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Management of symptomatic fibroids: conservative surgical treatment modalities other than abdominal or laparoscopic myomectomy

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Approximately 50% of women of reproductive age have fibroids, and at least 50% of these women have significant symptoms. However, until 15 years ago, the only surgical options available were hysterectomy and myomectomy, and as yet there are no proven effective long-term medical therapies. Fortunately, the past decade has witnessed the emergence of highly sophisticated diagnostic and therapeutic technologies for fibroids. Magnetic resonance imaging and high-resolution ultrasound are non-invasive, high-quality diagnostic procedures. The new treatment modalities include: laparoscopic and vaginal myomectomy; uterine artery embolization (UAE); magnetic-resonance-guided focused ultrasound surgery (MRgFUS); hysteroscopic resection where the fibroids are submucous; myolysis by heat, cold coagulation and laser; laparoscopic uterine artery occlusion; and temporary transvaginal uterine artery occlusion. It is, however, abundantly clear that there is no panacea that suits every woman, nor are all treatment types universally available to all women, even in the developed world. Laparoscopic surgery requires skills that are not common place, and there are limitations on the size and number of fibroids that can be treated by this modality. Much the same applies to vaginal myomectomy. UAE is now widely used in the USA and Western Europe, and has been recommended by the National Institute for Clinical Excellence (NICE) in the UK as an alternative therapy to hysterectomy. However, UAE is still under evaluation in terms of comparison with myomectomy. UAE has a range of complications including premature ovarian failure, chronic vaginal discharge and pelvic sepsis, and may have limited efficacy when the fibroids are large. Although there are a number of reports of successful pregnancy following UAE, the experience is limited and research is required in this area. MRgFUS was approved by the US Food and Drug Administration in 2004, while NICE recommended that the procedure should be used in an audit and research setting. Preliminary data following laparoscopic uterine artery occlusion

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suggest that outcomes are similar to those with UAE, but these data are derived from studies involving relatively small numbers. Temporary uterine artery occlusion is also promising, but has yet to be evaluated robustly. Thus there is no room for complacency; research involving the available treatment modalities is urgently needed, while innovations in search of newer and more effective therapies must continue. This chapter will review surgical treatment modalities other than hysterectomy and abdominal or laparoscopic myomectomy.

Key words: fibroids; laparoscopy; hysteroscopy; uterine artery; occlusion.

INTRODUCTION

Incidence and biology

Fibroids are the most common benign uterine tumours, with an incidence range of 5.4–77% in women of reproductive age depending on the diagnostic method.¹ They increase in incidence towards the end of a woman's reproductive life. Fibroids are particularly common in Black populations, with a nine-fold increase compared with Caucasian populations.^{2,3} Macroscopically, they are firm, round or oval-shaped tumours composed of smooth muscle bundles in a whorl-like pattern. They often appear singular but are generally multiple, varying in dimensions and locations. Fibroids can occur within the myometrial layer (intramural) of the uterus, in the inner aspect of the myometrium (submucosal) and outside the myometrium (subserosal). Occasionally, fibroids can obtain a blood supply separate from the myometrium and are then known as 'parasitic fibroids'. They can occur at unusual locations such as the uterine cervix or within the layers of the broad ligament.⁴ Histologically, they are composed of a mixture of connective tissue and smooth muscle fibres. The aetiology of fibroids is unknown. It is believed that they are derived from a single cell which has undergone a growth control genetic mutation. Many chromosomal re-arrangements have been noted in fibroid cells, and it is hypothesized that these abnormalities contribute to the loss of normal cellular growth.^{5,6} Fibroids are oestrogen-dependent tumours, which shrink after the menopause and also in response to downregulation treatment with gonadotrophin-releasing hormone (GnRH) agonists. There is also evidence that progesterone plays a pivotal role in the growth of fibroids.⁷ Although fibroids have receptors for oestrogen and progesterone, it is believed that action of the hormones is mediated via local growth factors such as epithelial growth factor and vascular endothelial growth factor.⁸ These growth factors are hormone signals that communicate with fibroid tissues and cause fibroids to increase in size. Oestrogen and progesterone increase their quantity, and hence fibroid growth. The growth factors are present at higher concentrations in fibroids compared with local myometrium. It is not fully understood what triggers this tumourigenesis, but work in the field of molecular biology has identified vascular endothelial growth factor-A, upregulation of types I and III collagen, transforming growth factor⁹ and interleukin 8¹⁰ as important factors. In addition, there appears to be a genetic predisposition.¹¹ At least one gene, *HMGIC*, appears to be implicated in a subgroup of fibroids where 12:15 translocations have been identified.¹²

