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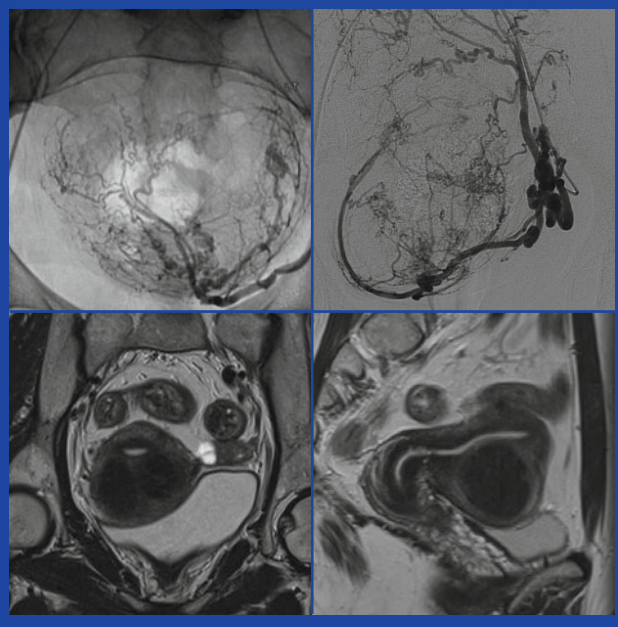
# Radiological Interventions in Obstetrics and Gynaecology



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# Medical Radiology

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# Radiological Interventions in Obstetrics and Gynaecology

Springer

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*For NOC*

—John Reidy

# Foreword

## Embolization of Uterine Myoma

In the last few decades, interventional radiology has revealed many unexpected therapeutic possibilities, and is now developing worldwide. In obstetrics and gynecology, arterial embolization is the most widely used procedure; its efficacy was proven first in the treatment of post-partum hemorrhage, then of uterine myoma. We had the opportunity to participate in the development of these treatments—a wonderful scientific adventure indeed. This opportunity was the result of the fortuitous meeting of two medical teams conducting apparently unrelated activities. When I joined the Lariboisière Hospital's maternity ward in 1988, I met J. J. Merland, chief of the interventional neuroradiology department. He convinced me that there was a role for embolization in the treatment of post-partum hemorrhage. Brown and Païs had initiated the technique in 1979–80, but few had followed their footsteps. From 1988 to 1990, we became convinced of the great efficacy of embolization; at this time, we were the only hospital in France to offer this life-saving treatment, day and night. The credit goes to J. J. Merland's team, whose skills and availability were essential in dealing with this unpredictable emergency. We then took on the challenge to spread the word, at first facing indifference, then a growing worldwide support for this technique.

We first took an interest in uterine myoma in the 1990s, by studying their vascularization, previously described by Sampson (1912). In 1994, we presented the first fibroid arteriogram, at the European Society of Gynecology Congress in Dublin. The poster received an award. Our main concern then was to avoid blood loss during complex myomectomies, which can sometime be so great as to lead to hysterectomy in young women still wanting children. We believed that preoperative embolization could be a solution, and we carried out a preliminary study in collaboration with the Bichat Hospital's maternity ward. The resulting lack of bleeding brought comfort and safety to both surgeons and patients. In France, this innovative approach was not welcomed. It was while operating in these cases that I became aware of the uselessness of the surgical procedure. This came as a shock: if embolization had already provided a cure, why remove an inactive fibroma?

J. J. Merland and I then decided to assess the efficacy of embolization on its own, and we offered this alternative to surgery to our patients suffering from symptomatic myomas, informing them that it was an experimental technique. My young surgical colleagues were astonished by that choice, and their eyes reflected their great concern as to my mental health. For three reasons, we took this decision without asking an ethics committee for approval. The approval was not mandatory, we had acquired an experience that no one else possessed and—most importantly—we had observed no harmful effects of embolization on the uterus. Finally, we were sure that we would face refusal from these committees that loathe the exploration of unknown territories.

It was then that N. Ciraru-Vigneron remembered that we had treated by embolization seven women with fibroids and severe bleeding who were unfit for surgery. The results were, at the very least, modest: three failed catheterizations, one early revascularization, three improved patients who were lost to followup. When we called back there patients we

observed results that exceeded our expectations: they were cured. By the end of 1994 we had treated 16 patients by embolization. In September 1995, The Lancet published our short report on these patients. I am very grateful to the Lancet reviewers for being so open-minded. One wrote “I do believe that is an interesting and important paper” whilst the second wrote “I had certainly not heard of fibroids treated by embolization before and feel privileged to have read this account”. They had recognized that our paper was groundbreaking!

A new therapeutic approach to uterine fibromas was born; it was totally unexpected by the gynecologic community. In France, where hormones were much counted on, the particles were ignored. Very few gynecologists took interest in it. They were not prepared for it, and very satisfied with their surgery—they did not hear their patients’ requests: to keep their uterus. Fortunately, our article raised the interest of a few Anglo-Saxon teams, and with us they contributed to developing and improving this treatment. They were pioneers. The first team to get in touch with us was the one of John Reidy and Robert Forman from Guy’s Hospital, who was working on a similar research project and was waiting for the approval of their ethics committee to start the trials. The first to visit us was Bruce McLucas, from UCLA. He introduced the method in the USA and published the first American article on the subject. We became close friends. In the meantime, the teams of Hutchins and Worthington-Kirsh in Philadelphia, and of Sutton and Walker in Guilford, convinced of the potential of embolization, also participated in the development and success of the technique. Soon, other teams—Spies in Washington, and Pron in Canada—contributed to the improvement and generalization of this new therapeutic approach and to its spreading throughout the world.

Today, the efficacy and advantages of fibroma uterine arterial embolization (UAE) are universally recognized. UAE has resulted in over 2000 referenced publications, it is used in the entire world and it has cured a great number of women. We, J. J. Merland and I, our co-workers, D. Herbreteau, N. Ciraru-Vgneron, J. M. Bouret, E. Houdart, and A. Aymard, are aware of the good fortune we were granted. Discovering something both unexpected and meaningful, which brings progress, is something always to be hoped for but rarely happening. This chance was given to us; fortunately we did not let the opportunity escape when it was in our grasp. Today, in this book, John Reidy and the distinguished international authors shows us the importance radiology has taken in the diagnosis and treatment of gynecologic and obstetric conditions, bearing testimony to the irrepressible human urge: the search for progress.

Jacques-Henri Ravina

# Preface

One of the curious facts regarding the emergence of uterine artery embolization (UAE) in 1996 as a significant minimally invasive interventional radiological treatment for the common condition of fibroid disease was that the technique was led and championed by Dr. Jacques Ravina, a Parisian gynaecologist and that the radiological expertise was supplied by a team of neuroradiologists.

After early concerns by the gynaecological community, UAE has become widely accepted and practiced and is now regarded in most countries as a significant treatment option for fibroid disease.

Though there have been some technical refinements the embolization technique has remained largely unchanged but what has changed is the clinical evaluation, assessment, and overall management of these cases.

Myomectomy as the surgical uterus-conserving alternative to UAE, perhaps spurred by the uptake of UAE has also undergone developments. This textbook in addition to giving state of the art accounts of many clinical aspects of fibroid embolization has also reviewed current myomectomy techniques and practice. Gynaecologists and interventional radiologists when discussing treatment options with women need to have a working knowledge of the alternative treatment options in order to make the optimal treatment decision. Thus, in this textbook the UAE chapters will give gynaecologists a working knowledge of fibroid embolization whilst similarly the myomectomy chapters will be of value to the interventional radiologist.

Though UAE for fibroids is the most commonly performed vascular intervention in Obstetrics and Gynaecology less common vascular interventions are also covered.

We are very grateful to Dr. Jacques Ravina who in his retirement has written a foreward detailing how he came about to pioneer this procedure and of the early days.

John Reidy

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# Part I

# Medical Radiology: Radiological Interventions in Obstetrics and Gynaecology (Gynaecologist)

# The History and Epidemiology of Fibroids

Christopher J. G. Sutton

## Contents



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**Abstract**

Although fibroids are the commonest tumours to afflict the pelvic organs of women and have been recognised and named since ancient times they were not amenable to treatment until the first laparotomy was performed just over 200 years ago. Without the benefit of modern imaging techniques there was considerable confusion between massive fibroids and large ovarian tumours and the diagnosis was often wrong, the mortality rate was extremely high and before the advent of anaesthesia the pain and suffering was appalling. The history of fibroid therapy is reviewed from this horrific start through safer and more conservative surgery to the modern approach using sophisticated imaging techniques and minimal access approaches to therapy. The epidemiology is reviewed with regard to clear racial differences, being much more common among those of African−Caribbean descent and a possible hypothesis is presented to try to explain this. Other factors such as age, parity, oral contraceptive use, the progesterone intra-uterine system and smoking are discussed along with medical diseases such as obesity, diabetes and hypertension and other disorders resulting in the production of unopposed oestrogen.

## 1 Introduction

Trying to fathom the history of female pelvic diseases is a difficult task and the lack of data is compounded by a certain mystique about female anatomy exemplified by the fact that the ancient Greeks regarded the uterus (hysteros) as the seat of the soul. The Pythagoreans believed that the uterus was bifid which almost implies a knowledge of embryology but probably arose from the fact that they were permitted to dissect animals but human dissection was forbidden. They hypothesised that the left uterine horn represented the west, or darkness from which females were

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derived whereas the right side represented the east, or light in which males developed. They believed that the uterus wandered around the abdominal cavity and that when the organ was displaced the poor woman developed signs of hysteria (O'Dowd and Philipp 1994). Such male orientated thinking persisted until the late nineteenth century allowing gynaecologists to perform ovariotomy—the removal of normal ovaries popularised by the American Surgeon Robert Battey—for a range of dubious indications ranging from hysteria, menstrual madness, insanity and even nymphomania and masturbation (Studd 2006). Such a practice performed at a time when operative mortality was around 70 % represented the zenith of morality in the specialties of surgery and psychiatry and was probably the greatest scandal in medical history (Barker-Benfield 2000).

Even a relatively common condition such as endometriosis only appears as a vague reference in the literature as late as 1690 when a German Physician, Daniel Schroen writing in his Disputato Inauguralis Medica de Ulceritus Ulceri describes it as "a female disorder characteristic of those who are sexually maturing" (Shroen 1690). Almost a century later it is described more graphically by William Smellie from Edinburgh in his textbook Dissertatio medica inauguralis de utero inflammatione ejusdem: "An affliction that permeated the whole female system … producing morbid symptoms that manifestly change the disposition of the entire body" (Smellie 1776). Although it was referred to sporadically in texts from the seventeenth to eighteenth centuries (Knapp 1999) it has never been mentioned in the great encyclopaedias of medical history (Kiple 1993; McGrew 1985; Porter 1997). It is possible that this is due to the extreme rarity of this disease in ancient times when women were subjected to much less retrograde menstruation than their modern counterparts. Thus, in Roman times, girls usually married at 14 or younger and were expected to become pregnant within a few months. Multiple pregnancies and universal breast feeding resulted in a postpartum amenorrhoeic state until they met with an early demise, either in childbirth or naturally, since the average age of death was 35 (Sutton 2006).

## 2 Fibroids

The situation is completely different with Myomas which are the most common tumours to afflict the pelvic organs in women, and references have been made to them since antiquity. Radiography of some of the remains of Egyptian mummies revealed several instances of calcified myomas which can be seen in the Egyptology Section of the British Museum in London (Sutton 2004).

### 2.1 Nomenclature

The lesions were certainly recognised at the time of the ancient Greeks, and Hippocrates (460–375 B.C.) who practiced on the island of Kos in the Aegean, called them "womb stones". Although he did not write specifically on female anatomy he theorised that the uterus went wild if not fed on semen and his followers practiced an elementary form of gynaecology and performed internal examinations. While Galen, a Roman physician who lived in the second century AD described them as "scleromas" (O'Dowd and Philipp 1994).

The term "fibroids" was introduced by Karl Von Rokitansky (1860) who was one of the triad of gynaecologists who described the Rokitansky-Kuster-Hauser syndrome characterised by congenital absence of the vagina and later by Klob (1863). The famous German pathologist Virchow demonstrated their derivation from smooth muscle and introduced the word "myoma" (Haines and Taylor 1975). Both these terms are semantic misnomers if one is referring to the cell of origin and they should more correctly be referred to as leiomyomas because many contain varying amounts of fibrous tissue which is believed to be secondary to degeneration of some of the smooth muscle cells (Droegmueller 1987). Fibroids are the commonest of all pelvic tumours and since this is the most popular name for them it will be often used throughout this text (Jeffcoate 1967).

## 3 Epidemiology

Although they are usually benign, uterine fibroids are associated with a significant morbidity and are the leading indication for hysterectomy in the United States (Wilcox et al. 1994; Farquhar and Steiner 2002) and most developed countries (Vollenhoven 1998; Progetto Menopausa Italia Study Group 2000). Considering how common they are there is very little data on their epidemiology.

### 3.1 Age at Menarche

The peak frequency of fibroids is in the 40–50 year age group (Cramer and Patel 1990). An increased risk of developing fibroids has been reported in women who have an early menarche (Marshall et al. 1997; Parazzini et al. 1988). And this may represent increased exposure to endogenous oestrogens since these benign tumours are responsive to both oestrogens and progesterone, (Windham et al. 2002).

### 3.2 Race

Fibroids are some 3–4 times more common among those of Afro-Caribbean origin in the United States (Marshall et al. 1997) and based on ultrasound evidence the lifetime risk among US black women is estimated to be in the order of 80 % (Day Baird et al. 2003). This black–white disparity in incidence cannot be explained by established risk factors (Kjerulff et al. 1996) and an interesting prospective hypothesis-generating study has been published recently which suggests that it may be due to hair relaxers intended to straighten hair which have been used for many years by millions of US black women (Wise et al. 2012). The Food and Drug Administration (FDA) in the United States has no regularity authority over cosmetic products and listing of ingredients is not mandatory but many contain hormonally active agents such as phthalates which are often listed as "fragrances" or "perfume" (Houlihan et al. 2002). Phthalates from cosmetic products can be absorbed by the skin or inhaled (Romero-Franco et al. 2011) and have been shown to have oestrogenic effects in cell models and experimental animals but the role of phthalates in humans is less clear (Hauser and Calafat 2005). Although the influence of phthalates, diethyl stilboestrol and dioxins is interesting nevertheless at this moment in time it is conjectural and it is possible that greater African ancestry simply increases their genetic predisposition to the development of fibroids (Stewart and Morton 2006).

### 3.3 Parity

In case-control and cohort studies it has consistently been reported that parous women are at a lower risk of developing fibroids (Parazzini et al. 1996) but it is difficult to know if sterility causes fibroids or vice versa. Certainly pregnancy and breast feeding reduce the time of exposure to unopposed oestrogens which appear to increase the risk of leiomyomata. In the Victorian era it was generally considered that a uterus deprived of pregnancy consoles itself by developing fibroids hence the popular expression at that time that "Fibroids are the reward of virtue, babies the fruit of sin" (Jeffcoate 1967).

### 3.4 Oral Contraceptives

Several cohort, case–control and population studies on the risk of oral contraceptive (OC) use and the development of fibroids have produced inconsistent results with some showing an increased risk and others a protective effect (Parazzini and Chiaffarino 2006). A cohort study on 162 women conducted by the Royal College of General Practitioners (1974) in the UK showed a significantly lower risk compared with non-users but past users showed no association. A much larger cohort study, the Walnut Creek (1981) study from the United States, reported on 505 women found that the risk of fibroids increased with duration of use whereas a similar study from the Oxford Family Planning Association in the UK showed a significantly decreased risk with duration of use (Ross et al. 1986).

### 3.5 Intrauterine Devices

The Mirena intra-uterine system which releases a small amount of norgestrol per day has been reported to reduce the risk of uterine fibroids (Baird 2004).

Although this is almost certainly due to the effect of the progesterone other IUDs have been associated with an increased risk of fibroids but this is likely to be due to the increased chance of detection due to investigation of the abnormal uterine bleeding which is a side effect of these devices (Parazzini et al. 1988).

### 3.6 Smoking

The effect of increased progestin levels due to smoking is also associated with a 40 % reduced risk of fibroids (Baron et al. 1990) this could also be explained by the unopposed oestrogen theory since there is a lower concentration of bioavailable oestrogen among smokers (Parazzini et al. 1996).

### 3.7 Hypertension, Obesity, Diabetes and Insulin Resistance and Anovulatory Infertility

Similarly higher oestrogen levels in overweight women and those with anovulatory infertility are associated with increased risk and of fibroid development and lower levels among marathon runners with a decreased risk (Marshall et al. 1998). It has been suggested that there is a recognised syndrome involving the combination of hypertension, obesity and uterine fibroids particularly with long standing hypertension (>5 years) and hypertension diagnosed in women under 53 years old (Summers et al. 1971). There is often co-existing Type 2 diabetes and it has been suggested that the related insulin resistance and hyperlipidaemia can result in fibroid formation in much the same way as they contribute to the formation of atheromatous plaques which is also due to smooth muscle cell proliferation of monoclonal origin (Faerstein et al. 2001).

Fig. 1 Ephraim McDowell (1771–1830): the father of abdominal surgery. Performed the first laparotomy on Christmas Day 1809. Painting by P.W. Davenport in McDowell House. (Photo: Chris Sutton with permission from McDowell House, Danville, Kentucky)

(FIGURE NO. 20)

Jane Todd Crawford (1762-1842)

From a painting of young Jane of unknown origin
McDowell House, Danville, Kentucky.

Fig. 2 Jane Todd Crawford (1763–1842). From a painting of young Jane of unknown origin. Reproduced courtesy of McDowell House, Danville, Kentucky

## 4 Surgical Treatment of Fibroids

### 4.1 The First Laparotomy: Christmas Day 1809

Until the beginning of the nineteenth century there was no possible way of removing a large fibroid because it was considered that the surgical opening of the peritoneal cavity resulted in certain death. A little over 200 years ago an event took place which has had a momentous impact on our survival as a species and yet it has been remembered by relatively few. That day saw the birth of operative abdominal surgery which has saved countless lives, yet it did not take place in one of the great University Teaching Hospitals but in the front parlour of the house of an American country doctor in the small town of Danville in the State of Kentucky.

On the morning of Christmas Day 1809 the brave surgeon Ephraim McDowell (Fig. 1) performed the world's first elective laparotomy to remove a massive tumour from the equally brave patient, Jane Todd-Crawford (Fig. 2). When I say the patient was brave, it was because she had to withstand the horrific pain of a large abdominal incision without the benefit of an anaesthetic and the doctor was brave because the abdominal cavity had never been deliberately opened with a surgical knife before and it was widely accepted that such an intervention would inevitably

result in death. Legend has it that the townsfolk of Danville had gathered in the square outside his house on the morning of the operation and were erecting a gallows so that if Jane Todd-Crawford died at the hands of the "dreadful doctor" he would be hanged in public (Sutton 1993).

## 4.2 The Surgeon: Ephraim McDowell

McDowell's family were of mixed Irish and Scottish extraction and he was born in Rockbridge County, Virginia in 1771, the ninth of 12 children (Othersen 2004). When he was 13 years old the family moved to Danville, a frontier town that was the first capital of the State of Kentucky, where his father was appointed Judge of the small community of some "150 homes and some tolerably good buildings" (Ellis 2009). This was before the era of Medical Schools in the United States of America and the young Ephraim decided on a career in medicine early in his life and served as an apprentice to a family physician, Dr Alexander Humphreys in Staunton, Virginia (Gray 1987). When he was 22 he spent 2 years studying anatomy in Edinburgh under Alexander Munro and surgery under the tutelage of John Bell. For financial reasons he had to return home to Danville without earning a medical degree but even without the letters after his name the prestige of being educated at one of the most famous medical schools in the world ensured that he rapidly built up an extensive surgical practice and he came to be regarded as "the best doctor west of Philadelphia" (Tan and Wong 2005). He was renowned for his swift amputations, hernia repairs and lithotomies and would typically operate in the homes of patients with family members gathered round to hold the unfortunate sufferer down. One of his patients was James Polk who, as a 14-year-old boy had several bladder stones removed, and later became the 11th President of the United States (Graham 1981; Bernhard 1980). McDowell's fame spread locally among the frontier people because this was an area that was expanding rapidly after Dr Thomas Walker had opened up the Wilderness Trail through the Cumberland Gap from Virginia into Kentucky accompanied by frontiersmen and Indian fighters such as Daniel Boone and Davy Crockett (Gray 1987).

**Fig. 3** Massive ovarian cyst. When removed weighed half of the patient's weight (Photo: Chris Sutton. St. Luke's Hospital, Guildford)

## 4.3 The Patient: Jane Todd-Crawford

Jane Todd-Crawford lived with her family of five children in a small log cabin in Motley's Glenn near Greensburg, Kentucky, some 60 miles from Danville and at the age of 44 she was thought to be carrying another child and was causing concern with the local doctors and midwives because she was 2 months beyond her due date. The attending physicians were in despair and had tried various potions and enemas used to induce labour and in desperation had even employed two midwives to jump up and down on her extremely distended abdomen. All this was to no avail and the poor woman had such a swollen abdomen that she could barely breathe and in desperation they decided to summon the "surgeon from Danville".

Although the journey from Danville to Greensburg can nowadays be easily accomplished in an hour or so using modern highways, in 1809 it required a lengthy and difficult journey on horseback, crossing many mountain ridges and fording deep rivers and when McDowell set out on this arduous journey the snow had already fallen deeply and there were added hazards from bands of skirmishing Indians, to say nothing of predatory wolf packs and bears. When he arrived he quickly appraised the situation and saw that the swollen abdomen did, indeed, have the appearance of a pregnancy, possibly a multiple one, with a size that was indeed making it difficult for the patient to breathe.

Without recourse to sophisticated imaging techniques it is often difficult clinically to distinguish a massive fibroid from a large ovarian tumour or, indeed, from a term pregnancy (Fig. 3). Possibly because of his education in Edinburgh under the tutelage of the anatomist Alexander Monroe (Secundus), he performed a more thorough examination than had been performed by the local physicians and this included a vaginal examination where he found that the mass was inclined to one side and was mobile and his examining finger felt a normal sized uterus and cervix which were pushed to the other side, all of which indicated that the mass was an "enlarged ovarium".

Clearly, he was very depressed by his findings and in an account written many years later to a medical student he wrote "I told the lady that I could do her no good and candidly stated to her, her deplorable situation; informed her that John Bell, Hunter, Hay and A Wood, four of the first and most eminent surgeons in England and Scotland, had uniformly declared in their lectures that such was the danger of peritoneal inflammation that opening the abdomen to extract the tumour led to inevitable death." She was clearly devastated by this pronouncement but told him that it was impossible to continue to live in her present situation since she was almost unable to breathe and felt that she would die anyway. He therefore continued "but, notwithstanding this, if she thought herself prepared to die, I would take the lump from her if she would come to Danville." He ended this account by stating simply "she appeared willing to undergo an experiment." (Gray 1987). This must surely be the first documented case of informed consent.

**Fig. 4** Jane Todd Crawford as an old lady holding a locket with a portrait of Abraham Lincoln, a distant cousin by marriage to one of her older sisters (Photo: Chris Sutton with permission from McDowell House, Danville, Kentucky)

## 4.4 The Operation

Dr. McDowell returned to Danville expecting to hear no more from her because even the journey with the increasing snowfall that winter was long and difficult and dangerous by horseback, but she was a tough frontier woman and a few days later appeared on his doorstep. Unfortunately the arduous journey had caused considerable bruising over the lower abdomen, where she had rested the enormous tumour on the pommel of her saddle. He therefore determined to wait for a few days before deciding to perform the operation and, being a deeply religious man, he timed the procedure to occur on the morning of Christmas Day when many of the townsfolk were in church so that they could bring the efforts of their combined prayers onto his endeavour. He was joined by his nephew, Dr James McDowell, who had graduated a few months previously from the first medical school in America in Philadelphia to join the practice as a partner and he did his best to dissuade his uncle from "the experiment". The kitchen table was dragged into the front room and Jane Todd Crawford was placed on her back on the table and tilted slightly to the right side and then "he removed all her dressing which might in any way impede the operation". Many years later when he wrote about the procedure he described it as follows:

> I made an incision about 3 inches from the rectus abdominus muscle on the left side, continuing the same 9 in length, parallel

> with the fibres of the above-named muscle, extending into the cavity of the abdomen … the tumour then appeared full in view but was so large that we could not take it away entire. We put a strong ligature around the fallopian tube near the uterus and then cut open the tumour, which was the ovarium and fimbrious part of the fallopian tube, very much enlarged. We took out 15 lbs of a dirty gelatinous-looking substance, after which we cut through the fallopian tube and extracted the sac, which weighed 7 lb and one-half… As soon as the external opening was made the intestines rushed out upon the table and so completely was the abdomen filled by the tumour that they could not be replaced during the operation which was terminated in about 25 min. We then turned her upon her left side so as to permit the blood to escape, after which we closed the external opening with the interrupted suture, leaving out at the lower end of the excision the ligature which surrounded the fallopian tube.

During the whole of this ghastly painful procedure Jane Todd-Crawford remained motionless and merely recited the Psalms in order to calm herself during her ordeal.

She stayed in McDowell's house and the bed in which she lay can still be seen because the entire house and gardens have been turned into a museum to commemorate this amazing feat of pioneering surgery. Ephraim McDowell visited her on a daily basis but on the 5th day he found her making her own bed and reprimanded her severely. She continued to make an excellent recovery and 25 days later she returned home in good health by the same route that she had come, which is now a long distance path named "The Jane Todd Crawford Trail".

The two of them never met again during their lives. Ephraim McDowell died at the age of 59 years of "an acute attack of inflammation of the stomach" which was probably appendicitis and long before the time when a laparotomy could be performed to remove the infected organ. Jane Todd Crawford outlived him and died at the age of 78 years and a picture of her in her old age (Fig. 4) shows her displaying a locket with the picture of Abraham Lincoln, who was born in a log cabin at Sinking Spring Farm very close to where she grew up in Greensburg County and to whom she was related as a cousin when he married one of her sisters.

Unlike his modern counterparts, Ephraim McDowell did not immediately rush off to get this operation published and waited until he had performed two more successful ovariotomies in 1813 and 1816 before reporting it in a journal with a limited readership, "The Eclectic Repertory and Analytical Review of Philadelphia". Two years later he published two further cases in the same journal, one of whom survived, but the other died of peritonitis on the third post-operative day. During his lifetime he performed three further ovariotomies between 1822 and 1826. One involved merely drainage but the patient lived for a long time afterwards, the second underwent complete excision, but the third had to be abandoned because of extensive adhesions.

**Fig. 5** Charles Clay (1801–1893) who performed the first successful abdominal hysterectomy in Europe on 2 January 1863. Reproduced with permission of the Royal College of Obstetricians and Gynaecologists of London

There were a further three that are mentioned in letters and on reading his descriptions it does seem that, although he styled himself an ovariotomist, at least two of his cases were large pedunculated myomas (Ricci 1945; Graham 1950).

News of great surgical advances took a long time to percolate across the Atlantic and even in America McDowell's achievement was greeted with a certain amount of scepticism and even outright disbelief (Gray 1987). It was 14 years later that the first ovariotomy was carried out in Europe by John Lizzars, a fellow student from

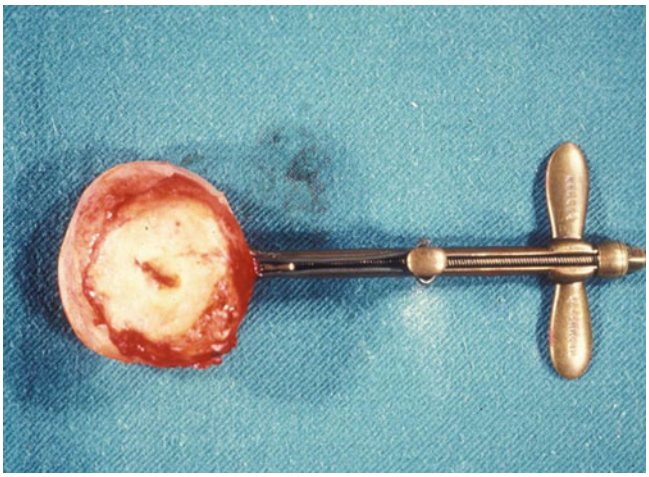

**Fig. 6** Massive fibroid exposed at laparotomy (Photo: Chris Sutton from drawing by Medical Illustration Department, St. Luke's Hospital , Guildford). Reproduced with permission

Edinburgh, but the patient died and he then made three more successful attempts in 1825. The initial years of abdominal surgery were associated with an enormous mortality rate, mainly due to uncontrolled haemorrhage or peritonitis and sepsis.

## 4.5 The First Abdominal Hysterectomy on November 17, 1843

The greatest of the ovariotomists in Europe was Charles Clay of Manchester, in the North of England. He studied at the Manchester Royal Infirmary and, like Ephraim McDowell received part of his medical education in Edinburgh. Like McDowell he also started in surgical practice in a small rural community, Ashton-under-Lyne under the shadow of the Pennines in Cheshire. After 16 years he moved to the industrial city of Manchester where he established his surgical reputation. He was a member of the Reform Club and was a friend of my great grandfather, William Sutton, who was a successful businessman in this thriving Victorian metropolis. He is shown in Fig. 5 at the peak of his surgical career, profoundly confident and appearing dapper with his top hat. He was the first to introduce the word 'ovariotomy', a strange choice for the name of this operation in an age when most surgeons were reared in the classics and therefore etymologically correct (Morton 1965).

The first four of his ovariotomies survived but with the fifth he was not so lucky and this turned out to be the first abdominal hysterectomy recorded and it turned out to be a compete disaster. The operation was performed on 17 November 1843 in the first floor room above his Consulting Rooms in Piccadilly, the large square in the centre of Manchester. As was usual in those days he was accompanied by several friends and medical students as spectators and since it was before the time of Pasteur or Lister no one wore masks or surgical gloves and the patient was given brandy and milk to alleviate the pain of the operation since this was a long time before anaesthesia was introduced by WRT Morton in 1846. He was certain that he was dealing with a massive ovarian cyst so he made a long 60 cm surgical incision from the xiphisternum to the pubis. Unfortunately once the peritoneum was entered the patient coughed and the massive tumour was extruded (Fig. 6) and he realised to his horror that it was a huge fibroid and since the patient was now struggling and had to be forcibly restrained by the medical students and it was impossible to replace the hugely enlarged uterus back in the abdominal cavity he had no option but to proceed and performed a subtotal hysterectomy. By an extraordinary coincidence a few days later on the 21st of November, A M Heath who was also an ovarian surgeon in Manchester, found himself in a similar situation operating on a huge fibroid instead of an ovarian cyst. Unfortunately both patients died of a massive haemorrhage a few hours later (Sutton 1997; Benrubi 1988).

The next year, he was more successful with a similar case but on this occasion he placed a ligature of Indian hemp around the supra-vaginal cervix to prevent haemorrhage from the uterine arteries. The patient lived for 15 days, when she fell out of bed in a coma and never regained consciousness. Although this was tragic for the patient it was also sad for Clay since she had survived the critical post-operative period and not succumbed to sepsis, the usual cause of death (Benrubi 1988; Bachman 1990).

From reading contemporary accounts of this woman's post-operative course it is difficult to determine the exact mode of death. She could have had a pulmonary embolus or she could have fallen out of bed in uraemic coma due to occlusion of both ureters by the ligature but popular Mancunian folklore suggests that she was dropped on the floor by a couple of incompetent porters while the nurses changed her bed linen. If this is true then her death was entirely unrelated to the operation and Charles Clay could have claimed to have performed the first successful hysterectomy in the world.

In fact it was not for a further 20 years that he attempted another hysterectomy and this time the patient survived. Interestingly he mentioned this almost as an aside during his important presentation to the Obstetrical Society of London in 1863 when he presented his experience of 395 ovariotomies with only 25 deaths (Clay 1863).

## 4.6 The First Successful Hysterectomy in the World

The first successful removal of a fibroid uterus was by Walter Burnham in Lowell, Massachusetts in 1853 (Speert 1980). This operation took place in the early days of anaesthesia and the ether caused the patient to vomit so when he made a massive incision from the sternum to the pubis, a large fibroid uterus was extruded through the incision when in fact Burnham was anticipating a massive ovarian cyst. It proved impossible to replace the massive fibroid and he had little choice but to proceed with a subtotal hysterectomy tying off both uterine arteries. The patient recovered and the fact that the original diagnosis was incorrect should not detract from his achievement. He performed a further 15 hysterectomies during the following 13 years but only three survived—the rest succumbing to sepsis, peritonitis, haemorrhage and exhaustion.

Later that year in September, in the same town of Lowell, Gilman Kimball carried out the first deliberate hysterectomy for a fibroid tumour with the patient surviving the operation (Matthieu 1985; Kimball 1855).

It is interesting that these two surgeons came from a small town in rural Massachusetts and considering that hysterectomy is the second most common operation performed on women, second only to caesarean section, that enquiries at the tourist office as to where these operations actually took place lead nowhere and it seems that the burghers of that small town are quite unaware of the fame that should be the just due of these two pioneering surgeons.

## 4.7 The First Successful Hysterectomy in Europe

Eugene Koeberle from Strasbourg was one of the greatest surgeons in Europe in the latter half of the nineteenth century and the French usually claim that he performed the first successful hysterectomy in Europe. The operation was for fibroids and the diagnosis was correct and in order to obtain haemostasis he used a device of his own invention called a serre-noeud which was a wire loop tightened by a screw device that held the cervix like a clamp and allowed it to be exteriorised through the wound (Fig. 7). Eventually the avascular cervical stump necrosed and fell back into the pelvis. This operation took place on 2 April 1863 and was certainly the first in continental Europe but in his lecture to the Obstetrical Society of London Charles Clay had briefly mentioned a successful case of "the entire removal of the uterus and its appendages" which he had performed in Manchester a couple of months earlier on 3 January 1863 (Clay 1863). Anaesthesia was employed regularly and

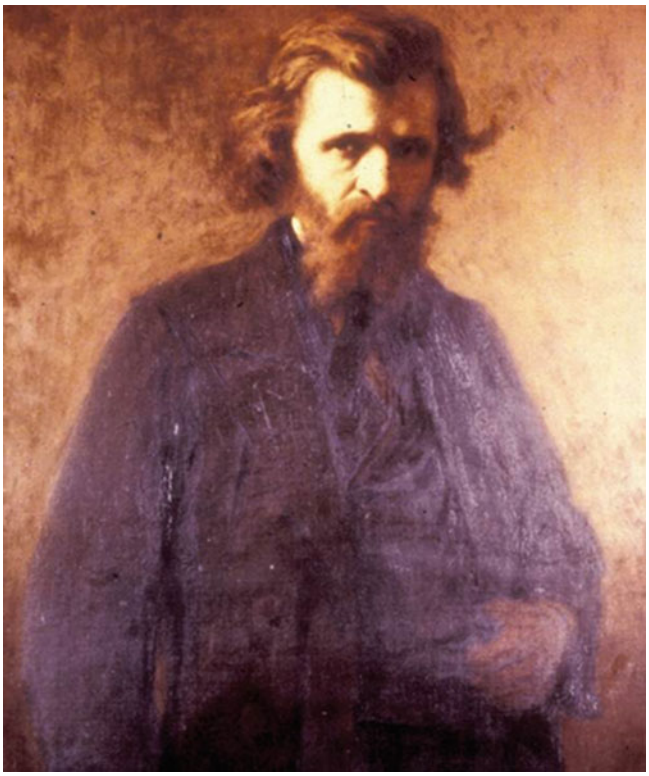

**Fig. 7** The serre-noeud introduced by Koeberle of Strasbourg, who performed the first successful hysterectomy in continental Europe on 2 April 1863 (Photo: Chris Sutton taken at St. Luke's Hospital, Guildford)

Lister had promulgated the theory of antisepsis and had devised a carbolic spray as an early method of combating it, although there is no actual reference in Clay's writings that he used these methods. In this particular case, which was deliberately undertaken to remove a uterine fibroid, he determined to cut through the cervix and not to open the vagina. The case is well authenticated by three doctors from Preston, Sheffield and Manchester, and immediately after the operation, Professor J Y Simpson, the inventor of chloroform, arrived unexpectedly from Edinburgh. He was greatly interested in the case and took the specimen back to Edinburgh from whence, some time later, he returned a description and a sketch, ending his letter with 'your case may turn out as a precedent for operative interference in some exceptional cases of large fibroids of the uterus and I congratulate sincerely on the happy recovery of your patient' (Sutton 2010).

## 4.8 Surgery in the Late Nineteenth Century

The initial mortality in these operations was extremely high since many of the early abdominal surgeons employed the long ligature hanging out of the lower part of the incision in

**Fig. 8** Thomas Keith from the Manse of St Cyrus, Melrose, Scotland, who drastically reduced the mortality and morbidity of hysterectomy by his treatment of the cervical stump. Reproduced with permission of Manse of St Cyrus

order to drain "laudable pus" from within the peritoneal cavity in much the same way as it was employed when amputating limbs during battlefield surgery. As late as 1876 surgeons such as Spencer Wells from St Mary's Hospital in London had a mortality rate of 75 % and it was only when Thomas Keith, a dour Scot from the manse of St. Cyrus near Melrose and a lifelong sufferer from cysteine stones realised the folly of this, and by cauterising the amputated cervical stump and letting it fall back into the abdominal cavity, reduced mortality and morbidity to acceptable levels (Sutton 1995). He also vigorously opposed the technique of blood letting and produced the best results with only six deaths in 156 cases (3.8 %). His hysterectomy results were no less impressive and by the time he left Edinburgh to emigrate south to London he had recorded 33 cases with only three deaths. Lawson Tate, an aggressive, outspoken character but, nevertheless, a brilliant surgeon was a bitter opponent of Spencer Wells and certainly did not mince his words when he said "the ovarian tumour was the battlefield whereon the first abdominal engagements were fought, whereas ovariotomy undoubtedly opened the gateway to abdominal surgery, Spencer Wells by his outmoded technique and resultant mortality of 75 % undoubtedly held back progress because no-one would submit women to such fearful risk unless life were already threatened. Dr Keith ended this dark period by showing us how to operate on the abdomen without fear and with little risk" (Sutton 1997) (Fig. 8).

## 4.9 The First Myomectomy

The first report in the scientific press of a myomectomy appeared in the American Journal of Medical Science in 1845, and the operation was performed by Dr Washington Atlee in Pennsylvania (Atlee 1845). Atlee was professor of medical chemistry in the hospital medical department, but clearly his remit spread beyond this and he was allowed to perform abdominal surgery. He was consulted by a young lady with a large abdominal swelling and he operated on her ostensibly for removal of an ovarian cyst. As was the custom in those days, the patient had no anaesthesia, and the operation was attended by 14 doctors and "our medical students." Atlee made a long midline subumbilical incision, and to the surprise of him and the other attendants, found an 18-inch pedunculated myoma. He transfixed the pedicle with three wax silk sutures and closed the abdomen with 15 through-and-though sutures and the woman survived.

## 4.10 Early Reports of Myomectomy in England

Adam Alexander from Liverpool, England, presented 11 cases of abdominal myomectomy to the British Gynaecological Society of London in 1898 (Alexander 1898; Cramer and Patel 1990) He claimed to have removed as many as 25 tumours from a single uterus. Unfortunately Alexander's presentation was met with great hostility from the distinguished audience, because of the hazard of bleeding and the fact that hysterectomy was by then an easier and safer operation. It is almost certain that, because of this response from the higher echelons of the gynaecologic profession myomectomy went out of favour for many years until it was revived by Howard Kelly (1907) and Noble (1906), and the Mayo brothers in the United States (Mayo 1922) and Victor Bonney in England (Bonney 1928). In fact Alexander's work was not referred to again until 1922 when Bonney looked up the literature on the subject.

## 4.11 Victor Bonney: Advocate and Pioneer of Conservative Surgery

Victor Bonney was a true gentleman and a master surgeon, and for personal reasons was a great believer in conservative surgery, not only for the removal of myoma, but also in conserving ovarian tissue at the time of ovarian cystectomy (Bonney 1937, 1923).

He invented the Bonney myomectomy clamp (Bonney 1923; Baskett 1998) that was designed to reduce blood loss during myomectomy, and his book on operative gynaecology published in 1946 is brilliantly written and a pleasure to read (Bonney 1946). The opening of one of his last papers that he gave on conservative surgery explained the driving force that he had in encouraging a more conservative approach in gynaecologic surgery: "in my early years as a gynaecological surgeon, a case occurred which profoundly affected my outlook. A lady, recently married, wishing above all things to have a child, underwent a subtotal hysterectomy on account of a single submucous fibroid. Being a woman of strong character and reticent fortitude, she accepted the blow without complaint and by assuming a proud indifference to children held her insistent mother instinct at bay and none but those who knew her well perceived the tragedy. I was among this number and the grief of it is still keen in me today." He was describing what had happened to his own wife (Bonney 1946).

Bonney was a resident gynaecologic surgeon at the Chelsea Hospital for Women in London, and it was there that he met Annie, who was a ward sister at the same hospital. They married in May 1905, but in 1907 Annie developed very heavy periods leading to severe anaemia, and after consultations, several senior gynaecologists at the Middlesex Hospital in London had the opinion that she needed a subtotal hysterectomy. At that time, myomectomy had fallen into disuse because of blood loss during surgery and infections that commonly followed the procedure. This was before the time of blood transfusions and antibiotics, and Bonney, stimulated by this personal tragedy in his own family, championed the cause of myomectomy and showed ways of avoiding these problems. By 1930, he reported on 403 consecutive myomectomies with low mortality and morbidity (Chamberlain 2000, 2003). It is salutary to think that had his wife been fortunate enough to have consulted a modern gynaecologist, she would have been treated by hysteroscopic resection of the myoma under light anaesthesia with only a few hours in a hospital.

## 4.12 Records and Curiosities in the History of Fibroids

In 1973, the largest recorded myoma with the patient surviving the operation was weighed 45.5 kg. The weight determined after about 1500 mL of blood had drained from the vascular network. The patient was a 58-year-old woman who had gradually developed abdominal enlargement over 20 years. When she went to her doctor she stated that the Lord had spoken to her saying, "Child, the time has come and I am going to deliver you." (Ferguson et al. 1982). An even larger myoma, weighing 63 kg, was removed in America in 1888, but the patient died.

I have personally removed 112 myomas from a patient at one operation, but at the time I was unaware of the world record achieved by Bonney of 125 fibroids during a single myomectomy operation in 1930 (Ferguson et al. 1982). My patient became pregnant 3 months later, and had three children born by caesarean section and two subsequent myomectomies. She had a rare form of myomatous disease called "multiple fibromatosis" whereby the uterus is completely infiltrated with a huge number of small myomas and shortly before retiring from surgical practice I operated on her daughter for the same condition.

## 4.13 Other Approaches to the Treatment of Fibroids

The Italian gynaecologist Ciniselli from Cremona popularised electrical treatment of fibroids in 1869 (O'Dowd and Philipp 1994) and this remained in use until the end of the nineteenth century although I have never seen a series of results from such treatment but it remained popular because the mortality from surgery was horrific (Table 1).

Various medications were prescribed such as potassium bromide or iodide either orally or as vaginal pessaries but Marion Sims stated in 1866 that he had never seen any worthwhile effect from such treatment (O'Dowd and Philipp 1994).

Progesterone was used as long ago as 1946 to slow the growth of fibroids (Goodman 1946) but it was only with the introduction of GnRH analogues, as described in the next chapter, that there was a realistic way of inhibiting myoma growth and, even then, the effect was only temporary and growth continued once the medication was discontinued (Matta et al. 1989).

**Table 1** Mortality rates of hysterectomies performed for fibroids (1880–1884)

| Operator | Date | Cases | Deaths | Mortality (%) |
|---|---|---|---|---|
| Pean | 1881 | 51 | 18 | 35 |
| Lawson Tait | 1882 | 30 | 10 | 33 |
| Spencer Wells | 1882 | 40 | 29 | 73 |
| Koeberle | 1882 | 19 | 10 | 52 |
| Schroder | 1884 | 100 | 32 | 32 |
| Keith | 1883 | 25 | 2 | 8 |

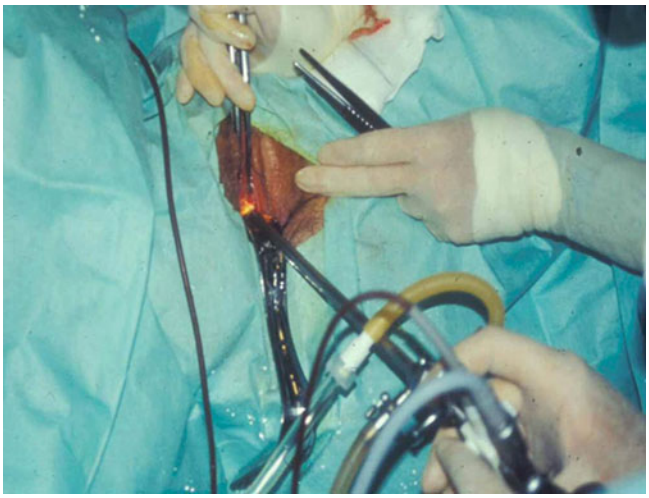

**Fig. 9** Hysteroscopic resection of submucous fibroid (Photo: Chris Sutton)

## 4.14 Minimal Access Therapy

With the development of minimal access therapy, we have witnessed successful techniques to remove submucous myomas by hysteroscopic surgery (Hart 2006) and intramural and subserous myomas by laparoscopic myomectomy (Dubuisson et al. 1998). Because of the difficulty of laparoscopic myomectomy and the need to suture the uterine wall carefully to withstand contractions of a subsequent pregnancy to avoid uterine rupture, others have searched for alternative methods to destroy the tumours, including laparoscopic myolysis with a bipolar needle, developed by Adolph Gallinat in Hamburg, and by the Nd:YAG laser (Gallinat 1993). More recently treatment has been wrested from the hands of gynaecologists with the development of uterine artery embolisation (Ravina et al. 1995) and the still experimental approach of high-intensity focused ultrasound under magnetic resonance imaging guidance (Stewart et al. 2003). Gynaecologists have understandably squirmed at this encroachment on their territory and have attempted to regain control by occluding uterine arteries either at laparoscopy (Liu 2000) or by a transvaginal Doppler-directed uterine artery clamp (Istre et al. 2004).

This book outlines the different therapeutic approaches to a common problem and one cannot fail to be impressed by the accelerated rate at which technological advances are introduced made possible by the introduction of minimal access therapy helped by sophisticated imaging techniques. By reading this book gynaecologists and general practitioners will be able to judge for themselves the appropriate technique to use and to recommend to their patients.

At this moment in time, the therapeutic approach is in an interesting state of flux but it is interesting to reflect that the first laparotomy allowing access to the peritoneal cavity only occurred just over 200 years ago which is a relatively short time in the evolution of Homo Sapiens. Before this there was no prospect of treating women with fibroids and they were often regarded as witches.

