertility after UAE are needed as well as information on fertility after surgery have low rate of serious complications (except for a high abortion rate) (Mara et al. 2012).

Hysteroscopic examination of the uterine cavity revealed that patients previously treated for intramural myoma(s) by uterine artery embolization had a significantly higher incidence of abnormal findings compared with patients treated by laparoscopic occlusion of uterine arteries (59.5 % vs. 2.7 %). In particular, there was a higher incidence of necrosis in the uterine cavity of patients subjected to uterine artery embolization (43.2 %) compared with patients after surgical uterine artery occlusion (2.7 %) (Kuzel et al. 2011).

UAE is used to treat postpartum hemorrhage (PPH) and fibroids. This effective therapy is replacing surgery in many cases. One of the main

goals of UAE is to preserve the uterus and therefore fertility (pregnancies, menses, and ovarian reserve). Pregnancies after this technique have been described. The main complications encountered during these pregnancies are not only PPH but also miscarriages and cesarean deliveries after UAE for fibroids. Conflicting results varying from completely well tolerated to serious complications such as definitive negative effect on endometrium and ovary function have been reported. Nevertheless, the series differ in that they included women of different ages and used different materials for vessel occlusion (definitive microparticles of varying sizes, temporary pledgets of gelatin sponge, etc.).

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Another new advanced technology is ExAblate 2100 system (Insightec Ltd, Haifa, Israel) for magnetic resonance imaging (MRI)-guided focused ultrasound surgery on treatment outcomes in patients with symptomatic uterine fibroids, as measured by the nonperfused volume ratio.

A retrospective analysis of 115 women (mean age, 42 years; range, 27–54 years) with symptomatic fibroids who consecutively underwent MRI-guided focused ultrasound treatment in a single center with the new generation ExAblate 2100 system from November 2010 to June 2011. Mean ± SD total volume and number of treated fibroids (per patient) were 89 ± 94 cm and 2.2 ± 1.7, respectively. Patient baseline characteristics were analyzed regarding their impact on the resulting nonperfused volume ratio. Magnetic resonance imaging-guided focused ultrasound treatment was technically successful in 115 of 123 patients (93.5 %). In 8 patients, treatment was not possible because of bowel loops in the beam pathway that could not be mitigated ($n = 6$), patient movement ($n = 1$), and system malfunction ($n = 1$). Mean nonperfused volume ratio was 88 % ± 15 % (range, 38–100 %). Mean applied energy level was 5,400 ± 1,200 J, and mean number of sonications was 74 ± 27. No major complications occurred. Two cases of first-degree skin burn resolved within 1 week after the intervention. Of the baseline characteristics analyzed, only the planned treatment volume had a statistically significant impact on nonperfused volume ratio (Trumm et al. 2013).

13.6 Temporary Artery Occlusion

A new exciting device, utilizing the principle of interference with the blood circulation, has recently been developed (Vascular Control Systems, Inc., San Juan Capistrano, CA) (Flowstat) for the treatment of fibroids with nonincision, only compression. However, there were few clinical centers who managed to adopt and control the device and therefore it has been removed from the market, but still I believe it could gain some clinical application in the future.

The system consists of a guiding cervical tenaculum, a transvaginal vascular clamp with integrated Doppler ultrasound crystals, and a small, battery powered transceiver that generates audible Doppler sound (Fig. 13.5). The clamp slides along the guiding tenaculum to the level of the lateral vaginal fornices at the 9:00 and the 3:00 cervical positions. When the crystals on the arms of the clamp contact

Fig. 13.5 The transvaginal vascular clamp with integrated Doppler ultrasound crystals and Doppler receiver

the vaginal mucosa, they return audible signals from the right and left uterine arteries. When the clamp is further advanced along the guiding tenaculum, the clamp displaces the uterine arteries superior to their points of insertion into the uterus. When closed, the clamp occludes the uterine arteries bilaterally by squeezing them against the lateral borders of the uterus, and the clamp is remained in place for 6 h (Fig. 13.5).

13.7 In Vitro and In Vivo Studies

After uterine artery occlusion, pH falls and when clot lyses and reperfusion occurs, pH returns to baseline. This has been investigated and monitored continuously before, during, and 24 h after laparoscopic occlusion of uterine arteries (Lichtinger et al. 2003). In patients with symptomatic fibroids, pH was measured with a catheter electrode embedded in the endometrium and in others in the myometrium. In 62 % of the patients pH dropped 0.4–0.8 units, while in 38 % the drop was greater, and the minimum was reached between 5 and 73 min. The return back to baseline was on average 5 h. After the uterine artery is occluded, blood reaches the myometrium by secondary pathways and for most women, these vascular pathways are insufficient to maintain aerobic metabolism. Until clotting occurs, blood continues to flow and supply oxygen to the myometrium, although at a new and slower speed.

13.8 Clinical Studies

We presented the first publication with this new technique in 2004 where a 43-year-old woman with menorrhagia, dysmenorrhea, and pelvic pain of several years duration with the uterus enlarged by fibroids to the size of a 16-week pregnancy was treated (Istre et al. 2004). Her uterine arteries were noninvasive transvaginally identified and occluded for 6 h with a clamp that was guided by audible Doppler ultrasound. Following removal of the clamp, blood flow in the uterine arteries returned immediately. Three months following treatment, the uterine volume had decreased by 49 % and the dominant fibroid volume by 54 % (Fig. 13.6).

Thirty patients treated with this technique were presented in 2006. Two alternatives of analgesic was chosen (para cervical and epidural block was utilized in 17 and 13 patients, respectively), menorrhagia was reduced in both groups, however in the para cervical group fibroid reduction was 12–24 % and in the epidural group 24–45 %. Two cases of hydronephrosis were observed and they were treated successfully with a stent (Vilos et al. 2006). The explanation of additional fibroid reduction in the epidural group could be related to a more stable tenaculum placement, lesser pain, and consequently constant compression of the uterine artery during the treatment time.