Clinical presentation of fibroids

It is estimated that 50% of fibroids are asymptomatic and are an incidental finding at the time of clinical or ultrasound examination. When fibroids are symptomatic, they

present in a variety of ways including menorrhagia, dysmenorrhoea, pressure symptoms and subfertility. Vegienka et al studied the relationship between self-reported bleeding symptoms and the size and location of uterine leiomyomas¹³ in a random sample of women aged 35–49 years. Abdominal and transvaginal ultrasound were used to measure the size and location of leiomyomata, and the women were asked about symptoms of heavy bleeding in a telephone interview. Reported use of eight or more pads/tampons on the heaviest days of menstrual bleeding increased with leiomyoma size, with a nearly 2.5-fold risk for women with large leiomyomata compared with women without leiomyomata (Figure 1). Non-submucosal fibroids were associated with essentially the same increase in heavy bleeding as submucosal fibroids of similar size. The authors concluded that small leiomyomata were associated with increased risk of heavy bleeding, and risk increased with size. Contrary to published articles, non-submucosal fibroids were associated with heavy bleeding to the same extent as submucosal fibroids.

Approximately 0.1% of fibroids present as a sarcomatous fibroid; this is a rare but serious smooth muscle malignant tumour.¹⁴ Submucous fibroids or intramural fibroids in close relation to the uterine cavity are found in 40% of patients with heavy and/or prolonged menstrual bleeding.^{15–18} The therapeutic goal for fibroids and debilitating menorrhagia must take into account the needs and desires of the patient in terms of her lifestyle (e.g. days lost from work because of symptoms) and childbearing plans.

Treatment modalities – a historical perspective

The traditional surgical treatments for symptomatic fibroids are laparotomy with hysterectomy or myomectomy, both of which involve considerable morbidity.^{19–21} Hysterectomy for benign indications has been associated with an increased risk for lower urinary tract sequelae.²² The authors looked at 165 260 women who had undergone hysterectomy and a control group of 479 506 individuals who had not had this procedure in Sweden. During the 30-year observation period, the rate of urinary stress incontinence surgery per 100 000 person-years was 179 [95% confidence interval (CI) 173–186] in the exposed cohort versus 76 (95%CI 73–79) in the unexposed cohort, irrespective of surgical technique. Risk for urinary stress incontinence surgery varied slightly with time of follow-up; the highest overall risk was recorded within 5

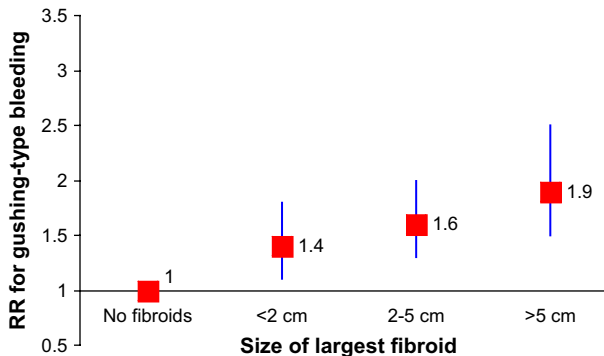


Figure 1. The presence and size of fibroids correlates with the severity of bleeding; therefore, even women with undiagnosed fibroids are likely to have symptoms. RR, relative risk.

years of surgery. The authors concluded that hysterectomy for benign indications, irrespective of surgical technique, increases the risk for subsequent urinary stress incontinence surgery. They also found that hysterectomy increased the risk of having subsequent pelvic prolapse surgery at a later stage. Therefore, women should be counselled regarding associated risks related to hysterectomy, and other treatment options should be considered before this major intervention.

Hysterectomy continues to be more costly, in both monetary terms (billions of dollars are spent annually) and the more fundamental terms of morbidity and mortality, than the less invasive alternatives of myomectomy, ablation and myolysis.²⁰ 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.²³ Although morbidity is reduced with endoscopic surgery, this technique is not widely available and has limitations.

Endometrial ablation is now more common than hysterectomy for heavy menstrual bleeding, and second-generation methods are now more commonly performed than hysteroscopic endometrial ablation. There is every indication that endometrial ablation will continue to increase in practice in England²⁴, and consequently there has been a decline in the number of hysterectomies performed in the UK.