Medieval texts record several instances of women passing a bird's egg per vaginum, and often these were likened to the egg of a thrush or a wren. In those times, when society was preoccupied with sorcery and witchcraft (Labarge 1986), these poor women were often regarded as being possessed of evil spirits and were often tried and sentenced by secular courts. Their punishment ranged from humiliation, torture or being burned at the stake (Heresy trials in the diocese of Norwich. Archives of Norwich Assizes 1428) whereas their only sin was that of expelling a calcified submucous myoma that, in modern times could be identified by an X-ray or ultrasound scan and removed hysteroscopically by electrosurgical resection (Fig. 9) or an Nd:YAG laser having spent only a few hours in the hospital or even, in some centres, treated in the hysteroscopy suite.

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# The Medical Treatment of Uterine Fibroids

David L. Olive

## Contents




**Abstract**

Uterine fibroids are the most common benign tumor in women, and cause many symptoms. The treatment for these tumors has traditionally been surgical. However, a variety of medical therapies are now available for use. These drugs are primarily utilized as preoperative adjunctive therapy to ease the difficulty of surgery. However, some may have potential as long-term medical treatments, allowing the patient to delay or even avoid surgery. Current medications include GnRH analogs, selective estrogen receptor modulators, aromatase inhibitors, progesterone receptor modulators, and a variety of other less thoroughly evaluated medications. In addition, a number of drugs are in development that are designed to attack novel, specific targets in the leiomyoma growth, and maintenance process.


## 1 Introduction

Uterine leiomyomata, also known as fibroids, are the most common benign tumors in women of reproductive age. The prevalence of these benign tumors increases with age, and by the age of menopause, ultrasonographic evidence of fibroids can be found in 80 % of African–American women and 70 % of Caucasian–American women (Baird et al. 2003). These tumors can produce a variety of symptoms, including abnormal uterine bleeding, dysmenorrhea, pressure effects such as constipation, urinary frequency, and pelvic pain, and reproductive issues such as infertility, recurrent pregnancy loss, preterm labor, fetal malpresentation, and obstetrical hemorrhage.

The principle treatment for uterine fibroids, when symptomatic, has traditionally been surgical. Hysterectomy is commonly employed in the woman no longer desiring reproductive potential, while those wishing to conserve fertility generally opt for myomectomy (laparotomic or

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laparoscopic). Recently, minimally invasive interventions such as uterine artery embolization and myolysis via ultrasound, electrosurgical heat, or cryotherapy have been investigated and implemented (Olive 2000).

Medical therapy for uterine fibroids has long been desired and considered. However, lack of understanding of the biology and biochemistry of myomas, as well as discouraging data from a few available treatment trials led to sparse enthusiasm for this approach. Fortunately, our knowledge of the mechanisms of growth of uterine fibroids has increased dramatically in recent years, as has the available armamentarium for medical interventions. Today, there are numerous potential directions for both the clinician and researcher to proceed when trying to attack these tumors medically.

This chapter will review the bioendocrinology of fibroids as well as the available medical treatments and evidence of their effectiveness. Finally, a rapid review of experimental treatments, currently being investigated in animal models or cell culture, will be included.

## 2 Potential Roles for Medical Treatment

Medical therapy for fibroids is often used for short-term relief of symptoms. Abnormal uterine bleeding can often be treated effectively for a period of time until either menopause occurs or a more permanent treatment is instituted. Mass effects from large fibroids, such as constipation, bladder frequency or urgency, or ureteral obstruction with resulting hydroureter and hydronephrosis, can also be relieved for a time.

The primary use for this approach today is in the preoperative patient. Reduction of symptoms prior to surgery may improve the patient's course; a common example is the cessation or reduction of bleeding in the anemic patient. In addition, preoperative medication may allow for the conversion of a technically difficult procedure into an easier surgery by reducing the size of the tumors.

Long-term therapy, although infrequently used, has significant potential. The role of such treatment has been infrequent to date, due to a lack of data to support its use as well as concerns regarding adverse effects and costs. Exploration of this concept in the future, especially with newer, more targeted therapies, will inevitably occur.

A final role proposed for medical therapy of leiomyomata is for prophylaxis against development of the tumors in those at high risk, or recurrence in women previously treated. To date there has been little work in this arena. As we increase our understanding of the endocrinology, biochemistry, and genetics of fibroids, prophylaxis may begin to have a prominent role in research and clinical practice.

## 3 Endocrinology of Fibroid Growth and Maintenance

Fibroids are clearly affected by the hormonal environment of the patient, as confirmed by the clinical observation that they generally first develop during reproductive years and regress following menopause. Estrogen clearly plays a role in fibroid growth and development. The growth of these tumors is up-regulated by estrogen (Walker 2002). Leiomyomata contain estrogen receptors, and more are present in the tumor than in surrounding myometrium (Otubu et al. 1982; Rein et al. 1990; Brandon et al. 1995; Bakas et al. 2008). In addition, aromatase is present in significant amounts (Bulun et al. 1994). These factors produce a hyperestrogenic environment within the fibroid.

Progesterone too seems to have a growth-promoting effect upon fibroids. Peak mitotic activity can be found in the luteal phase (Kawaguchi et al. 1989; Tiltman 1985) and high doses of progestational agents will enhance mitotic activity. Progesterone receptor levels are elevated in fibroids, probably because of up-regulation by the high levels of estrogen.

Estrogen and progesterone induce tumor growth by a variety of mechanisms. Progesterone increases BCL2 gene expression, which results in the production of bcl-2 protein, an inhibitor of apoptosis and a stimulator of cell replication (Yin et al. 2007). In addition, the expression of a large number of growth factors is induced by steroid hormones. Epidermal growth factors, insulin-like growth factors, and their receptors are overexpressed in these tumors, a direct result of high levels of estrogen exposure (Fritz and Speroff 2011).

Knowledge of these pathways for fibroid growth has given researchers a bevy of potential targets for medical treatment of the tumors. The results are a wide variety of drugs, each designed to target some aspect of this hormonal cascade within the fibroid.

## 4 Available Medical Treatments

### 4.1 GnRH Analogues

#### 4.1.1 GnRH agonists

Ovarian hormone secretion is dependent upon the functionality of the hypothalamic-pituitary-ovarian axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which stimulates pituitary secretion of the gonadotropins follicle-stimulating hormone (FSH) and leutinizing hormone (LH). These hormones, in turn, stimulate the ovary, resulting in follicular growth, ovulation, and the

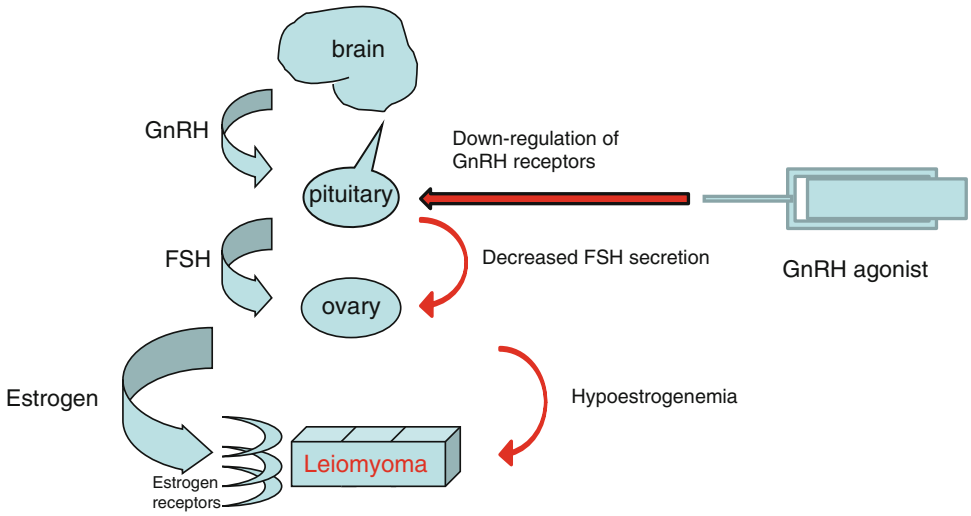


**Fig. 1** Mechanism of action of Gonadotropin-releasing hormone agonists (GnRH-agonists) on the hypothalamic-pituitary-ovarian axis in the presence of uterine fibroids

production of steroid hormones. GnRH release is pulsatile, and precise amounts and rates of GnRH secretion are required for optimal stimulation of FSH and LH production and release.

GnRH agonists are peptides that are modifications of the native GnRH molecule. Several agents have been developed that differ from the native hormone with respect to the specific amino acid sequence. All are designed to either increase receptor affinity or decrease GnRH degradation. Their use, therefore, leads to persistent activation of GnRH receptors. This activation results in an initial release of gonadotropin previously produced and stored in the pituitary. However, the release is rapidly followed by down-regulation of the GnRH-receptor expression and profound suppression of gonadotropin secretion. As a result, sex-steroid production in the ovary falls to levels similar to those seen after castration. This hypoestrogenic, hypoprogestogenic state creates an adverse environment for the fibroid (Fig. 1).

Three GnRH agonists are currently approved by the Food and Drug Administration for the treatment of endometriosis in the United States: leuprolide acetate, goserelin acetate, and nafarelin acetate. They differ with respect to dose and mode of administration. Leuprolide comes in a depot form and is administered intramuscularly at a dose of 3.75 mg monthly or 11.25 mg every 3 months. Goserelin can be administered as a monthly 3.6 mg subcutaneous implant or a 3 month 10.8 mg implant. Nafarelin is an intranasal spray, with 200 mcg administered per pump; the daily dose ranges from 400 to 1600 mcg.

Most adverse effects of GnRH-agonist therapy are related to hypoestrogenemia and include vasomotor symptoms, insomnia, and urogenital atrophy (vaginal dryness, urinary urgency and frequency, and painful intercourse). Other common side effects include headache, decreased libido, irregular vaginal bleeding, depression, arthralgia, myalgia, irritability, fatigue, and decreased skin elasticity (Table 1) (Olive 2008).

The most worrisome effect of the drug is loss of bone mineral density, which occurs at a rate of roughly 6 % annually (Hornstein et al. 1998). This side effect is largely responsible for the hesitancy to use GnRH agonist for extended periods of time. Another concerning side effect is memory impairment, which effects up to 44 % of those treated. Fortunately, this adverse phenomenon is completely reversible with discontinuation of the drug (Newton et al. 1996; Sherwin and Tulandi 1996).

An adverse effect unique to the use of these drugs for the treatment of fibroids is significant vaginal hemorrhage roughly 5–10 weeks after initiation of medication. This event is due to degeneration and necrosis of submucous myomas, and occurs is approximately 2 % of treated women (Friedman 1989).

The long-term side effects of GnRH agonists can be minimized or eliminated by adding back a small amount of sex steroids, similar to the replacement hormone dosages for menopausal women. A number of different regimens have been utilized, including estrogen/progestin, progestin alone (medroxyprogesterone or norethindrone), and androgen (tibolone). All reduce vasomotor symptoms, but progestins derived from progesterone (such as medroxyprogesterone) tend to preserve bone less well than norethindrone, whose breakdown products include ethinyl estradiol (Chwalisz et al. 2012). Such therapy can begin with the initiation of the medical therapy, or can be delayed for a period of time to allow for unopposed GnRH action.

GnRH agonists are most commonly used as a preparatory treatment for surgery. When treated for at least 3 months, uterine size is reduced to 30–65 % (Friedman et al. 1988; Carr et al. 1993; Minaguchi et al. 2000). Symptomatic relief is often achieved during this time, as bleeding is generally reduced and pressure effects relieved

**Table. 1** Adverse effects of gonadotropin-releasing hormone agonist therapy

| |
|---|
| *Common (>60 % of patients)* |
| Hot flashes |
| *Less common (20–60 % of patients)* |
| Headache, insomnia, memory disorder, and significant temporary bone mineral density loss (if used 6 months or less) |
| *Infrequent (2–19 % of patients)* |
| Significant and persistent bone mineral density loss, anxiety, dizziness, asthenia, depression, vaginal dryness, dyspareunia, weight change, arthralgias, myalgias, alopecia, peripheral edema, breast tenderness, irritability and fatigue, decreased skin elasticity, decreased libido, nausea, altered bowel function, and irregular vaginal bleeding |
| *Rare (<2 % of patients)* |
| Vaginal hemorrhage, allergic reactions |

(Benagiano et al. 1996). When patients are anemic from excessive uterine bleeding, the use of GnRH agonist preoperatively has been a strategy used to allow increase in hemoglobin levels. Furthermore, this approach often decreases blood loss at surgery. However, one caveat often mentioned by surgeons (but heretofore undocumented in the literature) is that pretreatment softens the myomas, making complete removal more difficult.

For the hysteroscopic removal of submucous myomas, GnRH pretreatment has several particular advantages. First, when removing fibroids by pieces (as with a resectoscope) rather than as a single, intact entity, a reduction in volume becomes much more meaningful. Second, endometrial atrophy will improve visualization. Finally, decreased vascularity should minimize blood loss and fluid intravasation.

It must be kept in mind that the effect of GnRH agonist reduces leiomyoma cell size and is not cytotoxic. With cessation of the drug there is a return in fibroid size within 3–4 months. This would imply that its use as a stand-alone therapy would be extremely limited. One such situation would be the use of GnRH agonist to treat women close to menopause in an attempt to avoid surgical intervention. However, intermittent, long-term use in women with fibroids may be feasible; in a study of women treated with the medication for abnormal uterine bleeding attributable to fibroids, there was symptomatic improvement in half for up to 6 months following discontinuation (Scialli and Levi 2000). Further investigation is clearly needed to evaluate this interesting concept.

### 4.1.2 GnRH Antagonists

GnRH antagonists are analogs of the GnRH molecule that act by directly competing for and occupying pituitary GnRH receptors. This blocks access of the GnRH molecule to these receptors, resulting in immediate pituitary suppression of gonadotropin secretion. This avoidance of the initial gonadotropin flare seen with GnRH agonists allows the antagonist to cause a clinical effect much more quickly, generally within 2 weeks. It is also rapidly reversible with discontinuation of the drug.

Similar amounts of shrinkage of fibroids are seen with antagonists as with agonists (Felberbaum et al. 1998, 2001; Gonzalez-Barcena et al. 1997; Flierman et al. 2005). Currently, long-acting antagonists are not available in the US, but should they become available this drug class will likely supplant GnRH agonists as a preoperative therapy, due to the more rapid onset. Exactly this pattern is seen in countries where GnRH antagonists are available and have begun to cause a decline in usage of GnRH agonists.

## 5 Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) are nonsteroidal estrogen receptor ligands that act as estrogen agonists in some tissues and as receptor antagonists to block estrogen action in others. Different SERMs behave differently in each tissue in which they act; the specific action is determined by their structure, the estrogen receptor to which they bind, and other interacting molecules in the tissue. As an example, tamoxifen and raloxifene, two well-known SERMs, both have estrogen antagonist effects upon mammary tissue. However, raloxifene is also an estrogen antagonist in endometrium, whereas tamoxifen is an agonist in uterine tissue.

The ability to block estrogen action means that this class of drugs has a potentially therapeutic effect in the treatment of fibroids. However, it is critical to find the SERM with the correct combination of actions in other locales. Tamoxifen has not been used in the treatment of myomas because of its tendency to produce endometrial hyperplasia (Neven et al. 1989). In addition, case reports suggest that tamoxifen may be agonistic in myometium and fibroids as well. Conversely, raloxifene's agonist/antagonist profile seems much better suited to this purpose.

As should be expected, the side effect profile of a SERM is primarily dependent upon its actions in various tissues. For raloxifene, the principal side effect is vasomotor symptomatology, as the antagonistic effect predominates in the central nervous system. The most critical side effect, however, is the thrombogenic nature of this medication, an estrogen-like activity in the liver that raises the risk of a thromboembolic event threefold (Ettinger et al. 1999). For this reason, leg pain and respiratory complaints must be taken seriously in women treated with this drug, and it is likely contraindicated in women with known thrombophilias.

Initial studies with raloxifene demonstrated that 60 mg daily was sufficient to significantly decrease the size of the tumors for up to a year in postmenopausal women (Palomba

EFFECTIVENESS OF COMBINED GnRH ANALOGUE PLUS RALOXIFENE ADMINISTRATION IN THE TREATMENT OF UTERINE LEIOMYOMAS: A PROSPECTIVE, RANDOMIZED, SINGLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL

| | GnRH-a + raloxifene | GnRH-a + placebo | P value |
|---|---|---|---|
| Patients | 50 | 50 | |
| Non-fibroid uterine volume | 39% decrease | 37% decrease | N.S. |
| Fibroid uterine volume | 70% decrease | 39% decrease | <0.05 |

**Fig. 2** The effect of GnRH-agonist plus raloxifene versus GnRH-agonist alone on uterine volume and leiomyoma volume. Data from Palomba et al. 2002b

et al. 2001). However, in premenopausal women, this dose was ineffective; doses as high as 180 mg daily were required to even see a marginal response in some women (Palomba et al. 2002a). It appears that raloxifene is capable of blocking the effect of estrogen on fibroids when levels are relatively low, but when premenopausal levels are present the blockade is ineffective.

The conflicting data from pre-and postmenopausal women led to the notion that raloxifene might be efficacious if premenopausal women could be "converted" via a medical menopause. Palomba and colleagues combined raloxifene with GnRH agonist treatment in an attempt to do just that (Palomba et al. 2002b). A randomized trial comparing GnRH agonist plus raloxifene 60 mg daily versus GnRH agonist plus placebo demonstrated that after 6 months substantially more fibroid volume reduction was seen with combination therapy than the control arm (Fig. 2). The size reduction remained stable for an additional 12 months of treatment, and myoma symptoms also remained improved (Palomba et al. 2004). The primary side effect, as expected, was hot flashes, but endometrium remained atrophic and there was no significant decrease in bone mineral density. Thus, the combination therapy proved superior in fibroid treatment to either drug alone, and also ameliorated a major adverse effect of GnRH agonists by protecting bone density. This regimen may prove to replace solo GnRH agonist therapy when medical therapy is desirable.

## 6 Aromatase Inhibitors

Aromatase inhibitors are molecules that directly inhibit estrogen synthesis by either blocking or inactivating aromatase, the enzyme responsible for synthesizing estrogens from androgen precursors. While estrogen is principally produced in the ovary premenopausally, the aromatase enzyme can be found elsewhere, such as in adipose tissue and endometriosis. Aromatase is also produced in many fibroids, which may explain why some tumors do not regress in hypoestrogenic states (Ishikawa et al. 2009).

Given the above facts, it would be anticipated that aromatase inhibitors would be of value in pre- and postmenopausal women. Side effects in such patients would be those expected in a hypoestrogenic state: Hot flashes, vaginal dryness, and bone loss. However, the utility in women with functioning ovaries might be expected to be poor, in that a hypoestrogenic state would likely stimulate the hypothalamic-pituitary-ovarian axis, with greater levels of FSH production, and resultant follicular development; such developing follicles would be unable to ovulate due to an absent LH surge (as estrogen, the surge trigger, is low) and ovarian cysts would result.

Data are limited for the use of these agents in the treatment of fibroids. Most publications are case reports or small uncontrolled series. However, there is currently one randomized trial comparing the aromatase inhibitor letrozole 2.5 mg/day to GnRH agonist in the treatment of uterine fibroids (Parsanezhad et al. 2010). In this study, premenopausal women with a single fibroid >5 cm in diameter were treated for 12 weeks. The patients treated with letrozole had 45 % reduction of volume of the fibroid, a result that did not differ from the GnRH agonist group. However, the patients treated with letrozole had a more rapid onset of size reduction, saw no changes in steroid hormone or gonadotropin levels, and also had no development of ovarian cysts. The long-term or preoperative use of their medication may well prove superior to the existing medications.

## 7 Progesterone Receptor Modulators

As progesterone has been shown to be critical to the growth of fibroids, a logical pharmaceutical approach to the treatment would be better to inhibit the action of progesterone on these tumors. Progesterone receptor modulators are a class of compounds that interfere with the progesterone–progesterone receptor interaction. Two types of such inhibitors have been developed: (1) the pure progesterone receptor antagonist, and (2) the selective progesterone receptor modulator, which has either agonist or antagonist activity depending upon the site of action.

### 7.1 Progesterone Antagonists

Mifepristone is a progesterone receptor antagonist with little or no agonist activity. It binds to the progesterone

receptor with high affinity, and also binds to the androgen and glucocorticoid receptors. The drug has been shown to reduce the progesterone receptor number in fibroids (Bouchard et al. 2011).

Side effects of this medication include vasomotor symptoms, nausea, and fatigue, but all are relatively infrequent. High doses can produce anti-glucocorticoid effects, and thus have been avoided in recent trials. The most concerning adverse effect is the effect of the drug on the endometrium. The inhibition of progesterone action on the endometrium creates a milleu of pure estrogen stimulation, resulting in histologic changes resembling hyperplasia. This was noted in 28 % in one of the original studies (Steinauer et al. 2004), although re-evaluation of the biopsies later reduced this rate to 14 % (Eisenger et al. 2003). Nevertheless, this finding raises concern for the value of progesterone antagonists in the long-term treatment of uterine fibroids.

Mifepristone has been shown to reduce fibroid volume consistently, by around 50 % in most studies with a dosage range of 5–50 mg/day (Steinauer et al. 2004). The studies also report a high rate of symptom relief (up to 75 %) and a 91 % rate of amenorrhea. Recently, a randomized trial comparing 5 and 10 mg daily doses for 6 months again demonstrated significant volume reduction, but also found that 1-year posttreatment in the majority of women remained asymptomatic (Esteve et al. 2012). Also interesting is an open-label study of the utility of 2.5 mg mifepristone daily. While the uterine volume was reduced only 11 % over the 6-month trial, the improvement in quality of life was similar to that seen with higher doses (Eisinger et al. 2009). This raises the possibility that effective medical treatment may not hinge upon reducing fibroid size in many women.

Ulipristal is a pure progesterone antagonist with no agonist activity. It binds progesterone receptors, but not estrogen receptors, and has less antiglucocorticoid activity than mifepristone (Hild et al. 2000; Attardi et al. 2000, 2002). The drug has been shown to reduce progesterone receptors, and downregulate growth factors and their receptors in cultured leiomyoma cells (Wang et al. 2006; Xu et al. 2006).

The side effect profile of ulipristal shows it to be extremely well tolerated. Estrogen levels are maintained in the mid-follicular range, and thus vasomotor symptoms are infrequent and less profound. There is no evidence of effect upon bone mineral density, and anti-glucocorticoid effects seem to be rare. The effect on the endometrium, a major concern for these medications, has been thoroughly investigated. Over 60 % of women treated with ulipristal show changes typical of this class of drugs after 3 months: Glandular dilatation and dyssynchronous glands and stroma. However, these changes resolved after a 6-month drug-free period (Donnez et al. 2012a). This leads to the intriguing possibility that intermittent therapy might eliminate the concerns of endometrial hyperplasia with this medication.

A number of small studies had previously suggested the value of ulipristal in the treatment of myomas, but two recent randomized clinical trials highlighted the value of this drug. In one, a randomized trial compared ulipristal 5 and 10 mg daily to placebo preoperatively in women with anemia (Donnez et al. 2012b). Bleeding was controlled in over 90 % of those treated with active medication, and there was a significant (but small) decrease in fibroid volume. A second trial compared ulipristal to a GnRH agonist. Compared to the GnRH agonist, ulipristal-induced amenorrhea more rapidly and produced a greater increase in hemoglobin levels in treated patients. While GnRH agonist produced a greater size reduction in the fibroids, the effect of ulipristal appeared to be more sustained. This had been suggested in prior studies (Eisenger et al. 2005).

Thus, ulipristal appears to be a drug worthy of consideration in the preoperative treatment of uterine fibroids; furthermore, its value as a long-term medical treatment via intermittent use is conceivable, and is in need of investigation.

## 7.2 Selective Progesterone Receptor Modulators

As stated earlier, some progesterone receptor antagonists have agonistic properties in some tissues, organs, or hormonal milleus. These medications are termed selective progesterone receptor modulators, or SPRMs. The most intensely investigated of this class is asoprisnil. This medication exhibits a mixture of agonist and antagonist actions, with a high degree of uterine selectivity. It induces amenorrhea and suppresses endometrial growth (Chwalisz et al. 2006). In addition, it has no antigluticorticoid effects. In culture, asoprisnil produces an anti-proliferative effect upon cultured leiomyoma cells (Chen et al. 2006).

Phase 1 trials with asoprisnil demonstrated reversible suppression of menstruation. Phase 2 trials showed, via multicenter randomized trials, that the drug reduced fibroid size by 36 % and menorrhagia in a dose-dependent manner, with an amenorrhea rate of up to 83 % with a dose of 25 mg daily (Chwalisz et al. 2007). The drug has also been shown to reduce uterine artery blood flow (Wilkens et al. 2008).

Asoprisnil appeared to have relatively few and mild side effects in the above-mentioned trials; however, endometrial histologic changes were seen typical of progesterone

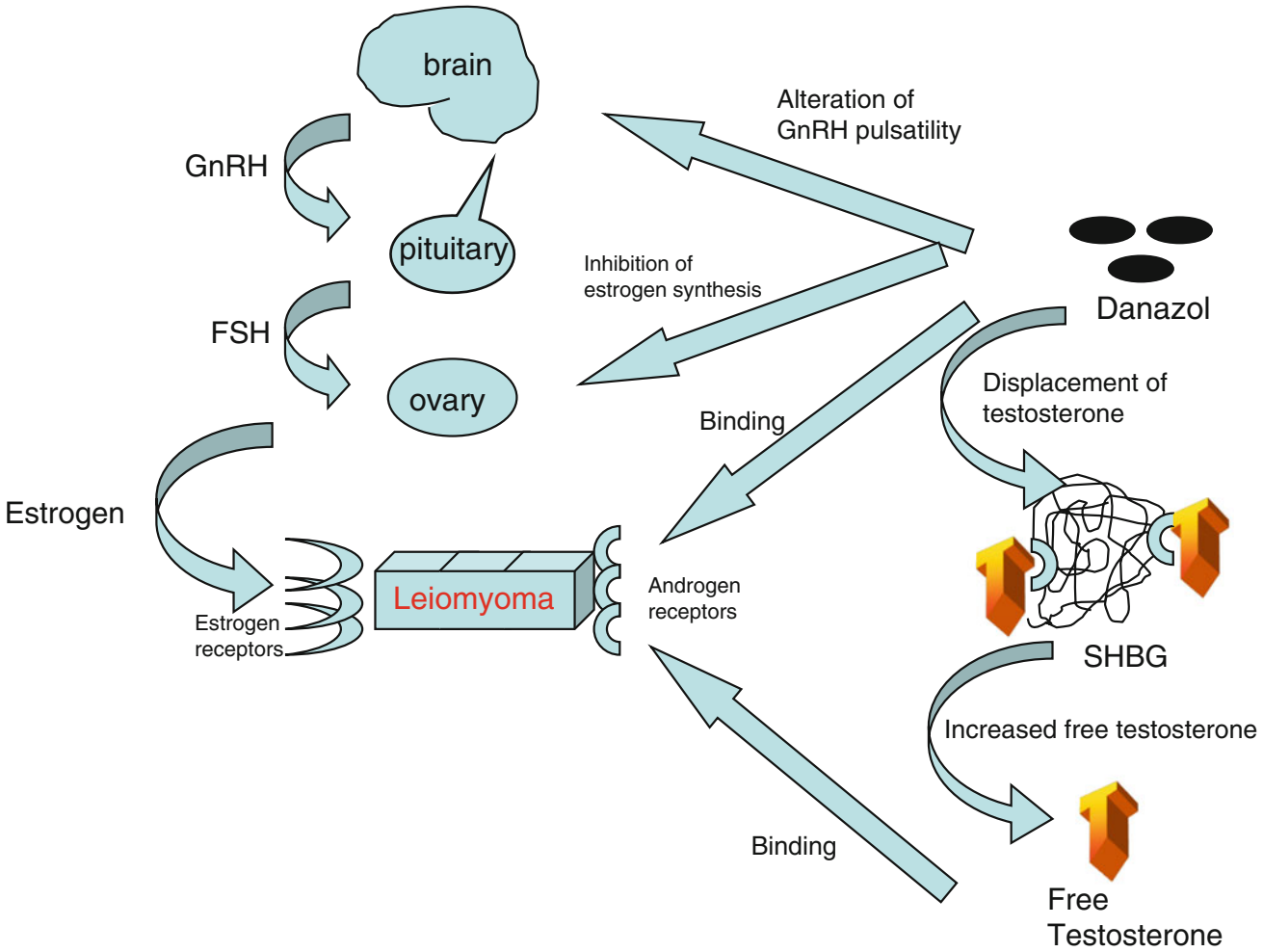


**Fig. 3** Mechanism of action of danazol upon uterine fibroids

receptor antagonists. As a result, phase 3 trials of the drug were abandoned despite the encouraging results.

## 8 Other Available Therapies

### 8.1 Danazol

Danazol is an isoxazole derivative of 17-alpha-ethinyltestosterone, and functions in a number of different ways that may inhibit the growth and maintenance of uterine fibroids. The drug alters GnRH pulsatility, resulting in ovulation dysfunction (Panidis et al. 1994), and also creates hypoestrogenemia by inhibiting multiple enzymes in the steroidogenic pathway, including aromatase (Barbieri and Ryan 1981; Ishihara et al. 2003) (Fig. 3). Furthermore, by binding to SHBG, testosterone is displaced and the amount of free testosterone rises. This combination of anti-estrogenic, anti-progestogenic, and androgenic effects seems to be beneficial in reducing fibroid size. Additionally, danazol appears to increase the uterine artery impedance to blood flow.

Clinical studies suggest that the medication is efficacious while being administered, and perhaps for a period of time thereafter. Danazol 400 mg/day produced a 24 % decrease in uterine volume by 4 months; the size was still significantly reduced 6 months after discontinuation of treatment. Symptom reduction was noted in all women treated (De Leo et al. 1999). A lower, more tolerable dose of the androgen has also been tried; women were treated with 100 mg daily for 6 months resulting in a mean myoma volume decrease of 38 % (La Marca et al. 2003).

Unfortunately, danazol has multiple androgenic side effects such as weight gain, acne, inappropriate body hair growth, oily skin, and decreased breast size. These and other less frequent symptoms may be reduced or eliminated, however, with lower doses of the drug, and trials of 50–100 mg daily for extended lengths of time are currently being planned.

### 8.2 Cabergoline

The dopamine agonist cabergoline has also been trialed in an attempt to medically treat myomas. The drug is believed to produce its effect via decreased uterine artery blood flow. In randomized trails against a GnRH agonist, this drug appears to cause comparable shrinkage of the tumors with few side effects (Melli et al. 2007; Sayyah-Melli et al. 2009). Further studies are definitely needed to better evaluate the potential usefulness of this drug in the long-term medical treatment of fibroids.

### 8.3 Gestrinone

Gestrinone is another androgenic steroid used to treat myomas. Like danazol, the medication is anti-estrogenic and anti-progestogenic. Studies suggest that the drug reduces uterine volume up to 40 % with 6 months of usage (Coutinho et al. 1986; Coutinho and Goncalves 1989). Of interest is that the treatment effect appears to be fairly durable, with a persistence in volume decline lasting for 18 months (Coutinho and Goncalves 1989).

### 8.4 Oral Contraceptives

Many publications have stated that estrogen–progestogen oral contraceptives are contraindicated in women with uterine fibroids; this conclusion is based upon in vitro studies of both hormones acting as stimulants for growth of myoma cells. There are very limited data regarding the clinical applicability of this conclusion, however. Oral contraceptives are associated with a decrease in duration of menstrual flow, and in at least one small study there was no associated change in myoma size (Friedman and Thomas 1995). This is not the case, however, with pure progestin therapy, as several studies have documented this class of medications when given alone will in fact cause tumor growth (Harrison-Woolrych and Robinson 1995).

### 8.5 Ascorbic acid

Ascorbic acid, also known as vitamin C, has a known role in tissue repair, as well as in platelet activation and aggregation. It has been proposed that many patients may have suboptimal levels of vitamin C producing a propensity to have greater blood loss during and after surgery. This has been tested in a randomized trial of patients undergoing abdominal myomectomy, where intravenous administration during and after surgery reduces blood loss, duration of surgery, and days of hospitalization (Pourmatroud et al. 2012).

## 9 Experimental Therapies

In addition to the above-mentioned medications, there are numerous agents in the early stages of investigation which may hold promise in the medical treatment of fibroids.

Catechol-O-methyl transferase (COMT) catalyzes the conversion of hydroxylated estrogen metabolites into their methylated forms. 2-hydroxyestradiol, a substrate for COMT, acts as an anti-estrogen in the body. Fibroids are known to have high levels of COMT and thus are able to eliminate 2-hydroxyestradiol from the local environment, promoting the growth stimulating effect of estradiol. It has been theorized that inhibition of COMT will result in a decrease in the estrogen effect upon fibroids, possibly resulting in tumor shrinkage. This hypothesis has been tested in the Eker rat model, a species that spontaneously produces uterine fibroids. Ro 41–0960, a COMT inhibitor, produced a dramatic reduction in fibroid volumes in Eker rats over 4 weeks (Hasson et al. 2011). However, contradictory data are provided by studies utilizing the COMT product 2-methoxyestradiol, which has also been shown to decrease leiomyoma cell proliferation in culture (Salama et al. 2006). Further studies are clearly needed to determine the validity of this approach in the human.

As stated earlier, epidermal growth factor (EGF) seems to play a role in fibroid growth. Selective inhibitors of the EGF receptor have been studied for their effect upon fibroids, with positive results. AG1478 and TKS050, two such receptor inhibitors, have been shown in vitro to block leiomyoma cell growth (Shushan et al. 2004, 2007).

Genestein, a naturally occurring phytoestrogen and known tyrosine kinase inhibitor and activator of PPAR gamma, also has been shown in multiple studies to inhibit leiomyoma cell growth. The mechanism is as yet unclear (Shushan et al. 2007; Miyake et al. 2009).

Halofuginone is an antifibrotic drug that inhibits collagen type 1 production, TGF betaI signaling, and cell proliferation in mesenchymal cells. When tested on leiomyoma cells in culture, the medication inhibited cell proliferation by inducing apoptosis, reducing collagen production, and reducing TGF levels (Grudzien et al. 2010).

Circumin is an active component of the spice Turmeric (Curcuma longa), and has been used for many years as a natural food supplement. This medicine suppresses the growth of several tumor cell lines in vitro, including uterine leiomyoma cells (Malik et al. 2009; Tsuiji et al. 2011). The mechanism seems to be through activation of PPAR gamma and alteration of the cell cycle. Investigation into this herbal

agent as a possible inhibitor of fibroid development and growth is needed, both in vitro and epidemiologically.

The Chinese herbal component Isoliquiritigenin is often touted as having anticarcinogenic properties. It is highly prevalent in licorice. In vitro, this drug inhibits myoma cell proliferation by initiating apoptosis through downregulation of Bcl-2 and other apoptosis inhibitors (Kim et al. 2008).

Interferon alpha, an anti-angiogenic cytokine, has been shown to inhibit leiomyoma cell growth in culture, as well as that of myometrial cells and endometrial stromal cells.

Pioglitazone, an insulin-sensitizing agent, acts through the PPAR gamma receptor to leiomyoma cell growth in vitro in a dose-dependant manner (Loy et al. 2005).

In summary, there are a variety of novel approaches being applied to the issue of limiting fibroid proliferation and/or producing a reduction in size. While many of these pathways look promising in the laboratory, more advanced investigation is needed prior to generating a significant level of enthusiasm for these medications.

## 10 Conclusions

It is astounding that the most common tumor in women, the uterine fibroid, to date has no widely accepted form of medical treatment. Nevertheless, the large number of forays into development of such an intervention have resulted in a number of medications of demonstrable value. Preoperative therapy is clearly of benefit in the anemic patient undergoing hysterectomy or myomectomy; the utility in the nonanemic patient is less clear.

Long-term therapy to avoid or significantly delay surgery is the remaining question mark for the medical approach to this disease. A number of drugs appear to have the potential to be used in this manner, but appropriately crafted long-term studies are sorely needed. Such investigations will not only need to determine the effect on fibroid volume and symptoms, but also side effects over time, quality of life measures, and cost-effectiveness. Approaches may include individual therapies, combinations (such as GnRH agonists with add-back hormonal therapy or GnRH agonist with raloxifene), and intermittent therapy.

More importantly, as our knowledge of fibroid growth, development, and maintenance increases, so does our collection of potential therapeutic targets. The development of highly specialized molecules to attack specific targets involved in an increasingly complex fibroid growth pathway will add substantially to our future capacity to control these tumors in a nonsurgical manner.

The treatment of uterine fibroids is, today, primarily surgical or via interventional radiology. However, the future lies in medical therapy. So let the surgeon beware: if you enjoy operating on uterine fibroids take advantage of your current opportunities, as your time may be limited!

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# Clinical Presentation of Uterine Fibroids

Mary Ann Lumsden and Salha Abukhnjr

## Contents




**Abstract**

Uterine fibroids are common benign tumours that occur in women of reproductive age. Over half appear to be asymptomatic although it is not clear why some are associated with symptoms and others not. In some instances it may be related to their position in the myometrium and it is assumed that those that distort the uterine cavity are more likely to be associated with menstrual disorder and sub-fertility than those that are intra-mural or sub-serosal although this is certainly not always the case. Fibroids are frequently associated with symptoms that impact on quality of life and require treatment although symptom severity does vary from one woman to another. Women with fibroids commonly present with menstrual problems, particularly heavy menstrual bleeding. Since the bleeding can be extremely heavy, anaemia can also occur. Intracavity lesions can also lead to unscheduled bleeding. Not all women present with menstrual problems, some have symptoms related purely to the size. This includes abdominal swelling or discomfort, hydronephrosis and other urinary symptoms. A pelvic mass may also be an incidental finding when imaging is performed for another reason. The relationship of fibroids with fertility is uncertain. Data from assisted conception suggest that implantation is affected by sub-mucosal fibroids and possibly intra-mural. They may also increase the risk of miscarriage and problems during later pregnancy. However, fibroids are commoner in older women in whom fertilisation rates and the likelihood of a successful pregnancy will already have decreased. Erroneous conclusions can also be drawn from case studies where successful pregnancy occurs after the fibroids have been treated, e.g. by myomectomy or uterine artery embolisation. Fibroids are an increasing problem since women are delaying pregnancy until their 30s and 40s. Consequently it is incumbent on us to continue to try and identify the cause of the clinical symptoms and develop means of preventing fibroid development.



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## 1 Introduction

Uterine fibroids, the most common tumour in women, are asymptomatic in at least 50 % of affected women (Divakar 2008; Zimmerman et al. 2012). However, in the remainder, they cause significant morbidity and affect quality of life (Gupta et al. 2008). Risk factors for fibroids include obesity, having no children and women who have not used the oral contraceptive pill for any length of time.

Clinically, they present with a variety of symptoms: such as menstrual disturbances including heavy menstrual bleeding (HMB), dysmenorrhoea and inter-menstrual bleeding and may lead to pressure symptoms such as a sensation of bloating, increased urinary frequency and bowel disturbance (Lumsden and West 1989; Gupta et al. 2008). In addition, they may compromise reproductive function, possibly contributing to sub-fertility, early pregnancy loss and later pregnancy complications such as pain, preterm labour or malpresentations (Ortiz et al. 2011).

Their growth is under the control of steroid hormones, particularly oestrogen and they do not appear before the menarche and shrink after the menopause (Buttram and Reiter 1981; Lumsden et al. 1994) since they are dependent on the presence of oestrogen for their growth.

## 2 Heavy Menstrual Bleeding

HMB may present in a number of ways such as an increase in the amount of blood lost per cycle or prolonged vaginal bleeding.

There is evidence that HMB is common with women with uterine fibroids (Fraser et al. 1986; Lumsden and West 1989; Lethaby and Vollenhoven 2011). If menstrual blood loss is measured in women without fibroids who complained of HMB then as many as half are likely to have a normal blood loss but perceive it as heavy (Chimbira et al. 1980). However, if the same procedure is taken with women with fibroids then a vast majority will have heavy loss and on occasions this may be excessive resulting in severe iron deficiency anaemia. Many research studies have used the definition of blood loss in excess of 80 ml per period but since menstrual blood loss is rarely measured, this is not useful in day-to-day practice. Clinically, it is defined as blood loss that reduces the quality of life of a woman because of social and/or medical compromise (NICE 2007). HMB may also be associated with embarrassment and difficulties with leaving the house or getting to work because of the need to change sanitary towels frequently and the occurrence of flooding (Warner et al. 2004). It is reported that nearly one-third of the patients with fibroids suffer from HMB. This is significantly greater in women with fibroids than in those who have a normal uterus. In women with a normal uterus, over half of those who complain of HMB will have loss within the normal range (Chimbira et al. 1980). However, in the presence of fibroids, the proportion with very heavy loss is considerably increased.

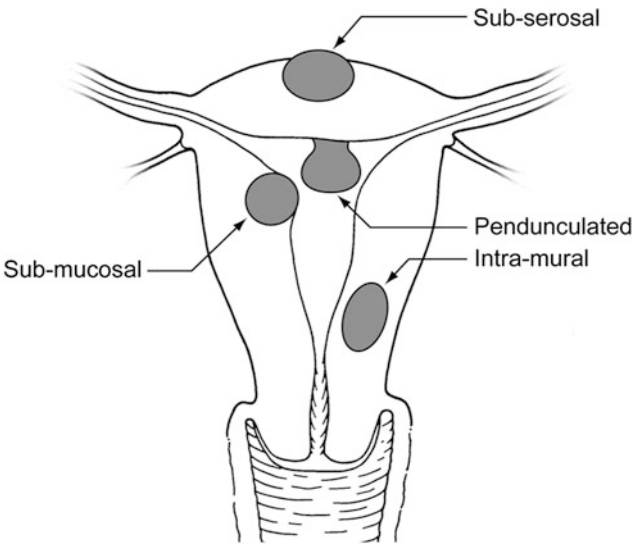


**Fig. 1** The position of fibroids in the uterus

### 2.1 Importance of Position

Fibroids can occur in different sites (Fig. 1). Sub-mucous fibroids that distort the cavity of the uterus are often assumed to be symptomatic, whereas those that are intramural or sub-serosal are considered less of a problem unless they cause symptoms related to their size or site. Fibroids can also occur outside the uterus to which they might be attached by a stalk (pedunculated, sub-serosal).

It is usually assumed that fibroids only impact on HMB if they are sub-mucous. However, this is an over simplification in that HMB has been reported in those with subserosal fibroids, although it is not known if this is causation or association (Sulaiman et al. 2004). Intra-cavity fibroids can also be associated with irregular bleeding since the surface blood vessels may be large and prone to bleed. These are more likely to cause intra-menstrual and irregular bleeding rather than HMB although the evidence for this is circumstantial.

Much of the data comes from 'before and after' studies of myomectomy that are difficult to interpret as the site and size may not be clearly defined. Recently, studies looking at the impact of some of the newer treatments such as MR guided high-intensity focused ultrasound that necessitate detailed imaging, suggest that submucosal fibroids do impact on menstrual blood loss. These techniques require absolute definition of the fibroids and allow the relationship

with the uterine cavity to be very clearly visualised. HMB has even been reported in the presence of subserosal fibroids, although it would appear that this is less common. The reasons why fibroids at different sites may cause HMB is unclear. It is quite possible that a fibroid within the myometrium might produce cytokines and vaso-active factors that will impact both on the blood supply to the uterus and also endometrial function.

### 2.2 Importance of Size

It appears that the size of fibroids does not impact on symptoms of HMB or sub fertility to any great extent. It is more the site and the relationship with the endometrium that is of importance. This may not be the case of an intra-cavity fibroid where the surface blood vessels may be large and might be prone to bleed. These are more likely to cause intra-menstrual and irregular bleeding rather than HMB.

### 2.3 Theoretical Explanation of HMB in Women with Fibroids

There is research data to support an association between heavy periods and uterine fibroids (Fraser et al. 1986). The mechanism by which uterine fibroids increase the blood loss during menstruation is still not fully understood and there are several possible explanations.

1. Disturbance in the ovarian hormones, it was thought that the number of anovulatory cycles increased leading to an excess of oestrogen. However, no difference in circulating concentrations of steroid hormone has been found between women with fibroids and women with out fibroids.
2. Increased size of uterine cavity leading to an increased surface area. Studies in dysfunctional uterine bleeding where fibroids are absent have failed to demonstrate any conclusive association.
3. High vascularity of the uterus associated with fibroids. The fibroids themselves are relatively avascular and only have immature blood vessels running through them. However, there are often very large vessels supplying the fibroid and these are found in the 'cavity' between the fibroid and the myometrium.
4. Venous pooling due to pressure from the fibroids. Compression of fibroids on the venous plexus of the adjacent tissues causes congestion to the myometrium and endometrium lead to abnormal uterine bleeding.
5. Abnormal uterine contractility in the presence of fibroids may lead to dysmenorrhoea (period pain).
6. The presence of a uterine factor.

It is well documented that there is a role for factors produced by the endometrium in HMB. The best studied of these are the prostaglandins but others such as endothelin and inflammatory mediators may also be involved (Downie et al. 1974; Maybin et al. 2011). Their role is much less clear than where heavy bleeding occurs in the absence of fibroids and it is also noted that medical treatment does not appear to be so effective in those with fibroids or other pathology.

Endometriosis and adenomyosis are often associated with fibroids especially those that are sub-mucous. Women with fibroids who have HMB should always be investigated to exclude other pathology.

Recent reports suggest that there is a relationship between development of fibroids and the dysregulation of several growth factors or their receptors, leading to vascular dysfunction and angiogenesis which contribute to abnormal vascular function or structure in the uterus, and subsequently to HMB (Munro 2011).

## 3 Role of Fibroids in Fertility

The place of fibroids in contributing in sub-fertility has been controversial for many years (Farquhar 2009; Latharby and Vollenhoven 2007). Many clinicians assume that if fibroids are present, they must be the cause of the problem but this is not necessarily the case as will be demonstrated in the next section. It is well-known that fibroids are extremely common in women of reproductive age, and therefore it is not surprising that many of those presenting with sub-fertility are found to have them within their uterus. On the other hand, many of those who achieve a pregnancy also have fibroids and do not experience any difficulty in becoming pregnant. It is difficult to be sure of the exact incidence of fibroids as the studies depend on the population involved and also the enthusiasm with which fibroids have been identified. The widespread use of ultrasonography has resulted in an increase in the diagnosis of uterine fibroids in those who are asymptomatic and have unexplained infertility

There is very little evidence that fibroids impair fertilisation itself. This might occur in the presence of an anatomical distortion of the tubal ostia or if fibroids produced factors that impaired the process although there is no evidence of this. Fibroids that impinge on the cavity could lead to abnormalities of endometrial function which would inhibit implantation or may alter uterine contractility, although the role in fertility is unknown.

Much of the evidence has been obtained by looking at the results of myomectomy. These are largely uncontrolled, and therefore make the drawing of conclusions very difficult. Some clarity has been introduced to the discussion by studying the role of fibroids on the results of assisted conception which gives a greater insight into their role in implantation and will be discussed in greater detail below.