13.9 Complications

A disadvantage of the noninvasively transvaginal clamping technique is fibroid location close to the cervix, in which there are some difficulties to apply the clamp location correctly. In addition, possibility of clamping the urethers with subsequent hydronephrosis and possible damage of the renal function is of concern.

Another possible application of the temporary artery uterine clamp is during and after myomectomy operations. Thereby, we can reduce peri- and postoperative bleeding. In addition, the clamping may act as adjuvant therapy of possible residual fibromas. However, few results exist so far, and further studies of this therapeutic approach are needed to prove its long-term value.

13.10 Use and Indication of Uterine Artery Techniques

The application of techniques like uterine artery occlusion is primarily for women who will avoid hysterectomy. Many women do not wish to undergo an operative procedure, as they may not accept the associated risks of the operation, and therefore prefer the less invasive procedures.

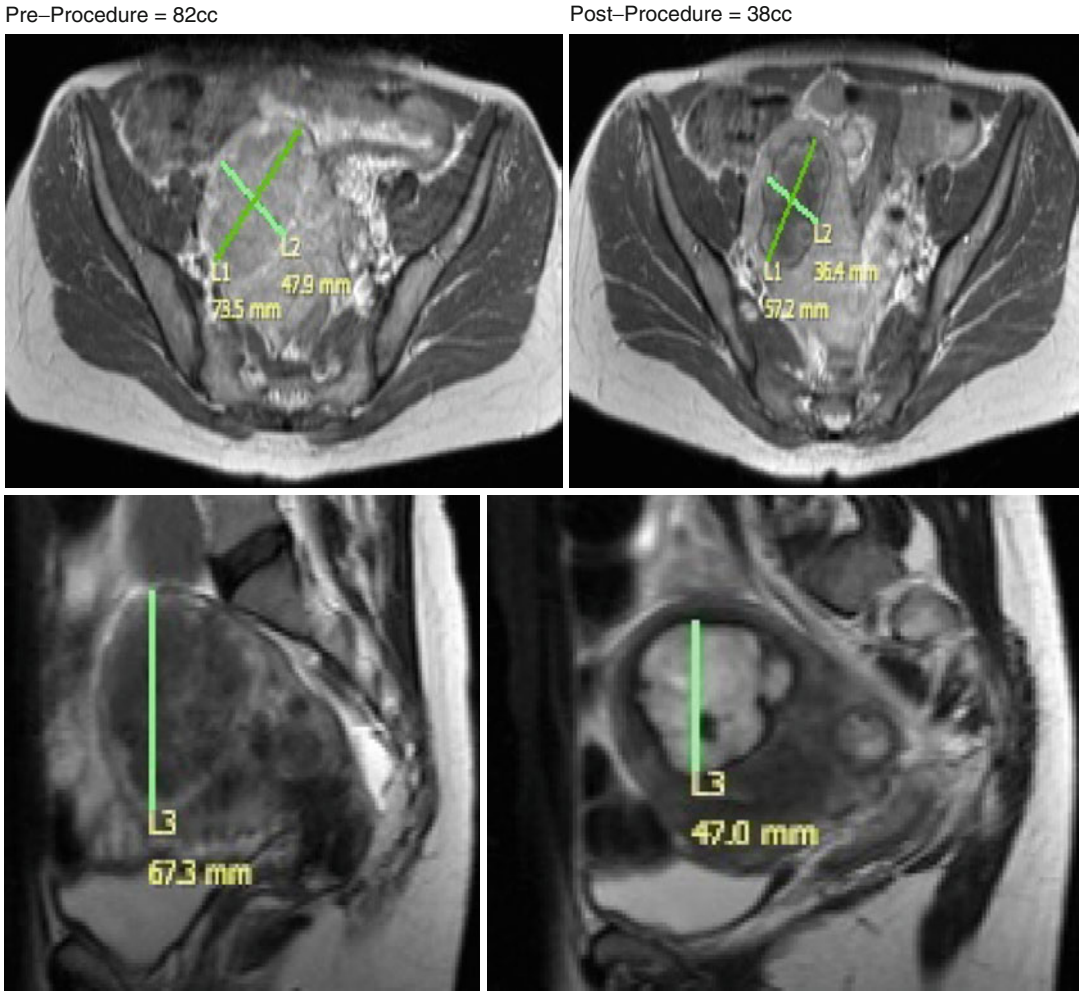

Fig. 13.6 MRI showing *Major Fibroid reduction 54 %*

Both radiological and laparoscopic occlusion techniques are potential treatment options in the treatment of fibroids. However, insufficient long-term follow-up results do not exist at present. Furthermore, both techniques are associated with a high level of skill, and consequently they should be performed only in special centers with interest in this field. Anyhow, counseling of the patients is of utmost importance before they make their own treatment choice (Hald et al. 2004).

Conclusions

Fibroids present with different symptoms in different patients, i.e., infertility, bleeding problems, pressure and pain, single or multiple, different ages, which should be treated differently. In bleeding problems, an important issue is the location of the fibroid, and in cases with submucosal fibroids hysteroscopic resection is the method of choice. In cases with intramural, subserosal, and even multiple fibroids, uterine artery therapy with embolization or laparoscopy seems to achieve good results on both bleeding problems and pressure symptoms. The temporary uterine clamp performed by general gynecologist without incision may replace the more complicated procedures like embolization performed by radiologist and laparoscopic uterine artery closure performed by skilled endoscopist.

In infertility patients, the single fibroid should be removed, while when multiple fibroids are present medical or circulation therapy may be the only option for uterus saving therapy.

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