The demand for alternative treatments has increased during the last decade, pushed forward by women resisting hysterectomy and physicians looking for less invasive procedures.

The past decade has witnessed highly sophisticated diagnostic and therapeutic technology for fibroids. Currently available tools permit greater management flexibility, which must be tailored to the individual clinical situation. Uterine fibroid embolization has become one such alternative procedure, while laparoscopic occlusion of uterine vessels is another alternative.

CONSERVATIVE SURGICAL TREATMENT MODALITIES OTHER THAN HYSTERECTOMY AND ABDOMINAL OR LAPAROSCOPIC MYOMECTOMY

Vaginal myomectomy

In a prospective study published in 1999, Davies et al²⁵ demonstrated the feasibility of performing myomectomy via the vaginal route. Out of 35 women with symptomatic fibroids requiring myomectomy, it was completed vaginally in 32 (91.4%) women, none of whom required a hysterectomy. The overall operating time was 78 mins, estimated operative blood loss was 313 mL, and mean postoperative hospital stay was 4 days. Pelvic haematomas developed in four patients, and one colpotomy required resuture. Seventy-four percent of the women reported symptom relief at 3-month follow-up. Thus, for well-selected patients in good surgical hands, vaginal myomectomy is feasible and well tolerated. The use of fibroid 'morcellation' also renders it feasible to perform the procedure even in cases of large, numerous and intramural fibroids. Unlike with laparoscopic myomectomy, conventional suture of myoma dead spaces and closure of serosa allows optimal reconstruction of the uterine wall. Randomized trials are required to establish the place of vaginal myomectomy in comparison with the open transabdominal procedure, especially with regard to the issue of postoperative adhesion formation, risk of recurrence and blood loss in comparable cases.

Fibroid myolysis

Ablation techniques reported for the treatment of symptomatic fibroids have included the use of temperature to destroy tissue, including myolysis, cryomyolysis and laser. Despite reports of apparently successful outcomes^{26–28}, these techniques have not enjoyed widespread popularity and use. The techniques require placement of probes into the fibroid, usually via laparoscopy, and the fibroid tissue is destroyed by heat (unipolar or, preferably, bipolar), cold coagulation (cryomyolysis) or laser. It appears that in women with symptomatic fibroids and menorrhagia, myolysis can be combined with other procedures such as endometrial ablation or resection, markedly improving the success rates of these minimally invasive alternatives to hysterectomy.²⁹ Myoma coagulation combined with endometrial ablation also reduces all subsequent surgery rates compared with endometrial ablation alone.

Power colour Doppler imaging was performed pre- and postoperatively to determine the effectiveness of cryomyolysis in reducing or eliminating the primary blood supply, as well as regression of the myomas (Figure 2). Myomas regressed by up to 80%, and the major blood supply to the myomas was eliminated. Another study reported that cryomyolysis is able to maintain (or slightly reduce) uterine fibroids at post-GnRH agonist size, whereas all other uterine tissues return to their pre-treatment size.³⁰

In the event of pregnancy occurring after myolysis, intensive surveillance is required. The author would advocate elective caesarean section delivery at term, and certainly emergency caesarean section if there are any signs of uterine rupture, or if the woman goes into labour prior to the planned caesarean section.

Magnetic-resonance-guided focused ultrasound surgery for the treatment of uterine fibroids

Magnetic-resonance-guided focused ultrasound surgery (MRgFUS) is a non-invasive thermo-ablative technique that uses focused high-energy ultrasound to ablate fibroid tissue. As in conventional diagnostic ultrasound, the ultrasound waves pass through the anterior abdominal wall. Significant heating only occurs where the waves converge at the focus. Magnetic resonance guidance provides continuous imaging of the fibroid and other vital structures such as bowel, bladder and sacral nerves.³¹

Significant improvement in quality-of-life parameters has been reported in women undergoing MRgFUS. Given considerable symptoms at enrolment and a large decrease in mean symptom levels, this appears to be a clinically significant result. The volume reduction after treatment is small compared with the mean levels seen after both myomectomy and uterine artery embolization (UAE). MRgFUS appears to be a safe intervention for uterine fibroids.³¹ None of the MRgFUS-treated patients had urgent surgical procedures or bowel injuries, which are reported in many early studies of new investigational devices for uterine fibroids.³² Furthermore, women who have treatment with MRgFUS do not appear to develop symptoms similar to the postembolization syndrome symptoms associated with UAE.