## 4 Non-medical Treatment of Fibroids and Impact on Fertility

### 4.1 Myomectomy

It would appear that overall, the myometrium heals well after a myomectomy, although there is a fear that hysteroscopic myomectomy can lead to extensive damage and scarring in the uterine cavity. Removal of intramural or subserosal fibroids will often lead to some bleeding. If this is very heavy then hysterectomy may be required as a life saving procedure. However, even the smallest amount of bleeding can lead to adhesion formation, which could impair fertility in the future.

There are few data on the outcome of myomectomy beyond these already alluded to, so that the place is very uncertain and further research is undoubtedly required.

### 4.2 Uterine Artery Embolisation

The impact of uterine artery embolisation on fertility is extremely controversial, and thus there are many who believe that it should not be used in women wishing to conceive. However, as the above discussion has outlined, this is often because studies do not compare like with like since they have not been randomised. There have been successful pregnancies in women following uterine artery embolisation, but it would appear there might be an increased incidence of problems in pregnancy, although it is difficult to know whether the increase is due to the technique itself or the fact that the women has uterine fibroids. The role of embolisation increasing fertility is discussed elsewhere in this book and will not be further developed here.

## 5 Outcomes in the Studies of Infertility

When studying fertility, there are multiple outcomes reported in most papers. These start with what are called 'chemical pregnancy rates', which act as a surrogate for implantation since there is a rise in human chorionic gonadotrophin (the hormone used to diagnose pregnancy). This level may drop before the time of a missed period but can be used to confirm that 'pregnancy' did occur. The next parameter tends to be 'on going' pregnancy rate in relation to the gestation of the pregnancy which usually relates to miscarriage rates that are defined as first trimester (up to 12 completed weeks) and second trimester (from 13 completed to 28 weeks of pregnancy). Preterm labour occurs before 37 completed weeks and then term from 37 to 42. Live or 'take home' baby rate at term are obviously the most important outcomes for the women in question.

There have been three systematic reviews of the role of fibroids and reproductive outcomes (Klatsky et al. 2008; Pritts et al. 2009; Somigliana et al. 2007). In addition, a consensus statement was produced from a group in Australia that included that all these reviews and also additional studies, but did not generally alter any of the conclusions (Kroon et al. 2011). These investigated the importance of fibroid position as well as the different stages of pregnancy.

## 6 The Importance of Position

### 6.1 Submucous Fibroids

Data on implantation have been derived from the outcome of IVF and there are many small publications that have been reviewed and metaanalysed. These conclude that there is a decrease in implantation rate. This being the case, hysteroscopic resection of Sub-mucosal fibroids might be a logical treatment. This involves removing the fibroid through the cervix usually by resecting it with a diathermy loop. It avoids any abdominal incision. It would appear that after hysteroscopic myomectomy, patients should achieve pregnancy rates that are comparable with control groups without fibroids. However, implantation rates from 3 to 11.5 % ongoing pregnancy rate and an increased miscarriage rate between 22 and 47 % are quoted. Caution must be exercised with all these studies that comparison is made with infertile women of the same age without fibroids since age has a major impact of miscarriage rates.

### 6.2 Intra-Mural Fibroids

The role of intramural fibroids is extremely contentious (Sunkara et al. 2010). This is partly due to difficulties in diagnosis, since it can be difficult to determine if they impinge on the endometrium or not. It is probable that they have little impact unless they are in contact with it. Pritts summarises studies where there has been hysteroscopic examination of the uterine cavity and these confirm the importance of this characteristic. Also, more information will become available as more accurate imaging studies are undertaken. Consequently, there has been considerable debate as to whether intramural fibroids should be removed.

**Table 1** The incidence of late pregnancy complications

| Complication | No fibroids (%) | Fibroids (%) |
|---|---|---|
| Abnormal Lie e.g. breech | 8 | 13 |
| Pre-term, premature, rupture of membranes and preterm labour | 13 | 19 |
| Risk of lower segment caesarian section | 21 | 49 |
| Post partum haemorrhage | 3 | 8 |

Adapted from Manyonda et al. 2004

### 6.3 Sub-Serous Fibroids

There is general consensus that sub-serous fibroids do not impair fertility and should not be removed unless they are of sufficient size to cause other symptoms for this reason.

## 7 Miscarriage

There are several old reviews concentrating on the impact of myomectomy on miscarriage concluding that it may decrease the symptom by about a half (Buttram and Reiter 1981) However, although this paper set the scene for the debate that has gone on since, as has already been discussed, small fibroids might have been missed because of the lack of good imaging. In addition, women who conceive with fibroids are often older and so not only should comparison be made with infertile women without fibroids, but also those whose age is late 30s or early 40s. However, in spite of these concerns, current opinion is that it is very probable that sub-mucosal fibroids do impact on miscarriage rates.

## 8 Impact of Fibroids on Later Pregnancy

Fibroid size, location and relation to the site of implantation of the placenta are of importance (Ahmed and Ash 2011). Sub-serosal and intra-mural fibroids probably impact on the pregnancy itself less than sub-mucosal fibroids, but they can make caesarian section much more difficult. Fibroids that distort the cavity can cause complications (Ortiz et al. 2011; Zaima and Ash 2011).

### 8.1 Symptoms and Complications in Pregnancy

1. Fibroids are usually asymptomatic in pregnancy.
2. Pain is the commonest symptomatic presentation and up to 15 % women may require admission to hospital (Ouyand et al. 2006). The risk tends to increase with size. It may occur due to torsion of the fibroid or 'red degeneration' where the fibroids infarct, because they have suffered an impairment of their blood supply.
3. Pressure symptoms may occur particularly on the bladder with increased frequency of micturition. Urinary retention can occur but is rare. Constipation, which is present in a vast majority of pregnancies, is not made worse by uterine fibroids that impact little on bowel function.
4. Complications of labour and delivery are outlined in Table 1. Fibroids may interfere with rhythmical contractions, and thus lead to a less effective labour and also increase the likelihood of a post-partum haemorrhage. However, dysfunctional labour is not a uniform finding and many women achieve delivery without any difficulty. Several investigators have reported obstetric outcomes with positive associations with increased caesarean section rates in particular, as well as malpresentation and post-partum haemorrhage (Ouyand et al. 2006; Zaima and Ash 2011). Unfortunately, none of these have the power to evaluate uncommon outcomes and the risk of ascertainment bias of some positive studies prohibits more definite conclusions.

Caesarian section is more often performed in the presence of large fibroids and the number seems to be of little importance.

### 8.2 Diagnosis in Pregnancy

Asymptomatic fibroids may be identified on a routine ultrasound scan since these are normally performed in early pregnancy. They can be followed during the pregnancy in the same way and rarely grow significantly.

### 8.3 Treatment

Fibroids rarely require treatment in pregnancy. Very occasionally, a myomectomy will be performed if there is a torsion; for example, if not symptoms are treated with analgesics as required. Myomectomy is rarely performed at the time of caesarian section as the blood supply to the uterus is significantly increased and this would make the operation extremely hazardous.

## 9 Presentation Due to Size

Fibroids can grow to a very large size and may reach a diameter of 20 or 30 cm. Obviously, this takes up a lot of space within the abdominal cavity and may cause symptoms alone because of size. A slim woman may appear to be pregnant and if she is indeed wishing for fertility, this is a very distressing symptom. Also fibroids can be uncomfortable and impair mobility. Fibroids will change in size during the menstrual cycle which is quite likely to be due to alterations in blood supply and lead to an increase in size pre-menstrually. This may also be accompanied by a feeling of bloating even in women who do not have particularly large fibroids.

Large Fibroids and those in particular position within the uterus may compress the ureters leading to hydronephrosis and potentially to renal damage in the long term, although the latter is very uncommon. Anterior fibroids regardless of size may lead to urine frequency simply due to irritation of the bladder.

Unusual presentations may occur. Some occasions when the size of the uterus changes suddenly; for example when the uterus is treated with GRNH agonist, then impaction in the pelvic brim and urinary retention has been reported.

## 10 Conclusion

Fibroids are extremely common and occur in many women who attend gynaecological out patients. Most will present with menstrual disorders but in some this may be associated with sub-fertility. In the latter group, the fibroids may also be asymptomatic. Myomectomy may be performed to improve fertility and on occasions to help HMB but due to the complexity and skill set required to do this operation, it is far less common than hysterectomy which is the treatment of choice even now with some gynaecologists even though it means an end to fertility.

Alternative treatments, such as UAE, have been developed but have yet to achieve general acceptance. Menstrual problems can be treated medically but this does not lead to a cure and often the best treatments for HMB result in amenorrhoea and anovulation, again not appropriate for those wishing to achieve a pregnancy.

Symptoms are affected by site and size in particular and large studies are needed to determine the cause of the symptoms as well as the best way of relieving them.

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# Gynecological Assessment Prior to Uterine Artery Embolization

Linda D. Bradley

## Contents




**Abstract**

Benign uterine fibroids, or leiomyomas, are the most common benign tumors found in women in a gynecologic practice. Approximately 50–80 % of women have fibroids. Most women with fibroids are asymptomatic. Women with symptomatic fibroids may present with heavy menstrual bleeding, pelvic pain, leukorrhea, pressure and bloating, increased abdominal girth, and severe dysmenorrhea. However, these symptoms can mimic other gynecologic and non-gynecologic conditions. It is imperative that physicians take an excellent history and perform a thorough pelvic examination prior to recommending uterine fibroid embolization for therapy. The patient's desire for future pregnancy should be ascertained. As a part of the evaluation it is important that the patient does not have other indications for surgical intervention such as the presence of an adnexal mass, abnormal pap test, or endometrial malignancy/endometrial hyperplasia that would be treated with surgical intervention or other necessary therapy. Hysterectomy has long been utilized as a definitive method to treat fibroids in women. Medical therapy often requires long term use of single or multiple medical therapies to alleviate fibroid-related symptoms. Uterine fibroid embolization (UFE) using particulate emboli to occlude the uterine arteries, thereby disrupting the blood supply to fibroids and leading to devascularization and infarction, has been reported to be effective in alleviating fibroid-related symptoms. Excellent gynecological assessment is essential prior to referring a patient for uterine fibroid embolization.



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## 1 Introduction

Uterine leiomyomata are the most common neoplasm found in gynecologic practice. According to the American College of Obstetrics and Gynecology (ACOG), fibroids occur in

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approximately 25–80 % of all women, most commonly in those ages 30–40 years, and affect African American women in higher numbers than their Caucasian counterparts. (ACOG 2008) Fibroids are commonly the underlying cause of such symptoms as heavy menstrual periods, pelvic pain, pressure, and bloating, increased abdominal girth and severe dysmenorrhea; other associated complaints may include dyspareunia, leukorrhea, reduced fertility, miscarriage, acute or intermittent urinary retention, and/or constipation. Given the characteristics and severity of such symptoms, leiomyomas are likely to have a detrimental effect on quality of life.

Surgery has been the traditional treatment for fibroids. Myomectomy, surgical removal of leiomyomata without hysterectomy, is an option for women who wish to retain their uteri. Current surgical approaches for myomectomy include abdominal, laparoscopic, or robotic. The size, number, and location of the fibroid, as well as surgeons' skill set, determine the route of the procedure. Surgical approaches may be associated with bleeding, postoperative fever, delayed intra-abdominal adhesions, infertility, or uterine dehiscence during pregnancy or labor. Rarely, intraprocedural bleeding may occur during a myomectomy procedure, resulting in emergency hysterectomy. Additionally, myomectomy is associated with fibroid recurrence and further surgery in 23–51 % of patients evaluated via ultrasound during a follow-up period of up to 5 years (Rossetti et al. 2001; Fauconnier et al. 2000). Given these disadvantages, myomectomy is performed less often than hysterectomy, which has been considered the definitive treatment for fibroids, as there is no possibility of post procedure recurrence.

More than 600,000 hysterectomies are performed in the United States each year, with uterine leiomyomata as the leading cause. Because it is classified as major surgery, hysterectomy for benign disorders has a number of drawbacks, not the least of which is an overall complication rate of 17–23 % regardless of approach—abdominal, transvaginal, or laparoscopic (Mäkinen et al. 2001).

Hysterectomy is not appropriate for women who wish to retain their fertility; moreover, it has significant negative impact on psychosexual health compared with less invasive procedures, even in those who have no plans for future childbearing (McPherson et al. 2005).

Hysterectomy is more expensive than UFE. The Vaginal, Abdominal, Laparoscopic Uterine Excision (VALUE) study, undertaken to assess the rates of serious complications associated with hysterectomy in more than 37,000 women in the United Kingdom, found that individuals with symptomatic fibroids experience more intraoperative and postoperative complications than women with dysfunctional uterine bleeding (McPherson et al. 2004).

Trial researchers also observed that younger women are at most risk for experiencing severe complications with hysterectomy and recommended a less invasive alternative treatment for symptomatic fibroids in this patient group (Goldberg 2007).

UFE, also known as uterine artery embolization, or UAE, has emerged as an excellent option which is nonsurgical, minimally invasive therapy that, with accruing clinical experience, is gaining widespread acceptance in North America and in Europe as a safe and effective treatment for reducing the symptoms of uterine leiomyomata. Uterine artery embolization has a high patient satisfaction rate similar to hysterectomy and myomectomy, with quicker return to work, shorter hospital stay, and return to normal activities (Gupta et al. 2012). An estimated 250,000 UFEs have been performed since 1995, when this procedure was first utilized by Ravina and colleagues (Ravina et al. 1995).

UFE involves the injection of particles, typically sized 500–900 μm, into the uterine arteries to cause occlusion, thereby disrupting the blood supply to fibroids and leading to devascularization and infarction. The result is improvement in fibroid-associated symptoms, preservation of the uterus, avoidance of general anesthesia, and obviation of the potential complications and lengthy recovery associated with surgery.

Two multicenter studies with combined cohorts totaling more than 2,200 patients recently reported long-term follow-up data for UFE-treated symptomatic leiomyomas (Goodwin et al. 2008; Spies et al. 2007). Both support the conclusion that UFE is effective and safe, with durable symptom control, few complications, and improved health-related quality of life (HRQOL).

## 2 Selecting Patients Most Likely to Benefit

The Task Force on Uterine Artery Embolization and the Standards Division of the Society of Interventional Radiology (SIR) recommend that UFE be offered only to women with symptomatic uterine leiomyomas who are of reproductive age but who are not interested in childbearing (Andrews et al. 2004). In this patient subpopulation, UFE is indicated for individuals with clinically documented fibroids and fibroid-related symptoms who wish to avoid surgery, particularly hysterectomy, who refuse blood transfusion for health or religious reasons; and/or who have failed medical or surgical therapy. Contraindication to general anesthesia may be another consideration.

Of the numerous treatment options available, patient selection for UFE is generally based on such factors as bulk symptoms, bleeding symptoms, and desire for future fertility

or uterine preservation A patient's ultimate choice among available fibroid therapies may depend upon the fibroid-related impact on her HRQoL, the length of convalescence that is acceptable to her, and the importance she assigns to tolerable invasiveness and symptom resolution (Manyonda et al. 2012).

## 2.1 Pre-Procedure Evaluation

A cooperative relationship between the obstetrician/gynecologist (OB/Gyn) and interventional radiologist (IR) is essential for effective diagnosis, treatment, and follow-up of patients who are potential candidates for UFE, and the combined efforts of these specialists contribute to the establishment of optimal clinical guidelines for patient care (Usadi et al. 2007). Collaboration begins with the screening and selection of patients, as both specialists must contribute their skills when choosing appropriate candidates.

Preoperative consultation with an OB/Gyn is necessary to confirm the diagnosis of fibroids, to ensure a patient's overall gynecologic health, exclude preexisting infection, and to exclude other conditions that mimic fibroid symptoms or that may require surgical intervention. The presence of atypical symptoms or an unusual pattern of bleeding may necessitate additional gynecologic assessment to exclude endometriosis, pelvic adhesive disease, or diffuse adenomyosis.

Additionally, collaboration with an Ob/Gyn who has hysteroscopic expertise is essential to manage post UAE leukorrhea, prolapsing leiomyomas, or intracavitary leiomyomas weeks to years after the procedure. A hysteroscopist can treat intracavitary leiomyomas hysteroscopically and avoid hysterectomy in women who may present with extrusion of leiomyomas into the uterine cavity (AAGL 2012).

## 2.2 Diagnostic Imaging

For patients who are interested in UFE, pelvic magnetic resonance imaging (MRI) with and without intravenous gadolinium contrast is the diagnostic method of choice (Cura et al. 2006). Fibroid size, number, and location are critical in determining a patient's candidacy for UFE; MRI depicts these variables, which are predictors of the success and safety of the procedure, more accurately than ultrasound, has less intraobserver variability, and identifies those patients who will benefit most. Additionally, after the procedure, post-UFE contrast-enhanced MRI, reliability detects fibroid viability and tissue perfusion (enhancement) which is predictive of procedure success or failure.

Although the majority of leiomyomas can be treated with UFE, exceptions include exophytic subserosal fibroids with a stalk of <2 cm or submucosal intracavitary pedunculated fibroids that may detach and lodge in the uterine cavity or abdominal cavity after embolization and, single dominant, fibroids larger than 10 cm may be associated with greater failure rates (Cura et al. 2006). Fibroids that are pedunculated and on a narrow dangling stalk of <3 cm may be at risk of detachment if treated with UFE. They can then become free floating masses in the abdomen and increase risk for adhesions or bowel obstruction. Fibroids that are broad-based do not possess this risk. MRI imaging helps to identify patients with a narrow pedunculated who should be excluded from this procedure. Exophytic fibroids with a stalk are better treated with myomectomy to avoid torsion, degeneration, and prevention of the leiomyoma from becoming a free floating intra-abdominal mass. Intracavitary, type 0 fibroids that are exclusively limited to the intracavitary portion of the uterus can usually be treated hysteroscopically.

Assessing the morphology of these relative contraindications to UFE is more practicable with the use of MRI. MRI is also efficient in detecting the presence of possible co-existing pathologic and anatomic factors, such as adenomyosis, prior tubo-ovarian pathology, or large fundal leiomyomas with aberrant ovarian or collateral blood supply that would predispose patients to treatment failure with UFE (Cura et al. 2006). In fact, reported data have shown that the initial diagnosis and subsequent treatment plan for 18 % of cases being evaluated for UFE were changed following MRI (Cura et al. 2006).

## 2.3 Presurgical Evaluation with MRI

MRI of the pelvis reliably characterizes soft tissue masses as well as size, and location of uterine leiomyoma. MRI differentiates leiomyomas from other pelvic masses. Less intraobserver variability exists between MRI compared to ultrasound. MRI of the pelvis, compared to transvaginal ultrasound is very sensitive in detecting adenomyosis, location, size, and number of uterine fibroids. Also it is particularly helpful in identification of fibroids that are pedunculated or connected to the uterine serosa by a stalk. Particularly, for patients seeking minimally invasive surgical procedures such as laparoscopic myomectomy or UFE, the number of suspected fibroids is important in recommending a particular therapeutic intervention, predicting outcome, and determining success of surgery. When inclusion criteria are met for laparoscopic myomectomy (4 fibroids <8 cm, size <16 weeks) or leiomyomas which enhance on MRI and are therefore particularly suitable for

UFE, increased success rates are the norm. MRI should be considered complementary to abdominal ultrasound or TVUS when results are equivocal.

## 2.4 Presurgical Evaluation of the Patient for Uterine Fibroid Embolization

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Especially for patients who desire UFE, MRI facilitates the triage of patients who will most likely benefit from this excellent alternative to hysterectomy. Many academic centers require MRI of the pelvis with and without contrast as an integral component of the work-up of patients desirous of UFE. During the consultation of women who are potential candidates for UFE, it is vital to determine if the leiomyoma(s) contribute to symptoms, determine the anatomic position, size, location, presence of degeneration, presence of a stalk, and vascularity. Additionally, pelvic masses mimicking fibroid symptoms such as adenomyosis can be reliably excluded. All of these factors may contribute the outcome, success, failures, or complications of UFE. Additionally, similar information helps detect the ease of performing laparoscopic, robotic, vaginal, or abdominal hysterectomy.

A frequent fibroid-related symptom includes abnormal uterine bleeding which can be regular, irregular, prolonged, or infrequent. Evaluation of uterine health is important when women present with irregular menstruation or anovulatory cycles. Endometrial assessment with and office endometrial biopsy reliably excludes global endometrial pathology such as endometrial hyperplasia and endometrial malignancy. Endometrial biopsy should be considered in women greater than age 45 years with irregular, prolonged, or anovulatory bleeding patterns.

Office hysteroscopy or saline infusion sonography (SIS) can also be used to evaluate the endometrium for polyps or intracavitary pathology. In general, however, MRI of the pelvis with and without contrast is currently recommended, when equivocal hysteroscopy or SIS can be helpful.

Patients should also have a normal pap test prior to having a UAE. Patients with abnormalities in their pap test should be evaluated and treated prior to referral for UFE.

Cultures for sexually transmitted diseases such as gonorrhea or Chlamydia should be obtained on a case by case basis.

## 2.5 MRI Reliably Predicts UFE Outcome

Increasingly, UFE is advised for the treatment of symptomatic uterine fibroids. Many institutions utilize MRI of the pelvis to determine if the patient is a suitable candidate for UFE. Unlike CT scans which evaluates only a single tissue parameter—X-ray attenuation, MRI does not utilize ionizing radiation and has excellent soft tissue resolution. When scheduling patients for MRI of the pelvis, contrast is usually requested. As uterine size increases, abdominal ultrasound is less reliable in detecting differences between enlarged uterus and adnexal masses. The disparity increases as uterine size increases when ultrasonography is solely used. Excellent capacity to differentiate between tissue types, adnexal masses, and size is particularly the characteristic of MRI imaging.

## 2.6 MRI Technical Findings in UAE Failures: Repeat Procedures, the Importance of Re-imaging With MRI

Many studies have published the benefits and effectiveness of uterine artery embolization in improving bulk symptoms, menorrhagia, pain, and other symptoms associated with UAE (Spies et al. 2005). Although most patients improve, not all patients respond equally as well or have recurrent symptoms. Collective review of the literature demonstrates 20 % repeat intervention within 5 years of UAE. Intervention strategies include: repeat embolization, hysterectomy, or myomectomy. The etiology of these failures is uncertain and little studied, however MR imaging can triage patients and help determine if a repeat uterine artery embolization would be beneficial in cases of failure. Yousefi et al. reviewed factors predisposing to recurrence after treatment of UAE among 25 patients. These patients had recurrent pressure and/or bulk symptoms (n = 15), recurrent heavy bleeding (n = 12), and pelvic pain or cramping (n = 7). Findings included: new fibroid growth, incomplete infarction of tumors after the first embolization, and 9/25 (37 %) required ovarian artery embolization to occlude aberrant ovarian supply to the uterus. Follow-up was available for 21 patients, of whom 19 (90 %) had symptom control. MRI imaging in most cases of repeat embolization demonstrated that nearly 50 % of the fibroid was infarcted, but that even minor residual viable tumor could result in recurrent symptoms. In nearly all cases of incomplete infarction, MR imaging demonstrated an increase in the extent of viable tissue in incompletely treated tumors between the two embolization procedures (Yousefi et al. 2006). Pelage et al. demonstrated symptom recurrence when perfusion of the tumor was still present, regardless of the decline in the size of the fibroid (Pelage et al. 2004). Marret et al. described recurrence rates among 81 patients treated with the possible etiologies of failure including: increasing dominant fibroid size, increasing number of uterine fibroids, pedunculated serosal fibroids, possible adenomyosis, and in one case endometrial cancer. Recurrence rate was 17.2 % by 30 months. A larger study of 233 patients demonstrated,

repeat intervention in 9.4 % of patients, with a mean follow-up of 30 months (range, 34 days–36 months). The causes of failure were not described.

When a patient presents with recurrent symptoms or failure of an initial UFE, repeat pelvic MRI with and without contrast of the pelvis is necessary, if the patient inquires about the feasibility of a repeat UFE procedure. Information collected including size, number, location of fibroids, presence of pedunculated serosal leiomyomas, adenomyosis, and collateral blood flow from ovarian vessels will help determine whether a repeat embolization is likely to be successful.

The technical aspects of embolization will need to be clarified in the future. Additionally, an MRI classification system that is standardized would be helpful in comparing future studies and potentially able to identify subgroups of patients prone to success, failure, or recurrence. Tumor perfusion studies are just in its adolescence and its importance may not be fully understood (Spies et al. 2004).

## 3 Summary

Uterine fibroid embolization (UFE) is an established option for the treatment of symptomatic premenopausal women with uterine fibroids. UFE is an effective and safe alternative to traditional surgical intervention in the appropriate patient. Careful triage of patients is important to determine successful outcome and exclude patients who would not benefit or have contraindications to therapy. The patient's symptoms should correlate with expected clinical outcomes well established for UFE. Assessment with MRI imaging, endometrial biopsy, and pap is important before proceeding with a uterine sparing option. Excellent collaboration between gynecologists and interventional radiologists will improve the outcome of the patient.

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# Imaging Fibroids Pre and Post Uterine Artery Embolisation

Audrey E. T. Jacques

## Contents




**Abstract**

Fibroids are common in women of reproductive age and non-surgical management with uterine artery embolisation for symptomatic patients is increasingly performed. In this chapter, the role of diagnostic radiology, in particular MRI, in the diagnosis, mapping and assessment of fibroid disease prior to embolisation is discussed. While ultrasound is readily available, MRI has been shown to be more accurate at characterising fibroids and defining their number and location. In particular fibroid vascularity prior to embolisation is well demonstrated with Gadolinium-enhanced MRI. Contraindications to embolisation such as pedunculated fibroids on a narrow stalk or non-vascular, degenerated fibroids are also readily identified with MRI. Following embolisation, early change in fibroid vascularity can be demonstrated which has a prognostic implication to long-term response. Post-embolisation appearances such as intrafibroid gas, infection and fibroid passage are also discussed and demonstrated. Given that uterine artery embolisation is increasingly being performed, diagnostic radiologists therefore need to be familiar with pre-treatment diagnosis and assessment and typical post-embolisation appearances.


## 1 Introduction

Fibroids are common in women of reproductive age, increasing in prevalence up to the fifth and sixth decades. They may often be asymptomatic but for patients who suffer distressing or unmanageable symptoms of pain, menorrhagia, dysmenorrhoea or irregular menstrual bleeding, treatment options including uterine artery embolisation (UAE) may be considered. UAE is an accepted alternative to surgical or medical management and is routinely performed in many institutions. Diagnostic radiologists are therefore being increasingly involved in the pre- and post-treatment

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assessment and follow up of these patients. Prior to treatment, imaging is used to diagnose, localise and define volume size of fibroids and to identify any relative contra-indications for embolisation, in particular, endometriosis, pelvic malignancy and pedunculated fibroids. Given that the symptoms of fibroid disease are relatively non-specific, other gynaecological conditions such as, adenomyosis, endometriosis and endometrial polyps need to be excluded. Following embolisation, imaging is used to monitor response and identify possible complications of the procedure.

Ultrasound (US), and increasingly magnetic resonance imaging (MRI) are the two most accurate modalities utilised for the assessment of fibroids. Given that it is readily available, of relatively low cost and well tolerated, ultrasound is the initial imaging modality of choice for women presenting with gynaecological symptoms. Transvaginal ultrasound (TVUS) has improved visualisation of pelvic organs compared with transabdominal ultrasound, particularly in obese patients or when a large amount of overlying bowel gas is present. However, US is operator dependent and diagnoses are made in 'real time'. The referring clinician is dependent on the written scan report, which if performed as an initial screening test, may not always define the fibroids in detail required prior to UAE. It may therefore be necessary to repeat the US or perform an MRI for specific fibroid mapping prior to embolisation. MRI has been shown to be more accurate at characterising fibroids, in particular for defining fibroid number and location (Spielmann et al. 2006; Rajan et al. 2011). In addition, early studies showed MRI prior to UAE lead to a significant change in management in up to 22 % of patients (Omary et al. 2002; Spielmann et al. 2006; Rajan et al. 2011).

Computed tomography (CT) has limited tissue contrast resolution in the pelvis and fibroids are not visualised discretely, unless calcified. CT therefore has no routine role in the assessment of uterine fibroids although may be used in the acute setting in the investigation of potential post-treatment complications. Given its wider body coverage, contrast-enhanced CT imaging of the thorax, upper abdomen and large vessels can be useful when malignancy is suspect or if a diagnosis of disseminated peritoneal, intravascular or benign metastasising leiomyomatosis is considered.

## 2 Pre-embolisation Imaging

### 2.1 Fibroid Appearances

Fibroids are seen as well-defined masses with both US and MRI with or without associated uterine enlargement, contour abnormality and endometrial compression or distortion. Sonographically, they are heterogeneous in echotexture and typically hypoechoic compared with surrounding myometrium (although can be iso or hyperechoic to myometrium). They transmit sound waves relatively poorly, resulting in areas of posterior acoustic shadowing which may obscure deeper structures. Areas of calcification further increase overall heterogeneity and posterior shadowing (Fig. 1). Doppler ultrasound assessment of fibroid vascularity does not aid the diagnosis and is not routinely performed.

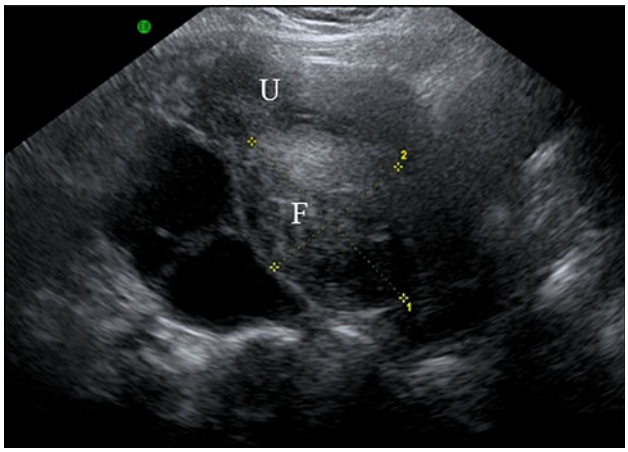


**Fig. 1** Transvaginal ultrasound scan (TVUS) showing a transverse view through the uterus (U). There is a large, well marginated subserosal fibroid (F) posteriorly which is heterogeneous and hyperechoic to surrounding myometrium

At MRI, fibroids are well defined and of markedly low T1 and T2 signal intensity. Given its improved soft tissue resolution, fibroids are best defined using T2 weighted sequences (Fig. 2). Areas of cystic degeneration are seen as fluid signal intensity, low on T1 and high on T2 weighted sequences. Areas of high T1 signal intensity due to the T1 shortening effect of methaemoglobin indicate haemorrhagic degeneration (Fig. 3).

Fibroid vascularity can be accurately assessed using contrast enhanced MRI. This involves the use of fast dynamic scanning before and at least 3 time points after the intravenous administration of Gadolinium. Three-dimensional volumetric sequences with fat suppression are used and obtained in either a coronal or sagittal plane Fibroids typically enhance avidly, usually iso or hyperintense to surrounding myometrium (Fig. 2). Degeneration within fibroids is visualised as complete or heterogeneous areas of non-enhancement (Figs. 3, 4). Patients with a significant volume of non-vascular fibroids are clearly unsuitable for UAE.

### 2.2 Fibroid Mapping

In order to measure post-embolisation response, it is important to accurately assess the volume and location of dominant fibroids prior to treatment. Volume measurements

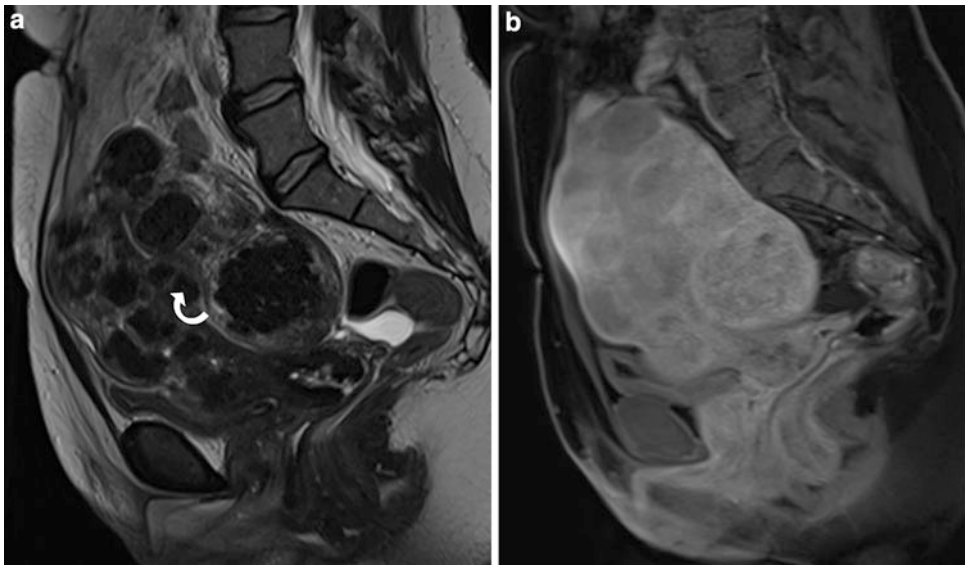


**Fig. 2** MRI **a** T2 sagittal and **b** T1 fat saturated (T1FS) following contrast medium administration showing enlarged uterus with multiple fibroids. Note the submucosal fibroids indenting the endometrium (*curved arrow*). Although small these are often the cause of menorrhagia. Following contrast medium administration all of the fibroids enhance avidly, similar to the surrounding myometrium

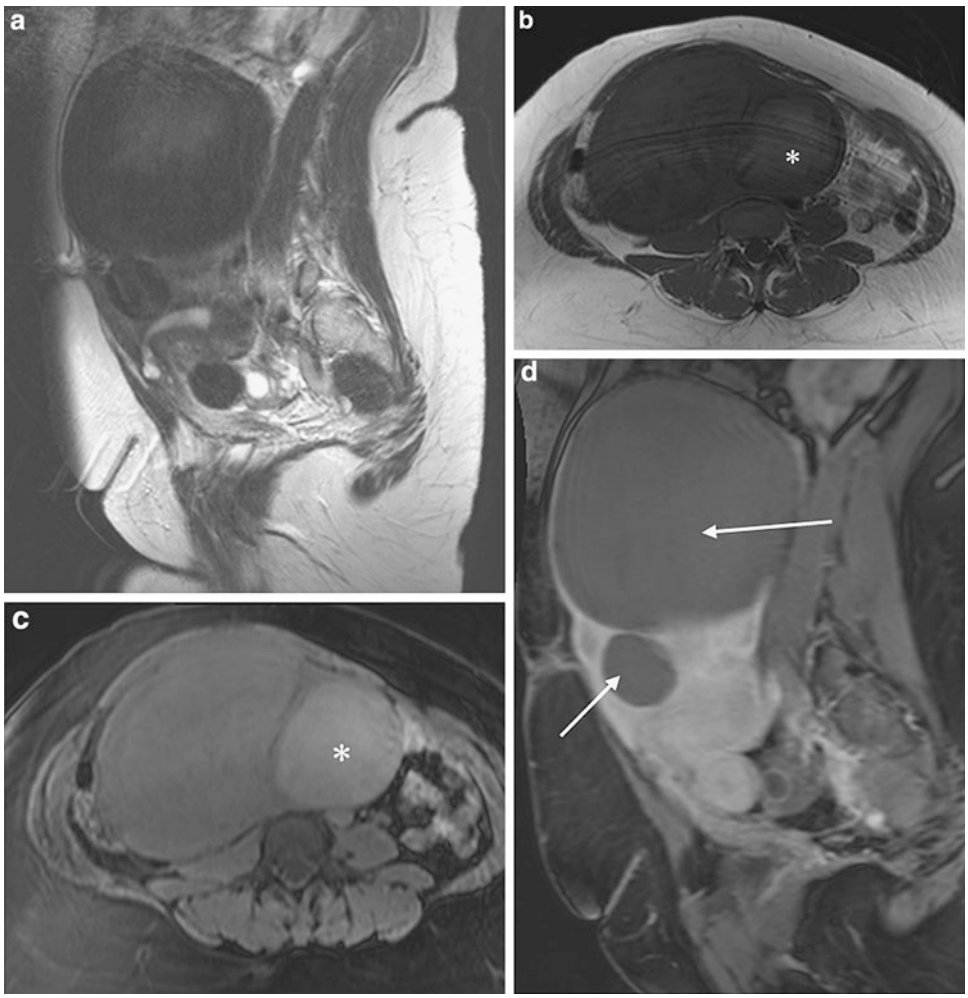


**Fig. 3** MRI in a patient referred for assessment for UAE. **a** T2 sagittal, **b** T1 axial, **c** T1 axial with fat saturation (T1FS) before and **d** after contrast medium administration. Images show well marginated intramural and subserosal fibroids which are low signal intensity on T2 and T1 images. There is T1 hyperintensity in at least one of the fibroids in keeping with haemorrhagic degeneration (*). Following contrast medium administration the dominant fibroids do not enhance at all (*arrows*) and this patient was therefore unsuitable for treatment with UAE

of the dominant fibroids can be readily made with both US and MRI. However, for the purpose of post-embolisation assessment, MRI provides more standardised and easily comparable images for follow up. Fibroid location as well as volume should be correlated with patient's symptoms. For example, submucosal fibroids, even when small, are

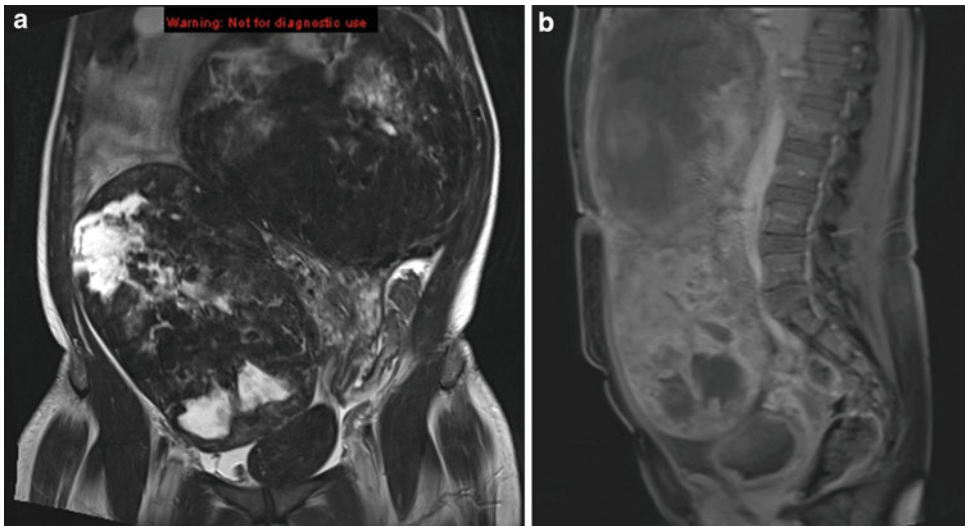


**Fig. 4** MRI **a** T2 coronal and **b** sagittal T1FS after contrast administration in a patient with large, broad-based pedunculated fibroids. There are prominent areas cystic degeneration which are of high T2 signal intensity and contrast enhancement is patchy

typically responsible for abnormal uterine bleeding (Buttram and Reiter 1981; Spies et al. 2002a), whereas large intramural or subserosal fibroids are typically responsible for pressure symptoms (Fig. 4).

Pedunculated subserosal fibroids, defined as those having a stalk diameter 50 % narrower than the fibroid diameter (Goodwin et al. 2001) have long been recognised as a relative contraindication to UAE (Fig. 5). Primarily there is potential risk of the stalk undergoing infarction causing either fibroid torsion or detachment and potential peritonitis. This risk however is rare. More commonly however, pedunculated fibroids, which may have a dual blood supply parasitised from adjacent organs, have been shown to respond less well to UAE and be a cause of treatment failure (Katsumori et al. 2005; Toor et al. 2008). It is important therefore for radiologists to identify pedunculated subserosal fibroids in the context of the other fibroids present and patient's symptoms. If there are widespread fibroids in all locations, the patient may still benefit from UAE. Conversely, a patient with mainly pressure symptoms and a dominant pedunculated subserosal fibroid might be best treated with myomectomy. Pedunculated subserosal fibroids, particularly in a large uterus can be significantly under reported with US. If transvaginal US alone is performed, subserosal fibroids located outside of the pelvis will not be visualised. MRI however, provides a large imaging field of view in multiple planes and thus, pedunculated subserosal fibroids and their stalks can be accurately identified (Fig. 5).

Fibroid location may also provide prognostic information regarding potential complications or side effects of embolisation. Submucosal fibroids or intramural fibroids with a submucosal component are at risk of becoming endocavitary and sloughing off, reported in up to 3 % of dominant submucosal fibroids in one study (Verma et al. 2008). In particular, fibroids which have a higher ratio between their endometrial interface and longest dimension are more at risk of becoming endocavitary (Fig. 6). Fibroid passage, although a consequence rather than true complication of the procedure, can be accompanied by pain and infection which may require hospital admission for treatment. It can therefore be useful to identify these potential higher risk patients prior to embolisation.

## 2.3 Making the Diagnosis

Fibroids are a common cause of menorrhagia but may also present with dysmenorrhoea, irregular uterine bleeding or pelvic pain. Given that fibroids are common and their symptoms non-specific it is important to consider alternative or concurrent pathologies prior to embarking on treatment.

### 2.3.1 Adenomyosis

Adenomyosis is defined as the presence of heterotopic endometrial glandular and stromal tissue within the myometrium with surrounding smooth muscle hypertrophy and hyperplasia. It can result in uterine enlargement and abnormal uterine bleeding and be clinically, demographically and sonographically indistinguishable from fibroid disease, with which it may co-exist. Differentiation between the two conditions however can be achieved with almost 100 % accuracy with MRI (Togashi et al. 1989; Ascher et al. 1994). With T2 weighted MRI, adenomyosis is visualised as either focal or diffuse widening of the innermost layer of myometrium (the junctional zone). This low signal intensity interface between the endometrium and deep myometrium is normally symmetrical in appearance and less than 8 mm in thickness (Fig. 7). Greater than 12 mm is highly suggestive of adenomyosis. In many cases quite marked areas of ill-defined low signal intensity within the

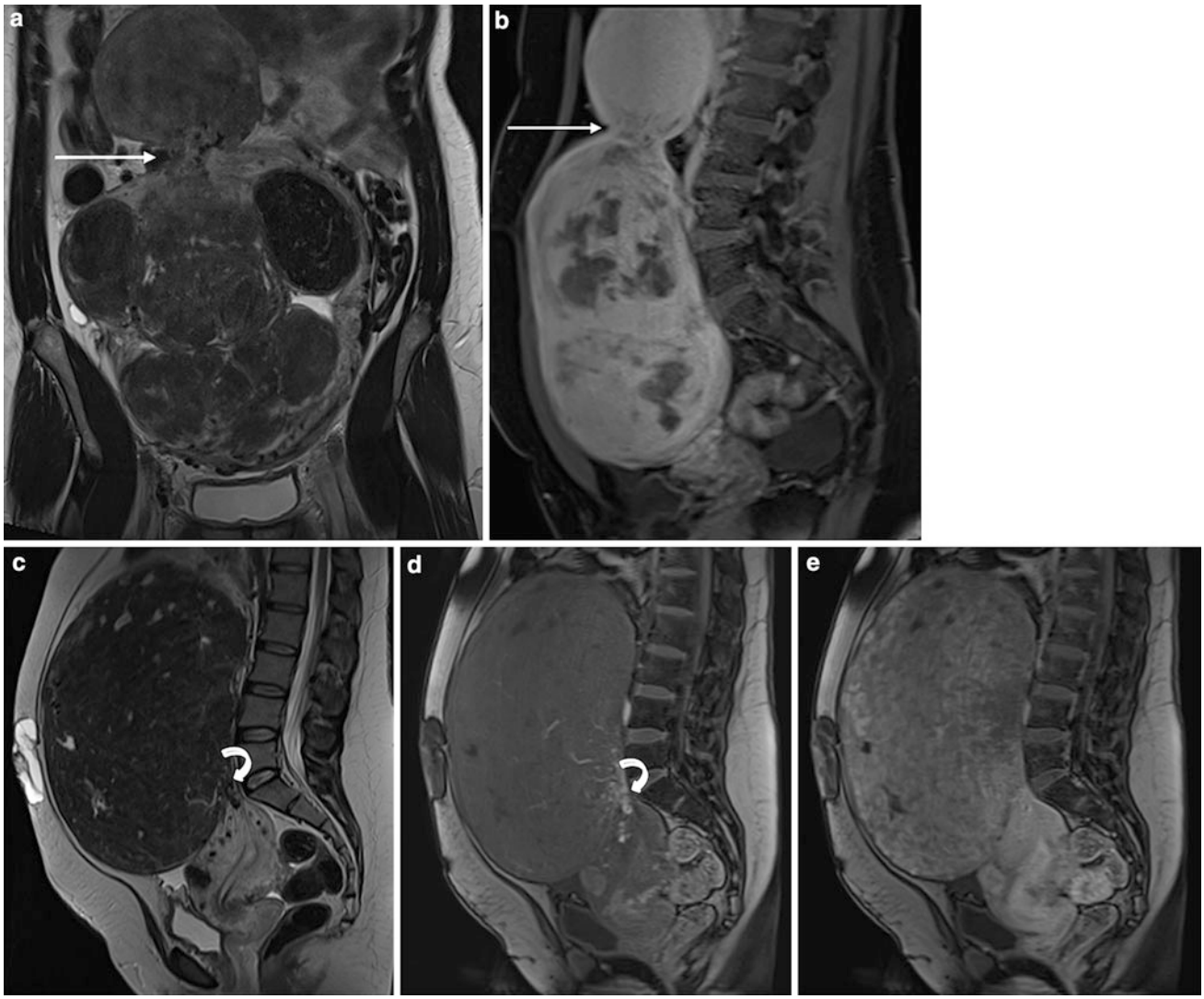


**Fig. 5** **a** Coronal T2 and **b** Sagittal T1FS contrast-enhanced MRI in a patient with multiple fibroids. There is a dominant pedunculated fibroid on a narrow stalk (*arrow*) arising from the uterine fundus which is markedly vascular. Despite this, the patient was referred for UAE given the presence of multiple other fibroids and a combination of bleeding and pressure symptoms. **c** T2 sagittal MRI in a different patient with a large, almost solitary pedunculated fibroid. There is a very narrow (1 cm) vascular pedicle (*curved arrow*) which is well demonstrated on the early arterial post-contrast MRI (**d**) and the fibroid enhances avidly (**e**). Myomectomy might be considered a more favourable treatment option for this patient given the lack of other fibroids and predominance of pressure symptoms

myometrium can be seen. In contrast to fibroids, the areas are less well demarcated and are in contact with the endometrial interface. Foci of T2 high signal intensity in keeping with dilated endometrial glandular tissue is frequently present. Less commonly, T1 hyperintense foci corresponding to areas of haemorrhage may also be seen.

Adenomyosis was previously thought of as a cause of failed UAE for fibroids. However, following UAE, reduction in junctional zone thickness and corresponding improvement in patients' symptoms occurs, at least in the short term. More recent evidence suggests that UAE can also be an effective long-term treatment for adenomyosis in a proportion of patients (Kim et al. 2007). Therefore now in most institutions, where fibroids and adenomyosis co-exist, UAE is still considered.