The mean time of return to work after MRgFUS was approximately 1 day, compared with 13 days after UAE and approximately 6 weeks after abdominal myomectomy or hysterectomy.³³ However, the true place of MRgFUS has yet to be established in comparison with the other available treatment modalities by way of randomized controlled clinical trials.

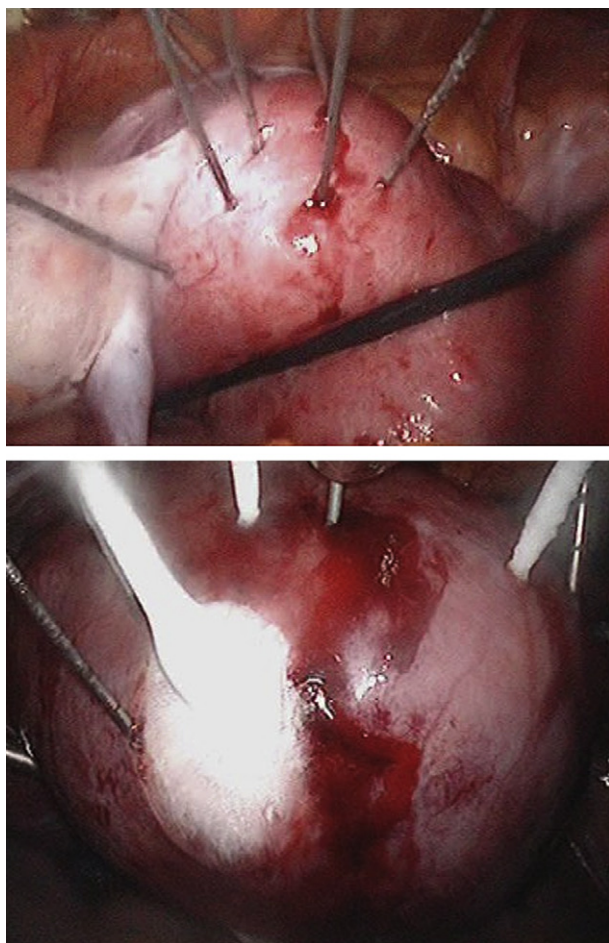


Figure 2. Needle placement in fibroid before and after freezing.

Hysteroscopic resection

Hysteroscopic resection, in appropriately selected cases, can provide excellent results and eliminate the need for major surgery.

The first resectoscopes were unipolar electrodes that required non-electrolytic solutions (such as glycine 1.5%, sorbitol or mannitol) to distend the uterine cavity. These fluids have the potential to cause non-physiological excessive fluid absorption, causing changes in serum electrolyte levels leading to hyponatraemic encephalopathy and brain oedema.^{34,35} General fluid overload may cause pulmonary oedema, especially in elderly patients or patients with right-sided heart failure, kidney or liver disease. During the last decade, technological improvements have led to the production of new instruments using bipolar rather than monopolar energy. The most important benefit of bipolar resection is the use of saline solution rather than non-ionic distension media, as well as the reduction of energy spread through the tissue during resection. In addition

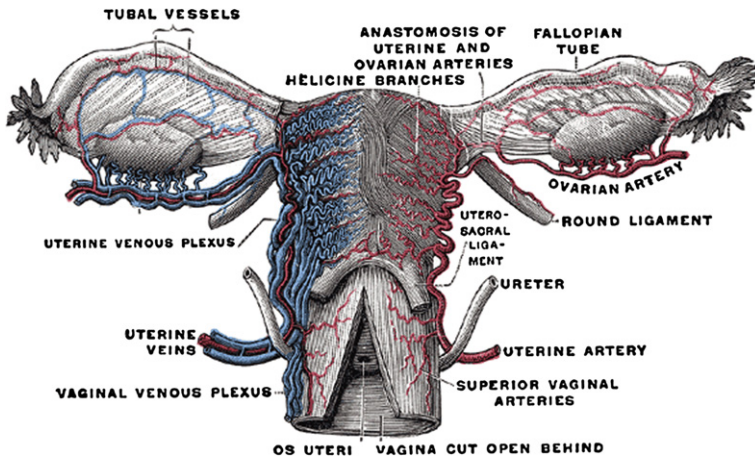


Figure 3. Uterine blood supplies.

to the irrigation media used, the main difference between different types of equipment is the loop size. Theoretically, smaller loops will cut more superficially and remove a smaller amount of tissue. Consequently, it may be necessary to resect twice at the same level to remove the basal layer. The endometrium has a remarkable ability to regenerate and, in order to achieve an effective result, it is necessary to go beneath the basalis or destroy the endometrium to a depth of at least 5 mm when considering the early to mid-proliferative phase of the cycle.

Versapoint (Gynecare Inc, Menlo Park, CA, USA) bipolar equipment has been available since 1999, and TCRiS (Olympus, Hamburg, Germany) bipolar equipment became available in Europe in 2004. The loop size of TCRiS is smaller than that for monopolar equipment, but larger than the Versapoint loop.

Interference with blood supply to the uterus

Treatments interfering with blood supply to the uterus or fibroids include UAE performed by an interventional radiologist, or laparoscopic uterine artery occlusion performed by a gynaecologist.³⁶ Before discussing these in detail, it is important to describe the uterine (and therefore fibroid) blood supply.

Uterine and fibroid vascular supply

The uterus has a very rich blood supply through two extrinsic arterial systems, the uterine and ovarian arteries (Figure 3). Intrinsic uterine arteries consist of ascending uterine, arcuate, radial and peripheral arteries providing free flow through the uterus. Fibroids receive their blood supply from the intrinsic arteries, primarily from branches of the arcuate arteries, and the vessels are located in the pseudo capsule around the fibroid. The ipsilateral uterine and ovarian arteries are connected via a communicating (anastomotic) branch. In addition to its primary (uterine artery) and secondary (ovarian artery) extrinsic blood supply, the uterus has a vast network of lesser known arterial collaterals.³⁷ If the blood supply from the right or left uterine artery is occluded, blood from the left or right artery supplies the myometrium by vascular communications

through the arcuate arteries. If both uterine arteries are occluded, the ovarian arteries provide a blood supply to the myometrium via the anastomoses. 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.³⁸

To occlude primary blood flow, uterine artery occlusion must be more distal than the internal iliac artery, in case occlusion of both internal iliac arteries does not stop antegrade blood flow.³⁹ As such, it does not cause uterine ischaemia, and the Doppler flow remains unchanged after bilateral internal iliac artery ligation.⁴⁰ When bilateral internal iliac occlusion is performed distal to the posterior division, reverse flow in the middle haemorrhoidal artery reconstitutes antegrade flow in each uterine artery. Under these conditions, the antegrade flow in each uterine artery persists and pulse pressure is damped, resembling a venous system instead of an arterial system; consequently, it does not cause uterine ischaemia.

Uterine artery embolization

There is a whole chapter devoted to UAE in this issue; therefore, this section will be brief and is only included for completeness. There can be no doubting the immense popularity that UAE has gained in the USA and Western Europe over the past decade. It is performed by highly skilled interventional radiologists, and studies and reports to date indicate significant efficacy in inducing fibroid shrinkage, improving fibroid-related symptoms and improving quality of life. A number of issues are still to be resolved, and definitive studies to compare UAE with myomectomy or MRgFUS are awaited. The key to success in the provision of a UAE service lies in close collaboration between interventional radiologists and gynaecologists. This allows for optimal patient selection and preparation for the procedure, and for appropriate pre- and post-treatment care of women, since interventional radiologists are not trained in gynaecology, and gynaecologists cannot perform UAE. Some practitioners insist that women should have endometrial sampling and/or hysteroscopic imaging prior to UAE, since women with submucous fibroids may be better served by hysteroscopic resection than UAE. Others require bacteriological screening and removal of intra-uterine devices prior to UAE, and all these interventions are within the domain of gynaecologists. In routine practice in the UK, radiologists rarely have inpatient admitting beds, and the women would therefore need to be admitted under the care of gynaecologists. When complications occur, such as chronic vaginal discharge, fibroid extrusion through the vagina, premature ovarian failure or severe pelvic sepsis, women will present to gynaecologists. Therefore, the importance of close collaboration between gynaecologists and radiologists cannot be overemphasized.