### 2.3.2 Endometriosis

Endometriosis, defined as the presence of ectopic endometrial tissue outside of the uterus, commonly manifests as symptoms of pelvic pain, dysmenorrhoea and bloating similar to that of symptomatic fibroid disease. Repeated bleeding into endometriotic implants can lead to the formation of endometriomas within the ovary. These gelatinous and haemorrhage filled cysts are well visualised with TVUS (Fig. 8). However, tiny peritoneal implants throughout the pelvis will not be visualised with TVUS and require either

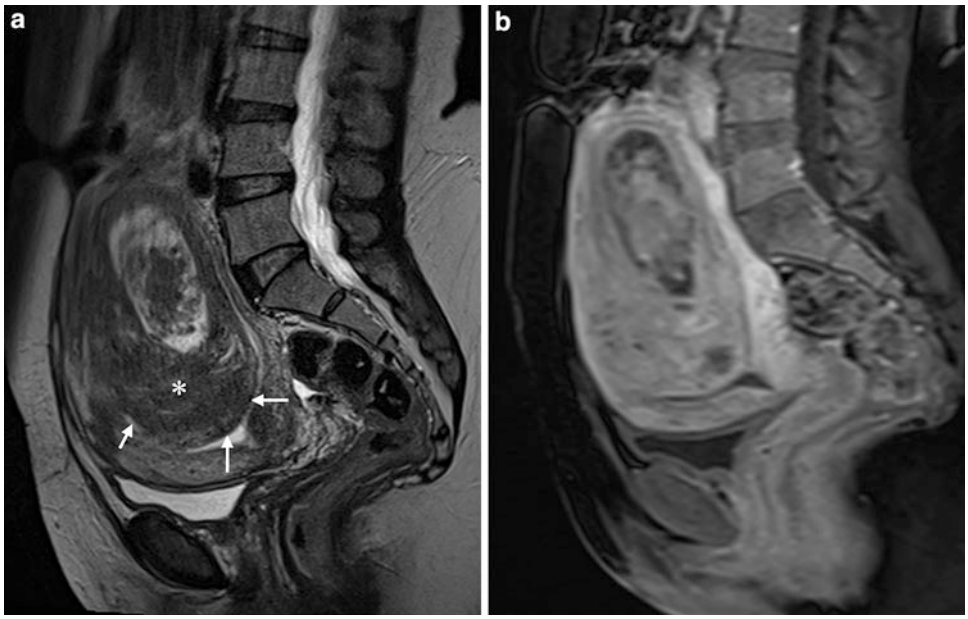


**Fig. 6** Intracavitary fibroid. **a** Sagittal T2 and **b** Sagittal T1FS with contrast enhancement MRI showing a dominant submucosal fibroid (*) with a large intracavitary component. Compressed endometrium is seen indented by the fibroid (*short arrows*). Although there is some central degeneration, the remainder of the fibroid enhances avidly and would be suitable for UAE, although risk of sloughing off is high and the patient should be informed of this possible outcome

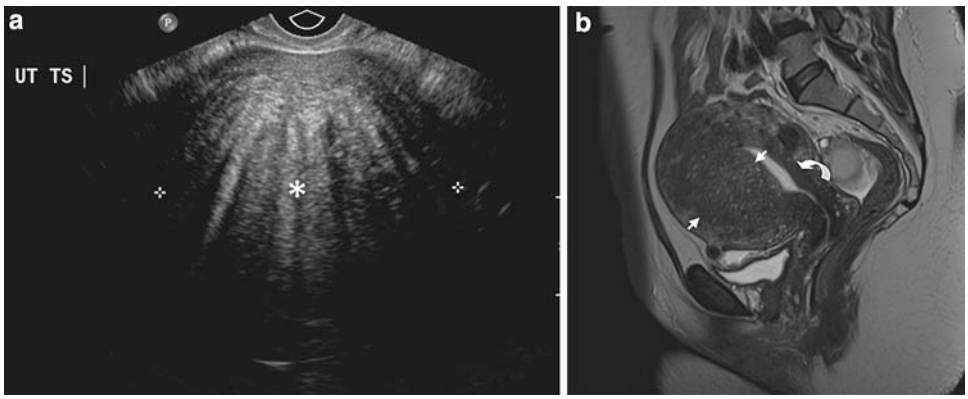


**Fig. 7** Adenomyosis **a** TVUS showing what appears to be a heterogeneous circumscribed mass. There are multiple area of linear posterior shadowing, a typical feature of adenomyosis. **b** Sagittal T2 weighted MRI confirms myometrial enlargement anteriorly, containing areas of T2 hyperintensity (between *arrow heads*), characteristic of adenomyosis. There is marked widening of the junctional zone anteriorly which is within normal limits posteriorly (*curved arrow*)

MRI or laparoscopic examination for diagnosis. T1 weighted sequences with fat saturation have high sensitivity for the demonstration of tiny haemorrhagic foci which are seen as markedly hyperintense to surrounding tissue (Fig. 8). Using this technique, even tiny foci of superficial endometriosis can be demonstrated non-invasively. Repeated bleeding leading to chronic inflammation in these areas can lead to pelvic fibrosis and adhesions between the pelvic organs, bladder and sigmoid colon. The resulting symptoms can be severe and surgical intervention can be difficult. As fibroids may co-exist in these patients it is important to identify the primary cause of the symptoms as management of the two conditions is greatly different. The multiplanar imaging ability of MRI readily enables demonstration of areas of fibrosis and adhesions.

Other causes of irregular menstrual bleeding and menorrhagia include polycystic ovarian syndrome, endometrial polyps and hyperplasia and TVUS can aid the non-invasive diagnosis of these conditions.

### 2.3.3 Uterine Sarcoma

Uterine sarcomas are rare, accounting for less than 3 % of all uterine malignancy. Carcinosarcoma is the commonest histological subtype, followed by leiomyosarcoma, and rarely, endometrial stromal sarcoma and adenosarcoma. Leiomyosarcomas can arise de novo or from malignant degeneration, however, this is rare, occurring in less than 1 % of benign fibroids. Malignant degeneration, in the early stages can be multifocal, with benign and malignant elements combined. Differentiation from a benign fibroid with imaging may not be possible. Similarly, due to sampling error, histological evaluation following biopsy is also unreliable. MRI features including loss of the normal low T2 signal intensity, areas of high T2 cystic change and avid contrast medium enhancement have been described (Tanaka et al. 2004) (Fig. 9). While malignancy can be considered, these appearances are also seen in atypical and degenerating fibroids, and these occur much more frequently (Cornfeld et al. 2010). Similarly, malignant foci can be found histologically in fibroids

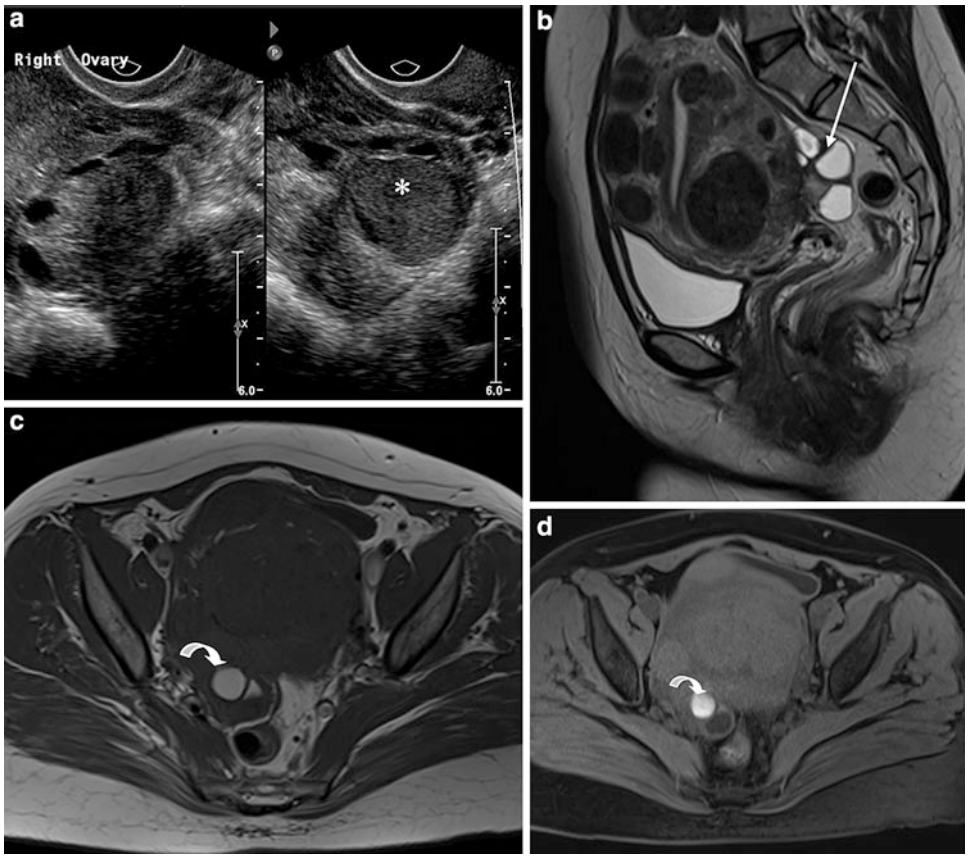


**Fig. 8** Endometriosis. **a** TVUS showing a slightly hypoechoic rounded lesion (*) within the right ovary which contains homogeneous low level internal echoes throughout. There is posterior acoustic enhancement, confirming the lesion is cystic rather than solid. **b** Sagittal T2 weighted **c** axial T1 weighted and **d** axial T1FS MRI in a second patient. In addition to the multiple uterine fibroids, there is a multiloculated cystic adnexal mass posterior to the uterus (*arrow*). It contains high signal intensity material on both the T1 and T1FS sequences, confirming the presence of blood products in this endometrioma

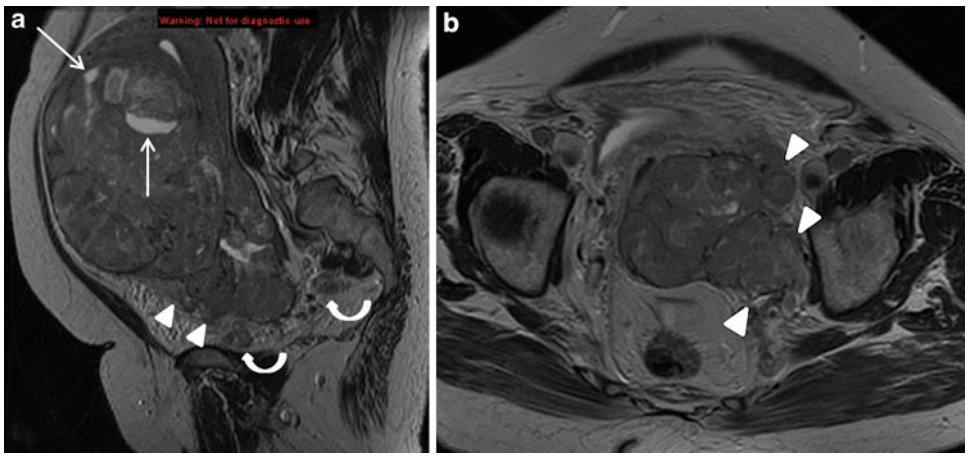


**Fig. 9** Uterine sarcoma. **a** Sagittal and **b** axial T2 weighted MRI showing an enlarged uterus. The normal uterine architecture is almost completely replaced by an intermediate signal intensity mass which contains pockets of high T2 signal intensity (*arrows*). Inferiorly the mass replaces the cervix and the outer serosal margin anteriorly has been breached by tumour (*arrow heads*). There is lateral tumour extension to the left pelvic sidewall and discrete tumour deposits in the pelvis (*curved arrows*)

which demonstrate a typical MRI appearance. Clinical suspicion should be raised in a patient with a rapidly enlarging uterus, particularly in a post-menopausal patient. Functional imaging techniques such as diffusion weighted MRI and PET-CT may aid diagnosis but again there is overlap with atypical and degenerating fibroids (Namimoto et al. 2009). Indeed, mild to moderate tracer uptake by benign fibroids is a well-recognised finding at PET-CT (Kitajima et al. 2008, 2010). Imaging finding of locally invasive or distant metastatic disease are the only definitive indicators of malignancy (Fig. 9).

## 3 Post-embolisation Imaging

Imaging following UAE is performed at varying intervals in different centres. An accepted recommended follow up period is typically at 3, 6 and 12 months after embolisation.

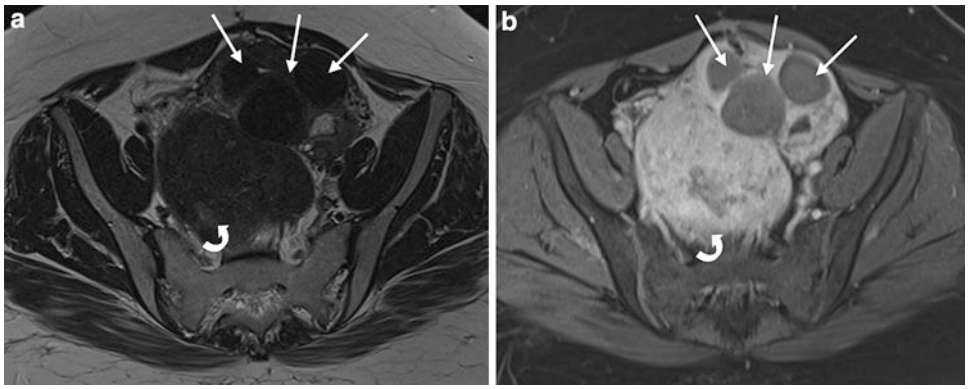


**Fig. 10** MRI performed 6 months following UAE. **a** Axial T2 weighted MRI and **b** T1FS MRI following contrast medium administration showing 3 uterine fibroids anteriorly (*arrows*) which are uniformly non-enhancing following UAE and have responded well. The large, posterior pedunculated fibroid (*curved arrow*) however, demonstrates persistent, avid contrast medium enhancement and has failed to respond to UAE

MRI is used to evaluate change in uterine and fibroid volume, change in fibroid location and degree of fibroid infarction or persistent vascularity. Fibroid shrinkage typically occurs in the first 6 months following UAE, with continuing reduction in volume up to 1 year (Walker and Pelage 2002). Follow up studies show 30–83 % reduction in the volume of the dominant fibroid and correlates with improvement in symptoms (Worthington-Kirsch et al. 1998; Walker and Pelage 2002; Pron et al. 2003; Gupta et al. 2006). Ultrasound and CT are used in the acute setting in the investigation of potential complications. Given that UAE has become a fairly widespread technique, radiologists need to be aware of the typical post-embolisation appearances and that of potential complications.

## 3.1 Typical Post-embolisation Appearances

### 3.1.1 Vascularity

Successful embolisation results in complete fibroid infarction and this is best assessed with contrast-enhanced MRI (Katsumori et al. 2001). Initially, haemorrhagic infarction may be visualised as higher signal intensity on T1 weighted MRI images and variable signal intensity on T2 weighted images. Over an increasing time period of typically more than 3 months, progressive necrosis of the fibroid can be seen as higher T2 signal intensity in keeping with liquefaction (Fig. 10). Complete lack of contrast medium enhancement signifies fibroid necrosis and successful embolisation. This can be evident as early as 24 h after UAE (Pelage et al. 2004; Katsumori et al. 2008) and prior to significant reduction in fibroid size. The degree of fibroid infarction has been shown to correlate with both short- and long-term symptom control (Katsumori et al. 2008; Kroencke et al. 2010). Long-term studies have shown that where some residual enhancing fibroid tissue remains on the post UAE contrast-enhanced MRI subsequent growth can lead to recurrence of symptoms and ultimate treatment failure. In a large prospective study of 113 patients, those whose fibroids demonstrated complete infarction at 24–72 h after embolisation showed significantly better clinical outcome at 24 months compared with those whose fibroids demonstrated partial and almost complete infarction (Kroencke et al. 2010). This held true for both re-intervention rates (none in the complete infarction group vs 50 and 20 % re-intervention in the almost complete and partial infarction groups) and persistence or recurrence of menorrhagia and bulk-related symptoms. Re-intervention may include hysteroscopic resection, myomectomy, hysterectomy or further UAE. Repeat imaging therefore is recommended in patients who experience persistence or recurrence of symptoms. Given that ultrasound cannot accurately assess fibroid vascularity, contrast-enhanced MRI should be performed.

### 3.1.2 Gas

Gas can be seen within the uterine cavity and fibroids following UAE. As a fibroid infarcts and breaks down, gas can be seen filling potential spaces within it in a linear or branching pattern (Fig. 12). This appearance has been well described in other tumours treated with radiofrequency ablation or chemoembolisation (Ghai et al. 2005) and can be seen from 1 month after UAE. This appearance does not necessarily signify infection and it is important to correlate with clinical and laboratory findings.

## 3.2 Imaging of Complications

### 3.2.1 Infection

Significant infection requiring intervention or more specifically endometritis is a well recognised but rare complication following UAE, occurring in less than 1 % (Spies et al. 2002b). It should be considered in a patient with protracted or late onset of pain, fever, offensive discharge or bleeding and may occur in association with passage of infarcted fibroid tissue. In one study post-embolisation infection occurred only in patients with submucosal fibroids. Early treatment is imperative if widespread septicaemia is to be avoided. MR imaging may demonstrate

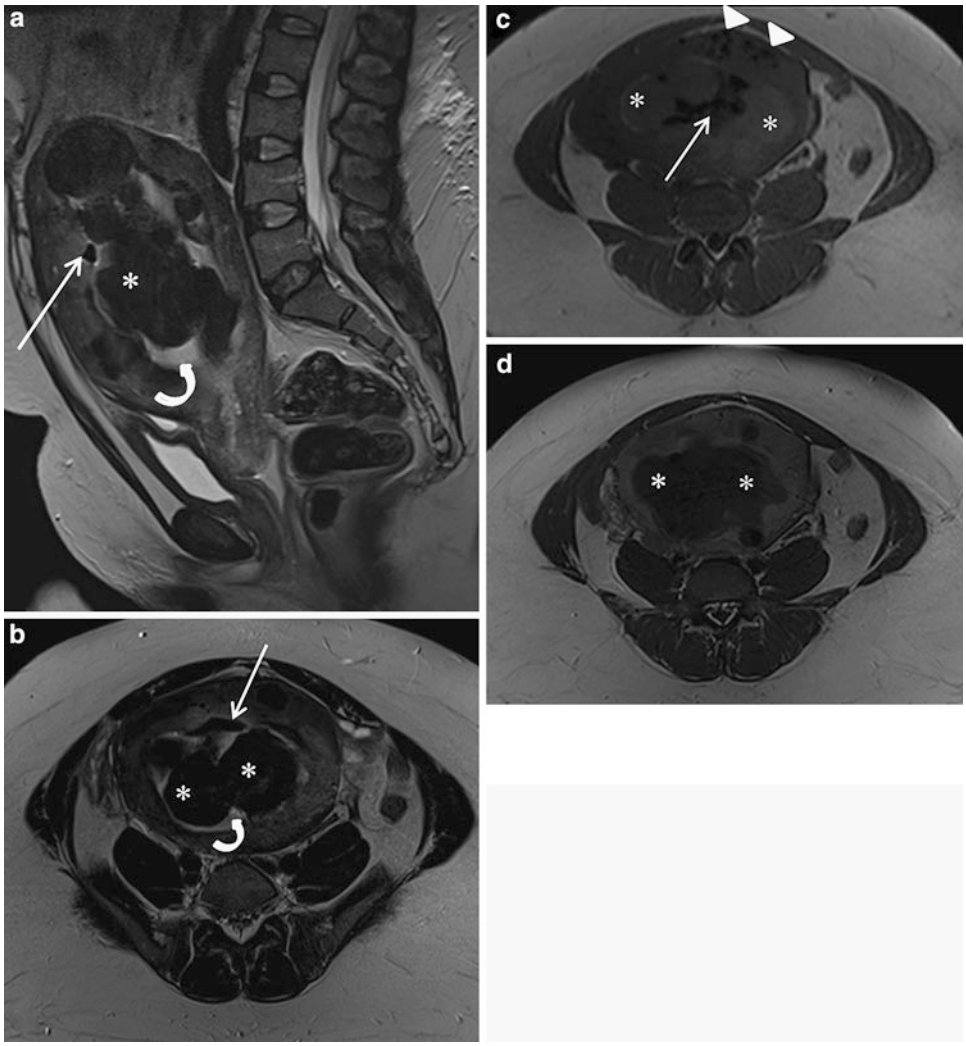


**Fig. 11** MRI in a patient presenting with pyrexia, pain and raised inflammatory markers, 6 weeks after UAE. **a** Sagittal and **b** axial T2 weighted MRI, **c** Unenhanced axial T1 and **d** axial T1 weighted MRI following contrast medium administration. There is sloughed off non-enhancing, fibroid tissue within uterine cavity (*) which also contains a high T2 signal intensity fluid collection (*curved arrow*). Gas is seen within the collection (*straight arrows*) and within the myometrium (*arrow heads*) in keeping with associated infection

uterine enlargement, heterogeneous, non-enhancing intrauterine collections which are typically of high T1 and intermediate to high T2 signal intensity. Gas within the collection is seen as punctate foci signal voids on all sequences (Fig. 11). This is distinct from the branching, linear gas seen normally within infarcted fibroids post-embolisation. However, appearances should always be interpreted alongside the clinical profile of the patient.

### 3.2.2 Fibroid Expulsion

Expulsion of infarcted fibroid tissue following embolisation is a frequent occurrence. Fibroid expulsion, while reported in up to 3 % of cases (Spies et al. 2002b), occurs much more commonly in submucosal fibroids or intramural fibroids with a significant submucosal component which are in contact with the endometrial surface. In one small series, 50 % of dominant submucosal fibroids were completely expelled following embolisation (Radeleff et al. 2010). Symptoms include severe pain, infection and bleeding. Fibroid passage can occur anytime from a few days to up to a year after embolisation (Spies et al. 2002b). It may or may not be accompanied with infection and correlation with the clinical picture is imperative for planning treatment. Imaging with MRI can help define location and vascularity of the infarcted fibroid. When infarction has been complete, a non-enhancing fibroid of low T2 weighted, fluid signal intensity may be seen within the uterine cavity (Fig. 12), expanding the endocervix or within the vagina. Many of these will be expelled spontaneously. MRI can be used to identify persistent fibroid enhancement indicating incomplete infarction and define any residual viable attachment to the uterus. In these cases, hysteroscopic resection may be warranted. MRI can also be used to demonstrate complete restoration of a normal looking uterine cavity following fibroid passage (Park et al. 2005) (Fig. 12).

### 3.2.3 Adhesions

Intrauterine synechiae can occur following embolisation but are typically clinically silent. In one study, where hysteroscopic evaluation of the uterine cavity was performed in

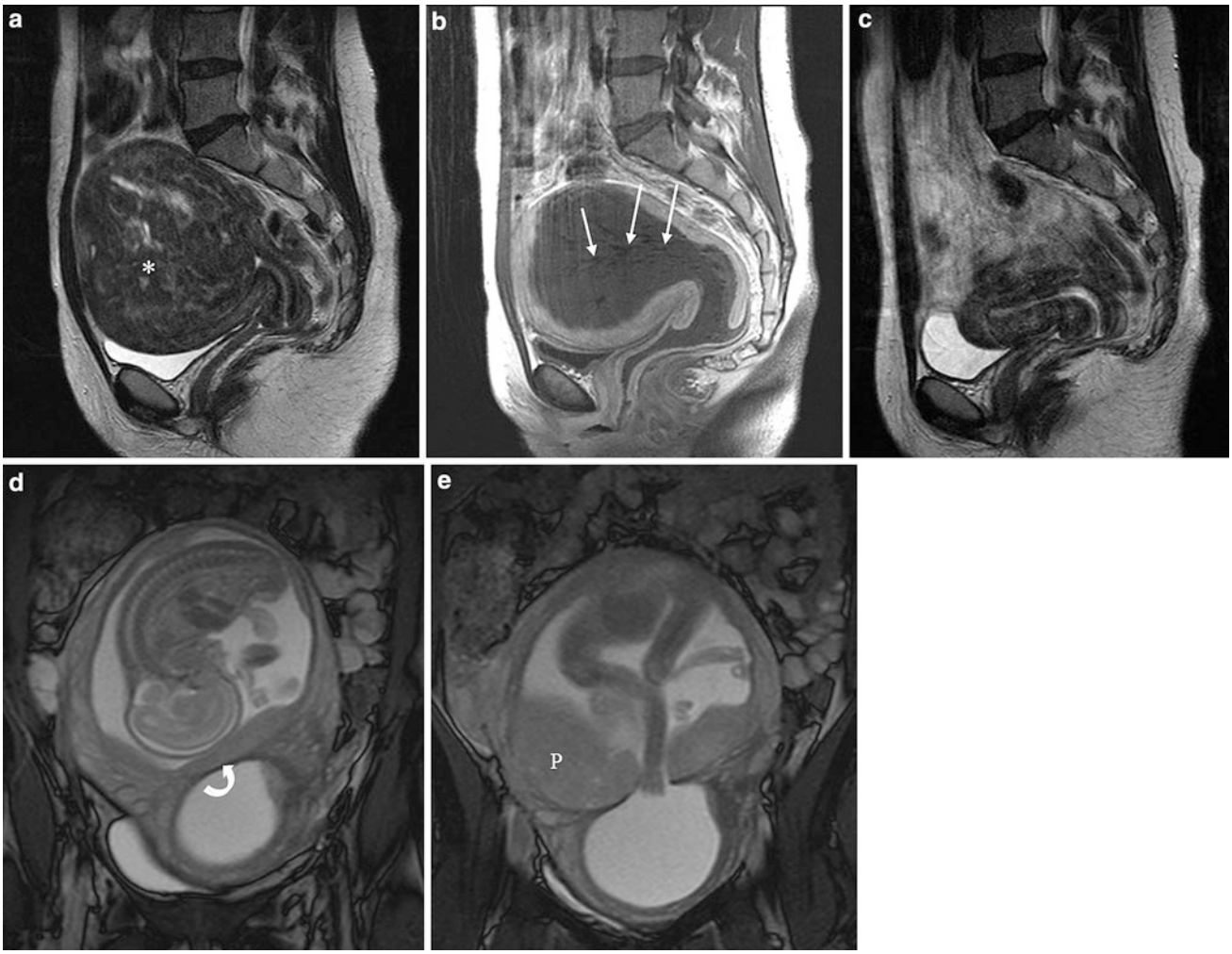


**Fig. 12** Sagittal T2 weighted MRI (**a**) before UAE showing large intracavitary fibroid (*). **b** Contrast-enhanced T1FS MRI performed 3 months after UAE. The uterine cavity is still expanded by the fibroid which is now completely de-vascularised and non-enhancing. There are linear areas of signal void within the fibroid in keeping with gas within the degenerated fibroid (*arrows*). **c** Sagittal T2 weighted MRI performed 18 months after UAE. The patient clinically passed the fibroid and there is restoration of a normal looking uterine cavity. **d** and **e** coronal True-FISP MRI. The patient is 21 weeks pregnant. There is now a linear adhesion across the mid uterine cavity (*curved arrow*), onto which the placenta (P) has implanted. The pregnancy has developed in the 'aneurysmal' superior portion of the cavity. The band-like adhesion did not extend across the whole of the cavity and there was herniation of the foetal arm into the lower cavity. The baby was delivered successfully at 26 weeks following premature rupture of membranes at 23 weeks and bleeding (Images courtesy of Dr Nigel Hacking)

asymptomatic women up to 9 months following UAE, intrauterine or cervical adhesions were seen in 14 % (Mara et al. 2007). Fibroid expulsion and infection are particular risk factors for the development of adhesions which if severe, can lead to amenorrhoea, infertility or obstetric complications (Fig. 12).

### 3.2.4 Uterine Infarction

Uterine infarction leading to necrosis is a very rare but life-threatening complication of UAE. There are few case reports in the literature describing uterine necrosis occurring between 4 days and several months after UAE (Torigian et al. 2005). Uterine infarction is invariably associated with early or late infection and possibly aetiologies include superadded infection and poor collateral circulation (Godfrey and Zbella 2001). The imaging descriptions in the literature are limited but MRI with contrast medium administration is the imaging modality of choice to assess uterine vascularity and viability, if infarction is suspected. Necrotic uterine tissue demonstrates intermediate to high T1 and high T2 signal intensity with or without the presence of gas. Complete absence of endometrial and myometrial enhancement is diagnostic of uterine infarction, and is the key differential feature in these patients who may present with non-specific symptoms of pain, fever and discharge. Of note, persistent areas of subserosal enhancement indicating spared

viable myometrial tissue has been described and is presumed to be due to the presence of a superficial collateral blood supply (Torigian et al. 2005). This finding should not preclude the diagnosis of uterine infarction.

## 4 Conclusion

Imaging before UAE is important for establishing the diagnosis, fibroid mapping and patient selection. Imaging appearances following embolisation vary with time and success of the procedure. MRI, in particular is best suited to assess fibroid appearances and vascularity. Prior to embolisation, diagnostic radiologists should be familiar with the important features of fibroids, in particular location and vascularity which can help plan treatment and may have prognostic implications. Following embolisation, radiologists need to be familiar with the range of normal appearances and those of complications. In particular, the finding of gas can be a normal post-embolisation appearance and does not always indicate infection. Close communication with clinical colleagues is vital to aid correct diagnosis and management.

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# Uterine Artery Embolization Indications and Contraindications

James B. Spies

## Contents




**Abstract**

Uterine artery embolization (UAE) has become accepted as an effective therapy for most women with symptomatic fibroids (ACOG Practice Bulletin 2008). And while the vast majority of patients would be well treated with embolization, the decision as to whether it is the best choice for any individual patient requires a consideration of the extent of the fibroids and also patient-related factors, such as interest in future childbearing, preferences toward surgery, and the relative risks of differing therapies for individual patients. Therefore, the decision as to whether UAE is appropriate for a patient is based on a multilayered consideration of factors. This chapter will review what is known about the patient selection for UAE, including the indications and contraindications of the procedure, as well as medical conditions in which patient care may be a particular challenge. We also will review the anatomic limitations of UAE, with regard to uterine and fibroid size and specific subtypes of fibroids that may have diminished results. The hope is to provide the reader with all the tools needed to appropriately guide patients in the decision of whether UAE is a good choice for them.


## 1 Basic Considerations in UAE Patient Selection

### 1.1 History and Physical Examination

As outlined in earlier chapters, the first step is an appropriate evaluation of the patient with the completion of a medical history, physical examination, and review of imaging. The medical history is particularly important in that the first decision in patient selection is whether the patient has symptoms and, if so, if those symptoms are likely due to fibroids or another gynecologic pathology. There have been considerable efforts to develop structured approaches to the


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medical history as a tool to direct further evaluation (Munro et al. 2011), recognizing that at least with abnormal uterine bleeding, there are a large number of potential causes. A pelvic examination is the initial means of confirming the presence of fibroids, with an enlarged uterus with an irregular contour the typical finding. Based on the history and physical examination, a presumptive diagnosis of fibroids is possible, although the diagnosis should be confirmed with imaging.

### 1.2 Imaging

The diagnosis requires imaging confirmation, particularly since the history and physical examination does not exclude other uterine pathology, such as adenomyosis, endometrial polyps, or other endometrial pathology that can mimic the symptoms of fibroids. While either pelvic ultrasound or MRI can be used for imaging evaluation, there are caveats. MRI has greater anatomic resolution, makes localizing fibroids and determining the extent of their perfusion much easier than ultrasound and adenomyosis is better detected than with ultrasound (Fig. 1). It has poorer ability to assess the endometrial lining than ultrasound, particularly sonohysterography. Regardless of imaging modality used, confirmation of the diagnosis of fibroids and exclusion of other important gynecologic pathology with imaging is important.

The decision to routinely use MRI or to use it in selected cases in which ultrasound is not sufficient is based as much on resource availability as on medical necessity. It appears that MRI has some advantages over ultrasound in the preprocedure evaluation of patients, but that advantage is not so great that MRI must be used. If ultrasound is to be the primary imaging tool, the study should be of high quality and the images made available for review. If there is uncertainty about the location or extent of fibroids, the degree to which they are in the uterine cavity or whether adenomyosis is an important part of the presenting condition, then MRI may be a valuable adjunct and should be considered.

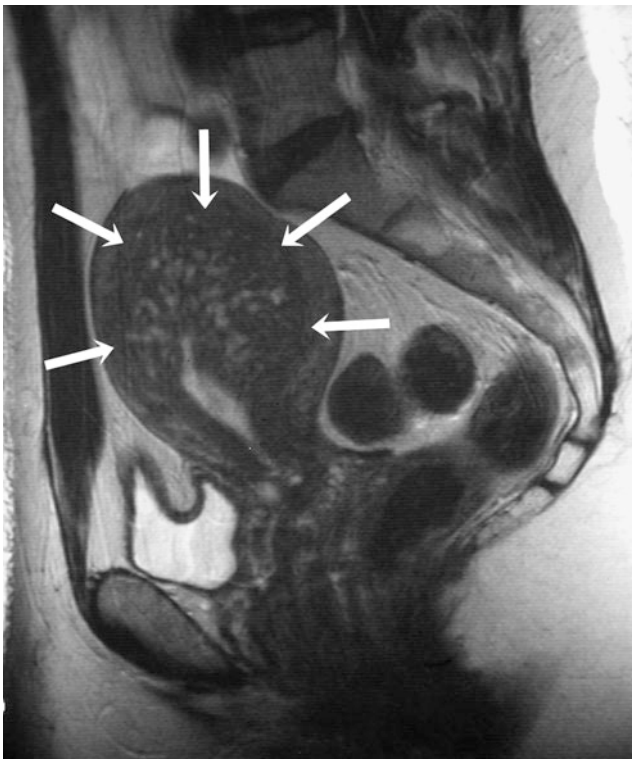

**Fig. 1** MRI imaging for pre-procedure evaluation. Sagittal T2-weighted MR image of the pelvis demonstrating adenomyosis (*arrows*) in a patient previously diagnosed as having fibroids based on an ultrasound examination

## 2 Indications

Once a diagnosis has been confirmed, the first question is whether the fibroids detected in a patient require treatment. Many likely do not. The majority of women with fibroids do not have any fibroid-related symptoms and therefore conservative management, is the most appropriate approach (Parker 2007). Perhaps 20–30 % of women with fibroids will eventually develop symptoms that require therapy, but most transition into menopause without the need for therapy. In general, UAE is indicated for patients of reproductive age with symptomatic fibroids who wish to avoid surgery or for whom surgery is contraindicated.

### 2.1 Heavy Menstrual Bleeding

Heavy menstrual bleeding is the most common symptom among women seeking treatment for fibroids. Fibroids usually present with menorrhagia without interperiod bleeding, though submucosal fibroids can present with both menorrhagia and metrorrhagia. Symptomatic fibroids commonly increase the length of the menstrual cycles, the number of days with heavy bleeding, as well as the frequency of change of sanitary protection on the heaviest days. Typically, heavy menstrual bleeding is caused by fibroids that are either submucosal or intramural (Fig. 2). Serosal fibroids do not cause alterations to menstrual bleeding (Wegienka et al. 2003).

The evaluation of the patient with menorrhagia varies depending on individual patient factors, but there are many causes for heavy menstrual bleeding beyond fibroids and these need to be considered carefully at the time of initial patient presentation. As indicated in the section above, a

structured approach to the medical history (Munro et al. 2011), as well as collaboration with a gynecologist, is the best way to complete an appropriate evaluation that will help ensure the best patient outcomes.

### 2.2 Pelvic Pain and Pressure

Pelvic pressure, bloating, and pelvic pain are common with uterine fibroids and often most prominent before and during the perimenstrual period. Pelvic pain due to symptomatic fibroids is often described as discomfort more than pain, and usually is low grade and aching. Dysmenorrhea may develop or worsen in the presence of fibroids. Severe pain is atypical, but can occur with spontaneous fibroid degeneration. This is quite uncommon and other causes of female pelvic pain, such as endometriosis, should be considered. Variations of pelvic pain, such as dyspareunia, may also be caused by fibroids. When assessing a woman with pelvic pain and fibroids, it is important to correlate the location of the fibroids with the location of the pain. A patient with pain on the left with right-sided fibroids may have a different cause for the pain and further evaluation may be needed.

### 2.3 Urinary Symptoms

Urinary symptoms can also be caused by fibroids, particularly if the symptoms are urgency, frequency, or retention. Incontinence is unlikely to be solely caused by fibroids, but may be worsened by bladder compression from the enlarged fibroid uterus. Hydronephrosis from the enlarged uterus occurs in about 10 % of patients presenting for uterine embolization and is more likely in patients with significantly enlarged uteri from fibroids (Alyeshmerni et al. 2011). The hydronephrosis resolves as the uterus shrinks after uterine artery embolization in nearly all cases (Alyeshmerni et al. 2011; Mirsadraee et al. 2008).

### 2.4 Asymptomatic Fibroids

There are relatively few circumstances in which asymptomatic fibroids should be treated with UAE. Perhaps the most common is in a woman who has fibroids without symptoms who wishes to become pregnant. The link between fibroids and infertility and subfertility is difficult to establish in many individual patients, but as a group, patients with fibroids have diminished fertility and are more likely to have pregnancy-related complications than women without fibroids (Klatsky et al. 2008). The role of uterine embolization in this group of patients is secondary to myomectomy in most patients who have not had prior therapy and who have a strong desire for pregnancy. In a randomized trial, women with fibroids interested in pregnancy were treated with either embolization or myomectomy, with better reproductive outcomes in the first 2 years after treatment among the patients treated with myomectomy (Mara et al. 2008). UAE may have a role in patients who are poor surgical candidates, who have had prior pelvic surgery, or who have a strong desire to avoid surgery. There is a much more detailed discussion of fertility and treatment options in the chapters on fertility.

## 3 Contraindications

### 3.1 Practice Guidelines

The contraindications to UAE have not been well-defined. While published practice guidelines have included contraindications, these have not been evidence-based. For example, the Society of Interventional Radiology published a policy and position statement on patient care and uterine artery embolization for leiomyomata in 2009 (originally published in 2004) (Andrews et al. 2009) that listed a range of potential contraindications, including immunocompromise, prior pelvic irradiation or surgery, adenomyosis, and serosal fibroids with a narrow attachment, all without clear evidence that these patients are at high risk. Even more conservative are the guidelines from the Society of Obstetrics and Gynaecologists of Canada, which state that since uterine embolization is known to have a very small but real chance of a complication leading to hysterectomy, UAE should not be offered to women who refuse hysterectomy (SOGC Clinical Practice Guidelines 2005). This begs the question of what options these patients might have, as most gynecologic procedures that might be alternatives to UAE have the same risk. Many of the recommendations in these guidelines have not been subjected to rigorous evaluation and, as is discussed in the sections below, there is some evidence gathering that embolization may be safe in some circumstances in which traditionally it has been avoided.

### 3.2 Pregnancy

Current pregnancy is one of the absolute contraindications and patients must be tested to exclude pregnancy before the procedure. As a pregnancy test is likely to be negative for the first few weeks of pregnancy, in ideal circumstances, the embolization should be performed within the first 10 days of the menstrual cycle, which would ensure that an early

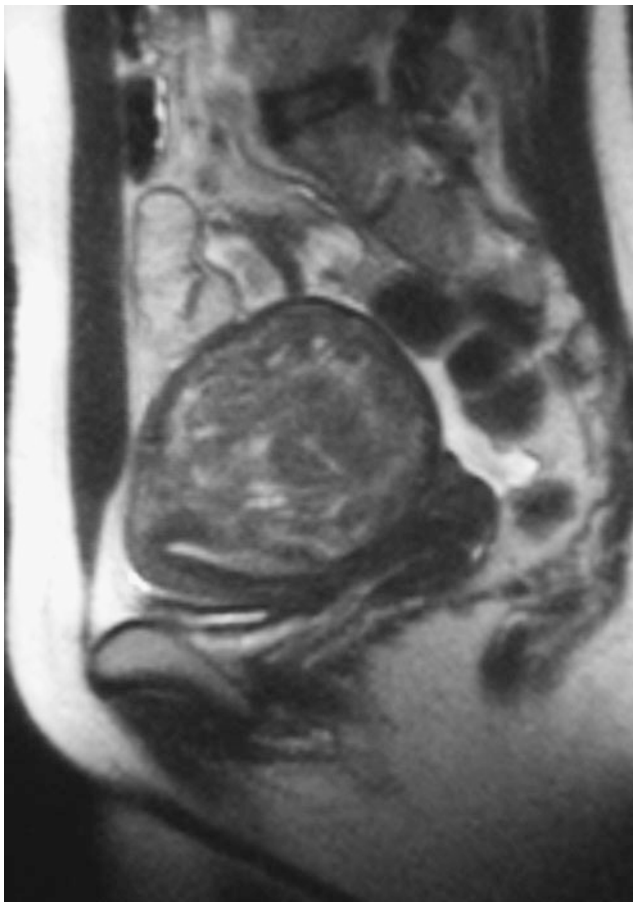

**Fig. 2** Typical fibroid location in a patient with heavy menstrual bleeding. Sagittal T2-weighted MR image of the pelvis in a patient with a transmural posterior wall fibroid with substantial compression of the endometrial cavity. Because of the distortion of the endometrial cavity, the fibroid is likely the cause

pregnancy is not present. Unfortunately, due to the irregularity of menstrual cycles in this population and the vagaries of scheduling, the ideal timing is often not practical.

## 3.3 Suspected Uterine or Adnexal Malignancy

Suspected uterine and adnexal malignancy should be evaluated before treatment. This often may be characterized on the MRI, but in some cases operative intervention is needed for diagnosis. The extent of the evaluation that should be performed has not been well-defined and depends on the level of suspicion. For masses that are highly suspicious for malignancy, the diagnosis should be clarified with biopsy (Fig. 3). There are several types of gynecological malignancy that might occur.

First and perhaps most common is endometrial cancer. This would be an unusual malignancy in a premenopausal patient but must at least be considered in patients with atypical bleeding. Menorrhagia associated with fibroids usually results in longer and heavier menstrual cycles. Interperiod bleeding is infrequent. Endometrial malignancy and potential precursors such as endometrial hyperplasia with atypia are more likely to present with irregular intermenstrual bleeding. Imaging may show thickening of the endometrial lining. Endometrial sampling, either via pipelle biopsy or dilatation and curettage, is necessary for a definitive diagnosis.

Leiomyosarcoma is the malignant counterpart of leiomyoma, a rare malignancy with an incidence of 0.13 and 0.29 % among women being treated for presumed fibroids (Leibsohn et al. 1990). Differentiating a leiomyosarcoma

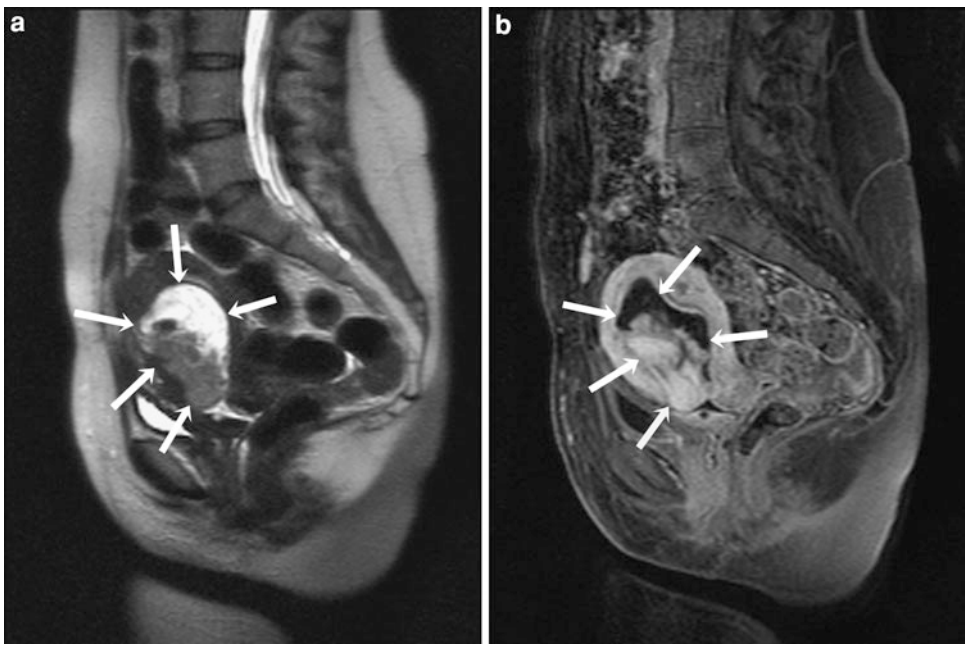


**Fig. 3** Probable endometrial cancer. **a** Sagittal T2-weighted MR image of the pelvis demonstrating a markedly heterogenous mass (*arrows*) in the endometrial cavity in a 48-year-old woman with irregular menstrual bleeding. **b** Sagittal T1-weghted contrast-enhanced MR image showing very variable contrast enhancement. The mass is irregular in contour and internal architecture more suggestive of a neoplasm than a fibroid


**Fig. 4** Large Fibroid and Uterus. Sagittal T2-weighted MR image of the pelvis showing an enormous uterus, well over 30 weeks size, with a single giant fibroid. By way of orientation, the arrow indicates the level of the navel. While embolization will likely infarct the fibroid, bulk-related symptoms, and abdominal wall distortion are unlikely to be satisfactorily resolved

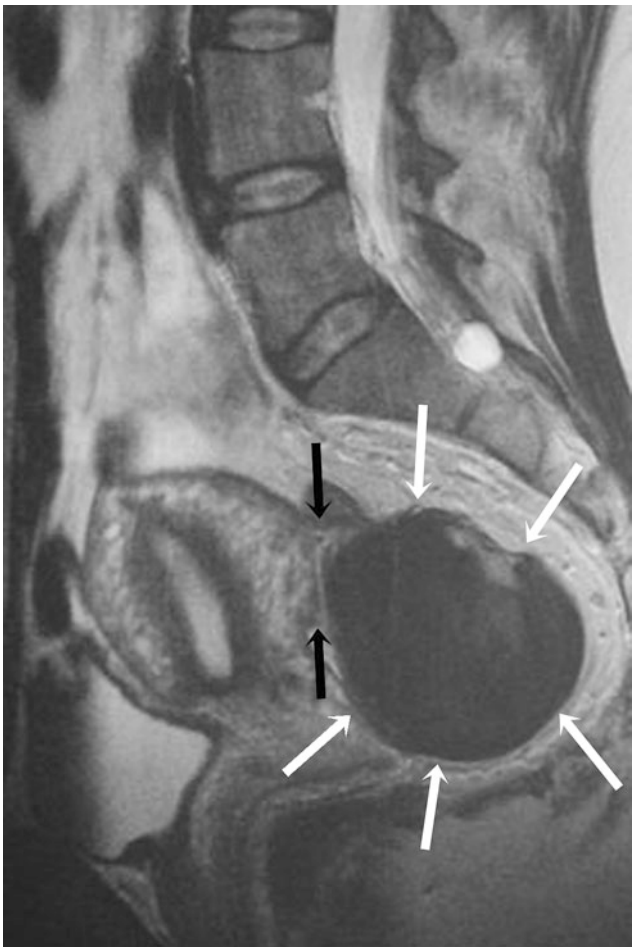

**Fig. 5** Narrow-based pedunculated serosal fibroid. Sagittal T2-weighted MR image of the pelvis with a posterior pedunculated serosal fibroid (*white arrows*). The narrow-based attachment is indicated by the *black arrows*

from a fibroid may be difficult based on clinical history or imaging findings. Clinically, the presence of a "rapidly growing" fibroid has been suggested as a marker for possible leiomyosarcoma, but in a series 371 patients with rapidly growing fibroids, only one had a sarcoma (Parker et al. 1994). On MRI, these tumors typically present as a single or dominant mass with a distorted internal architecture and variable enhancement. In a small series, Tanaka et al. 2004 found that they may be characterized by greater than 50 % high signal on T2-weighted images and foci of increased signal on T1-weighted images, suggesting hemorrhage (Tanaka et al. 2004). Unfortunately these findings are not specific. Unless there is local invasion of the myometrium or endometrium and adenopathy, it may be difficult to distinguish a sarcoma from an atypical benign leiomyoma. A high index of suspicion based on the imaging findings of the mass itself is needed to detect these lesions. If a fibroid is bizarre in architecture or shows a markedly atypical enhancement pattern, leiomyosarcoma should be considered, and the patient should be referred to a gynecologist or gynecologic oncologist for definitive diagnosis.