Laparoscopic uterine artery occlusion

Perhaps, in part, because of frustration at not being able to perform UAE, some innovative gynaecologists have developed what is effectively an equivalent procedure to UAE; laparoscopic bipolar coagulation of uterine arteries and anastomotic sites of uterine arteries with ovarian arteries.^{41,42} The peritoneum overlying the external iliac artery is incised with a T incision between the round ligament and the infundibulo-pelvic ligament. The iliac vessels are identified, and the retroperitoneal space is developed (Figure 4). The uterine artery is occluded with an endoclip at the level of the internal iliac artery. An identical procedure is performed on the opposite side. The collateral

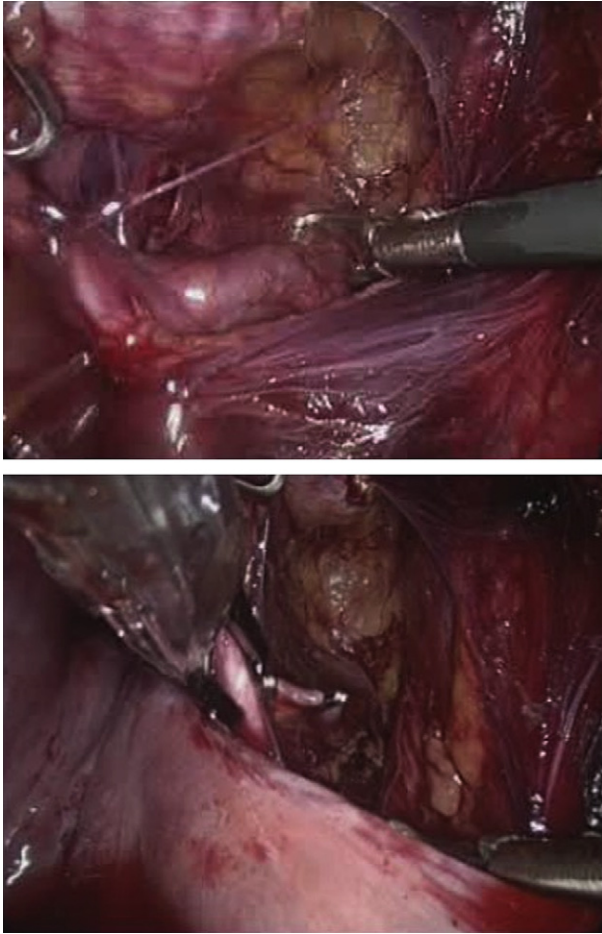


Figure 4. Uterine artery during laparoscopic occlusion before and after placement of clips.

arteries between ovaries and uterus (in the utero-ovarian ligament) are coagulated using bipolar forceps.

In the author's institution, 46 premenopausal women with symptomatic fibroids were studied, of whom 24 underwent UAE and 22 underwent laparoscopic occlusion of the uterine arteries.^{43,44} The picture blood assessment scores were reduced by 50% in both groups after 6 months, and uterine volume was reduced by 35–40% in both groups. Interestingly, less post-treatment pain, less nausea and shorter hospital stay were reported in the laparoscopic uterine artery occlusion group compared with the UAE group. On the downside, more women in the laparoscopic occlusion group experienced heavy menstrual bleeding at 6 months compared with the UAE group. It can be tentatively concluded that laparoscopic uterine artery occlusion therapy is a promising new method for treating fibroid-related symptoms, with outcomes at least comparable to UAE. However, it is recognized that the numbers in this study were small, and there is a need for a randomized trial of the two procedures before definitive conclusions can be made.

Temporary transvaginal occlusion of uterine artery

It is reasonable to assume that UAE and direct surgical uterine artery occlusion cause fibroid death due to ischaemia. It is also teleologically sound to suppose that fibroids, due to their more tenuous blood supply, are more sensitive to ischaemia than the myometrium. When the blood supply is interrupted, presumably the ischaemia thus created stimulates recruitment of the collateral circulation, but this may take some time. Thus, while the myometrium is able to 'hold its breath', the fibroids are unable to tolerate the ischaemia. The collateral flow occurs too late for the fibroids to survive, while the myometrium recovers from the temporary ischaemia. This may explain the recent finding by Banu et al of no serum markers of myometrial ischaemia following UAE.⁴⁵ This thinking leads to the supposition that temporary occlusion of the uterine arteries could cause fibroid death without affecting the myometrium, which would be subject to the temporary ischaemia but would be able to recover fully.

This hypothesis (effect of temporary uterine artery occlusion) was tested at the author's institution in 2004 on a 43-year-old woman who had a 16-week-size fibroid uterus and had suffered for several years with menorrhagia, dysmenorrhoea and pelvic pain.⁴⁶ Her uterine arteries were non-invasively identified through the vagina 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, uterine volume had reduced by 49% and dominant fibroid volume had reduced by 54%.