Ovarian cancer, usually presenting as a cystic or mixed cystic and solid mass, is the most common adnexal malignancy encountered in this population. A complete description of the imaging findings is beyond the scope of this chapter and if a suspicious ovarian mass is identified, then UAE should be deferred until a diagnosis is completed.

## 3.4 Contrast Allergy

An allergy to iodinated contrast is a relative contraindication, although these reactions may be less likely with intraarterial use. In some cases, gadolinium-based contrast may be used as a substitute, although the volume of contrast needed may exceed the safe dose of gadolinium.

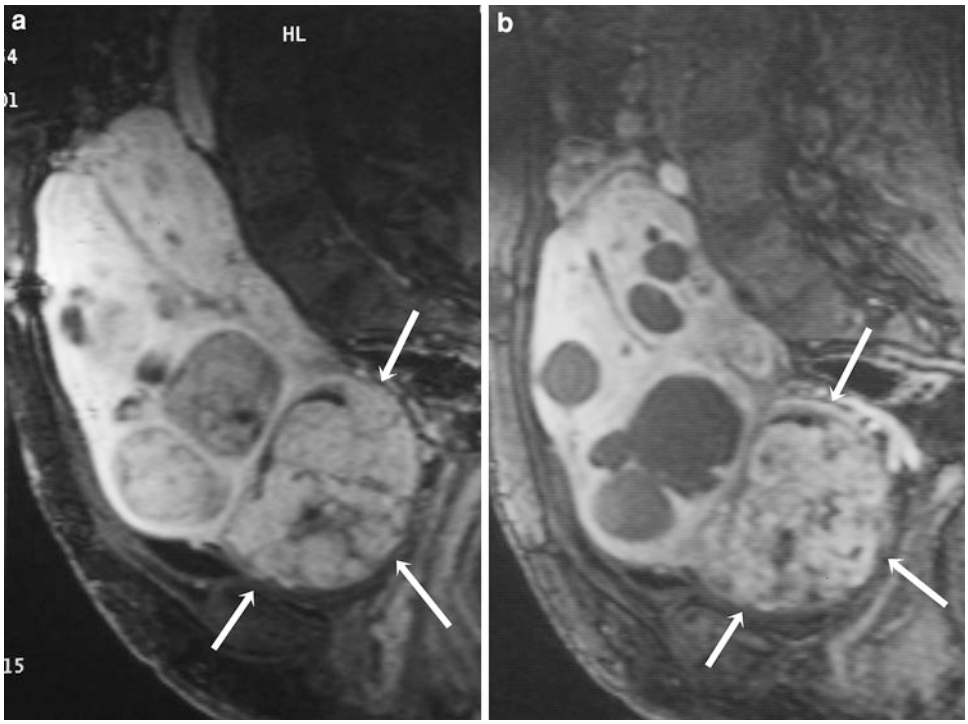


**Fig. 6** Cervical fibroid nonresponse to UAE. **a** Sagittal T1-weighted contrast-enhanced MR image with multiple fibroids in a patient with heavy menstrual bleeding and dyspareunia. *Arrows* indicate a large fibroid arising from the cervix, confirmed on other images. **b** Contrast-enhanced image showing infarction of most of the fibroids (nonenhancing masses), but the cervical fibroids (*arrows*) is unchanged

The risk of a reaction may be minimized with preprocedural administration of corticosteroids. Current American College of Radiology Guidelines provide recommended regimens for prophylaxis, including oral corticosteroids and oral diphenhydramine (ACR Committee on Drugs and Contrast Media 2010). Two options for oral corticosteroids are suggested: 50 mg of prednisone 13, 7, and 1 h before the procedure, along with 50 mg of diphenhydramine or 32 mg of methyprednisolone 12 and 2 h before the procedure, along with the diphenhydramine. All patients undergoing uterine embolization should have secure intravenous access and oxygen available in the room, as well as immediate availability of a resuscitation cart. In patients with severe contrast allergy, the procedure may best be completed with anesthesia assistance to ensure appropriate airway support.

## 3.5 Pelvic Infection

Active uterine or adnexal infection is also a UAE contraindication as it may predispose to fibroid infection. If unchecked, fibroid infection can lead to sepsis, so clearly avoiding infection is important. Embolization is safe after the infection resolves with appropriate therapy. Endometrial infections prior to UAE would be very atypical and the most likely concern would be active pelvic inflammatory disease. This clearly requires resolution prior to UAE.

Less certain is when there has been previous infection or possible infection. This would be most commonly seen in a patient with hydrosalpinx. Early in the UAE experience, reported a possible infection post-UAE in a patient with hydrosalpinx (Goodwin et al. 1997). Since that time, there has been a concern that the presence of hydrosalpinx might predispose to uterine infection after the procedure. There have been no further published studies on this issue. Hydrosalpinx presents with varying degrees of severity and chronicity. In a patient with a long-standing hydrosalpinx and no clinical evidence of infection, infection is unlikely to be present. The use of prophylactic antibiotics directed toward chlamydia and other potential tubal pathogens may be appropriate. In our practice, we use either oral doxycyline for 5 days prior to the procedure or a single intravenous dose of ceftriazone immediately before the procedure to provide a margin of safety in patients presenting with hydrosalpinx, although there are no controlled trials assessing the efficacy of antibiotics in this setting.

Another concern for infection is in those patients with intrauterine devices in place. These have routinely been considered as a contraindication to embolization, as they are feared to predispose to infection (Steen and Shapiro 2004). While the risk is likely very low in a population with a low prevalence of sexually transmitted diseases, it has been a concern for interventionalists. A recent study of 20 women undergoing uterine embolization with intrauterine devices found no increased risk of infection (Smeets et al. 2010).

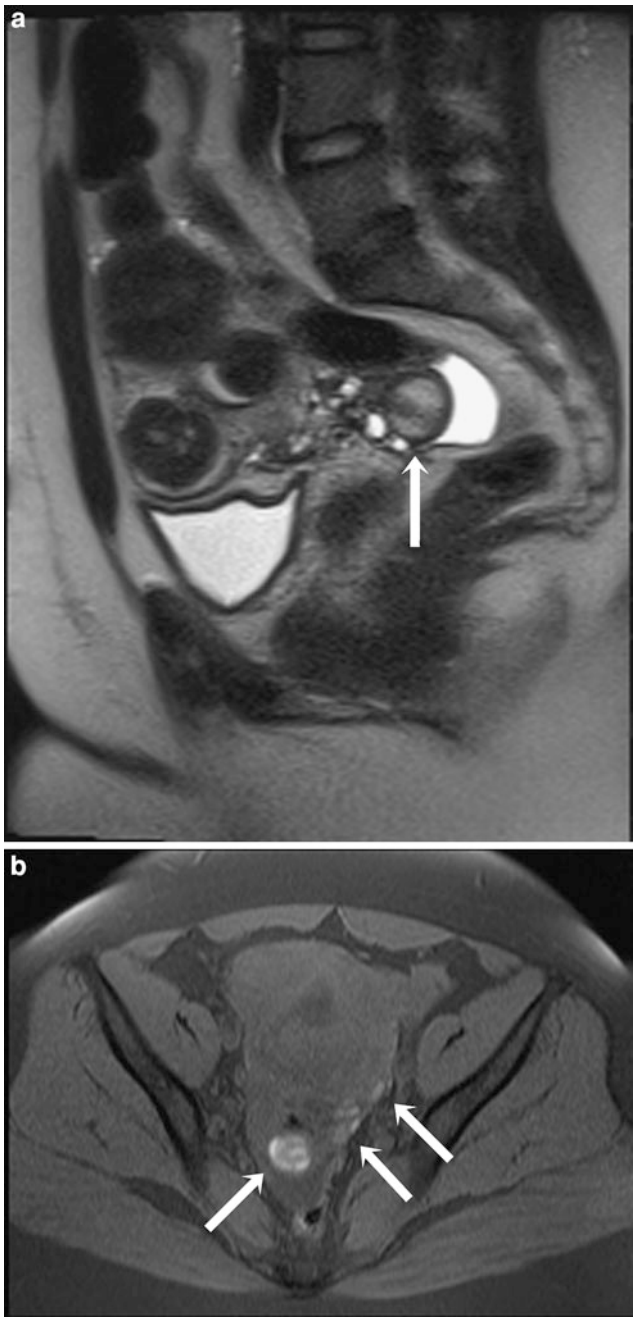


**Fig. 7** Fibroids and endometriosis. A 30-year-old with an interest in future pregnancy with heavy bleeding and severe perimenstrual pain. **a** Sagittal T2-weighted MR image demonstrating fibroids and a mixed signal complex cyst posteriorly, compatible with an endometrioma (*white arrows*). **b** Axial T1-weighted image with high signal small cyst and other foci of high signal, corresponding to the endometrioma and additional endometriosis implants. In this patient, menstrual bleeding was only mildly increased and the primary complaint was severe menstrual pain. Patient was referred for management of endometriosis, with treatment for fibroids deferred until they are more symptomatic

At a mean follow-up of 20.5 months, none of these patients developed an infectious complication. One hysterectomy was done for persisting pain and the pathologic examination of the uterine specimen showed no unusual inflammation. These authors suggest that the presence of an IUD should not be a contraindication to embolization. Because of the discomfort and expense of removal and subsequent replacement, as well as the need for temporary use of other contraceptive methods, we do not routinely remove intrauterine devices prior to UAE. We do use an antibiotic prophylaxis regimen in these patients aimed at common uterine and tubal pathogens, such as oral doxycycline or intravenous ceftriaxone.

## 4 Medical Conditions Requiring Caution

Some of the published guidelines list medical conditions as contraindications that would more properly be designated as comorbidities that require special attention or caution. Many of those listed are systemic medical conditions that also make the patient a poor candidate for surgery and in fact are often the reason the referral is made. With care, many of the patients with conditions discussed below can be safely treated, with less potential morbidity than might be associated with surgery.

Immunocompromised patients, such as those with HIV, may be at increased risk of infection after any intervention. The risk after surgery would likely be greater than UAE. The frequency of infections after UAE is very low and with ongoing monitoring and proper patient instruction, most patients can be treated safely. It is important to be alert to atypical presentations of infection while following these patients, as they may not develop typical signs and symptoms. It is probably appropriate to administer prophylactic antibiotics, although their efficacy in this circumstance has not been studied.

Guidelines have also suggested that patients with prior pelvic radiation or pelvic surgery may be contraindicated for UAE, on the basis of impaired healing or as an altered barrier to infection (Andrews et al. 2009). These concerns would of course also apply to the surgical alternatives and the morbidity of surgery in this type of patient would clearly be elevated. To date there are no data that these conditions predispose to UAE complications. In fact, prior myomectomy is one reason women are commonly referred for UAE instead of surgery. There was no evidence that prior surgery affected outcomes in the FIBROID Registry, one of the largest multicenter outcome studies for UAE (Spies et al. 2005a; Worthington-Kirsch et al. 2005). Our own experience suggests that patients with chronic inflammatory conditions, such as lupus erythematosis and multiple sclerosis, can be safely treated but may experience a flare of their underlying condition during their recovery. Beyond that, an increase in adverse events does not appear to occur.

Renal insufficiency is a condition that requires preprocedure hydration. The number of contrast injections and the volume of contrast used can be limited. Routine aortography can be avoided, as can preembolization iliac or uterine arteriograms. If the uterus is large and the need for a large volume of embolic material is anticipated, one might consider the use of particle polyvinyl alcohol (PVA) rather than a spherical product, as a comparison of PVA to tris-acryl gelatin microspheres showed similar outcomes but one third the volume of embolic for PVA (Spies et al. 2004). This translates into less contrast use.

Patients with coagulation defect must also be treated with caution. There are two groups to consider; those who are hypercoagulable and those who are anti-coagulated or who have hypocoagulable condition. Those who are hypercoagulable are the greater concern, as pulmonary embolus can occur after uterine embolization (Czeyda-Pommersheim et al. 2006), including fatalities after UAE (Baig et al. 2011; Hamoda et al. 2009) and these patients are perhaps at highest risk of thromboembolic events. Patients with a known hypercoagulable condition or who have a personal history of venous thromboembolism should have prophylactic low dose anticoagulation in the periprocedure period. If the risk is particularly high, therapeutic doses may be necessary, with care coordinated with a hematologist or internist. In some cases, temporary vena cava filtration may be considered.

For patients who are fully anticoagulated for the procedure, either short term or chronically, or who have a hypocoagulable condition due to clotting defect, the risk of bleeding from the arterial puncture site is the primary concern. In times past this might have required conversion to intravenous heparin ahead of the procedure, cessation at the time of the procedure, and then restarting intravenous and oral anticoagulation after a time-consuming and cumbersome process. One current approach is to leave a patient on their anticoagulation or without correction of the coagulation defect and use an arterial closure device for the procedure. This eliminates the gaps in anticoagulation and has minimal risk of a bleeding complication with today's closure devices.

## 5 Anatomic Considerations in Patient Selection

The size of the uterus and the size, extent and locations of the fibroid are important factors to consider when evaluating a patient for UAE. Some of these anatomic types have become adopted in practice guidelines, despite a lack of convincing evidence (Andrews et al. 2009). For some of these relative contraindications, there is evidence that UAE may provide acceptable outcomes. In any case, each patient's uterine anatomy needs to be evaluated in the context of the alternative therapies. For some patients, such as those with prior pelvic surgery or who are poor surgical candidates, UAE may clearly be the safest option, even when the fibroids present are not the ideal for embolization.

### 5.1 Large Uteri

Some UAE series have excluded very large uteri from treatment, with those greater than 24 weeks size not treated (Spies et al. 2001). This was done not based on prior knowledge of outcome, but with the concern that markedly enlarged uteri would shrink less than smaller uteri and might result in poorer outcomes (Fig. 4). One early small series called that presumption into question, with 12 women with uteri greater than 780 $cm^3$ compared with 49 women with smaller uteri (Prollius et al. 2004). There was no difference in complication rates and symptom control, but many of the patients with larger uteri did not have dramatic reduction in uterine volume and the authors suggested that this should be a part of counseling of patients with large uteri. Smeets and co-workers completed a similar but larger study of 71 patients with either a uterus greater than 700 $cm^3$ or a dominant fibroid greater than 10 cm in diameter (Smeets et al. 2010). They found no differences in this group compared with reported outcomes in patients with smaller uteri and concluded that uterine size should not be a barrier to UAE.

### 5.2 Large Dominant Fibroid

Similarly, a common concern is whether there is a limit to the size of fibroids that can be safely and effectively treated by UAE. McLucas has suggested that fibroids greater than 8.5 cm in diameter are likely to do poorly and this should be the limit of fibroid size treated (McLucas et al. 1999). Subsequent analyses by others have suggested large fibroids are not well-treated with UAE (Spies et al. 2002) and long-term failure leading to hysterectomy or myomectomy was more likely in larger fibroids (Spies et al. 2005b). This is in part is due to diminished patient satisfaction with less shrinkage that occurs with larger fibroids. The FIBROID Registry found that patients with large single fibroids tended to have poorer improvement in symptoms and satisfaction compared to a patient with a similar sized uterus but with multiple smaller fibroids (Spies et al. 2005a). Based on this considerable body of evidence, it is likely that patients with large fibroids may tend to have less satisfactory outcomes, but does that constitute a contraindication? The safety of treating large fibroids does not appear compromised compared to others, based both on the FIBROID Registry short-term outcomes (Worthington-Kirsch et al. 2005) and a study specifically assessing the safety of UAE

of these fibroids (Katsumori et al. 2003). These authors found no increased risk of complication in patients in a group of 47 women with fibroids greater than 10 cm. As noted above, Smeets did not find differences in women with large fibroids compared to those with smaller fibroids (Smeets et al. 2010). While caution may be indicated in women with large fibroids and patient counseling about the potential for somewhat diminished shrinkage and satisfaction is warranted in those with large fibroids, the treatment of them by UAE does not seem to be contraindicated.

### 5.3 Pedunculated Serosal Fibroids with Narrow Attachment

From the first report of UFE in 1995 (Ravina et al. 1995), there has been concern about potential complications associated with pedunculated serosal fibroids with a narrow attachment to the uterine body, with a fear of detachment of the fibroid after UAE (Fig. 5). This traditionally has been defined as a stalk with a diameter that is 50 % or less than the diameter of the fibroid itself. While there are anecdotes of detachment, there is little in the literature regarding these cases. We have also been concerned that this type of fibroid might predispose to bowel adhesions as the fibroid surface likely becomes inflamed after infarction and it would seem that this might be more likely the larger the fibroid.

There are some data to suggest that in fact the risk of complications may be low in these patients, including a recent published series on UFE in patients with pedunculated serosal fibroids, assessing the outcomes in 29 women (Smeets et al. 2009). These authors found similar outcomes in this group of patients as have been seen in other fibroid types, including similar infarction rates and no cases of fibroid detachment. Other studies have suggested less shrinkage for serosal fibroids (Spies et al. 2002), although no increase in complications. Thus, it seems clear that there is not a high rate of complications associated with pedunculated serosal fibroids and the proscription against treating these fibroids may be overstated.

Broad ligament fibroids may also be less likely to respond to uterine embolization, as they may have collateral sources of blood supply that makes complete treatment difficult. While there have not been studies published regarding broad ligament fibroids, a rare fibroid location, anectdotal experience suggests these are likely not to respond to UFE.

### 5.4 Cervical Fibroids

A recent study has specifically examined the outcomes of uterine embolization for cervical fibroids (Kim et al. 2012). Among a group of ten patients with cervical fibroids, only two of the ten had complete infarction of the fibroids and the authors also noted that cervical fibroids were commonly poorly vascularized. Although this is a small experience, it does suggest that this rare subset of fibroids may not be well-treated with embolization (Fig. 6). The difficulty is that these are often difficult to manage surgically and usually the only surgery that can be considered is hysterectomy. Thus, the best choice for patients with cervical fibroids is not clear in every case and coordination with the gynecologist is important to ensure the best choice of therapies.

## 6 Gynecologic Co-Morbidities

A final consideration is deciding on the best treatment when other gynecologic conditions are present in addition to fibroids. This is not an uncommon occurrence for fibroids to occur in women of late reproductive age, a group who also may develop adenomyosis, endometriosis, endometrial polyps, and other gynecologic conditions. The first question is which of the conditions is the primary cause for the patient's symptoms. When more than one gynecologic condition is present, a careful history combined with analysis of the imaging findings can often point to the pathology of greatest concern. While this often can be inferred from the history, it is not always clear. Unfortunately, symptoms caused by different conditions overlap and often the conditions coexist. Heavy and irregular menstrual bleeding may occur in a patient with both uterine fibroids and endometrial polyps and the cause for the problem could one or the other or both. Similarly, fibroids typically cause pelvic discomfort, aching pain or dysmenorrhea, while endometriosis causes severe burning perimenstrual pain. Yet a patient with pelvic pain may have both types of pain or be unable to distinguish the nature of the pain and it can be difficult to know which is the cause of symptoms (Fig. 7).

On many occasions, the true cause of the symptoms may not be discernable with certainty or symptoms may be caused by more than one condition. Our approach is to treat the key symptoms first, whether bleeding or pain. When fibroids are likely the primary condition, we approach their treatment first. If they do not appear to be the dominant problem, then it is best to recommend therapies for the other gynecologic condition and to address the fibroids later. On occasion, both conditions need treatment to have effective relief of symptoms. Medical decision-making can be quite complex when more than one gynecologic condition is present and it is important to complete the evaluation in collaboration with the patient's gynecologist to ensure appropriate consideration of all treatment options.

## 7 Summary

The key to appropriate patient selection is careful attention to presenting symptoms, physical findings, and imaging data. This will allow exclusion of those at risk and ensure the patients for whom UAE is offered the best outcomes, with a high likelihood of clinical symptom relief and a low risk of complications.

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# Clinical Results of Fibroid Embolisation, Trials and Registries

Reddi Prasad Yadavali and Jon. G. Moss

## Contents




### Abstract

Uterine fibroids are the most common tumour to affect women. Many are asymptomatic but when treatment is required there is almost always a choice. Uterine artery embolisation (UAE) is a relatively new minimally invasive technique and is usually one of the options. Initially slow to be accepted it is now a recognised, approved and funded procedure in most countries. It is the duty of any doctor to discuss all treatment options available with the patient. This discussion should be based on the best evidence available and it is the duty of the doctor to remain up-to-date with that information. The discussion should be fair, balanced and non-prejudicial. After the consultation patients should feel empowered to make an informed choice. The choice is usually between surgery and UAE and this chapter attempts to inform the reader of the current evidence base.


### Abbreviations

| | |
|---|---|
| EBM | Evidence-Based Medicine |
| HRQOL | Health-Related Quality of Life |
| SF-36 | Short Form (36) Health Survey |
| UAE | Uterine Artery Embolisation |
| UFS-QOL | Uterine Fibroid Symptom and Quality of Life |
| UK | United Kingdom |
| USA | United States of America |


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## 1 Introduction

Uterine artery embolisation (UAE) for fibroids was first reported in the English literature in 1995 by Ravina working in Paris (Ravina et al. 1995). He initially used it as a pre-operative procedure prior to myomectomy with the intention of reducing operative blood loss. When patients began reporting symptomatic relief before the myomectomy was scheduled attention was turned towards using UAE alone as definite treatment.

Although enthusiasts embraced UAE from the outset many were sceptical, particulary gynaecologists and activity levels varied widely from centre to centre and country to country. The drivers for more evidence were twofold; in some countries, for example, the U.K. government bodies such as the National Institute of Health and Clinical Excellence (NICE) began setting certain standards and criteria before a new procedure could be routinely used and secondly a joint report from the Royal College of Radiologists and the Royal College of Obstetricians and Gynaecologists (2000) following a death in London due to fulminating sepsis. The twenty-first century suddenly saw UAE being researched in a manner rarely seen with other Interventional radiology procedures. This chapter aims to distil the results of that work which includes national registries, cohort studies and randomised control trials. The final picture as always remains incomplete as more evidence appears and new trials start.

## 2 Evidence

Evidence comes in all forms and consequently varies in its strength and relevance. It is often displayed in pyramidal form (Fig. 1) where the best is in shortest supply there being many more "expert opinions" (lowest level) than meta-analyses (highest level). Collaborative groups such as the Cochrane initiative analyse the evidence and can produce drivers for more studies by indicating knowledge gaps or poor quality evidence.

### 2.1 EBM Pyramid

In Fig. (1) arrow indicates the direction of increasing quality of evidence with meta-analyses of randomised trials at the top and expert opinion at the bottom.

### 2.2 Levels of Evidence

*Scottish Intercollegiate Guidelines Network: Key to Evidence Statements* (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html)

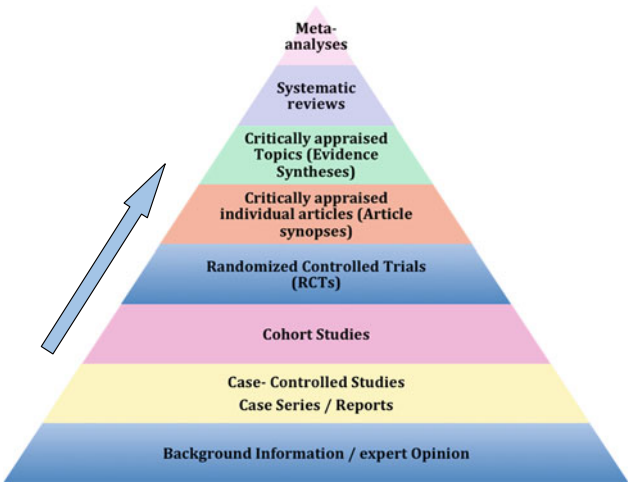


**Fig. 1** Quality of evidence

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1− Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort or studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2− Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies, e.g. case reports, case series
4 Expert opinion

### 2.3 Grades of Recommendation (http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html)

The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1+ , directly applicable to the target population, and demonstrating overall consistency of results

**Table 1** Outcome measures

| |
|---|
| **Safety data** |
| Mortality |
| Morbidity |
| **Efficacy** |
| Patient focussed outcomes (QoL) |
| Generic e.g. SF36, EuroQol5D |
| Disease specific e.g. UFSQol |
| Pelvic floor function scores |
| Qualitative research—patient satisfaction |
| Surrogate outcomes |
| Imaging outcomes (infarction rates, volume reduction) |
| Objective menstrual loss |
| **Long-term follow up** |
| Need for further treatment (hysterectomy, myomectomy, repeat UAE) |
| **Cost-effectiveness** |
| QALY |

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ , directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2+

**Good Practice Points**

Recommended best practice based on the clinical experience of the guideline development group.

## 3 Outcome Measures

One of the fundamental issues for any study is the setting and definition of appropriate outcome measures. These need to reflect the needs of all the stakeholders which include the patient, staff and healthcare providers. Table 1

Although from a purely scientific stance hard endpoints such as objective menstrual blood loss and volume reduction have their place they have been increasingly replaced by patient focussed outcomes. For example menstrual blood loss is a very subjective symptom and the objective reduction is of little interest to patients. Similarly the magnitude of uterine volume reduction is irrelevant unless associated with improvement of quality of life. The UFSQoL is the first and only fibroid specific questionnaire introduced in 2002 (Spies et al. 2002). This validated instrument consists of 38 questions, the first 8 give a symptom score and the remaining 29 a QoL score (6 domains, concern, activities, energy/mood, control, self-consciousness and sexual function.). The response options for the first 8 questions are presented as five point Likert scales where 1 = "not at all" and 5 = "a very great deal" in response to "how distressed were you by ?" For questions 9–37, the response options also are on a Likert scale where 1 = "none of the time" and 5 = "all of the time" in response to questions about health-related quality of life. Now considered the standard in assessing response to fibroid treatment it was not available for most of the randomised controlled trials.

## 4 Systematic Reviews and Meta-Analyses

### 4.1 Cochrane Review

The first Cochrane review of UAE was published in 2006 and then updated in 2011 (Gupta et al. 2006). Four trials were identified, two compared UAE with abdominal hysterectomy in 234 women (PINTO & EMMY). A third trial (REST) compared UAE with surgery (hysterectomy & myomectomy) in 157 women. The fourth trial (MARA) included 121 women and compared UAE with myomectomy in those wishing to preserve fertility.

The conclusions were that UAE significantly reduced hospital stay and time to resume normal activities. However UAE was associated with significantly higher rates of minor complications (OR 2.39, CI 1.55–3.7), unscheduled visits and readmissions after discharge (OR 2.5, 95 % CI 1.38–4.51). The re-intervention rate after 5 years follow up was significantly higher in the UAE group (OR 5.79, 95 % CI 2.65–12.65) and balanced out any earlier cost advantages of UAE over surgery. There was no difference in ovarian failure rates at long-term follow up. The only trial looking at fertility outcomes concluded that myomectomy appeared to have superior reproductive outcomes in the first 2 years.

The authors' conclusions were "UAE offers an advantage over hysterectomy with regards to a shorter hospital stay and a quicker return to routine activities. UAE appears to have an overall patient satisfaction rate similar to hysterectomy and myomectomy. Women opting for UAE should be counselled that there is a high surgical intervention rate in the longer term (at 5 years)".

The review points out the risk of detection bias due to no blinding of either participants or physician and that all the trials were small. Finally the single trial looking at fertility issues limits any conclusion to be made regarding the effects of UAE on fertility and future pregnancy.

### 4.2 Systematic Review and Meta-Analysis

The group in Holland who conducted the EMMY trial have recently (2011) produced a systematic review and meta-analysis of the current literature (Van der Kooij et al 2011). Only RCT's (REST, EMMY, MARA, PINTO) were included with a total pool of 515 women. There is much overlap with the Cochrane review but in summary short term outcomes such as blood loss, hospital stay and return to work were all significantly shorter than surgery. Mid- and long-term results showed similar health-related quality of life results but a significantly higher re-intervention rate after UAE. Both groups showed a similar and high degree of satisfaction with either surgery or UAE.

It was noted that a considerable number of the hysterectomies and myomectomies were carried out by an open abdominal approach skewing recovery times in favour of UAE. Advances in minimally invasive surgical approaches might narrow the gap.

## 5 Trials

The published trials are summarised in Table 2

### 5.1 PINTO

The first RCT from Spain published in 2003 was small, single centre and the methodology was unusual using the Zelen design (Pinto et al. 2003). Patients were randomly assigned to one of two groups: patients in the first group were informed about UAE and the alternative of hysterectomy and the other group was not informed of the option of UAE and underwent hysterectomy. All subjects had menorrhagia and fibroids >10 cm and those wishing to maintain fertility were excluded. Although initially 38 patients were assigned to first and 19 to second group, towards the end of study 40 patients underwent UAE and 20 hysterectomy. The primary outcome measure was length of hospital stay; secondary outcomes included satisfaction scores, return to work and complications. Although the primary outcome was assessed on the intention to treat principle (ITT) others such as safety and efficacy used the actual treatment received due to crossover from the groups. The technical success rate for the UAE arm was low at 88 %.

Complications occurred in 72 % (UAE group) and 45 % (hysterectomy group) respectively. Many of the UAE complications were minor and included the post embolisation syndrome. Hospital stay was significantly shorter in UAE group. A relatively high number of patients in both groups presented to the emergency department following hospital discharge, 32 % (UAE group) and 20 % (hysterectomy group). Five percent in each group were re-admitted to hospital. There was no further follow up beyond 6 months.

### 5.2 MARA

This single centre RCT from the Czech Republic randomised 121 patients between myomectomy and UAE. The initial results were published in 2006 with reproductive outcomes in 2008 (Mara et al. 2006; Mara and Maskova 2008). All had symptomatic fibroids and were planning to conceive. Exclusion criteria included the dominant fibroid being either submucosal or subserosal and any fibroid >12 cm. Of the 63 myomectomies 41 were laparoscopic and 21 open. Gonadotrophin levels were assayed.

The UAE group had a significantly shorter duration of procedure, hospital stay and recovery period. Imaging was performed at 6 months and if there were persistent fibroids >5 cm present then a myomectomy was recommended in both groups. This strategy resulted in a re-intervention rate of 33 % (UAE group) and 3 % (myomectomy group) respectively. No significant differences were seen in technical success rate, symptom control, re-intervention for fibroid recurrence or complications between the groups.

During the mean follow up period of 25 months, there were more pregnancies (33), labours (19) and fewer abortions (6) in the myomectomy group compared to UAE pregnancies (17), labours (5) and abortions (9). It was concluded the myomectomy group had a greater chance of pregnancy.

### 5.3 EMMY

This multicentre Dutch RCT randomised 177 patients between UAE and hysterectomy. The investigators have published 6 separate papers reporting a variety of different outcomes measures including follow up to 5 years (Volkers et al. 2006; 2007; Hehenkamp et al. 2005, 2007, 2008; Van der Kooij et al. 2010). Patients had menorrhagia and would ordinarily have undergone hysterectomy. Exclusions included those with submucosal fibroids with 50 % of their diameter in the uterine cavity and dominant pedunculated subserosal fibroids.

The primary outcome measure was control of menorrhagia at 2 years and the trial was powered assuming UAE would control the menorrhagia in 75 %. This trial in addition to the usual secondary endpoints (quality of life (SF36), satisfaction, hospital stay, complications) also used additional questionnaires (urogenital distress inventory, incontinence impact questionnaire and Wiklund menopause questionnaire). Gonadotrophin and antimullerain hormone were assayed in a subgroup.

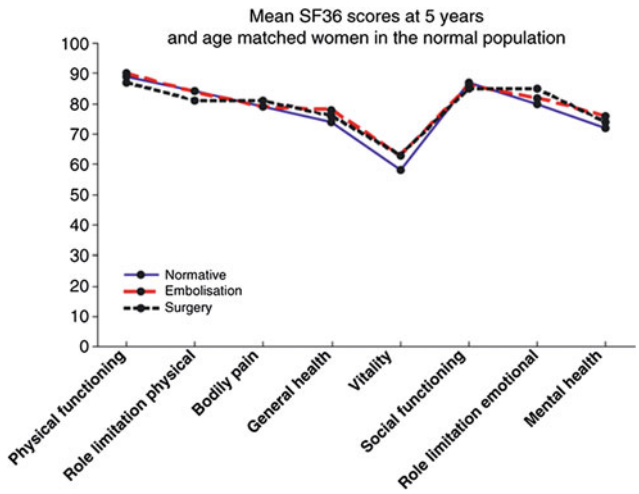


**Fig. 2** Mean SF36 scores at 5 years post-treatment and for age-matched women in the normal population. Reproduce by permission from BJOG

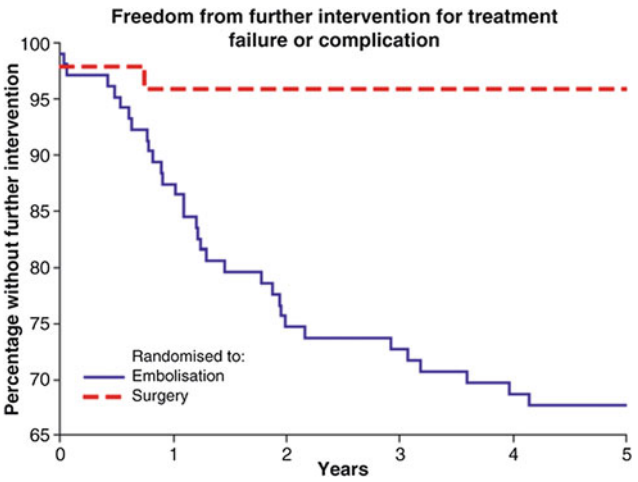


**Fig. 3** Kaplan–Meier curve showing freedom from further intervention for either treatment failure or complications Reproduce by permission from BJOG

An early publication reported a technical failure rate for UAE of 5.3 % and a procedural failure rate of 17.3 %. This very high overall failure rate was attributed to unfavourable anatomy but it is to be noted that this study had many operators who contributed only a very small number of cases. Length of hospital stay and time to resumption of normal daily activities were significantly shorter in the UAE arm. Complication rates at 30 days were similar but significantly higher in the UAE arm between 30 days and 6 months (62 vs. 41 %, $p = 0.01$).

Generic QoL (SF36, EuroQol 5D, Health utility Index), pelvic floor questionnaires and menopause outcomes were similar between groups at 1 year follow up. Satisfaction scores were high and similar in both groups.

Outcomes reported at 5 years in the final paper confirmed the earlier findings with the exception of the defaecation distress score which showed a significant difference between groups in favour of UAE ($p = 0.06$). The cumulative need for re-intervention by 5 years was significantly higher in the UAE arm (28 %) than the hysterectomy arm (11 %) ($p = 0.002$). The majority of the re-interventions following UAE were hysterectomies but curettage, myomectomy and endometrial ablation were reported. In the hysterectomy arm re-interventions included division of adhesions, oophorectomy and fistula repair.

## 5.4 REST

This multicentre U.K. RCT randomised 157 patients between UAE (106) and surgery (hysterectomy 43 and myomectomy 8). Twelve month outcomes were published in 2007 with final 5 year outcomes in 2011 (Edwards et al. 2007; Moss et al. 2011). Patients were symptomatic and would ordinarily have undergone surgery. Exclusions included pedunculated subserosal fibroids and where no fibroid was greater than 2 cm but there was no upper limit on size. All operations were open abdominal procedures. The primary outcome measure was QoL (SF-36). Secondary outcome measures included symptom and satisfaction scores, return to normal milestones, complications, adverse events and re-intervention for treatment failure. Gonadotrophin assays were separately reported at 1 year in a subgroup. A full economic analysis was carried out at 1 and 5 years.

Outcomes at 1 year showed no differences in QoL between groups. However, the symptom score improvement was significantly better in the surgery group ($p = 0.03$).The UAE arm had a significantly shorter duration of hospital stay (1 vs. 5 days, $p < 0.001$) and a significantly shorter time to regain normal lifestyle milestones which included return to work. Minor complication rates were similar 34 % (UAE group) and 20 % (surgery group) as were adverse events rates (UAE 12 %, surgery 20 %).

At 5 years, the improvement in QoL was maintained with no group difference (Fig. 2). Satisfaction scores were very high with again no group difference (UAE, 90 %) and (surgery, 87 %). Symptom score improvement was similar in both groups. The cumulative need for re-intervention at 5 years was significantly higher in the UAE arm (32 %) than the surgery arm (4 %) (Fig. 3). The initial cost benefit of UAE over surgery seen at 12 months was substantially reduced because of subsequent interventions, with treatments being cost neutral at 5 years.

## 5.5 FUME

This single centre U.K. RCT randomised 163 women with symptomatic fibroids between UAE (82) and myomectomy

(81) (Manyonda et al. (2011)). Women actively trying to conceive were excluded as were pedunculated fibroids and those extending above the umbilicus. All myomectomies were trans-abdominal. The primary outcome measure was quality of life using the UFSQoL. Secondary outcomes included hospital stay, complications and need for re-intervention.

The technical success rate for both procedures was high at 97 %. Hospital stay was significantly shorter after UAE (2 days) than myomectomy (6 days). Major complications rates were similar (3 % UAE) and (8 % myomectomy).

At 1 year there were significant and similar improvements in QoL across both groups.

At 2 years there were significantly more re-interventions in the UAE arm (14 %) than the myomectomy arm (3 %)

### 5.6 FEMME

This multicentre U.K. trial aims to randomise 650 women with symptomatic fibroids between UAE and myomectomy (http://www.hta.ac.uk/project/2378.asp). The primary outcome measure is QoL using the UFSQoL. Other outcomes include hospital stay, complications, pregnancy and need for re-intervention. It will include a cost benefit analysis. Funded by the National Institute of Health Research it commenced recruitment in 2012.

## 6 Registries

### 6.1 U.S.A. Fibroid Registry

This was a prospective multicentre registry which collected data from 72 sites over the period 2000–2002 (Worthinton-Kirsch et al. 2005; Spies et al. 2005; Goodwin et al. 2008). The majority of centres were from the U.S.A. with overseas contribution from the U.K. (4 centres), Canada (1 centre) and Hong Kong (1 centre). Three thousand hundred sixty patients were enroled with complete follow up data available for 1,278 patients at 36 months.

The technical failure was 4 %. Mean hospital stay was 1.68 days with 94 % of patients having one overnight stay. Adverse events during hospital stay were reported in 3 % of patients with the majority (79 %) being minor (Society of interventional radiology (SIR) class A or B). One femoral nerve injury did result in permanent leg pain (SIR class E).There were no deaths. Mean duration to resume normal activities was 14 days.

Thirty day follow up was available for 91 % of patients and the total adverse event rate was 26 % and major adverse event rate 4 % including emergency care or admission for recurrent pain or infection. The most frequent minor events were hot flushes and pain. One patient underwent a laparotomy and bilateral oophorectomy for pelvic pain (SIR class E). Follow up beyond 30 days included the UFSQoL questionnaire and re-interventions for fibroid-related symptoms by a central data collection centre using postal or/and telephone contact. At 12 month follow up, mean symptom score had improved from 58.6 to 19.2 ($p < 0.001$) and mean health-related quality of life score from 46.95 to 86.68 ($p < 0.001$). At 3 year (the final assessment) data was available for 1,278 patients and mean symptom scores improved 41.4 points ($P < 0.001$), and the quality of life scores 41.5 points ($P < 0.001$), both moving into the normal range for this questionnaire. About 29 % of the patients had amenorrhoea at 3 years, 79 % of these were aged >45 years with 5.5 % aged <40 years. It was not possible to determine causality in these cases. During the 3 years of the study, Kaplan–Meier estimates of re-intervention (hysterectomy, myomectomy, or repeat uterine artery embolisation) were 9.79, 2.82 and 1.83 % respectively.

Subgroups which seemed to have better outcomes included those presenting with menorrhagia as main symptom, those with smaller or submucosal fibroids, lesser symptoms at baseline and older patients with a lower BMI. Patients with cervical or lower uterine segment fibroids had poorer outcomes. Satisfaction scores were high 86 % would recommend the procedure to family members or friends.

### 6.2 BSIR/NICE UK Registry

A total of 59 centres in the United Kingdom contributed to this registry between 2003 and 2006. Thousand three hundred eighty seven patients were entered with initial follow up in 78 %. At 1, 2 and 3 year follow up was available for 48, 12 and 3 % respectively (http://www.bsir.org/Images/_Members/_Thomas_1303/File/uae_report_website.pdf).

Complications after discharge were reported in 14 % of patients most occurring within the first year and included fibroid expulsion, persistent vaginal discharge, deep vein thrombosis, uterine and urinary tract infections. One patient underwent small bowel resection to excise an adherent intramural fibroid. One patient was diagnosed with a uterine sarcoma 17 months after UAE and died 11 months later.

The complication rate was less in those receiving antibiotics.

In those with UFSQol data available 84 % of patients had improvement in symptoms at 6 months, which was maintained in 83 % at 12 months. Outcomes were similar in patients with pressure symptoms or menorrhagia. Increasing age of the patient was shown to be a positive indicator of outcome.

Repeat embolisation was performed in 5.4 %, hysterectomy in 2.7 %, myomectomy in 0.7 %, endometrial ablation in 0.3 % and other interventions in 6.7 % of patients. Seven pregnancies were recorded in the registry.

**Table 2** Trials summary

| | PINTO $n = 60$ | | MARA $n = 121$ | | EMMY $n = 177$ | | REST $n = 157$ | | FUME $n = 163$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Primary outcome measure* | Menorrhagia | | Pregnancy | | Menorrhagia | | QoL | | QoL | |
| *Procedure* | UAE | Surgery (H) | UAE | Surgery (M) | UAE | Surgery (H) | UAE | Surgery (H/M) | UAE | Surgery (M) |
| *Randomised allocation* | n/a[a] | n/a[a] | 58 | 63 | 88 | 89 | 106 | 51 | 82 | 81 |
| *Technical success* (%) | 90 | 100 | 90 | 92 | 83 | 100 | 97 | 98 | 97 | 98 |
| *Minor complications* (%) | 72[b] | 45[b] | 21[b] | 16[b] | 64[c] | 56[c] | 47[e] | 28[e] | 13[d] | 11[d] |
| *Major complications/Adverse events* (%) | | | | | 5[c] | 3[c] | 19[e] | 25[e] | 3[d] | 8[d] |
| *QoL* | n/a | n/a | n/a | n/a | ns[e] | ns[e] | ns[e] | ns[e] | ns[d] | ns[d] |
| *Re-intervention rates* (%) | 10 | n/a | 33[d] | 3[d] | 28[e] | 11[e] | 32[e] | 4[e] | 14[d] | 3[d] |

*ns* not significant, *n/a* not applicable, *H* hysterectomy, *M* myomectomy

[a] Zelen randomisation

[b] Minor and major complications at 1 month

[c] 6 weeks

[d] 2 years

[e] 5 years

## 7 Cohort Studies

### 7.1 HOPEFUL

A multicentre (18) retrospective cohort study from the U.K. comparing the safety, efficacy and cost-effectiveness of hysterectomy and UAE (Hirst et al. 2008). There were 459 hysterectomies and 649 UAE patients available with mean follow up of 4.6 years. Data was sought by case record review and direct contact with patients by postal questionnaire. Symptomatic relief was higher after hysterectomy than UAE (95 vs. 85 %, $p < 0.0001$) but fewer would recommend hysterectomy to a friend (70 %) than UAE (86 %) ($p = 0.007$). Complications were less frequent in UAE cohort (17.6 %) than the hysterectomy cohort (26.1 %). Infective complications were less common after UAE in those receiving prophylactic antibiotics. There was a 23 % (95 % CI 19–27 %) chance of requiring further treatment after UAE at 4.6 years.

The cost-effective analysis favoured UAE even allowing for re-interventions but this advantage could be eroded in younger patients if the re-intervention rate increased further.

## 8 Ovarian Function

Premature ovarian failure is defined as occurring aged <40 years. Amenorrhoea is defined as the absence of menstrual bleeding for at least 1 year. Ovarian function is classically assessed by a standard gonadotrophin hormone profile (FSH, LH & oestradiol). However these markers only become abnormal as the ovary finally fails. The REST, EMMY and MARA trials have all reported gonadotrophin outcomes. A new assay—antimullerian hormone gives a surrogate assessment of follicular reserve and is much more sensitive in detecting potential ovarian damage. Unfortunately only the EMMY trial used this assay and then only in a subgroup ($n = 63$).

REST and EMMY used an FSH level >40 IU/L and MARA FSH >20 IU/L to indicate ovarian damage. Results from REST and EMMY when pooled showed an elevation in these hormone levels but no group difference between UAE and hysterectomy (Hehenkamp et al. 2007; Rashid et al. 2010). The small subgroup having AMH levels measured showed a reduction after both UAE and hysterectomy with partial recovery in the hysterectomy group. There was no significance between group differences. The MARA trial showed no significant hormonal elevation from baseline in either group and no group difference.

A small prospective cohort study ($n = 36$) of women aged 26–39 years undergoing UAE were compared with a matched cohort of 36 control women over a 5 year period (Tropeano et al. 2010). Standard gonadotrophin assays and ultrasound ovarian volume and follicle measurements were taken. Although there was a significant loss of ovarian volume and function over time there was no group difference suggesting UAE does not lead to accelerated decline in ovarian function.

It would appear therefore that ovarian function deteriorates after both hysterectomy and UAE. The aetiology is unclear, interruption to ovarian blood supply is a strong possibility with both procedures but the natural history cohort study suggests it may simply be due to natural age-related ovarian attrition (Tropeano et al. 2010). Data from

the MARA trial showed no evidence of ovarian decline in either group.

It is important to keep an open mind on ovarian function bearing in mind the flaws in both the assays and relative small patient numbers. Larger trials such as FEMME using AMH in several hundred women should provide further information.

## 9 Fertility and Pregnancy

In 2004 the American College of Obstetricians and Gynecologists recommended that UAE should be considered investigational or relatively contraindicated in women wishing to retain fertility. The latest guidance from NICE in 2010 states "patients contemplating pregnancy should be informed that the effects of the procedure on fertility and on pregnancy are uncertain".

There has been one RCT (MARA) designed to look at fertility outcomes and it was small ($n = 121$) (Mara et al. 2006; Mara and Maskova 2008). The only other myomectomy trial (FUME) specifically excluded patients wishing to actively conceive (Manyonda et al. 2011). A third publication is a systematic literature review of 227 pregnancies reported after UAE which were compared with a group (matched for age and fibroid location) who became pregnant but had untreated fibroids (Homer and Saridogan 2010). This included the MARA trial data.

The MARA trial reported that 50 % of women who tried to conceive after UAE became pregnant compared with 78 % after myomectomy ($p < 0.05$). The live birth rate was 19 % (UAE group) and 48 % (myomectomy group) ($p < 0.05$). The rate of spontaneous abortion was 64 % (UAE group) and 23 % (myomectomy group) ($p < 0.05$).

The systematic review showed a significantly higher miscarriage rate in those who had undergone UAE (35 %) compared with the untreated fibroid group (16 %) ($p < 0.001$). However there was no difference in obstetric complications rates which included preterm delivery, malpresentation and intrauterine growth retardation (IUGR).

The Cochrane review stated that the MARA trial limits any conclusion to be made regarding the effects of UAE on fertility and future pregnancy (Gupta et al. 2006).

## 10 Complications/Adverse Events

Different publications have used different definitions for complications making it difficult to compare and summate the data. An example of a recognised classification system is that produced by the quality improvement and standards committee of the SIR (Sacks et al. 2003). This was used by the REST, EMMY and FUME trials, and U.S.A. Fibroid registry (Table 3).

**Table 3** Society of interventional radiology (SIR) Classification System for Complications by Outcome

| *SIR Classification System for Complications by Outcome* |
|---|
| *Minor Complications* |
| A. No therapy, no consequence |
| B. Nominal therapy, no consequence; includes overnight admission for observation only |
| *Major Complications* |
| C. Require therapy, minor hospitalisation (<48 h) |
| D. Require major therapy, unplanned increase in level of care, prolonged hospitalisation (>48 h) |
| E. Permanent adverse sequelae |
| F. Death |

The details of the types of both minor and major complications and adverse events are discussed in detail in Complications of fibroid embolisation. The REST trial found that the nature and timing varied between surgery and UAE; major adverse events in the surgical group occurred during the hospital stay, whereas in the UAE group, such events more commonly occurred after hospital discharge.

## 11 Deaths

There were no procedural-related deaths in any of the five RCTs. One death reported in the U.K. registry was due to a uterine sarcoma [http://www.bsir.org/Images/_Members/_Thomas_1303/File/uae_report_website.pdf]. No cause was specified for three deaths reported in the USA registry and one death mentioned in EMMY trial (Van der Kooij et al. 2010; Goodwin et al. 2008).

However additional deaths have occurred almost certainly related to the UAE procedure. Five have been published (Vashisht et al. 1999; de Blok et al. 2003; Lefebvre et al. 2004; Hamoda et al. 2009) but there are additional anecdotally recognised unpublished cases (Lanocita et al. 1999; 2001). Four patients have died secondary to pulmonary thromboembolism (Lefebvre et al. 2004; Hamoda et al. 2009; Lanocita et al. 1999) and two from sepsis-related complications (Vashisht et al. 1999; de Blok et al. 2003).

## 12 Cost-Effectiveness

Cost-effectiveness is an increasingly important issue with any medical treatment but particularly so for new technologies. There have been several publications from France, U.S.A. Netherlands (EMMY) and the U.K. (REST). Some of these use complex economic modelling and make various assumptions for different scenarios. However the basic

ingredients are cost and QoL with subsequent calculations of quality adjusted life years (QALYs). Costings can vary between different healthcare models and needs to be acknowledged if applying to another country.

A study from a single French hospital showed at 6 months UAE to be more cost-effective than vaginal hysterectomy (cost-effectiveness ratios were €2,300 and €2,789 per successfully treated case respectively) (Pourrat et al. 2003).

A study from the U.S.A. using a decision model comparing UAE with hysterectomy showed UAE to be the dominant strategy being more effective (8.29 vs. 8.18 QALYs) and less costly (US$6916 vs. US$7847) (Beinfeld et al. 2004). The HOPEFUL study using a probabilistic model showed UAE to be less costly (£2,536) than hysterectomy (£3,282) with a small reduction in QoL (8.203 vs. 8.241 QALYs) (Wu et al. 2007).

The EMMY trial reported the 24 month cumulative cost of UAE to be lower than that of hysterectomy and from a societal economic perspective claimed UAE to be a superior treatment strategy (Volkers et al. 2008). The REST trial reported (at 12 months) UAE to be substantially less costly than surgery by £951 (Edwards et al. 2007). However at 5 years this advantage had been eroded due to re-interventions in the UAE arm with both options being cost neutral (Moss et al. 2011).

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# Complications of Fibroid Embolisation

Joo-Young Chun and Anna-Maria Belli

## Contents




**Abstract**

Uterine artery embolisation (UAE) is a well-established procedure in the treatment of uterine fibroids. It is a safe procedure in experienced hands, but is not without serious complications. As our experience with the procedure has grown, our understanding of the nature and timing of these complications has also improved. A large number of observational studies and comparative studies of UAE versus surgery have reported a range of complication rates. Two large multicentre registries with the largest patient cohorts have also presented their data on adverse events. These complications are classified according to the Society of Interventional Radiology (SIR) guidelines and the evidence for each category is presented in this chapter. It is important to understand the causes of these adverse events and to maintain awareness during and after UAE, in order to ensure prompt diagnosis and appropriate management should they occur.


## 1 Introduction

As experience with uterine artery embolisation (UAE) has increased, our understanding of the nature and timing of complications has improved. Whereas most complications related to surgery are expected within 30 days and often before the patient has been discharged, complications associated with UAE may be delayed for months. Therefore, it is important for clinicians and patients to be aware of this difference in timeframe. The EMMY trial reported that the majority of UAE complications occurred following discharge, within the first 6 weeks (Volkers et al. 2006). Another large series reported up to a quarter of all complications occurring after 30 days and within the first year of treatment (Spies et al. 2002).


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**Table 1** Definition of complication class according to the Society of Interventional Radiology (Goodwin et al. 2003)

| | SIR class | Description |
|---|---|---|
| Minor | A | No therapy, no consequences |
| | B | Nominal therapy, observation, no consequences, includes overnight admission for observation only |
| Major | C | Required therapy, minor hospitalisation (<48 h) |
| | D | Major therapy, unplanned increase in level of care, prolonged hospitalisation (≥48 h) |
| | E | Permanent adverse sequelae |
| | F | Death |

The most comprehensive and widely used classification of complications is that recommended by the Society of Interventional Radiology (SIR) (Goodwin et al. 2003). All complications occurring within 30 days of the procedure are deemed to be procedure related. Each complication is graded according to severity (Table 1) and divided into general categories as follows:

- Complications of angiography
- Non-target embolisation
- Post-embolisation syndrome (PES) requiring prolonged admission, readmission or escalation of care
- Pelvic infection
- Fibroid passage requiring intervention
- Ovarian failure
- Sexual dysfunction
- Radiation injury
- Adverse drug reaction
- Pulmonary embolism (PE)/Deep vein thrombosis (DVT).

## 2 Overall Complication Rates

There are a large number of observational studies of UAE and comparative studies of UAE versus hysterectomy or myomectomy. The largest patient cohorts to date are two prospective, multicentre registries: UK Uterine Artery Embolisation for Fibroids Registry set up by the British Society of Interventional Radiology (BSIR) (O'Grady et al. 2009), and the Fibroid Registry for Outcomes Data (FIBROID) registry established by the SIR (Worthington-Kirsch et al. 2005). The 59 centres that participated in the BSIR registry recorded data on 1387 procedures and found an overall pre-discharge complication rate of 2 %, of which only 1 % resulted in delayed discharge, and 14 % post-discharge adverse events. The FIBROID registry consists of 3160 patients from 72 sites and reported an in-hospital complication rate of 0.66 % and 30 days post-discharge rate of 4.8 %.

A large prospective series of 400 patients by Spies et al. reported an overall complication rate of 8.5 % and a major complication rate of 1.25 %. (Spies et al. 2002). Several randomised controlled trials have described major complications in up to 15 % of patients following UAE (Pinto et al. 2003; Mara et al. 2006; Volkers et al. 2006; Manyonda et al. 2011; Dutton et al. 2007; Edwards et al. 2007) and smaller observational studies have also reported higher complication rates of 11–26 % (Razavi et al. 2003; Goodwin et al. 2006; Siskin et al. 2006). On the other hand, the most recently published prospective randomised trial (FUME) reported a much lower major complication rate of 2.9 % (Manyonda et al. 2011). A summary of complication rates from various reports are outlined in Table 2.

The joint standards of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) and the Society of Interventional Radiology (SIR) have produced quality improvement guidelines for UAE (Hovsepian et al. 2009). The reported complication rates and suggested threshold rates are outlined in Table 3.

## 3 Complications of Angiography

These are immediate complications related to the technical aspects of the procedure and include haematoma, contrast reaction, arterial dissection/rupture and femoral nerve injury. Such complications are rare in UAE as the patients are young with no underlying arterial disease and procedural anticoagulation with heparin is not required. Groin haematoma has been reported in 0.25–20 % of patients (Pinto et al. 2003; Spies et al. 2002; Manyonda et al. 2011; Goodwin et al. 2006; Siskin et al. 2006; Dutton et al. 2007), arterial injury has been seen in up to 0.5–10 % (Pinto et al. 2003; Spies et al. 2002; Pelage et al. 2000), femoral nerve injury in up to 1.6 % (Razavi et al. 2003; Spies et al. 2002) and adverse reaction to contrast medium in up to 2.5 % (Spies et al. 2002; Manyonda et al. 2011; Dutton et al. 2007).

The majority of these complications are minor requiring either no secondary intervention or overnight stay for observation. However, one of the largest case series of 400 consecutive patients reported a case of bilateral iliac artery thrombosis, which occurred during embolisation and required thrombolysis and intensive care therapy (Spies et al. 2002). This is a highly unusual complication which has not been reported elsewhere and unfortunately no detailed explanation has been offered by the authors.

**Table 2** Complication rates of observational and comparative studies of UAE

| Study | Years | N | Complications n (%) | | Reported complications |
|---|---|---|---|---|---|
| | | | Total | Major | |
| Goodwin et al. (1999) | 1999 | 60 | 13 (21.7) | 1 (1.7) | Hysterectomy for infection 1 |
| Siskin et al. (2000) | 2000 | 49 | 2 (4.1) | 2 (4.1) | Uterine/fibroid necrosis 1, prolonged fever 1 |
| Spies et al. (2001a) | 2001 | 200 | 14 (7) | 1 (0.5) | PE 1 |
| Spies et al. (2002) | 2002 | 400 | 34 (8.5) | 5 (1.25) | PE 1, arterial thrombosis 1, fibroid expulsion 3 |
| Pron et al. (2003a) | 2003 | 538 | – | – | Amenorrhoea 21 |
| FIBROID Worthington-Kirsch et al. (2005) | 2005 | 3160 | – | 20 (0.66)[a]<br>135 (4.8)[b] | Prolonged pain 6, infection/possible infection 17, fibroid passage 19 |
| Goodwin et al. (2006) | 2006 | 149 | 33 (22.1) | – | Fibroid expulsion 3, UTI 4, post-embolisation syndrome 4 |
| Mara et al. (2006) | 2006 | 30 | 18 (60) | 3 (10) | – |
| Siskin et al. (2006) | 2006 | 77 | 20 (26) | 0 | – |
| EMMY Volkers et al. (2006) | 2006 | 81 | 29 (35.8)[a] | (4.9)[a] | PE 1, fibroid expulsion 1, sepsis 1, UTI 2, post-embolisation syndrome 2 |
| | | | 51 (63)[b] | (11.1)[c] | |
| REST Edwards et al. (2007) | 2006 | 106 | – | 9 (12) | Pelvic infection 2, fibroid expulsion 3, necrotic fibroid 1, pelvic abscess 1, transient amenorrhoea 2 |
| HOPEFUL Dutton et al. (2007) | 2007 | 649 | 22 (19) | – | Amenorrhoea 1, sepsis 17 |
| BSIR registry O'Grady et al. (2009) | 2009 | 1387 | – | 15 (1)[a] | Respiratory arrest 1, fibroid expulsion 31, DVT 1, uterine infection 21 |
| | | | | 191 (14)[d] | |
| FUME Manyonda et al. (2011) | 2011 | 67 | – | 2 (2.9) | Pelvic sepsis 1, fibroid expulsion 1 |

*PE* pulmonary embolus, *DVT* deep vein thrombosis, *UTI* urinary tract infection
[a] during hospital stay
[b] from discharge until 6 weeks
[c] within 30 days of discharge
[d] following discharge

**Table 3** Complication rates for UAE (CIRSE and SIR quality improvement guidelines) (Hovsepian et al. 2009)

| Complication | Reported rate (%) | Suggested threshold (%) |
|---|---|---|
| Transient amenorrhoea | 5–10 | 10 |
| Permanent amenorrhoea <45yrs | 0–3 | 3 |
| Permanent amenorrhoea >45 yrs | 7–14 | 15 |
| Transcervical fibroid expulsion | 0–3 | 5 |
| Non-infectious endometritis | 1–2 | 2 |
| Endometrial or uterine infection | 1–2 | 2 |
| Deep venous thrombosis or pulmonary embolus | <1 | 2 |
| Uterine necrosis | <1 | 1 |
| Non-target embolisation | <1 | <1 |

## 4 Non-target Embolisation

There are multiple branches of the internal iliac artery which arise close together and there are known collateral communications with the ovarian arteries and contralateral uterine artery branches (Fig. 1). Therefore, it is important to be aware of the variations in normal anatomy and the presence of any arterial anastomoses that may open up during embolisation as the haemodynamics of the pelvic circulation is altered.

There are several reports of non-target embolisation during UAE. One woman was readmitted 8 days after bilateral UAE with profuse watery vaginal discharge and complete urinary incontinence, secondary to widespread cervical and vaginal necrosis with fistulation into the urinary bladder (El-Shalakany et al. 2003). She required hysterectomy and surgical closure of the bladder defect. The authors speculated that the extensive involvement of the vesical and vaginal blood supply may be secondary to thrombosis, occurring as a result of inflammation associated with ischaemic necrosis of the embolised fibroids. Another report described a patient presenting 4 days after-unilateral UAE with dysuria and purulent vaginal discharge, secondary to areas of necrosis in the cervix and ipsilateral lower vaginal wall (Löwenstein et al. 2004). She was successfully treated conservatively with analgesia and antibiotics.

**Fig. 1** Selective angiogram of the left uterine artery shows contralateral retrograde filling of the right uterine artery (Courtesy of Dr A Pankhania)

Another woman developed 2 areas of full-thickness buttock necrosis following UAE that required surgical debridement (Dietz et al. 2004).

It has also been suggested that UAE may reduce a woman's ability to achieve orgasm (Lai et al. 2000). The authors speculate that disrupting the uterine blood flow may result in altered perfusion of the uterovaginal plexus, which is responsible for sensory and autonomic innervation of the pelvic organs. Inadvertent non-target embolisation of the cervicovaginal branches, which arise from the uterine arteries, may contribute to the ischaemic effect. In contrast to this case report, a study of 141 premenopausal women who underwent UAE for symptomatic fibroids observed significant improvements in sexual function and well being while problems associated with orgasm and pain reduced (Voogt et al. 2008). Similar improvements in sexual activity and satisfaction following UAE have been described in other studies (Hehenkamp et al. 2007; Smith et al. 2004).

A fatal case of non-target embolisation has been reported in a patient that required 22 syringes of embolic particles to treat a 10 cm uterine fibroid. This patient developed multi-organ failure following UAE and the autopsy report stated the presence of an arteriovenous malformation within the leiomyoma, a patent foramen ovale and embolic particles in the lungs, heart and kidneys. Another fatal case was reported in a patient who underwent UAE with 11 vials of 500–700 μm (de Blok et al. 2003). The post-mortem showed diffuse necrosis of the pelvic organs and microspheres were found in the main uterine arteries as well as the smaller branches within the myometrium, leiomyomata, vagina and parametria.

As a general rule, large quantities of embolic agents and the use of small embolic particles should be avoided in order to minimise complications of non-target embolisation. The need for an unusually large volume of embolic agents should alert the operator of the possibility of an abnormal collateral supply or anastomotic communication. Careful scrutiny of images during embolisation should be performed to ensure the particles are being delivered to the appropriate end-organ, as evidence suggests that the amount of embolic particles is fairly similar in all cases and is not proportional to the fibroid or uterine size (Parthipun et al. 2010).

## 5 Post-embolisation Syndrome

Post-embolisation syndrome (PES) is characterised by low-grade fever, pain, leucocytosis and malaise. It occurs during the first 7–10 days following the procedure. And is an expected outcome after embolisation. PES should be anticipated in all women undergoing UAE and it becomes a complication only if the symptoms are severe i.e. necessitating readmission, prolonged admission beyond 48 h or unexpected escalation in the level of care (Goodwin et al. 2003; Bratby and Belli 2008). In early series of UAE, it was one of the main reasons for re-admission after discharge (Mehta et al. 2002). PES is now better understood although distinguishing this syndrome from an acute infection can be difficult as the signs and symptoms may mimic those of acute sepsis. Therefore, it is important to counsel women prior to UAE to warn them of PES symptoms in the early post-procedural period. In addition, they should be advised to seek urgent medical assistance if similar symptoms occur beyond the first 1–2 weeks in order to avoid delay in diagnosis of acute infection.

## 6 Pelvic Infection and Sepsis

Any pelvic sepsis is a contraindication to UAE. Although pelvic infection is uncommon following UAE, it can be a serious complication which may lead to sepsis, emergency hysterectomy or even death. Although there is no consensus on the use of prophylactic antibiotics, there is some evidence from the HOPEFUL trial and the BSIR registry that this may be beneficial (Dutton et al. 2007; O'Grady et al. 2009) and peri-procedural antibiotics are often administered in an effort to avoid infection.

It may be difficult to differentiate acute sepsis from PES as the clinical presentation is similar in the early stages. PES presents early, lasting from 7 to 10 days following embolisation with lower abdominal pain, fever and other flu-like symptoms.

Acute sepsis should be suspected in cases of delayed presentation with fever and pain beyond the expected period of PES. In order to avoid delay in diagnosis and appropriate management of sepsis, women should be counselled beforehand and there should be a low threshold for reviewing post UAE women by the radiologist or gynaecologist.

Hysterectomy has been performed for pelvic sepsis following UAE in 1–2 % of patients following embolisation (Edwards et al. 2007; Dutton et al. 2007; Pelage et al. 2000; Goodwin et al. 1999; Siskin et al. 2000). These include endometritis, which is an infection of the endometrium that has been reported in up to 1.6 % of UAE patients (Spies et al. 2002; Volkers et al. 2006; Goodwin et al. 1999). Magnetic resonance (MR) imaging may show uterine enlargement, thickened endometrium, intracavitary fluid or intrauterine gas. Although most patients respond well to intravenous antibiotics, hysterectomy may be necessary (Spies et al. 2002; Goodwin et al. 1999).

Fibroid abscess (pyomyoma) is a rare but serious complication where hysterectomy is the definitive treatment (Walker and Pelage 2002; Kitamura et al. 2005). It may be difficult to diagnose on imaging as gas in a fibroid can be a normal finding following embolisation.

Uterine necrosis is a rare but potentially life-threatening complication, which has been reported in up to 2 % (Pelage et al. 2000). Pelage et al. reported a case of acute septic uterine necrosis in a patient who presented 17 days post embolisation and required hysterectomy (Pelage et al. 2000). Siskin et al. reported another patient who underwent hysterectomy for pelvic sepsis which revealed necrosis of the fibroid and surrounding myometrium (Siskin et al. 2000). Possible causes include poor collateral circulation and small diameter embolic agents that occlude the distal branches. There is a general consensus that PVA particle sizes of less than 300 μm and microspheres of less than 500 μm should be avoided to lower the risk of ischaemic complications.

A common cause of pelvic infection is incomplete passage of fibroids, which may require hysteroscopic removal. This is most common with cervical and submucosal fibroids and may present with chronic vaginal discharge that does not settle. This is discussed in more detail in Sect. 7.

## 7 Fibroid Passage

Spontaneous expulsion of necrotic fibroids is one of the most common complications of UAE, occurring in 1.5–14.8 % of cases (Spies et al. 2002; Pinto et al. 2003; Edwards et al. 2007; Manyonda et al. 2011; Goodwin et al. 1999, 2006; Dutton et al. 2007; Pron et al. 2003b; Volkers et al. 2006; Abbara et al. 1999; Hovsepian et al. 2009; Pelage et al. 2000). Leiomyomas in contact with the endometrial surface, including submucosal fibroids and intramural fibroids with some submucosal component, are at increased risk of passage. Women at risk should be warned prior to UAE, especially if there are pedunculated fibroids (Hovsepian et al. 2009; Abbara et al. 1999; Dutton et al. 2007). A solitary pedunculated submucosal fibroid would therefore be more suitable for hysteroscopic removal than UAE.

Although the majority of cases do not require treatment, fibroid passage may be associated with pain as it is passed through the cervix. Surgical intervention may be required if the fibroid becomes impacted in the cervical canal, in order to treat/prevent infection or recurrent bleeding (Braude et al. 2000; Dutton et al. 2007; Abbara et al. 1999; Edwards et al. 2007; Manyonda et al. 2011; Volkers et al. 2006) (Fig. 2). A report describes a woman with heavy bleeding during fibroid passage who was, treated unsuccessfully with dilatation and curettage, and eventually required hysterectomy (Spies et al. 2002). Necrotic fibroids may also slough and pass as offensive vaginal discharge, which is seen in up to 25 % of cases (Spies et al. 2002; Pinto et al. 2003; Edwards et al. 2007; Goodwin et al. 2006; Dutton et al. 2007; Pron et al. 2003b; Volkers et al. 2006) (Fig. 3). In some cases, the vaginal discharge is profuse and may require hysteroscopic curettage to remove as much of the necrotic fibroid as quickly as possible.

## 8 Ovarian Failure

Ovarian dysfunction and menstrual disturbances are not uncommon following UAE. Although the exact mechanism remains unclear, it is thought to be due to undetected inadvertent embolisation of the ovaries via utero-ovarian arterial anastomoses (Razavi et al. 2002) and as a direct consequence of reduced uterine perfusion (Pron et al. 2003a). It has been shown in a surgical series that women who undergo hysterectomy with ovarian preservation experience premature menopause, thought to be due to disruption in the ovarian vascular supply (Siddle et al. 1987). In the same way, bilateral embolisation of the uterine arteries may compromise the ovarian blood supply via the utero-ovarian anastomoses, resulting in premature loss of ovarian function (Pelage et al. 2000).

The incidence of amenorrhoea following UAE appears to be age-related with women over 45 years of age at increased risk. The highest reported incidence of amenorrhoea following UAE is 15 % where 14 % showed biochemical and clinical features consistent with ovarian failure and presumed menopause (Chrisman et al. 2000). However, these findings were age-dependent with all 9 of 65 cases occurring in women over 45 years old. Another study assessed ovarian function using serial follicle


**Fig. 2** Five weeks after UAE, a large submucosal fibroid became impacted at the cervical os and required hysteroscopic removal with a good clinical result

**Fig. 3** Non-infected 'chicken soup' vaginal discharge following UAE (Courtesy of Prof J Reidy)

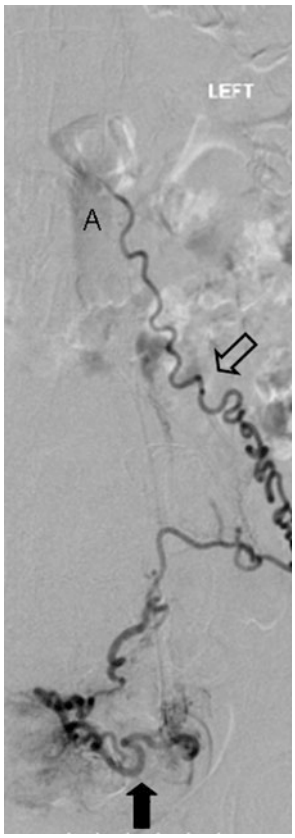


**Fig. 4** Contrast injection into left uterine artery (*filled arrow*) resulted in retrograde filling of the left ovarian artery (*unfilled arrow*) and opacification of the abdominal aorta (*A*)

stimulating hormone (FSH) levels following UAE (Spies et al. 2001b). Although none of these patients developed post-procedural amenorrhoea, women over the age of 45 a 15 % chance of increased basal FSH into the peri-menopausal range. A large multicentre prospective study of 538 patients undergoing UAE reported post-embolisation amenorrhoea in 8 % of cases (Pron et al. 2003). These findings were again highly age-dependent, with 3.9 % of women under the age of 45 versus 15.3 % of women over 45 developing amenorrhoea. Several suggested explanations for the higher risk of amenorrhoea in older women include a reduced overall ovarian reserve, increased sensitivity to disruptions in vascular supply and a natural consequence of ageing (Pron et al. 2003a; Chrisman et al. 2000). The presence of utero-ovarian anastomoses also increases the risk (Kim et al. 2007) (Fig. 3).

A recent study compared ovarian function following UAE versus surgery using FSH measurements (Rashid et al. 2010). The patient cohort was the same as in the randomised controlled REST trial (Edwards et al. 2007). The authors reported no significant difference in the rate of ovarian failure at 12 months between the two groups and highlighted that UAE does not have a detrimental effect on ovarian function in women below the age of 45 years (Fig. 4).

Although amenorrhoea is an unintended consequence of UAE and is therefore viewed as a complication, it may be a desirable outcome from the woman's point of view depending on the patient's expectations from treatment and the desire to maintain fertility following embolisation.

## 9 Pregnancy After Embolisation

UAE has been advocated in women wishing to preserve their fertility. However, there is relative lack of published data on the safety of pregnancies in women who have previously had UAE. A recent meta-analysis of 227 pregnancies from mostly small observational series suggests an increased risk of first trimester miscarriage and post-partum haemorrhage following UAE compared with control pregnancies with fibroids, but no difference in foetal growth and birthweight (Homer and Saridogan 2010). The reasons for these findings remain unclear but it has been suggested that this may be secondary to abnormal placental development following UAE resulting in a higher incidence of placenta accreta (Kitson et al. 2012). Although these observations raise concerns, there is lack of higher levels of evidence from larger randomised control to confirm these findings.

## 10 Deep Vein Thrombosis and Pulmonary Embolism

Patients with uterine fibroids are at higher risk of developing DVT due to an enlarged uterus compressing the iliac veins, which may result in venous stasis and thrombosis. UAE adds to this risk due to patient immobility due to pain and possible dehydration following the procedure. Therefore, prophylactic low molecular weight heparin and thromboembolism deterrent stockings are recommended before and after the procedure. DVT following UAE has been reported in up to 2 % of cases (Spies et al. 2002; Pinto et al. 2003).

PE is a rare complication of UAE with only two cases reported in the literature (Volkers et al. 2006; Spies et al. 2002). One patient presented 3 days after embolisation and required re-admission for anticoagulation and another patient required prolonged inpatient stay for anticoagulation.

## 11 Radiation Protection

Minimising radiation exposure is important in this group of patients, as the majority of women who are candidates for UAE are of childbearing age, some of whom wish to retain fertility for future pregnancies. It is therefore particularly important to adopt dose reduction techniques to avoid potential ovarian injury. Although the radiation dose associated with UAE is highly unlikely to result in acute or

long-term radiation injury to the patient or a measurable increase in the genetic risk (Nikolic et al. 2000), only modern angiographic equipment with dose reduction features should be used. Pulsed fluoroscopy with a low frame rate and careful coning should be used as the mainstay of intra-procedural imaging and angiographic runs should be avoided as much as possible (Bratby and Belli 2008; Braude et al. 2000; Goodwin et al. 2003).

Bilateral femoral arterial puncture technique has been shown to reduce fluoroscopy time and catheter manipulation compared to a unilateral access technique, with a 25 % reduction in simulated dose (Bratby et al. 2007). The same study demonstrated that the overall fluoroscopy time and patient dose are generally very low.

Women with large body mass indices are often referred for UAE as they are high risk for surgery. These women can receive large radiation doses during the procedure and should be warned that the procedure may have to be completed in two stages, one side at a time, if large radiation doses occur. It is helpful to apply a dose threshold in such cases, so that once this is reached, the procedure is stopped and re-scheduled.

## 12 Miscellaneous

Urinary tract infection is rare but has been reported in up to 5 % and urinary retention in up to 2 % (Spies et al. 2002; Pinto et al. 2003; Goodwin et al. 2006; Dutton et al. 2007; Volkers et al. 2006).

Small bowel obstruction has been reported in several cases following UAE (Payne and Haney 2003; Virmani et al. 2011; Goldberg et al. 2005). Necrotic subserosal fibroids lying adjacent to small bowel loops can result in intra-abdominal adhesions and subsequent bowel obstruction. One of these cases presented 7 months following embolisation with adhesions between a previously embolised subserosal fibroid and the pouch of Douglas, trapping a loop of small bowel (Goldberg et al. 2005).

In a rather unusual case, a patient presented 2 weeks post embolisation with extensive inflammatory changes adjacent to a subserosal fibroid. The patient was responded to antibiotics and was discharged but represented 7 months later with small bowel obstruction and a fistulous communication between the uterus and small bowel with an intraluminal mass at the transition point, which was later confirmed to be a hyalinised fibroid (Virmani et al. 2011). It is thought that the inflammatory changes around the subserosal fibroid caused bowel adhesions and fistula formation, and subsequent necrosis resulted in detachment of the fibroid and passage into the small bowel lumen.

## 13 Death

Two deaths have been reported in patients with uterine infection and severe sepsis. One patient developed acute sepsis and disseminated intravascular coagulation (DIC) secondary to a large necrotic fibroid 7 days after UAE with 355–500 μm polyvinyl alcohol particles (PVA) (Vashisht et al. 1999). Despite hysterectomy and intensive care management, the patient eventually died from multi-organ failure.

Two fatal cases of non-target embolisation have also been described in Sect. 4.

## 14 Conclusion

UAE is a safe procedure in experienced hands but, as with any intervention, it is not without serious complications. It is important to understand the causes of these adverse events and to maintain awareness during and after embolisation to ensure prompt diagnosis and appropriate management. The procedure, equipment and embolic materials should be standardised as much as possible in order to minimise technical and human error. Protocols and checklists may be useful.

All operators should be familiar with anatomical variations in the pelvic blood supply, especially the utero-ovarian anastomoses, and to actively look for these in order to avoid premature ovarian failure and non-target embolisation. All complications should be recorded and discussed as a team to encourage discussion and reflection, with the aim of identifying any patterns that led to the adverse incidents and implementing changes in practice to avoid future mistakes.

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# When to Consider Ovarian Artery Embolization in UAE

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## Contents



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**Abstract**

The ovarian artery is a major collateral pathway to the uterus and may act as a source of fibroid perfusion. This chapter gives an overview about the ovarian artery anatomy, imaging techniques to visualize collateral arterial supply to uterine fibroids, the technique of ovarian artery embolization (OAE) as well as the risks and benefits of supplemental OAE in the setting of uterine fibroid embolization.

## 1 Introduction

Uterine artery embolization (UAE) has become an accepted treatment option in patients suffering from symptomatic uterine leiomyomata (fibroids) with a high clinical success rate. Among other causes, incomplete devascularisation of uterine fibroids is considered to be an important negative prognostic factor for the long-term clinical outcome of the procedure (Pelage et al. 2004; Kroencke et al. 2006). Collateral arterial supply to uterine fibroids has been identified as a relevant cause for incomplete fibroid infarction and subsequent clinical failure (Nikolic et al. 1999; Matson et al. 2000). The ovarian arteries represent the major collateral pathway to the uterus with significant supply to uterine leiomyomata in up to 6 % of patients undergoing UAE for symptomatic fibroids according to the literature (White et al. 2007). In addition, the connection between the uterine and ovarian artery circulation, known as the uterine-ovarian anastomoses, represents a potential pathway for nontarget embolization of the ovary during UAE. Furthermore, supplemental ovarian artery embolization (OAE) has been advocated in selected cases of ovarian artery collateral supply to ensure complete fibroid infarction of targeted fibroids. Knowledge about the anatomy of the ovarian artery and recognition of this collateral pathway including types of uterine-to-ovarian artery anastomoses as well as knowledge about the technique, benefits,

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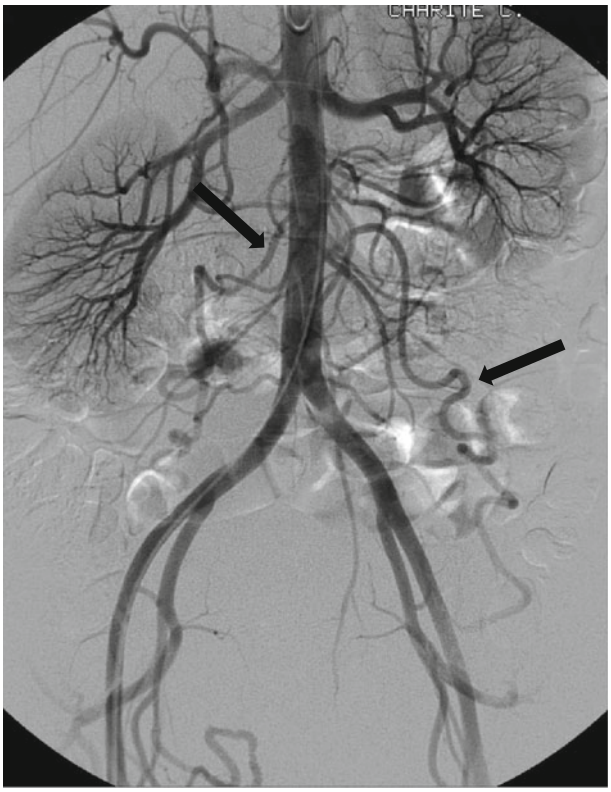

**Fig. 1** Flush aortography with a pigtail catheter positioned at the level of the renal arteries shows enlarged ovarian arteries (*black arrows*) which descend retroperitoneally into the pelvis and show the typical corkscrew appearance distally

and risks of ovarian artery embolization (OAE) is therefore of importance to interventional radiologists performing UAE.

## 2 Anatomy of the Ovarian Artery

The ovarian arteries generally originate as paired vessels from the anterolateral aorta below the renal arteries at the level of L2 (see Fig. 1).

They may also arise above or below the renal pedicle from L1 to L4. In cadaveric studies, it is reported that in 6–12 % of cases the ovarian arteries originate directly from the renal arteries, particularly from accessory renal arteries and most commonly from the right (Shoja et al. 2007). In cases where the ovarian artery comes off an accessory renal artery, associated anomalies, such as a common trunk to supply the adrenal gland or replacement of the inferior phrenic artery has been described (Notkovich 1956; Rahman et al. 1993). Seldomly, an ovarian artery may arise in an aberrant fashion from the inferior mesenteric artery (Smoger et al. 2010; Dixon et al. 2012), the common iliac (Kim et al. 2013), external iliac artery (Kwon et al. 2013), or internal iliac artery (Reed and McLucas 2012). The ovarian artery


**Fig. 2** Selective angiography of the right ovarian artery shows small branches to the retroperioneum (*black arrow*) and filling of the perifibroid plexus vessels of a leiomyoma

descends retroperitoneally on the psoas muscle, gives branches to the retroperitoneum (Fig. 2) and ureter, which it crosses anteriorly, and can be identified by its characteristical serpentinous ("corkscrew") distal segment before it enters the pelvis (Frates 1969). The ovarian artery then courses medially in the suspensory ligament of the ovary (Syn.: infundibulo pelvic ligament) toward the uterine cornu and gives of branches to the ovary on its lateral border. The tubal branch of the ovarian artery supplies the fallopian tube and variable anastomoses with the uterine artery (uterine-to-ovarian artery anastomoses), lateral and inferior to the junction of the uterine body, and to the fallopian tube (Sieunarine et al. 2005).

## 3 Classification of the Uterine-to-Ovarian Artery Anastomoses

Razavi proposed a classification of the ovarian artery-to-uterine artery anastomoses (Syn.: uterine-to-ovarian artery anastomoses, UOA) distinguishing three patterns based on selective angiography (Razavi et al. 2002).

According to this classification, a Type I pattern describes an ovarian artery that connects to the intramural uterine artery before branches supply the fibroid(s). Type I can be further subdivided into a Type Ia and Type Ib. In Type Ia, the ovarian artery is a major source of blood supply to the fibroids by means of anastomosis with the intramural uterine artery. In these cases, the flow is toward the uterus, without evidence of retrograde reflux in the direction of the ovary on selective uterine artery angiograms. In Type Ib, the ovarian artery supplies the fibroids in a similar manner as in type Ia. Flow is toward the uterus; however, reflux into the ovarian artery is seen on the selective uterine artery angiogram. In Type II, the ovarian artery supplies the fibroids directly. Although anastomoses to the intramural uterine artery may exist, the flow to the fibroids is anatomically independent of the uterine artery. In Type III, flow is continuous toward the ovary on selective uterine angiograms and washout of the contrast material does not occur from the direction of the ovary within the anastomosis. Theoretically, clinical failure after UAE is likely in patients with Type II and is possible in patients with Type I utero-ovarian anastomosis, whereas those with Type III may rather bear the risk of inadvertent (nontarget) ovarian embolization with resulting ovarian failure. It has to be kept in mind that the uterine-to-ovarian anastomosis has been directly observed in only 40–50 % of cases undergoing UAE using selective uterine artery angiography, while anastomoses between ovarian branches of the ovarian and uterine arteries have been observed in a constant fashion in cadaveric studies employing injection of contrast media under X-ray (Razavi et al. 2002; Kozik 2000; Kim et al. 2006).

Moreover, this classification does not include the anatomic relationship between uterus, fallopian tube, and ovary with variant supply of the fallopian tube which is part of the uterine artery-to-ovarian anastomosis (Dubreuil-Chambardel 1925). This calls into question if standard angiography is sufficient and reliable to visualize this vascular connection. The frequency of the types and the significance of these patterns, as described by Razavi et al., and the impact on fibroid perfusion as well as ovarian function is still debated. In a large study including 202 patients undergoing UAE for symptomatic fibroids Lanciego et al. did not find an association between clinical outcomes and any of the types of ovarian artery-to-uterine artery anastomoses (Lanciego et al. 2012). Other factors, such as patient age, may be far more important to ovarian function than visibility and type of ovarian artery-to-uterine artery anastomoses identified on an arteriogram during UAE (Hu et al. 2011) (see Table 1).

## 4 Uterine Artery-to-Ovarian Artery Anastomoses, Ovarian Perfusion, and Function in the Setting of UAE

Several articles address the role of the uterine artery-to-ovarian artery anastomoses in the setting of UAE with respect to subsequent ovarian function. Given the fact that embolic particles can reach the ovary via this anastomosis, the type of anastomosis, the flow direction during embolization, and the size of particles may contribute to the extent of nontarget embolization of ovarian stroma and subsequent reduction of ovarian function (Payne et al. 2002). It has been postulated that larger sized particles may prevent nontarget embolization of the ovary but this has not been substantiated in further studies. Coil embolization of prominent uterine artery-to-ovarian artery anastomosis has been proposed as a measure to prevent premature ovarian failure (Marx et al. 2003). This approach is possible only in a minority of cases where the anastomosis can be reached without difficulties and creating spasm.

Ryu et al. assessed the delayed effects of uterine artery embolization on ovarian arterial perfusion by performing ovarian sonography immediately before and after UAE, as well as several months later. They showed that although persistent loss of detectable arterial perfusion after UAE occurs in some women, most patients reestablish arterial perfusion and do not develop symptoms of ovarian failure (Ryu et al. 2003).

Kim et al. reported in a cohort of 124 women (mean age, 43.1 ± 5.7 years) undergoing UAE for symptomatic fibroids patent anastomoses between the uterine and ovarian arteries in 55 patients (44.4 %) detected by angiography (Kim et al. 2006). Changes in basal follicle-stimulating hormone (FSH) level obtained on day three of the menstrual cycle before and 6 months after uterine artery embolization (UAE) were more frequent in women with observed patent anastomoses but also highly age dependent. Salazar et al. compared the incidences of symptom recurrence and permanent amenorrhea following uterine artery embolization (UAE) for symptomatic fibroid tumors in patients with Type I and II utero-ovarian anastomoses with versus without supplemented ovarian artery embolization (OAE) and did not find a significant difference regarding permanent amenorrhea rates but higher symptom recurrence rates were observed when OAE was not performed in the setting of UOA (Salazar et al. 2013) (see Fig. 3).

**Table 1** Angiographic classification of Ovarian-to-Uterine Artery Anastomoses according to Razavi et al. based on selective uterine artery angiogram as well as pre- and post-UAE flush aortography

| | |
|---|---|
| Type I | The ovarian artery is a major source of blood supply to the fibroids by means of anastomosis with the intramural uterine artery |
| Type Ia | Flow within the anastomosis is toward the uterus. No evidence of retrograde reflux in the direction of the ovary on selective uterine artery angiograms |
| Type Ib | Flow within the anastomosis is toward the uterus but reflux into the ovarian artery is seen on pre-embolization selective uterine artery angiograms |
| Type II | The ovarian artery supplies the fibroid(s) directly |
| Type III | Flow in the anastomosis is continuously toward the ovary with an ovarian blush on selective uterine artery angiograms. Wash out occurs in the direction of the ovary |

Adapted from Razavi MK, Wolanske KA, Hwang GL et al. Angiographic classification of ovarian artery-to-uterine artery anastomoses: initial observations in uterine fibroid embolization. Radiology 2002; 224:707–712

**Fig. 3** Selective angiography of the left ovarian artery shows collateral perfusion of the uterus. Opacification of vessels supplying the left ovary (*black arrow*) is also noted

Although a plethora of prospective studies have been undertaken to assess the relation between UAE and ovarian function by using hormonal assays and ultrasound measurements, only three of these were comparative studies comparing UAE to surgical treatments such as myomectomy or Hysterectomy. These studies show no differences in FSH level between the treatment groups (Salazar et al. 2013; Healey et al. 2004; Hovsepian et al. 2006; Tropeano et al. 2010). Two studies including the randomized EMMY trial comparing UAE to hysterectomy showed, however, a decrease in anti-mullerian-hormone (AMH), a marker which is cycle independent and considered more sensitive to test the extent of ovarian reserve (Healey et al. 2004; Hehenkamp et al. 2007). Ovarian reserve is a term used to describe the functional potential of the ovary and reflects the number and quality of oocytes within it. To evaluate the extent of ovarian reserve reduction, day three FSH is of limited value since it is an indirect marker, reflecting the hormonal balance between the ovaries and the hypothalamo-pituitary axis and large intercycle variations in basal FSH occur (Maheshwari et al. 2006).

In the EMMY trial, FSH increased significantly compared to baseline at 24 months follow up after hysterectomy and UAE. No differences in FSH values between the groups undergoing UAE versus hysterectomy were found. AMH levels were significantly reduced during the entire follow up period only in the UAE group compared to the baseline values and expected AMH decrease due to aging. However, a significant difference between UAE and hysterectomy group was only observed at 6 weeks follow up but not during the later course of the study. A number of studies assessed clinical and hormonal outcome by age groups and concluded that UAE does not significantly affect ovarian function in women under age of 45 years (Tropeano et al. 2004, 2010; Spies et al. 2001; Tulandi et al. 2002). For an in-depth review on the issue see Kaump et al. (Kaump and Spies 2013).

## 5 Imaging of the Ovarian Artery and Indication for Ovarian Artery Embolization

As early as 1999, several reports have confirmed the possibility of clinical failure after UAE due to collateral supply of uterine fibroids by the ovarian artery (Nikolic et al. 1999; Matson et al. 2000; Andrews et al. 2000). Pelage et al. reported that ovarian artery supply of fibroids were more common in women with large fundal fibroids, previous tubo-ovarian pathology, or surgery (Pelage et al. 2003). Additional ovarian artery embolization has been advocated

for these selected cases (Andrews et al. 2000; Pelage et al. 2003; Barth and Spies 2003; Scheurig-Muenkler et al. 2011). The decision to perform ovarian artery embolization (OAE) should be based on the extent of collateral supply and includes careful analysis of pre-UAE MR angiography, if available as well as unselective and selective catheter angiography during the procedure. Appropriate counseling prior to adjunctive OAE is mandatory (Andrews et al. 2009).

Due to its high spatial and temporal resolution, flush aortography is the reference standard for imaging of the ovarian arteries. However, the standard use of flush aortography prior to UAE is of limited value. Binkert et al. demonstrated ovarian collateral arteries on *Pre-UAE* Aortography in 13/51 patients (25 %), but their detection influenced treatment in only 6 % of the reported cases (Binkert et al. 2001). Furthermore, it has to be kept in mind that flush aortography adds up to 20 % of the total radiation dose of a UAE procedure (White et al. 2007).

Abbara et al. concluded from their study on the use of flush aortography *after* UAE that the presence of residual fibroid perfusion is more likely if the ovarian arteries are large, have rapid flow, or have flow that extends into the pelvis and recommended selective ovarian artery evaluation in these cases to determine the extent of residual fibroid perfusion (Abbara et al. 2007).

In a retrospective study of 1,128 consecutive women undergoing UAE for uterine fibroids, White et al. reviewed *Post-UAE* flush aortographies performed in 1,072 patients (White et al. 2007). Based on the criteria published by Abbara et al., selective ovarian artery angiography was performed to confirm ovarian artery supply to targeted fibroids. Around 17 % of patients undergoing UAE in their retrospective study had at least one visible ovarian artery on Post-UAE flush aortography which either was visible down to the level of the ovaries and/or showed rapid arterial flow. Sixty two (5.8 %) patients were identified at selective ovarian angiography as having collateral OA supply of the uterus and embedded fibroids.

Overall, Post-UAE flush aortography identified fewer than 1 % of patients as having substantial ovarian artery collateral supply and had a sensitivity of less than 25 % in identifying patients with residual uterine perfusion from an ovarian artery. The authors concluded that post-UAE aortography rarely helps to identify patients with substantial residual OA supply to the uterus and is a poor predictor of the extent of that supply, and thus its routine use during UAE is not recommended.

It has been shown that magnetic resonance angiography (MRA) included in a pre-UAE MR imaging exam can visualize enlarged ovarian arteries (Kroencke et al. 2006; Mori et al. 2010). The size of these enlarged ovarian arteries, usually as large or larger than the diameter of lumbar arteries, is an important finding suggesting relevant collateral supply to the uterus (see Fig. 4).