The technique

The system for temporary uterine artery occlusion consists of a guiding cervical tenaculum, a transvaginal vascular clamp with integrated Doppler ultrasound crystals, and a small, battery-powered transceiver that generates an audible Doppler sound (Figure 5).

The clamp slides along the guiding tenaculum to the level of the lateral vaginal fornices at the 9 o'clock and 3 o'clock cervical positions. When the crystals on the arms of the clamp make contact with the vaginal mucosa, they return audible signals from the right

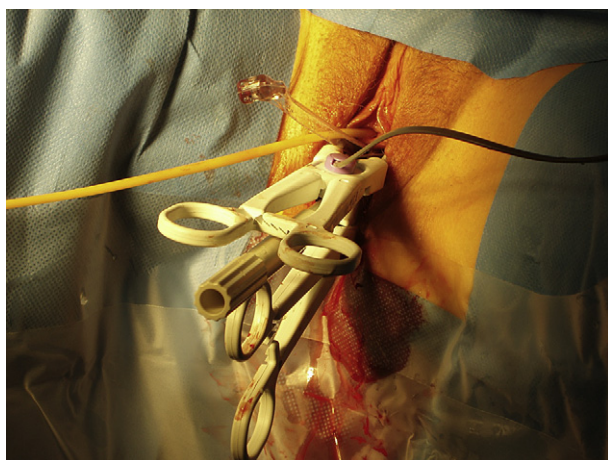


Figure 5. Transvaginal vascular clamp left in place for 6 h to treat fibroids.

and left uterine arteries. When the clamp advances further 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. The clamp remains in situ for 6 h.

It has since been demonstrated that temporary bilateral occlusion of the uterine arteries (for 6 h) is sufficient to treat multiple fibroids in several patients. This approach can also be used in other situations, such as during and after laparoscopic myomectomy in order to reduce peri- and postoperative blood loss, and as adjuvant therapy of residual myomas following other treatment modalities.

There is an ongoing multicentre trial of temporary uterine artery occlusion involving centres in Europe and the USA, that intends to recruit 300 patients with symptomatic fibroids.

Although promising and already of proven efficacy, the current methods of uterine artery occlusion, be it by embolization, permanent laparoscopic occlusion or the temporary procedure, have limitations in their potential for widespread use. These techniques require complex facilities and considerable skill, and this limits their availability to major medical centres with the requisite facilities and expertise.

CONCLUSIONS

At present, there is no surgical panacea for the treatment of uterine fibroids, which may present with a variety of symptoms, may be single or multiple, and may occur at different ages. Never has the need for the individualization of treatment been more pertinent than in this very common disease. Gone are the days when the only surgical options were hysterectomy or open myomectomy. Vaginal, laparoscopic and hysteroscopic myomectomy are just three invasive surgical options, while UAE, MRgFUS, and permanent and temporary uterine artery occlusion offer less invasive approaches. All of these treatments have been shown to be efficacious, but the degree of efficacy remains to be fully assessed. The challenge now is for definitive randomized trials to establish the true place of these newer treatment modalities, so that women can be offered therapies that are optimal to their specific clinical presentation.

Practice points

- until 15 years ago, the choice of surgical therapy available to women with symptomatic fibroids was confined to hysterectomy and abdominal myomectomy
- the armamentarium of therapeutic options for symptomatic uterine fibroids now includes: laparoscopic and vaginal myomectomy; hysteroscopic resection; ablative techniques that use heat, laser or cold coagulations; UAE; MRgFUS; laparoscopic uterine artery occlusion; and temporary transvaginal uterine artery occlusion
- ablative techniques using heat, laser or cold coagulation have failed to gain in popularity or widespread use
- laparoscopic uterine artery occlusion appears to have similar outcomes to those seen with UAE, but larger definitive studies are required for comparison
- temporary occlusion of the uterine arteries appears to result in symptom improvement and fibroid regression, but definitive studies are awaited
- the newer treatment modalities tend to require technical expertise or high-technology, expensive facilities, which limits their availability to large centres

Research agenda

- long-term outcomes of laparoscopic uterine artery occlusion in comparison with UAE
- randomized controlled trials of conventional surgical treatments (myomectomy) versus the newer treatment modalities (laparoscopic uterine artery occlusion)
- randomized controlled trials of permanent laparoscopic versus temporary transvaginal uterine artery occlusion in the management of symptomatic fibroids

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