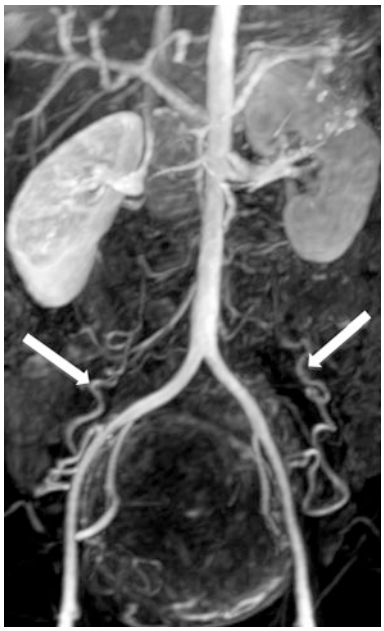

**Fig. 4** Contrast-enhanced (ce) magnetic resonance angiography (MRA) prior to UAE. Enlarged ovarian arteries (OA) are detected (*white arrows*). The size of both OA is equal or larger than lumbar arteries in their pelvic segments

However, the direct visualization of enlarged ovarian arteries is an imperfect predictor. It is known that dilated ovarian arteries seen on pre-UAE aortography may not be visible after the embolization of uterine arteries, presumably due to occlusion of the relevant fibroid supply resulting in a reduction in the "sump effect" of the fibroids with reduced demand through the uterine-to-ovarian artery anastomosis or embolic occlusion of the anastomosis after UAE (Binkert et al. 2001). This may be the case in Type I uterine-to-ovarian artery anastomosis representing an OA connected to the intramural UA. In these cases although markedly enlarged OA are identified on preinterventional contrast-enhanced MR angiography, a relevant OA supply may not be confirmed on post-UAE aortography.

A possible explanation is the reduced demand via this collateral pathway after UAE.

In a study conducted by Lee et al., the likelihood of supplemental OAE was significantly higher in those patients who had small or nonvisible uterine arteries on contrast-enhanced MR angiography (Lee et al. 2012). The uterine artery diameter and presence of enlarged ovarian arteries had a high specificity and negative predictive value for ovarian artery collateral supply, but the uterine artery diameter was a better criterion than the detection of enlarged ovarian arteries by MR imaging. CT Angiography with its unchallenged spatial resolution can delineate the ovarian and uterine arteries. It has been advocated for failed

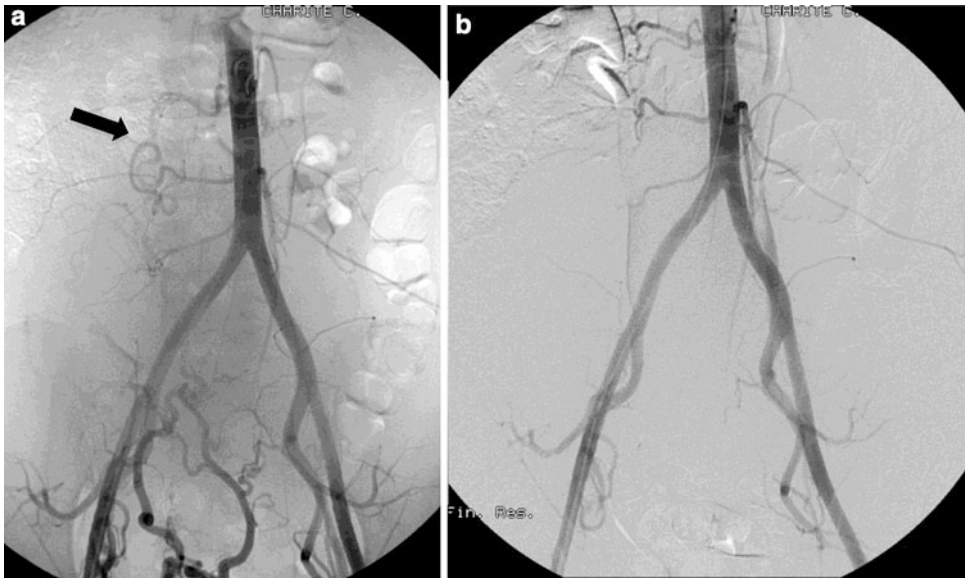


**Fig. 5** Flush aortography prior (**a**) and post uterine artery embolisation (**b**) After UAE the right ovarian artery (black arrow in Fig. 5a) is not opacified anymore.

UAE procedures to identify collateral and persistent uterine artery supply but it does add little information compared to MR Imaging and is associated with significant radiation exposure to the patient which does not seem to justify routine use (McLucas 2009).

In summary, integrating MR angiography into the *pre-interventional* imaging exam seems to be currently the best approach to determine the possibility of ovarian artery collateral supply. In case of clinical failure after UAE, interventionists have to look for the possibility of collateral supply of uterine fibroids by previously undetected ovarian arteries.

## 6 Technical Aspects

Catheterization of the ovarian artery is sometimes challenging due to the steep angle of origin from the abdominal aorta. Reversed-curve catheters such as a 0.038-inch inner lumen Sos-Omni or the Mikkaelsson type configuration give stability within the aorta but also allow to enter the orifice of the vessel (Fig. 6a, b). It is recommended to use a microcatheter which is coaxially advanced over a microwire into the usually straight first part of the ovarian artery. Tension on the vessel must be avoided since the ovarian artery is prone to spasm and spasmolytics should be given if necessary. In most cases, it is neither necessary nor advisable to advance the microcatheter as far as possible since this is usually resulting in spasm due to the tortuosity of the ovarian artery. Limitation of flow should be avoided to ensure that the particulate embolic agent is reaching the perifibroid plexus. Gelatine sponge, nonspherical PVA (355–550 μm), as well as spherical microspheres in the size range of 700 to 900 μm have been used as embolic agents (Hu et al. 2011; Barth and Spies 2003; Scheurig-Muenkler et al. 2011; Kim et al. 2007). The recommended angiographic endpoint for embolization is near-stasis (Fig. 6c, d) with occlusion of the branches feeding the uterus (Hu et al. 2011; Scheurig-Muenkler et al. 2011).

## 7 Clinical Outcome After Ovarian Artery Embolization

Very few studies have investigated safety and clinical outcome of ovarian artery embolization.

In early reports, the embolization of the ovarian artery was reported to be technically feasible, safe without affecting the menstrual cycle, and successful with alleviation of fibroid-related symptoms of treated patients (Andrews et al. 2000; Pelage et al. 2003). Salazar et al. compared the incidences of symptom recurrence and permanent amenorrhea following UAE for symptomatic fibroids in patients with Type I and II uterine-to-ovarian artery anastomoses with versus without ovarian artery embolization (OAE) and found no statistical differences in permanent amenorrhea rates in the groups studied, but a significantly higher symptom recurrence rate when OAE was not performed (Salazar et al. 2013) Barth et al. analyzed 6 patients treated by supplemental OAE and found no effect on the menstrual cycle of these women and reported clinical success in five of them (Barth and Spies 2003). Our group from Charité reported on 13 patients who underwent UAE and additional OAE and in 10 of the 13 patients, improvement or complete resolution of clinical symptoms was observed.

These women presented with regular menses. Two patients, 47 and 48 years, both treated with additional unilateral OAE, reported permanent amenorrhea directly after

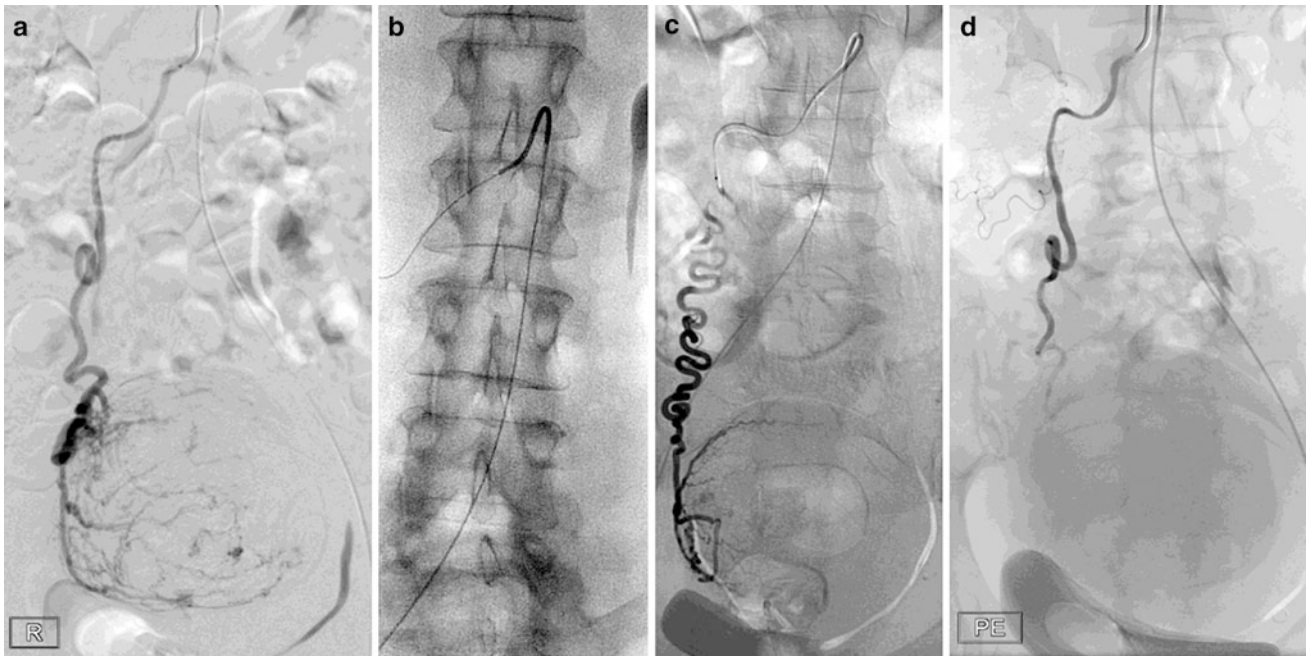


**Fig. 6** Selective catheterization of the right ovarian artery by a 0.038 inner lumen Sos Omni catheter (**a**). A microcatheter is coaxially advanced (**b**). Selective angiography through the microcatheter positioned in the straight part of the ovarian artery reveals collateral supply to a fibroid uterus (**c**). Post ovarian artery embolisation (OAE) angiography shows standing column of contrast within the OA and no opacification of terminal uterine branches (**d**)

embolization (Scheurig-Muenkler et al. 2011). In the largest series published to date, 77 patients of a cohort of 1,451 patients (5.3 %) underwent additional OAE (Hu et al. 2011). In this single-center case–control study, 51 patients undergoing OAE were compared to 49 control subjects using the Menopause Rating Scale (MRS), a validated menopausal symptom questionnaire. Compared with standard UAE, the addition of OAE did not precipitate the onset of menopause nor did OAE increase the menopausal symptom severity.

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# Early Post UAE Management

Elizabeth A. O'Grady and Geoff Shaw

## Contents




**Abstract**

Uterine artery embolization for fibroids provides a treatment with low morbidity, and short in-hospital stay. An understanding of the expected post procedure course, and of the potential problems that can occur is essential to manage patients in this period effectively, to reduce patient anxiety, and unnecessary re-admissions. In contrast to surgery (hysterectomy) most complications occur after discharge. Effective communication of the expected outcomes and potential serious complications is therefore required to both patients, and other clinicians.


## 1 Introduction

In this chapter, we will discuss the care of the patient after uterine artery embolisation (UAE) from the time the patients leaves the radiology suite, up to and including the first follow-up appointment, usually between 4 and 8 weeks post procedure.

## 2 In Hospital Care

The management of patients after UAE can be undertaken by either the gynaecologist, the interventional radiologist, or most effectively, by a combination of both specialists working together. Whoever undertakes care of the patient must however be fully aware of the expected normal post procedure course, of possible complications, and be able to impart clear information to the patient and to their primary care physician. Managing the patient's expectations is a key part to care during this period.

Where nursing staff are not used to caring for patients post transarterial embolisation, a brief programme of education will prove helpful; an understanding of the differences post UAE compared to post surgery will enable ward staff to care most effectively for these patients.


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## 2.1 Length of Stay

Many institutions admit patients post UAE for a single night. The main reason for this is to achieve adequate pain control. Some institutions will discharge the patient later the same day, if for example, they were treated early in the day, and are fit for discharge the same evening (Siskin et al. 2000).

It is our practice to admit patients for one night, with very few patients requiring a prolonged stay. The commonest cause for delayed discharge is for pain control.

A number of patients will choose to undergo UAE rather than surgery because of adverse social conditions or pre-existing co-morbidities. In our experience the majority of these patients will also be fit for discharge the following day. The presence of additional morbidities rarely necessitates prolongation of length of stay.

## 2.2 Care of the Puncture Site

Increasingly, interventional radiologists are becoming bed holders with admitting rights. If following UAE, the patients are admitted to a Gynaecology bed, rather than to an Interventional Radiology bed, nursing staff in gynaecology wards may be unused to caring for patients post angiographic procedures. It is important to give clear instructions regarding period of bed rest and time to mobilisation, the observations required and how to regain haemostasis in the event of bleeding from the puncture site.

Closure devices are small "plugs" used to seal the arterial puncture, and are commonly used if early mobilisation and discharge after angiographic procedures is required. In our practice, as patients are being admitted overnight post procedure for symptom control and pain relief we do not use closure devices. Use of a closure device does add to the consumable costs. If patients are to be discharged the same day, then these may be useful, with the cost being offset by the savings of no overnight stay.

## 2.3 Pain Control

Pain relief is the main issue in the management of patients in the first few hours post procedure. When establishing a UAE service it is useful to engage with your institution's existing pain relief team, and/or anaesthetic department. It is important to ensure that any pain relief protocols used are in line with those already in use elsewhere. Common protocols avoid confusion and improve compliance as they will be familiar to nursing and medical staff in departments outside of radiology.

The pain will usually commence whilst the patient is still in the Interventional Radiology room. Patients may on occasions, however, experience relatively mild pain until after they have left the interventional room, and if pain is not anticipated, the patient can become quite distressed during, for example, transfer to a ward. Regaining control of pain in an agitated patient is more difficult than controlling the pain adequately to start with. Adequate pain relief in the post procedure period is also likely to be a key determinant in the patient's overall satisfaction, or otherwise, with the whole procedure.

A number of different pain management regimens have been described, most using narcotic analgesics and Non Steroidal Anti-Inflammatory Drugs (NSAIDs), usually in combination. Our practice is summarised in Table 1.

The patient is premedicated prior to UAE with 50 mg Diclofenac PR before the procedure. We then commence a patient controlled analgesia pump (PCA) containing 100 mg Morphine in 50 ml syringe driver which administers with each patient request a 1 mg bolus with a 5 min lockout, whilst the patient is still in the interventional theatre and prior to transfer to the recovery area. Use of IV Paracetamol (1 g infusion over 5–10 min) given at this time is useful in reducing the patient's requirement for narcotic analgesia. The dose will need to be reduced if the patient weighs less than 50 kg, and should not be repeated within the next 4 h.

If pain is not controlled then additional pain relief can be given with boluses of IV morphine, given in 2 mg aliquots, every 2–5 min, up to a maximum dose of 10 mg, either via the PCA, or by IV injection, whilst monitoring pulse, blood pressure and oxygen saturation.

Relief of nausea with IV antiemetics will usually be required. It is our practice to use Cyclizine 50 mg IV. Other anti-emetics including Ondansetron (4 mg IV) can also be used.

Patient usage of the PCA is usually highest during the first few hours, with the PCA usually being discontinued the following morning.

It is important to maintain the patient on regular NSAIDs and Paracetamol for the next 5–7 days with these being tapered off after 5 days. It is important for both the ward nursing staff and patient to understand that these should be maintained on a regular basis for this time, rather than on an "as required" or "PRN" basis, so as to minimise the effects of the embolisation process.

Where the patient still finds pain control to be suboptimal once the PCA is discontinued, addition of Codeine phosphate on an "as required" (PRN) basis will usually be sufficient.

Dyspepsia and peptic ulceration secondary to NSAID use can be minimised by the addition of a short course of a proton pump inhibitor (PPI) such as Omeprazole 20 mg daily, or an H2 receptor antagonist such as Ranitidine 300 mg twice daily.

**Table 1** UAE pain management schedule

| | Drug | Dose | Route | Frequency |
|---|---|---|---|---|
| Pre procedure | Diclofenac | 50 mg | PR | Stat |
| In X-ray room | Paracetomol | 1 g | IVI | Stat (at time of second side embolisation) |
| | Fentanyl | 25–50 mcg loading dose | IV | Loading dose followed by aliquots of 25 mcg titrated against response |
| Post procedure | Morphine | 1 mg | IV via PCA | Bolus on patient demand, with 5 min lockout |
| | Morphine | 2 mg | IV bolus | In addition, in recovery staff can deliver bolus of 2 mg repeated up to 10 mg total, titrated against response. |
| | Ibuprofen | 400–600 mg | Oral | TDS for 5 days |
| | Paracetomol | 1 g | IV/oral | QDS (max dose 4 g in 24 h) for 7 days |
| | Cyclizine | 50 mg | IV | 4–6 hrly PRN |
| | Codeine | 30 mg | Oral | 4–6 hrly PRN |
| | Omeprazole | 20 mg | Oral | Daily |

### 2.4 In Hospital Complications

In-hospital complications are uncommon with an incidence of 2–3 % compared to post surgery of 15.6 %, with major complications after UAE of 0.7–1 % (Edwards et al. 2007, O'Grady et al. 2009, Worthington-Kirsch et al. 2005). In hospital complications that do occur include contrast reaction or other drug reaction, groin haematoma, urinary tract infection or retention, DVT and pulmonary emboli. None of these require any modification of the usual treatment of these conditions.

### 2.5 Post Embolisation Syndrome

Lassitude, low-grade fever and nausea with loss of appetite are key features of post embolisation syndrome. The patient, and nursing staff should be advised that this is an expected part of the normal post procedure course. The severity of these symptoms might be expected to relate to the volume of tissue embolised, with patients with very bulky fibroids experiencing more debilitating symptoms than patients with small fibroid load, but published data does not support this (Worthington-Kirsch et al. 2005). It is important that patients and clinicians do realise that this is a normal part of the course following the embolisation of any solid organ, and they should be re-assured that symptoms are usually self-limiting, commonly within 1–2 weeks. The differentiation of the normal post-embolisation events from complications such as developing infection can however be a difficult clinical problem. Measurement of markers of infection such as C-reactive protein (CRP) and white cell count (WCC) is required, but these are also elevated as part of the inflammatory response post-embolisation, and so are often of limited use in differentiating infection from post-embolisation syndrome, especially early post UAE.

## 3 Discharge

### 3.1 Medication

Patients are discharged with a tapering course of paracetamol and NSAIDs. GI tract protection in the form of PPI inhibitor, or H2 receptor antagonists may be added to cover the course of NSAIDs. Some patients will require additional pain relief on discharge; codeine is commonly used. Tramadol can also be helpful. Use of opiate analgesics can result in constipation, and simple laxatives may also be required.

### 3.2 Return to Activity

Patients should be warned that they will usually take between 1 and 2 weeks to return to full normal activity post procedure. We have not found it necessary to place any restrictions on general activity, other than that of warning patients to expect to feel generally rather tired for about the first 2 weeks. We have found it necessary to stress this point especially to patients who have no prior experience of surgery or significant illness. There is a subgroup of patients who perceive that because they are not undergoing surgery they will be able to return promptly to all normal activity; if not forewarned such patients may feel that either there is a serious problem or may feel dissatisfied with the whole procedure.

We do advise patients to avoid pregnancy for 6 months post embolisation. Contraceptive advice may be required. As

we have not instrumented the cervix we do not advise patients to abstain from sexual intercourse, but some practitioners may prefer to advise patients to abstain for 6 weeks.

Patients should be given clear instructions as to any symptoms after discharge that should cause concern and that might require medical attention. These include pyrexia >38 °C, rigours, offensive vaginal discharge and increasing pain despite adequate pain relief.

### 3.3 Written Instructions

Women desiring UAE will often need to travel some distance to a centre offering this treatment. If they experience problems after discharge they will however often seek advice locally. Experience of dealing with women after UAE may therefore be limited both amongst primary care physicians (GPs), Accident and Emergency (AED) staff and gynaecologists outside of these centres. We have found it useful to give patients written instruction for them to keep with them, at the time of discharge, in addition to the usually post-discharge clinical letters. These instructions sheets give details of the name and date of procedure, worrying features which should prompt a return to hospital/hospital admission, plus contact details for the Interventional Radiologist and the Gynaecology teams at our centre.

In addition, all patients are given daytime contact details for the Interventional Radiologist performing the procedure, and are encouraged to ring for advice at any time after discharge.

## 4 After Discharge

### 4.1 Follow-Up

Women on discharge are given a follow-up appointment between 4 and 6 weeks later and it is our practice for this to be at an Interventional Radiology clinic. Many other centres will follow-up women in a Gynaecology clinic. Where a joint Radiology/Gynaecology clinic exists, this is the ideal situation, but is one that is often difficult to achieve, especially if both services are not physically located on the same site. It is vital that, when follow-up is not via the gynaecology clinic, an identified gynaecologist is involved in the ongoing care of patients in case any complications requiring gynaecological input arise. The referring gynaecologist should as a minimum be included in all discharge and post discharge follow-up letters. Whatever follow-up arrangement is established, the responsible clinician must be clearly identified to both the patient and their primary care physician.

A number of patients will have concerns after discharge which can be dealt with by telephone consultation outside of outpatient clinic review. It is our practice to give patients contact details for the interventional radiologist, and they are actively encouraged to phone about any concerns they may have.

There are, however, a number of complications, after discharge which can present within the first 4–6 weeks requiring either prompt outpatient review or re-admission. In contrast to surgery, the majority of early complications after UAE occur post discharge, whereas after surgery most early complications will occur before discharge (Edwards et al. 2007; Spies et al. 2002).

### 4.2 Post Discharge Complications

The incidence of post discharge major adverse events is higher than after surgery but is overall low, with an incidence of 4.8 % within 30 days being described (Worthington-Kirsch et al. 2005). The commonest post discharge events are ongoing pain, passage of a necrotic fibroid and infections including pyometra.

#### 4.2.1 Pain Control

Reported rates of readmission for pain control after UAE in the literature of up to 4 % have been described (Worthington-Kirsch et al. 2005). In our experience the need is significantly less than this. The use of newer less aggressive embolisation techniques plus admission of patients post procedure for 24 h with a robust pain management regime as outlined above, means that re-admission for pain control is unusual. This may be more likely if patients are discharged the same day, as a number of patients may have significant pain a day or two after the procedure.

#### 4.2.2 Infection

Whilst post embolisation syndrome is common, it is important in the post procedure period to differentiate it from infection, whenever a patients presents with symptoms that could be due to infection. Very rarely serious infection can lead to fatal sepsis. (Vashisht et al. 1999). The use of prophylactic antibiotics at the time of embolisation has been shown to reduce the likelihood of infective complications post UAE (Hirst et al. 2008; O'Grady et al. 2009).

All our patients are given instructions to seek prompt medical advice in the event of increasing pain, a raised temperature >38 °C, rigours and/or feeling ill. Many such patients will merely have an extreme of the post embolisation syndrome or a less serious infection that settles with antibiotic therapy but all patients require admission with careful close observation. Investigations should include a septic screen (blood cultures, vaginal swabs, midstream urine analysis plus full blood count). Consideration should be given to early imaging. Magnetic Resonance (MR) scans

may give useful information relating to perfusion of the uterus and fibroids, and help exclude pelvic fluid collections but imaging may be confusing. Gas is a common finding on imaging certainly within the first week or so after embolisation of fibroids (and following embolisation of solid organs elsewhere in the body). The finding of gas does not therefore in itself indicate infection. The decision to proceed to urgent hysterectomy remains largely a clinical one, to be made by an experienced gynaecologist.

#### 4.2.3 Passage of Fibroid

Following UAE necrotic fibroids, typically those in a submucosal position, may be sloughed. Often, small pieces of fibroids will be passed mixed with menstrual flow, unnoticed by the patient. Passage of a whole necrotic fibroid may be prefaced by a vaginal discharge which may smell unpleasant, but the patient remains clinically well. Passage of whole fibroid is often accompanied by cramping low abdominal pain, but occasionally is unheralded. A partially sloughed fibroid may be incompletely expelled. If this is obstructing the cervix, a pyometra can develop.

Surgical intervention in the form of assisted passage or surgical division and transvaginal resection will be additionally required in cases of incomplete expulsion.

In some cases the patient may be troubled by persistent discharge, often described as "chicken soup" consistency whilst the necrotic fibroid is sloughed. High vaginal swabs (HVS) should be taken to exclude active infection. Any associated infection should be treated with the relevant antibiotic; commonly Metronidazole and/or a Cephalosporin are prescribed. There may be no associated infection, and if the patient remains clinically well this discharge will usually eventually settle, although it may take several months to do so.

Passage of necrotic fibroids may occur with 4–6 weeks of embolisation but can be late. Within 30 days of embolisation the rate of sloughing of fibroids has been reported at 5.2 %, and that of chronic PV discharge at 12.6 % (Worthington-Kirsch et al. 2005).

### 4.3 Bleeding

In our experience variable patterns of per vaginal (PV) blood loss may occur post procedure. Whilst patients often retain their usual menstrual cycle post procedure it is not uncommon for patients to experience transient disturbance in their cycle, with for them, unusual patterns of blood loss or amenorrhoea. Provided the patient remains well with no evidence of sepsis or systemic upset, then patients can be reassured that in most cases their cycle will settle without specific treatment. In some cases, treating successfully the menorrhagia associated with fibroids may unmask an irregular cycle, which if persistent may require gynaecological assessment and treatment. Amenorrhoea may become permanent, particularly if the patient is aged over 45 years (Goodwin et al. 2008).

### 4.4 Contraception

Whilst there is no specific guidance relating to attempting pregnancy after embolisation, it is our practice in common with other groups (Pron et al. 2005) to advise patients to avoid pregnancy for 6 months post embolisation. Appropriate contraceptive advice may be required.

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# Postembolization Problems and Management

Bruce McLucas

## Contents




**Abstract**

Many problems, ranging from mild to severe, may arise postembolization that can be reduced or prevented if properly managed. During the early post-procedure period many patients may experience groin, buttock, and leg pains that may range from a minor hematoma, to pseudo aneurysm , to arterial obstruction resulting in thrombosis. Postembolization fever may be the result of either postembolization syndrome or bacterial infection. Generally prophylactic antibiotics are given to prevent bacterial infection and infection is generally associated with late onset fevers and increasing pain. The rate of hysterectomy following embolization is 3 %, possibly occurring as a result of unilateral embolization, collateral blood supply to the fibroids resulting in failure, or incomplete embolization. Patients who do not experience symptom relief, have extreme postembolization symptoms, or experience severe infections or septicemia may also undergo hysterectomy. Myomata that do undergo necrosis may be passed if small enough, or patients may receive a myomectomy to remove prolapsed myomata. Early onset of menopause post-UAE is more likely in women over 40, and extremely uncommon in those younger than 40. Success of UAE is considered relief of symptoms; however an MRI should be performed in the months following UAE to check for complications including leiomyomasarcoma and adenomyosis.


## 1 Introduction

This chapter will deal with management of post-discharge problems after uterine artery embolization (UAE). Some of the problems may occur during admission for the UAE procedure, as well as post discharge. They will be mentioned in passing here as they are to be covered in detail elsewhere in this book. I have chosen to deal with problems in likely chronologic order following discharge, with the


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earliest occurring problems covered first. I will attempt to indicate the frequency and severity of the problems during their discussion.

Management of postprocedural problems will often mean the difference between success and failure of the UAE. In the few reported cases of death following UAE, early intervention would have yielded a different outcome. But less about generalities and on to specific instances.

## 2 Groin, Buttock, and Leg Pains

Gynecologists may encounter leg and groin pain, and buttock claudication during the early post-procedure period. In general, such presentations should be referred back to the operating physician. The groin pain may be a hematoma, or a pseudo aneurysm. If a sealing device is used, the pain may be a benign side effect from the device. The operator is best equipped to diagnose, and treat if necessary, such conditions. However, the patient should be surveyed for stable vital signs, and no sign of internal bleeding at the time of the visit.

Buttock claudication may result from nontarget embolization of the gluteal artery or arteries. While this problem is usually self-limited, physical therapy may aid the healing process. Leg pain may be the result of nerve compression, but arterial obstruction from nontarget embolization and phlebitis should first be ruled out.

### 2.1 Groin Hematoma and Pseudo Aneurysm

Groin hematoma or pseudo aneurysm may be problems after discharge (McLucas et al. 1997), thus gynecologists should be familiar with how to treat these problems. Groin hematoma is usually a minor angiographic complication seen in 14.8 % of patients (Volkers et al. 2006). Hematomas can be drained, however many may not need intervention. Even in the absence of a swelling in the common femoral artery groin pain should be evaluated for other potential complications.

Pseudo aneurysms are the result of separation of the arterial layers during the embolization procedure. While entering the common femoral artery either with initial puncture or dilator, the intimal and adventitia layers of the artery may become separated (Fig. 1). This results in blood flowing in and out of this area thus creating the pseudo aneurysm. Patients will usually complain of pain and swelling in the arteriotomy site. On examination of the groin area, it may be difficult to distinguish between a hematoma and pseudo aneurysm. Ultrasound examination with a Doppler flow probe will yield a clear movement of blood (Fig. 2). The so-called "ying and yang" sign refers to the pattern of movement of blood in and out of the pseudo aneurysm.

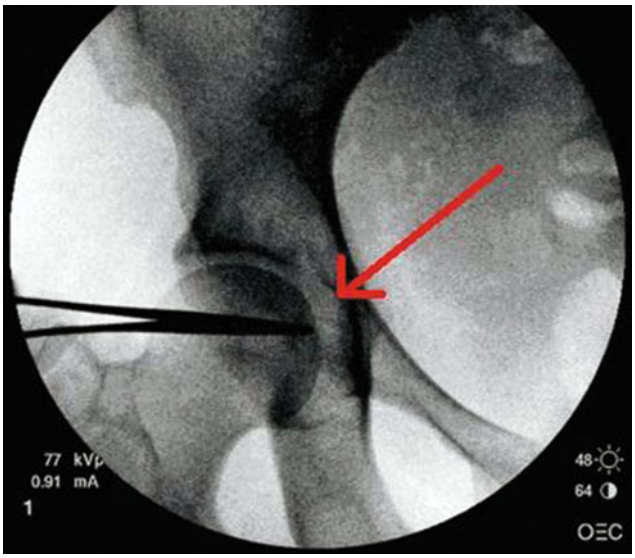


**Fig. 1** Hematoma formation

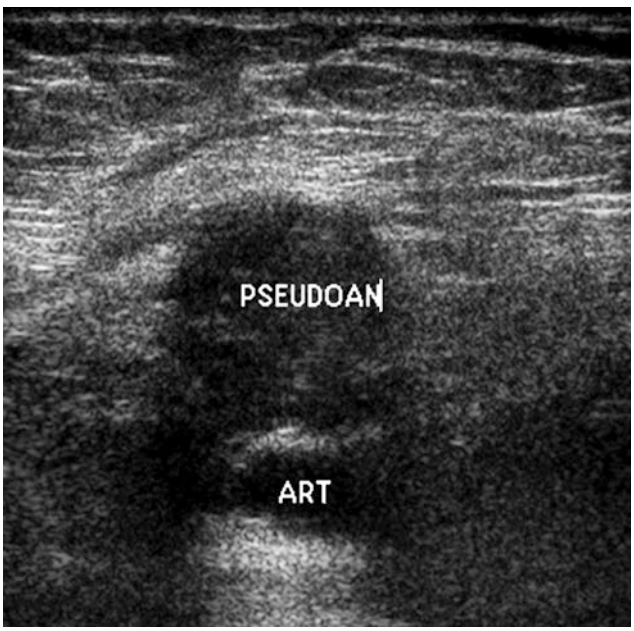


**Fig. 2** Ultrasound of pseudo aneurysm

Which pseudo aneurysms require treatment? Physicians will not commonly treat a pseudo aneurysm <2 cm which is stable in size. If expectant management is elected the patient must be examined again within 48 h to confirm that the area is not expanding. A pseudo aneurysm seldom requires surgical management. Instead thrombin will be injected under ultrasound guidance into the pseudo aneurysm to clot off the area of concern. Follow-up examination after injection is good practice to confirm the efficacy of treatment.

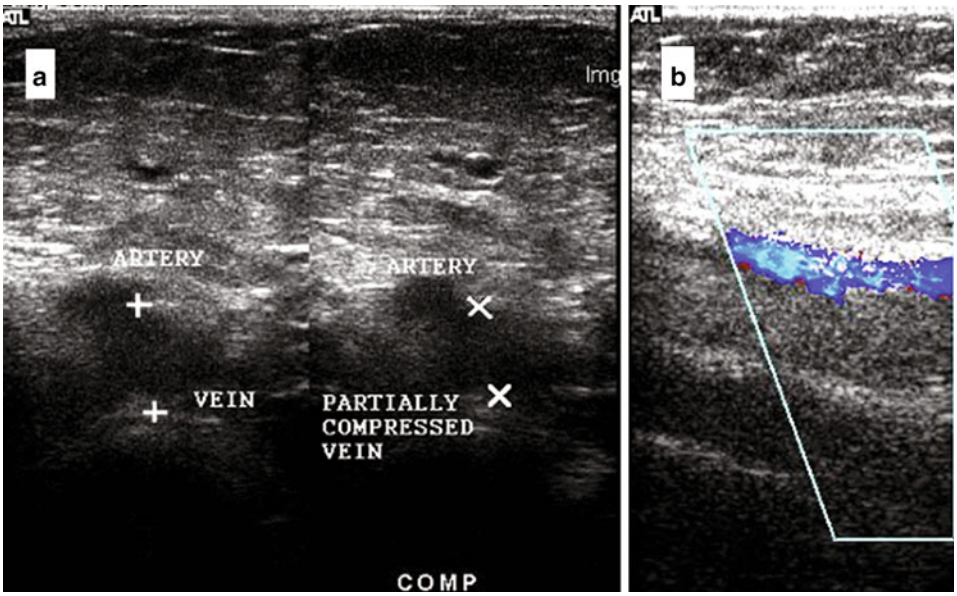


**Fig. 3** **a** Ultrasound image showing presence of a large clot, vessel walls not compressible with applied pressure **b** Doppler shows blood flow through artery (*blue*) but not through vein

## 2.2 Leg Pain

Just as particles may enter the gluteal arteries as a result of nontarget embolization, some particles may reflux around the end of the catheter and enter the common femoral artery. We will routinely order doppler studies of the arteries and veins of both legs when a patient complains of leg pain. Even in the absence of a swelling in the common femoral artery, pain must be evaluated.

The possibility of venous thrombus disease should be considered in all patients (Czeyda-Pommersheim et al. 2006). We have favored use of an arteriotomy closure device in our patients, although some authors question the efficacy of such device. Early ambulation after UAE goes a long way to preventing thrombotic disease. If a thrombus is discovered in the femoral vein, immediate therapy is indicated. Usual therapy is anticoagulation with heparin, followed by transition to coumadin. Unless there is evidence of pulmonary emboli, or high risk factors for the development of this complication, we have not placed caval filter devices (Fig. 3). Emboli must be carefully ruled out, proving to be a fatal postembolization problem on a few occasions (Hamoda et al. 2009).

Operators must be able to recognize dissections and punctures of arteries. We will not discuss management of these complications, as they are hardly unique to UAE procedures. Nonetheless such complications can be life-threatening, and require immediate recognition and treatment. Assuming these studies to be negative pulmonary obstruction and phlebitis should be ruled out. Patients will respond to therapy with exercise, physical therapy, and calcium within a few days.

# 3 Postembolization Fever

A potential source of fever after UAE is due to pelvic infection. To prevent fever associated with postembolization infection most doctors will use prophylactic antibiotics prior to the procedure as a precautionary measure. The most commonly used prophylactics for surgical procedures include cephalosporins (McDermott et al. 1997), first generation agents having better activity against both gram-positive and gram-negative bacteria. Coverage does not include anaerobes (McDermott et al. 1997).

Prophylactic antibiotics used in UAE typically include cephalosporins such as cefalozin or ceforozine (Spies et al. 2002) or a combination of antibiotics shown effective for use against aerobic and anaerobic bacteria such as gentamicin, ampicillin, metronidazole, or clindamycin (Al-Fozan and Tulandi 2002; Gall et al. 1981). For patients with a penicillin allergy vancomycin is used (Weed 2003). No study has shown that the use of prophylactic antibiotics prevents infection after UAE; however, it is suggested that prophylactic antibiotics reduce the risk of sepsis (Walker et al. 1999). In addition, no studies have shown increased risk based on type of particle used (Rajan et al. 2004). Some suggest the location of leiomyoma as submucosal as an increased risk for septicemia (Al-Fozan and Tulandi 2002).

Postembolization syndrome is a common and important early occurring complication after UAE, first being described as a postembolization problem after liver embolization (Slomka and Radwan 1992). Postembolization syndrome has also been associated with UAE patients (McLucas et al. 1999). The syndrome consists of temperature elevation, pain, and nausea. Leukocytosis is often pronounced. In our

experience, early occurrence of embolization syndrome within the first 72 h of the procedure is seldom a harbinger of infection. Nonetheless, we routinely question our patients about other sources of temperature elevation. We place an indwelling Foley catheter for the first 12 h after UAE. Could the patient have a urinary tract infection from this intervention? We also give prophylactic antibiotics to patients for the week following their procedure. Is there a change in bowel movements which could suggest the possibility of c difficile enterocolitis?

Once the fever work-up has excluded other sources of fever, we concentrate our work-up on the pelvis. We will routinely obtain a blood culture for a patient with temperature above 100.6 °F. We also will image the pelvis with a computed tomography study of that area including intravenous contrast. Following UAE we routinely see small amounts of air within the uterus (Fig. 4). Onset of symptoms later than 36 h post-UAE is more worrisome than onset prior to 36 h. One circumstance which will compel us to hospitalize a patient is increasing rather than diminishing pain (Table 1). The vast majority of our patients require no more narcotic management after 48 h following UAE. If pain is increasing and associated with fever, we are likely to admit the patient for further evaluation and intravenous antibiotic therapy (Nott et al. 1999). Once in the hospital setting management will depend on physical examination. Peritoneal signs will push a decision for surgery. Another worrisome sign will be rising rather than falling leukocytosis in the face of appropriate antibiotic choice and duration. Repeat imaging may be useful to demonstrate the direction of care.

Fever postembolization can be the result of either infection or postembolization syndrome , the difference being that infection is often associated with a discharge; however, distinguishing the two complications may be difficult (Spies et al. 2002). A discharge several weeks following embolization may simply be the sign of a submucosal myoma being passed. Both postembolization syndrome and infection will involve an increase in white blood cell count.

The first reported death as result of a complication of UAE was due to septicemia (Vashisht et al. 1999). In the case of a septic uterus hysterectomy is necessary. The rate of hysterectomy as a result of pelvic infection following UAE is <1 % (Walker and Pelage 2002). Early treatment of postoperative pelvic infections can prevent septicemia and more serious infections, and generally involves intravenous antibiotic treatment and hospitalization for a day or less.

Choice of antibiotics for coverage of febrile episodes after UAE will often be made in consultation with an infectious disease consultant based on the type of pathogen present. Treatment of infections of the female genital tract has focused on the prevalence of mixed anaerobic and aerobic bacterial infections, anaerobes generally outnumbering aerobic bacteria (Sweet 1981). The bacteria most associated with initial stages of infection are gram-negative facultative bacteria such as *E. coli* (Spies et al. 2002), suggesting that the use of prophylactic antibiotics may destroy gram-positive organisms but lead to a proliferation of gram-negative organisms (Walker et al. 1999). In addition, anaerobic bacteria such as *B. fragilis* are typically found in secondary phases of intraabdominal abscesses (Sweet 1981). For penicillin resistant bacteria such as *B. fragilis*, the antibiotics used for treatment include intravenous metronidazole, clindamycin (Gall et al. 1981) or cephoxitin due to broad range coverage for both anaerobic and aerobic bacteria. The use of antibiotics for a variety of organisms has been shown to be more effective in terms of recovery and incidence of severe infections (Sweet 1981). The use of single antibiotic therapy for polymicrobial obstetrical infections such as clindamycin, ticarcillin, and chloramphenical are as effective as compared to a multiantibiotic approach (Faro et al. 1982). Typically, while waiting for culture results we will choose a broad spectrum second or third generation cephalosporin.

**Fig. 4** Postembolization MRI showing normal air pattern in uterus

**Table 1** When to hospitalize for postembolization fever

| Onset of fever after UAE | Hospitalization | Treatment |
|---|---|---|
| <48 h | No | Oral antibiotics |
| | | Pelvic ultrasound or CT scan |
| 48+ h and increasing pain | Yes | Intravenous antibiotic therapy |
| | | Possible surgical candidate |


**Fig. 5** Air levels within myoma suggest abscess formations

An evolving abscess is often not clear on any kind post-UAE imaging, however, we have had some cases where the abscess within the myoma is obvious (Fig. 5). In such cases surgery is indicated. We have on many occasions removed necrotic myoma, leaving behind normal endometrium and other pelvic structures. Seldom is hysterectomy indicated. Having said this, bacteria often remain behind after myomectomy, requiring aggressive postoperative antibiotic therapy. To reduce the risk of bacterial infection post procedure it may be beneficial to extend the duration of time that antibiotics are given post procedure, especially in patients with a large or submucosal leiomyoma because these myomata are more susceptible to bacterial development post UAE (Brunereau et al. 2000). Infection is possible, so delayed fever post procedure should be carefully clinically monitored and examined via cross sectional imagining of the pelvis and antibiotic therapy depending on the results of the imaging and testing (Goodwin et al. 1997). If monitored early, surgical treatment of infections can be avoided.

## 3.1 Particle Load

Patients experience necrosis of myomata at different rates. We have tried to limit the particle load given to patients with large uterii to limit the possibility of rapid necrosis and abscess formation. The possibility of not accessing the uterine artery again must be weighed against the possibility of early necrosis and abscess formation. We often begin with 500 $\mu$ PVA particles, moving rapidly to a vial of 700 $\mu$ particles, followed by 1,000 $\mu$ particles, and even larger if necessary. Higher particle load and higher numbers of PVA vials used are associated with higher levels of peak systolic velocity (McLucas et al. 2002), which can be evaluated pre-embolization using Doppler flow sonography (Fig. 6). In addition, we are not hesitant to place a coil in one of the uterine arteries of patients with large uterii. Total uterine volume is calculated using the largest measurements in the anteroposterior, longitudinal, and transverse planes in the formula for a prolate ellipse (McLucas et al. 2002). Particle load is calculated by dividing the volume of uterus by the number of vials of PVA particles used. We have also used pledglets of gelfoam to occlude the arteries of patients with large myomata.

Another point to remember in management of the post-UAE patient with fever is that if a patient defervesces in the hospital, and is judged a candidate for outpatient oral therapy, she is still someone who can develop an abscess and require surgery. The patient must be followed up at least weekly, if not twice weekly with in-person visits. Worrisome signs include return of high pain levels and presence of malodorous vaginal discharge.

In summary, early onset of temperature within 48 h of embolization augers for a benign postembolization syndrome. These patients may be often managed as an outpatient, on oral antibiotics, after a reassuring pelvic ultrasound or CT scan. They will require frequent visits, at least weekly, to confirm the benign diagnosis, and rule out sepsis.

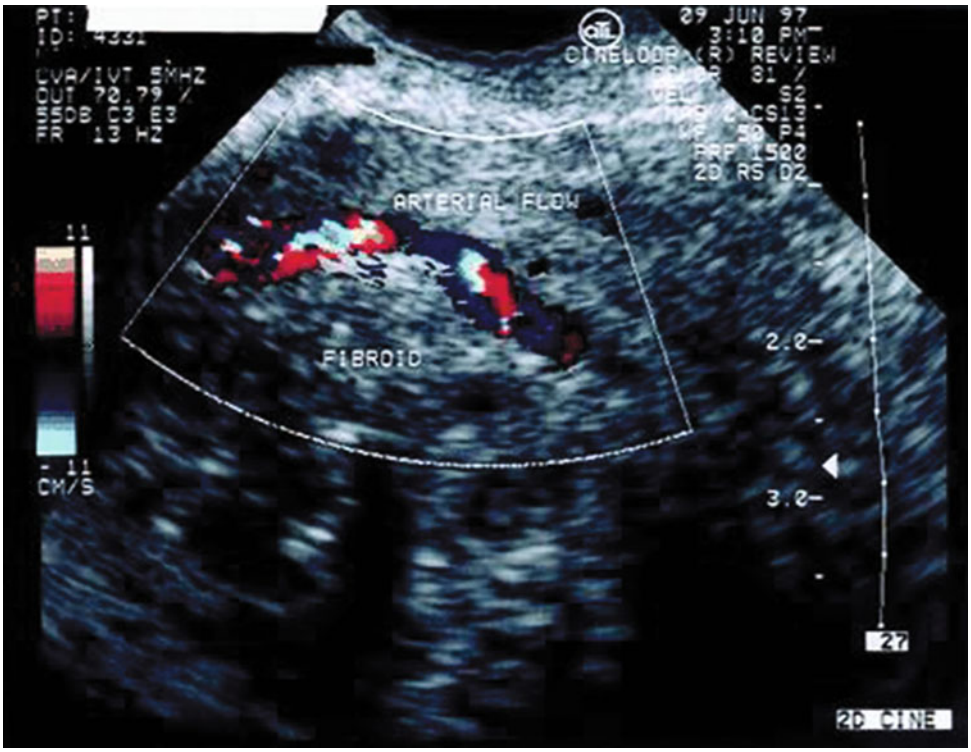


**Fig. 6** Right body of the uterus, high Doppler flow shown by *yellow*, *orange*, *blue*, *white*

Late occurring temperature elevations >7 days post procedure and accompanied with an increased pain level require hospitalization, aggressive intravenous antibiotic therapy, and are possible surgical candidates.

## 4 Hysterectomy Following Embolization

Hysterectomy is required infrequently postembolization. In a study of 1,797 patients from the Fibroid Registry of Outcomes Data, 2.9 % of women were found to require hysterectomy 1 year following uterine artery embolization (Spies et al. 2005a, b). From this study 86 % of those that required gynecological interventions within a year after embolization were 45 or older. After 5 years the subsequent hysterectomy rate was found to be 13.7 % in a study of 200 patients (Spies et al. 2005a, b). Intervention post UAE is more likely in those with very large uteri and large dominant leiomyomata. The factors that may affect recurrence of growth in fibroids include embolic agent used, incomplete embolization, and collateral blood supply to the uterus resulting in increased growth and recurrence of symptoms. Many studies agree that multiple factors may play a role in cases of subsequent hysterectomy; however, the exact causes are yet to be pinpointed. A higher risk for subsequent hysterectomy after UAE may exist for patients who cannot receive bilateral embolization. Hysterectomy after unilateral UAE is 2.19 times more likely than after bilateral UAE (Gabriel-Cox et al. 2007).

Hysterectomy following UAE is generally due to failure of the UAE to relieve symptoms, continued presence of myomata, or for severe postembolization syndrome or infection. Most frequently hysterectomy is due to failure of the UAE or recurrence of fibroids, as serious infections are rare (Walker and Pelage 2002). Fibroid size and number can be predictors of recurrence as large fibroids, those greater than 10 cm, and submucosal or partial mucosal fibroids are less likely to shrink (Marret et al. 2004).

## 5 Passage of Myoma, Per Vagina

We noted more than 10 years ago the association of submucous myomata pre-embolization with the possibility of prolapse of necrotic myomata post procedure (Goodwin and Reed 2000). Based on this information some operators have used the presence of submucosal pedunculated myoma as an exclusion criterion for UAE (Scheurig et al. 2006; McLucas et al. 2008) (Fig. 7). Menorrhagia associated symptoms should suggest the possibility of extension of an intramural myoma into the endometrial cavity, if not a sessile or pedunculated submucosal myoma. The collateral circulation for intramural myomata is not available for pedunculated myomata. Thus, a high risk of prolapse of a pedunculated submucosal myoma exists.

The instance of prolapse of a submucosal myoma is variable, and can potentially occur as soon as immediately following UAE. More commonly the prolapse will take

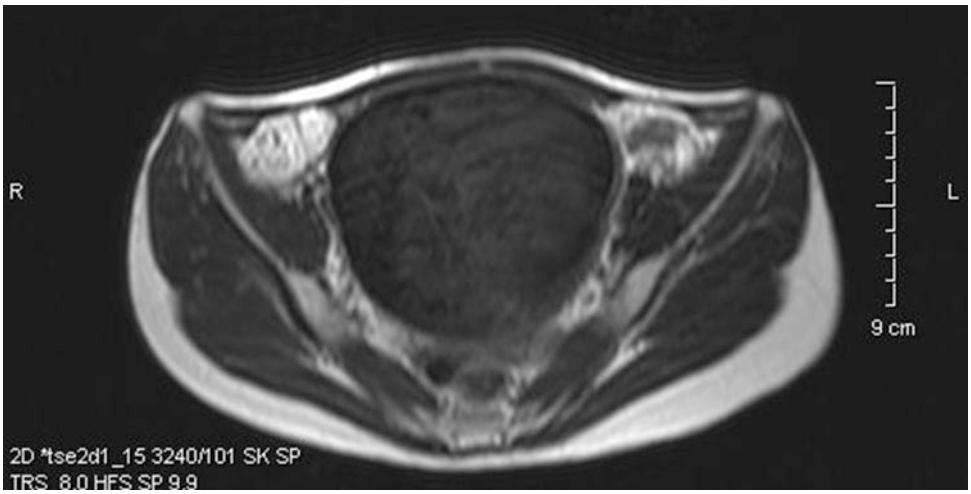


**Fig. 7** Pedunculated submucosal leiomyoma. Axial MRI Image showing fibroid dilating the cervix

place months after the embolization procedure. The symptoms are crampy pelvic pain, "chicken soup" foul smelling vaginal discharge, and a possible return of menorrhagia after abatement of the symptoms postembolization.

Despite the purulent discharge, the patients are usually afebrile. The white blood cell count is often within normal range. Ultrasound imaging is used to confirm the place and size of the myoma. Often the cervix is dilated on speculum examination with necrotic material visible in the cervical os.

Management will depend on the size of the myoma and the wishes of the patient. Small myomata may be allowed to pass spontaneously. We encourage the patient to preserve the necrotic myoma in a glass jar filled with salt water and to store it under refrigeration until it can be brought into the office for pathologic microscopic examination. After passage of the myoma we recommend a follow-up ultrasound to evaluate the endometrial cavity for residual tissue. Dilation and curettage may be necessary if partial extrusion of myoma is suggested.

The larger myoma presents a management challenge. In the case that it is over 5 cm in size we discuss the possibility of myomectomy with the patient. If the myoma is seen to be intracavitary, we may offer vaginal myomectomy. As the size approaches 10 cm, the likelihood of passage vaginally decreases, and the risk of infection rises. In these circumstances, we recommend abdominal myomectomy. Of the 5,000 patients we have treated, this surgery under these circumstances has occurred 5 times. Again, as discussed in the section on myomectomy for abscess formation after UAE, we recommend a vigorous debridement of the outer edges of the removed myoma. Antibiotic therapy beyond prophylaxis with broad spectrum coverage is recommended. Many of our patients have refused abdominal myomectomy despite being informed of the risks, and several have passed necrotic myomata approaching 10 cm. We inform patients about the likelihood of severe crampy pain if they elect such an approach. Of note we have seen numerous intramural myomata that have ruptured the endometrial cavity after UAE. This is less likely than passage of submucous myomata, but it can happen.

## 6 Oligomennorhea

While it is well known that menopause may occur following UAE, the period of time after UAE has not been extensively studied. It is possible for particles from the UAE to become lodged in the ovarian arteries (Ghai et al. 2005). If both ovarian arteries are thrombosed and cease to function, menopause may ensue. This phenomenon is more common in women over the age of 45 who undergo UAE, perhaps reaching 20 % in women closer to 50-years old. Under the age of 40, premature menopause is quite uncommon. In our group of more than 5,000 patients, we have never seen premature menopause occur in a patient under the age of 40. Our experience is similar to others who quote the overall chance of menopause at about 4 % (Walker and Pelage 2002).

The rapid rise of this phenomenon as patients approach menopausal age leads me to assume there is another force at work, aside from nontarget embolization. Perhaps the arteries supplying the ovaries are less able to withstand even a small vascular insult at that period. We know that women who undergo total abdominal hysterectomy are more likely to enter menopause than those who did not. During the first months after UAE, we have noted patients who experience either menstrual irregularities, or hot flashes. For the vast majority of such patients, follicle stimulating hormone levels were normal, and the patients returned to normal menses (McLucas et al. 2000).

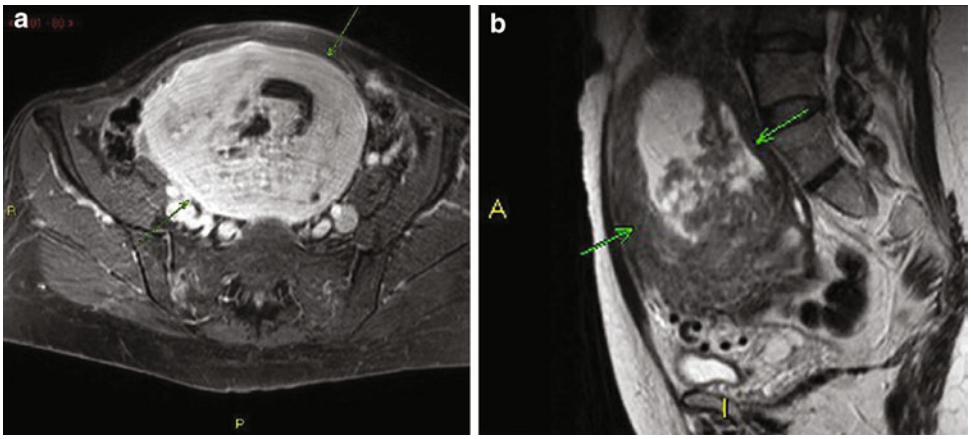


**Fig. 8** Leiomyomasarcoma **a** axial T1-wieghted MRI gradient echo fat saturated post contrast. **b** Sagittal T2-weighted MRI without contrast

## 7 Abdominal Pain

We first reported the presence of abdominal, omental, and small bowel adhesions after UAE in 1998 (McLucas et al. 1998). Since then others have noted the same phenomenon (Agdi et al. 2008; Godfrey and Zbella 2001; Goldberg et al. 2005; Payne and Haney 2003). However, we rarely see this occurrence, potentially because we screen our patients for any inflammatory process before suggesting UAE. Nonetheless, adhesions did develop in some patients whom we laparoscoped prior to embolization and had normal pelvic anatomy. As a result, we no longer tell patients they are less likely to experience adhesions than those women undergoing abdominal myomectomy.

Some operators refrain from performing UAE on patients with pedunculated subserous myomata. Just as those patients who have pedunculated submucous myomata may pass their necrotic myoma because of an accelerated infarction, the same pattern may occur with the subserous myoma. Indeed, this was an early described complication after UAE (Pelage et al. 2000) and we take a different course with this type of myoma.

When a patient presents with a pedunculated subserous myoma on a narrow stalk, we will urge consideration of a UAE procedure followed by a laparoscopic myomectomy. The patient will have the benefit of reduction of myomata, as well as the likelihood of no recurrence. UAE prior to laparoscopic myomectomy has been suggested as a way for surgeons to more safely use minimally invasive techniques for larger fibroids (Goldman et al. 2011).

## 8 Failure

Success after UAE is most often described as relief of symptoms, rather than an arbitrary amount of shrinkage (McLucas et al. 2002). If the patient has continued growth

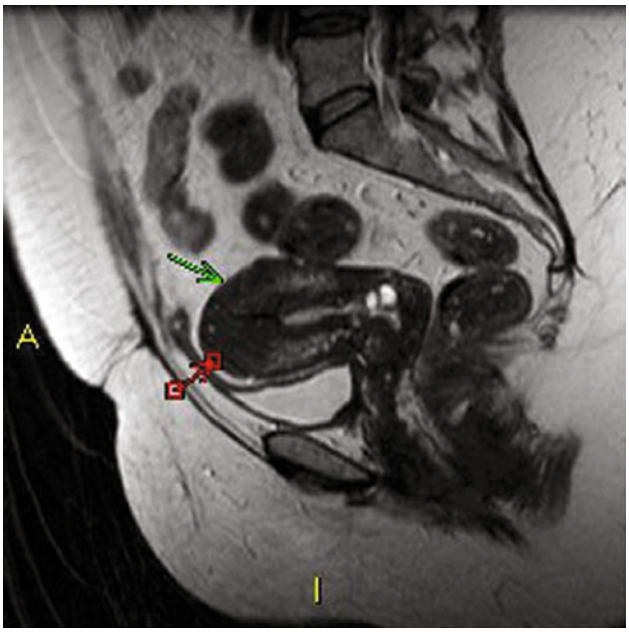


**Fig. 9** Adenomyosis. Sagittal T2-weighted MRI without contrast

of myomata, she will obviously be considered a failure. We, like others, perform a pelvic MRI with intravenous contrast 2 months after the UAE procedure. For the patient with persistent uptake of contrast into myomata, the first task of the operator is to confirm that the patient does not have a uterine malignancy. The most common malignancy of the myometrium is leiomyomosarcoma (Fig. 8). The appearance of this cancer when it is full blown may distinguish it from myomata; however, the earlier presentation of the sarcoma is not easy to distinguish.

On MRI, leiomyomasarcoma will not show a sharp line separating the tumor and the myometrium while myomata will be more clearly demarcated. Abdominal ultrasound and high Doppler flow have not been useful in distinguishing the two, however, central Doppler flow may suggest sarcoma, as myomata tend to have peripheral Doppler flow (McLucas 2008).

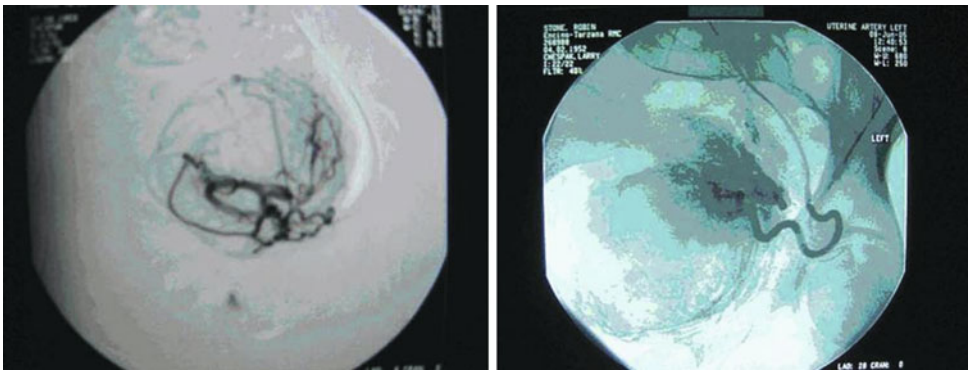

**Fig. 10** Blood flow around the fibroid

The clinical presentation of the tumor may distinguish a cancerous, rather than benign tumor. Leiomyomasarcoma tends to be rapidly growing, whereas in general, the myoma is more indolent. In addition to the rate of growth, a sarcoma tends to be solitary, rather than multiple, as often seen with fibroids. The onset of presentation will be often after menopause, compared to the benign myoma, which will grow during the fifth decade, classically (Silverberg 1971).

Having ruled out malignancy, the clinician may look for other benign growths which may mimic myomata. The most common would be the adenomyoma (Fig. 9). Signs of adenomyosis on imaging include a widened diameter of the junction between the uterine body and the cervix and lacunar lakes within the myometrium. Adenomyosis may be a coexistant disease, or the problem including the adenomyoma. The only known cure for this process is hysterectomy. Embolization may have a beneficial effect on adenomyosis (Kitamura et al. 2006), however, the duration of such an effect is unknown. Adenomyosis may also be a potential cause in the case of UAE failure (Smith et al. 1999).

If the disease is leiomyomata, and no other condition, then the search must begin with an MRI of the pelvis with contrast given intravenously. Persistent uptake of contrast into the myoma indicates continued blood supply (Fig. 10). We have used a CT angiogram of the abdomen and pelvis to help identify the source of the blood supply (Mclucas et al. 2002). A repeat UAE with ovarian or other artery supply embolization will often change the result to favorable for the patient.

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# The Role of a Repeat UAE Procedure

Robert L. Worthington-Kirsch

## Contents




**Abstract**

Patients who have been treated for fibroid disease by embolotherapy occasionally may not experience satisfactory symptom relief. Others, who initially do have relief from their fibroid-related symptoms may have those symptoms recur. Causes for clinical failure and symptom recurrence include incomplete fibroid infarction and interval growth of new fibroids. Many of these patients will respond to repeat embolization.


## 1 Introduction

Ideally, a Uterine Artery Embolization (UAE) procedure should cause complete or near complete infarction of all detectable fibroids (Katsumori et al. 2008). While patients with less than complete fibroid infarction may experience relief from symptoms in the short or medium term (Abramowitz et al. 2009), the risk of symptom recurrence in these patients is higher than for those who had more extensive infarction (Pelage et al. 2004; Kroenke et al. 2010). Unfortunately, embolotherapy does not change the pathology that leads to the formation of fibroids. Women may well go on to develop new symptomatic fibroids, even after the most thorough of embolizations. If a woman fails to respond to embolization or develops recurrent symptoms, one must consider whether or not a repeat embolization would be useful.

## 2 Indications for Repeat UAE

There are two clinical scenarios that can lead to a repeat UAE. Both situations pose different questions, which are largely answered by imaging. The procedure of choice is contrast-enhanced MRI of the pelvis (Table 1).

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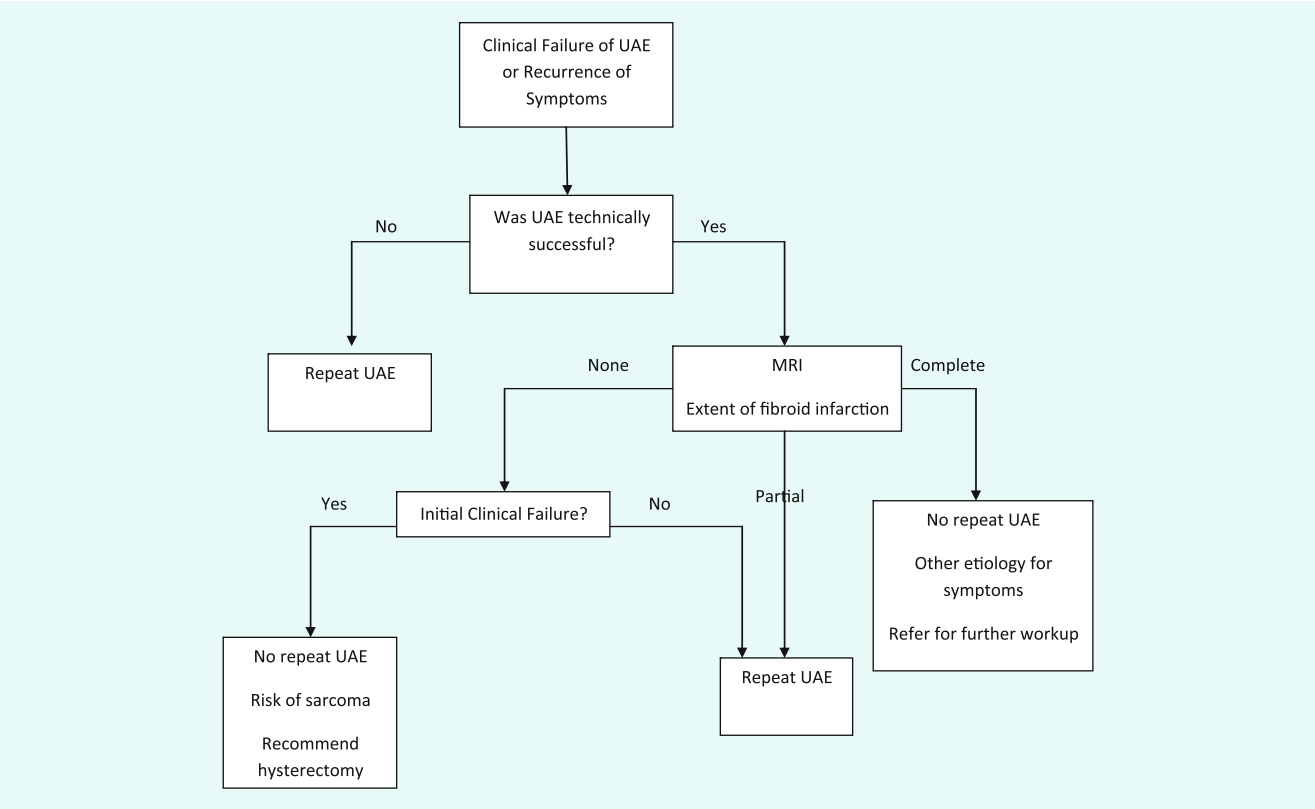
**Table 1** Repeat UAE decision algorithm




## 2.1 Scenario 1: Early Failure of UAE

Vignette—LK is a 43-year-old woman who works as a college professor. She has a 10-year history of increasing menorrhagia and pressure symptoms. Physical examination and MRI show an 18–20-week uterus almost completely occupied by 2 or 3 large fibroids which show homogeneous global enhancement. Endometrial biopsy is benign.

At UAE both uterine arteries were catheterized and embolized with a total of 12 ml of calibrated hydrogel microspheres (8 ml to the left uterine artery, 4 ml to the right uterine artery), achieving the desired endpoint[1]. The entire uterus was demonstrated during embolization. Her recovery was uneventful, with return to full activity levels within 1 week.

She was seen in the office 4 months after the UAE for follow-up. Her menstrual flow remained very heavy and she continued to have significant pressure symptoms, both essentially unchanged from before the UAE. MRI showed no change in uterine/fibroid size with minimal infarction of fibroids.

A woman who has had no improvement in her fibroid-related symptoms after embolization represents a clinical failure of the procedure. A woman who has an initial response to UAE and recurrence of symptoms within a short term (3–12 months) represents an early failure of the procedure. When evaluating these patients the first question that needs to be answered is whether or not the initial procedure was technically successful. Were both uterine arteries identified and selectively catheterized? Was the desired endpoint reached? Were adequate doses of embolic agent given? Was there a complete "uterogram"—was the entirety of the expected volume of the uterus seen during embolization?

If the answer to any of these questions is "no" then the first procedure should be considered a technical failure. Repeat arteriography and re-embolization to redress the technical problem with the procedure is appropriate. Technical failure of UAE should be a rare event, below 2% (Worthington-Kirsch et al. 2005). Overall, about 90% of patients experience at least short-term relief from symptoms (Spies et al. 2005). The causes of clinical failure in patients who have had technically successful procedures include

[1] The desired endpoint for UAE (Worthington-Kirsch 2011) is angiographic evidence that there has been a change in the flow pattern in the uterus suggesting that the fibroid/uterine vascular bed is largely embolized. These include any of the following findings: (1) Reflux into the ovarian artery that was not present on pre-embolization injection of the uterine artery. (2) Filling of cross-uterine collaterals that were not previously seen. (3) Retrograde flow of contrast in the uterine artery with injection. (4) Transient dilation ("plumping") of the uterine artery near the catheter tip with injection.

incorrect diagnosis for the cause of the patient's symptoms, unrecognized under embolization, sarcoma, and other causes which are yet to be defined.

If the first procedure was apparently technically adequate, then a contrast-enhanced MRI of the uterus is needed to decide on a course of treatment. If the MRI shows that all visible fibroids are globally infarcted, there is no indication for a repeat embolization. This suggests that the fibroid disease is not the cause of the patient's symptoms and another etiology needs to be considered. These patients should be referred to their gynecologist for further evaluation and management.

If the MRI shows that there has been partial infarction of the fibroids, then the embolization was probably inadequate. The uterine arteries may have been under embolized (due to poor choice of endpoint or spasm), or there may be accessory supply to the fibroids. This is most commonly from the ovarian artery. The pattern of fibroid infarction/preservation of flow may suggest which of these is responsible.

If the patient has had no improvement in symptoms after UAE despite what appears to be a technically adequate embolization and MRI shows no significant fibroid infarction (less than 10% of the overall fibroid burden), a repeat embolization should not be performed. There have been at least two reports of uterine leiomyosarcoma in this setting (Common et al. 2001; Papadia et al. 2007). In these cases it is important to explain to the patient that the risk of her having a malignancy is high enough that she needs to have a surgical procedure, which will most likely be hysterectomy. The author has referred two patients for hysterectomy under these conditions (out of a total of over 2,700 UAE procedures). In both cases no sarcoma was found. The reason for noninfarction of the fibroids in these patients is not clear.

Some would argue that a repeat UAE may be useful in this situation. It is true that many patients in this situation will not have a diagnosis of sarcoma after surgery. However, if the patient has a sarcoma the embolization and follow-up period could be interpreted as a 3-month (or longer) delay in diagnosis. It would be imprudent to delay the diagnosis by another 3–4 months or longer by attempting a repeat UAE.

Two of the three alternatives in this scenario require that the patient be referred back to her gynecologist for further management. It is essential to keep open communications between the IR and the gynecologist so that referrals like this can be managed in an efficient and collegial manner. The author personally makes every effort to speak directly with the gynecologist by telephone in addition to sending the relevant office notes, ideally calling and speaking with the gynecologist while the patient is still in the office and can listen to or participate in the discussion.

Vignette (continued) —After explaining the situation to her, I called Ms K's gynecologist while she was still in the office and reviewed the case. I explained to both the patient and her primary gynecologist that I did not think that this was a sarcoma, but that the risk of it being one was such that I did not think a nonsurgical procedure was wise. Ms K was referred to a gynecologic oncologist, who performed a TAH. The final pathology report was fibroids with no histologic evidence of sarcoma.

## 2.2 Scenario 2: Late Failure of Symptom Control

Vignette—FA had UAE in 1998, at age 35. She did well after the UAE, with complete resolution of symptoms. She was seen in follow-up at 3 months and 1 year post-UAE, after which she chose not to come for annual follow-up visits.

At age 46 she began to have recurrent menorrhagia and some urinary pressure. She came to the office 18 months after her menses became noticeably heavier. MRI revealed a 14–16 week-sized uterus with multiple enhancing fibroids.

The patient who has an initially good response to UAE and then experiences recurrent symptoms (either recurrent menorrhagia or bulk/pressure symptoms) in the medium to long term (arbitrarily more than 12 months) usually does so because of either an inadequate embolization or growth of new fibroids. It is important to recognize that menorrhagia may also develop because of pathology different from fibroids.

Repeating the contrast-enhanced MRI when symptoms recur is essential to making the diagnosis and planning treatment. The MRI is used to determine the extent and location of perfused fibroids and guide arteriography. This can provide information regarding the presence of collateral flow, especially from the ovarian arteries. The ovarian arteries typically will supply the fundal portion of the uterus. MRA can also define the ovarian arteries (Kirby et al. 2011).

Ideally, all patients have had a routine follow-up MRI done at 3–6 months post embolization. This is useful to define the extent of fibroid infarction or lack thereof and to advise the patient regarding the likelihood of symptom recurrence. If the MRI shows global fibroid infarction, it appears that the likelihood of recurrence is lower and that the clinical efficacy should be more durable than in those patients who have some preservation of enhancement in their fibroids.

It is important to note that if the follow-up MRI shows persistent fibroid perfusion the decision to intervene depends on how the patient is doing clinically. The imaging findings of persistent perfusion are not in and of themselves justification for a repeat arteriogram/embolization.

The decision tree for late recurrence is similar to that for early recurrence, with the exception of the patient who shows global fibroid enhancement. If the patient has had a good response to UAE for over a year and now has globally enhancing fibroids, repeat UAE is indicated.

Vignette (continued)—Ms A had a second UAE, receiving 1.5 ml of calibrated hydrogel microspheres to the left uterine artery and 6 ml of microspheres to the right uterine artery. Her recovery was uneventful, with return to full activity levels in 9 days. Since then she has had complete relief from her menorrhagia and pressure symptoms.

## 3 Technique for Repeat UAE

The technique for a repeat UAE is initially the same as a typical UAE, but requires additional arterial evaluation and, if necessary, embolization. Once arterial access is established, the internal iliac artery is selectively catheterized with the 4 or 5Fr catheter of the operator's choice. This author typically uses a 5Fr Levin I catheter (Cook Medical, Bloomington, IN, USA) for the majority of cases, with the 5Fr Roberts Uterine Curve catheter (Cook) for tortuous vessels. A mapping injection of the internal iliac artery is essential to evaluate for patency of the uterine arteries and the possibility of anomalous vessels such as aberrant origins or duplication of the uterine artery. It is important to inject enough contrast to reflux the common iliac bifurcation. This ensures that the entire internal iliac artery distribution is filled.

In patients previously embolized with calibrated microspheres or only regular PVA, the uterine arteries will almost always be patent (Razavi et al. 2000). The original published protocol for UAE (McLucas et al. 1996) called for large gelatin sponge pledgets to 'cap' embolization with irregular PVA particles. Some operators continue to use gelatin sponge for UAE. In the author's experience of repeat UAE in nine patients who had UAE under this protocol, 17 of the 18 uterine arteries were no longer patent, presumably due to the inflammatory reaction gelatin sponge incites.

Variations in the origins of the uterine artery, including atresia, have been well documented (Pelage et al. 1999; Worthington-Kirsch et al. 1999; Gomez-Jorge et al. 2003). Duplication of the uterine artery is apparently rare. The author has encountered only 2 cases in over 2,700 UAE studies.

If the uterine arteries are patent they should be selectively catheterized and re-embolized. The author uses the same criteria for choice of catheter[2], embolic particle, and endpoints as for initial UAE procedures. If the ovarian artery is not refluxed on initial injection of the uterine artery, embolization is started using either 500–700 micron trisacryl-gelatin microspheres (Embosphere, Merit Medical Systems, South Jordan, UT, USA) or 700–900 micron PVA hydrogel microspheres (Bead Block, Biocompatibles UK Ltd, Farnham, Surrey, UK). If the ovarian artery is refluxed, 700–900 micron microspheres are used. Once the uterine arteries have been evaluated and treated, the ovarian arteries should be examined. If there is flow to the uterus, embolization of one or both ovarian arteries should be performed. The author prefers to selectively catheterize the ovarian arteries for this purpose. Only if the ovarian arteries cannot be identified does he perform an aortogram to see if they can be defined (White et al. 2007). The left ovarian artery usually arises from the anterolateral aspect of the aorta, about one-third of the way caudal from the origin of the left renal artery on a line from the left renal artery to the inferior mesenteric artery. The right ovarian artery usually arises from the anterior aorta to the right of the midline a few centimeters caudal to the origin of the superior mesenteric artery. The ovarian arteries can be branches of the renal arteries, especially from inferior accessory renal arteries.

The ostia of the ovarian arteries are best engaged with a reverse-curve catheter (e.g., Levin I in Waltman Loop configuration, Roberts Curve, Simmons, Mickelson). A standard catheter should not be advanced into the ovarian artery beyond the ostium due to the small caliber and fragility of the vessel. If injection of the ovarian artery shows filling of vessels in the uterus a microcatheter is advanced into the descending portion of the ovarian artery and the vessel embolized with 700–900 micron-sized calibrated hydrogel microspheres (Barth and Spies 2003).

The author always discusses the possibility of ovarian artery embolization with patients, both when obtaining consent for the initial UAE and for any repeat studies. It should be noted that the vessels branching off the ovarian artery into the ovary itself are typically 600–650 micron in diameter (Sampson 1912), and 700–900 micron-sized particles would be expected to largely bypass the ovary and be distributed into the uterine vascular bed. In the author's experience patients who had embolization of one or both ovarian arteries showed no interruption in menstrual cycles or increase in vasomotor symptoms. The author is unaware of any published data that ovarian artery embolization increases the risk for ovarian failure after UAE.

If evaluation of the uterine and ovarian arteries shows supply to both sides of the uterus and that is treated, there is usually no point in further investigation. If vessels supplying the fibroids have not been demonstrated, other potential sources of accessory supply to the uterus need to be evaluated. The artery to the round ligament should be examined (Saraiya et al. 2002). This is a branch of the inferior epigastric artery. Given that it is conceivable that uterine supply may come from other pelvic vessels, repeat injection

[2] The author routinely performs UAE with a 5Fr diagnostic catheter, almost always either a Levin 1 curve or a Roberts Uterine curve. The catheter tip is positioned in the transverse segment of the uterine artery. The author only uses microcatheters in cases where the uterine artery is either too small or too tortuous to be catheterized with the 5Fr catheter.

of the internal iliac artery with prolonged filming or injection of the common or external iliac arteries may reveal previously unreported sources of supply to the uterus. A simple flush injection of the aorta is probably insufficient to fill these relatively small branch vessels, and is not worth the contrast load.

There are also reports of flow to fibroids from visceral and omental collaterals, particularly the inferior mesenteric artery (McLucas 2009b; Smeets et al. 2010). This appears to be most likely for large fundal fibroids, and may be associated with a history of previous surgery in the pelvis. Even if these unusual sources of arterial supply to the fibroids are identified the risk of nontarget embolization, especially to bowel, may preclude embolization.

## 4 Results of Repeat UAE

Given the challenges of identifying and catheterizing the various sources of supplemental vascular supply to the uterus, one would expect that technical results for repeat UAE would be poorer than for initial UAE. However, technical results of repeat UAE are apparently about as good as initial embolizations. Yousefi and colleagues report successful embolization of "all visible flow to the uterus" in 23 of 25 patients (92%) (Yousefi et al. 2006). They found supplemental ovarian artery supply to the uterus in addition to the uterine arteries in 6 of 15 patients (40%) and ovarian artery supply replacing one or both uterine arteries in 10 of 25 patients. McLucas reports successful embolization of all visible flow to the uterus in 19 of 22 (86%) patients whose initial UAE procedure was technically unsuccessful due to failed attempt at catheterization of a visible patent uterine artery (McLucas 2009a).

If all demonstrable supply to the fibroid uterus is successfully embolized, the results of repeat UAE appear to be similar to the results of initial UAE. The papers mentioned above show that 90–94% of patients who had successful repeat embolizations experienced relief from their fibroid-related symptoms (Yousefi et al. 2006; McLucas and Reed 2009; McLucas 2009a, b). Although the numbers are low, this appears to be the same as the 90–95% clinical success rate seen after initial UAE.

## 5 Conclusion

Patients whose initial UAE fails to relieve their fibroid-related symptoms or whose fibroid-related symptoms recur after successful UAE may well have residual/recurrent fibroids that remain amenable to embolotherapy. With appropriate clinical evaluation and a thorough approach to the embolization procedure, the majority of these women can be treated by repeat embolization. This allows them to continue to avoid major abdominal surgery for treatment of their fibroid disease.

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# Myomectomy Techniques

Adam Magos and Ioannis Tsibanakos

## Contents




**Abstract**

Uterine fibroids are common, and if symptomatic and the uterus is to be conserved for child-bearing, myomectomy is the traditional surgical solution. Myomectomy can be done by a variety of techniques, including by laparotomy (open surgery), laparoscopy, hysteroscopy and via the vagina. Each has its indication, and advantages and disadvantages. Open myomectomy is suitable for all cases and remains the only choice when the fibroids are numerous and/or large. Laparoscopic myomectomy is most suited to small to medium sized subserous fibroids but can also be used if the fibroid is intramural. Recently, robotically assisted laparoscopic myomectomy has been introduced into clinical practice, but whether it is cost effective remains to be seen. Hysteroscopic myomectomy is indicated for small intra-cavitary and submucous fibroids. Finally, vaginal myomectomy, widely practised in the nineteenth century, is undergoing a revival as an alternative to laparoscopic and hysteroscopic surgery.


## 1 Introduction

Due to their high prevalence and association with abnormal menstruation, subfertility, an abdominal mass and pressure symptoms, the management of uterine fibroids has traditionally represented a considerable workload for gynaecologists. While at least half the women with uterine fibroids remain asymptomatic, typically those with small leiomyomas, the absence of medical treatment which is both effective and suitable for long-term therapy coupled to the natural tendency of fibroids to enlarge during the reproductive years has meant that many women do ultimately require more invasive treatment. For the gynaecologist, this has essentially meant either conservative surgery (myomectomy) if fertility is to be preserved, or radical surgery (hysterectomy), when future childbearing was no longer an issue. However, it is increasingly the case that even women

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who do not desire pregnancy wish to retain the uterus and refuse hysterectomy. In such cases, myomectomy is the traditional surgical solution.

## 2 Preparation for Myomectomy

Adequate assessment prior to myomectomy is essential to ensure that the appropriate surgery is done and the surgery is made as safe as possible. Estimation of uterine size is the starting point, and this is easily achieved by abdominal and bimanual palpation, most gynaecologists describing the size of the uterus in terms or pregnancy equivalent. If vaginal myomectomy is a possibility, adequate vaginal access and good uterine mobility on vaginal examination should be sought. Although not a common finding, vaginal examination may reveal a cervical or prolapsed vaginal fibroid.

As it is rarely possible to conclude from palpation, how many fibroids there are and their precise position, something which may influence the route of surgery, clinical examination should be supplemented by appropriate imaging. In our practice, this typically involves ultrasound scanning as a cheap alternative to MRI, the aim being to document the number of fibroids, their position and size.

If the fibroids are relatively small and shown to be submucous on imaging, it is the practice of the authors to carry out an office (out-patient) hysteroscopy to confirm that the fibroid is suitable for hysteroscopic excision.

In view of the risk of intra-operative bleeding, it is important to diagnose and correct any pre-existing anaemia before surgery, so a full blood count is standard practice. This may simply involve treating with iron supplements, but could mean the use of GnRH analogues to stop menstruation, or more recently, ulipristal acetate. Hormone pretreatment can also be used to shrink fibroids to facilitate surgery, but this is not routine practice in our clinic for the reasons outlined in Sect. 4.

If imaging shows ureteric dilatation secondary to pressure from the fibroids, renal function tests are also done. Other investigations are only ordered if clinically indicated.

## 3 Techniques of Myomectomy

To many gynaecologists as well as patients, myomectomy equates with the excision of fibroids by laparotomy, laparoscopy or hysteroscopy (Mukhopadhaya et al. 2008). This ignores the fact that the earliest myomectomies were not done by any of these routes of surgery but via the vagina (for fibroids which were sited in the cervix or had prolapsed into the vagina). There are, therefore, four routes of surgery to remove uterine fibroids as summarised in Table 1.

**Table 1** Different types of myomectomy and our operative criteria

| Route of surgery | Uterine/fibroid size | Number | Position |
|---|---|---|---|
| Abdominal | Any | Any | Any |
| Laparoscopic | ≤15 cm total fibroid diameter | ≤3 | Subserous/intramural |
| Hysteroscopic | ≤5 diameter | 1 to a few | Intracavitary/ submucous |
| Vaginal | ≤14 weeks uterine size | 1 to several | Vaginal/ intracavitary/ intramural/subserous |

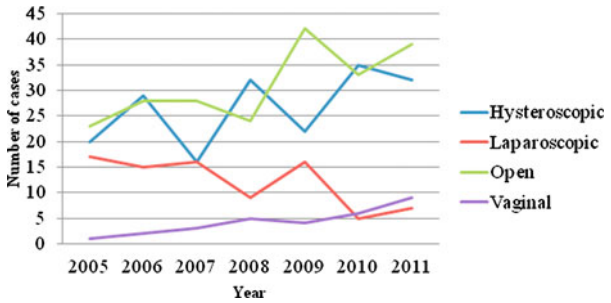


**Fig. 1** Myomectomies carried out under the care of the senior author (2005–2011)

The choice of which type of myomectomy to carry out is obvious in some cases, while in others it is a matter of the experience and preference of the gynaecologist. At one end of the spectrum, women with gross uterine enlargement secondary to multiple large fibroids have little option but to undergo open myomectomy. At the other extreme, there would be few who would disagree that hysteroscopic myomectomy for one or two small submucous fibroids is the best and most elegant technique in such cases, while laparoscopic myomectomy is most suited to women who have a few small to medium-sized subserous/intramural fibroids.

As is typical of all surgical procedures, individual surgical practice is not quite as clear cut. For instance, there are a handful of enthusiasts who carry out laparoscopic myomectomy in cases where, because of the size and number of fibroids to be removed, the majority of gynaecologists would not even consider it (Sinha et al. 2008). Another example is vaginal myomectomy, a technique which has been all but forgotten by the majority of gynaecologists; we consider that this technique has several important advantages over the other route of surgery, so offer it to suitable patients as a matter of routine as demonstrated in Fig. 1 (Thomas and Magos 2011).

## 4 Open Myomectomy

Open myomectomy is the traditional conservative procedure when the uterus is significantly enlarged by multiple, large fibroids (Breech and Rock 2008). While the advent of pelvic ultrasound scanning has meant that women are diagnosed with relatively small fibroids at an earlier age than previously, and indeed in many cases uterine fibroids are an incidental finding when imaging is done for some other reason, it is still the case that a significant proportion of patients who present to gynaecologists with a diagnosis of uterine fibroids and symptoms have an easily palpable pelvic mass in the abdomen. In the majority of such cases, open myomectomy is both the most appropriate and most thorough treatment if uterine function is to be preserved. About 40,000 open myomectomies are done each year in the USA, and 2,000 or so in England.

Having decided to carry out an open myomectomy, the next decision is whether or not to delay surgery and pre-treat with a GnRH analogue. Pre-treatment for 3 months is certainly popular for a number of reasons: there is a good chance that therapy will inhibit menstruation which may well have been abnormally heavy previously; amenorrhoea should lead to improved haemoglobin with correction any pre-existing anaemia, particularly if combined with iron therapy; it should reduce fibroid and uterine size, thereby allowing for a smaller laparotomy incision and possibly the use of a cosmetically and functionally superior low transverse laparotomy incision rather than a vertical one.

There are, however, disadvantages to GnRH pre-treatment. Quite apart from the need to delay surgery for the analogues to take effect, treatment is expensive and associated with menopausal side-effects such as hot flushes and night sweats (although this can be counteracted by concurrent oestrogen add-back therapy). Dissecting the fibroids from the myometrium tends to be more difficult as the tissue planes are often less distinct. There may be little or no benefit in terms of operative blood loss. Perhaps most importantly, there is good evidence that there is a higher fibroid recurrence rate in patients who have been pre-treated for the simple fact that small fibroids become so small with therapy that they are missed during surgery (Vercellini et al. 2003).

In consideration of the above, our protocol is to only prescribe GnRH analogue pre-treatment as an adjunct to correcting anaemia due to menorrhagia, and if shrinking the uterus will avoid the need for a vertical laparotomy incision. It may be that the recently introduced orally active selective progesterone receptor modulator, ulipristal acetate, may prove to be a more acceptable option to stop menstruation and shrink fibroids prior to surgery.

### 4.1 Patient Selection

Any patient is suitable for open myomectomy, but in reality, women who are offered this type of intervention are the ones who are judged to be unsuitable for the other approaches. This usually means that the typical woman who undergoes open myomectomy has multiple large fibroids, often extending to or above the umbilicus. Occasionally, open myomectomy is done on patients with relatively small or few fibroids when it tends to be a matter of patient preference. It is certainly true that, for instance, open myomectomy has more of a chance of removing all the fibroids with a stronger uterine repair for subsequent childbearing than laparoscopic myomectomy, and for some this is an important consideration.

### 4.2 Surgical Technique

The default incision for open myomectomy is a low transverse (Pfannenstiel) laparotomy. In some cases this is inappropriate because of the size of the fibroids, the presence of a previous midline incision or concern about adhesions, when a vertical laparotomy may be preferred. Quite apart from the cosmetic disadvantage of a vertical laparotomy, this incision has a considerably greater risk of breakdown and post-operative herniation. At the other end of the scale when there are relatively few, small fibroids to remove, surgery can be done via a mini-laparotomy (incision $\leq$7 cm) and even ultraminilaparotomy (incision $\leq$4 cm) as an alternative to laparoscopic myomectomy.

The aim of surgery is to remove as many of the fibroids as possible, ideally all of them, no matter how small. Rather than incising the uterus over each and every fibroid, the recommended technique is (a) to remove the fibroids through as few incisions as possible, and (b) to avoid posterior uterine incisions to reduce the chance of post-operative adhesions involving the fallopian tubes and ovaries risking subfertility (Breech and Rock 2008). It is for this reason that most procedures start with a single vertical anterior midline incision, and if a posterior incision is required, we prefer a "hood incision", originally described by Victor Bonney, arguably the most important figure in popularising open myomectomy in the UK (Chamberlain 2003).

Whatever the approach, we prefer to only open the endometrial cavity if this is unavoidable because of the presence of intracavitary or submucous fibroids. There are those, however, who advocate removing even posterior fibroids through an anterior uterine incision by cutting through the uterine cavity. Traditionally, if the uterine cavity has been opened at open myomectomy, any subsequent deliveries are done by elective Caesarean section.

**Table 2** Techniques which have been tried to reduce intra-operative blood loss at open myomectomy

| |
|---|
| *Pre-operative techniques* |
| GnRHa |
| Uterine artery embolisation |
| *Intra-operative techniques* |
| Hypotensive anaesthesia |
| Single midline uterine incision |
| Enucleation of coagulation cascade (e.g. tranexamic acid, aprotinin, aminocaproic acid, recombinant factor VIIa, gelatin-thrombin sealant) |
| Dissection techniques (e.g. laser electrosurgery chemical dissection with sodium-2-mercaptoethane sulfonate [MESNA]) |
| Uterotonics (e.g. ergometrine, oxytocin, misoprostol, sulprostone) |
| Hormonal tourniquet (e.g. vasopressin, terlipressin, epinephrine, bupivacaine + adrenaline) |
| Mechanical tourniquet (e.g. clamps, clips, electrocoagulation, single tourniquet, triple tourniquets) |

The major risk of open myomectomy is haemorrhage, which if severe may necessitate the greatest fear not only for the patient but the gynaecologist, namely hysterectomy. Various strategies, both pre- and intra-operative, have been advocated to reduce this risk (Table 2). Radiologists, of course, know the history of uterine artery embolisation (UAE) and are aware that UAE was originally introduced not as a definitive management, but as a precursor to open myomectomy to reduce the risk of intra-operative haemorrhage (Ravina et al. 1994).

Despite the long history of the operation, only a few of these strategies have been proven to be effective under controlled conditions. Table 3 summarises the results of randomized trials of various intra-operative techniques which have been studied, showing that the most effective strategy is the use of triple tourniquets to occlude uterine perfusion during surgery (Kongnyuy and Wiysonge 2011). The classic technique is to place tourniquets around the cervix and each infundibulopelvic ligament to occlude the uterine and ovarian arteries thereby rendering the uterus totally avascular during surgery (Breech and Rock 2008). Concern about prolonged ovarian hypoxia has meant that some gynaecologists release the ovarian tourniquets every 20 min or so, but this of course adds to the blood loss. To circumvent this problem, we have designed a special clamp (Ovarian Artery Clamp) which can be applied medial to the ovaries to occlude the ovarian blood supply to the uterus without crushing the fallopian tubes as would be the case with a standard clamp (Fig. 2a, b) (Magos et al. 2011). Preliminary results from our Institution show that this technique is as effective as conventional triple tourniquets.

As a further refinement of the technique, and a reflection of the fact that it can be difficult to apply an effective tourniquet around the cervix, we have reported the use of sterilised cable ties as an alternative to catheters and sutures (Al-Shabibi et al. 2010). Interestingly, the use of cable ties at surgery can be traced back to the 1970s!

**Table 3** Efficacy of various intra-operative techniques to reduce bleeding at open myomectomy

| |
|---|
| 12 randomized studies<br>674 women |
| *Not effective*<br>Intravenous *oxytocin*<br>Myoma enucleation by *morcellation* |
| *Effective*<br>Intramyometrial *bupivacaine + adrenaline* (MD-69 ml)<br>Intravaginal *misoprostol* (MD-149 ml)<br>*Single tourniquet* (MD-241 ml)<br>Intravenous *tranexamic acid* (MD-243 ml)<br>Intramyometrial *vasopressin* (MD-299 ml)<br>*Gelatin-thrombin matrix* (MD-545 ml)<br>*Triple tourniquets* (MD-1870 ml) |

*MD* Mean difference blood loss

On completion of the myomectomy, it is generally recommended that steps should be taken to reduce the risk of post-operative adhesions. A variety of anti-adhesive agents can be used for this, although in reality, their efficacy remains largely unproven (Ahmad et al. 2008). It is our usual practice to leave a drain in the pelvis both to monitor any oozing from the uterus and reduce the chance of a clinically significant post-operative haematoma. We also give prophylactic antibiotics during and after the surgery. Prophylactic anticoagulants are not given pre-operatively for fear that this will increase the risk of intra-operative haemorrhage, and instead we rely on anti-embolism compression stockings and pneumatic calf pumps during surgery to reduce the chance of deep vein thrombosis.

Drains and bladder catheters are usually removed after 2 days, and although variable, most patients are discharged from hospital after 5–6 days.

## 4.3 Operative Complications

Intra- and to some extent post-operative haemorrhage is the main risk of surgery. As noted above, triple tourniquets are a very effective technique for reducing bleeding complications, but even then around 10 % of our patients require a peri-operative blood transfusion (Taylor et al. 2005b; Al-Shabibi et al. 2009). Some may feel this rate of transfusion is unduly high, but the need for blood products very much depends on the size and number of fibroids removed. On average, we excise 15–20 fibroids per patient, a figure which is considerably more than reported in most published series (Hanstede et al. 2008).

Despite the extent of the surgery, we have never had to resort to hysterectomy because of intra- or post-operative bleeding. For instance, during the period 2005–2012, we only had to carry out two hysterectomies out of over 250 procedures, the indications for both being severe uterine

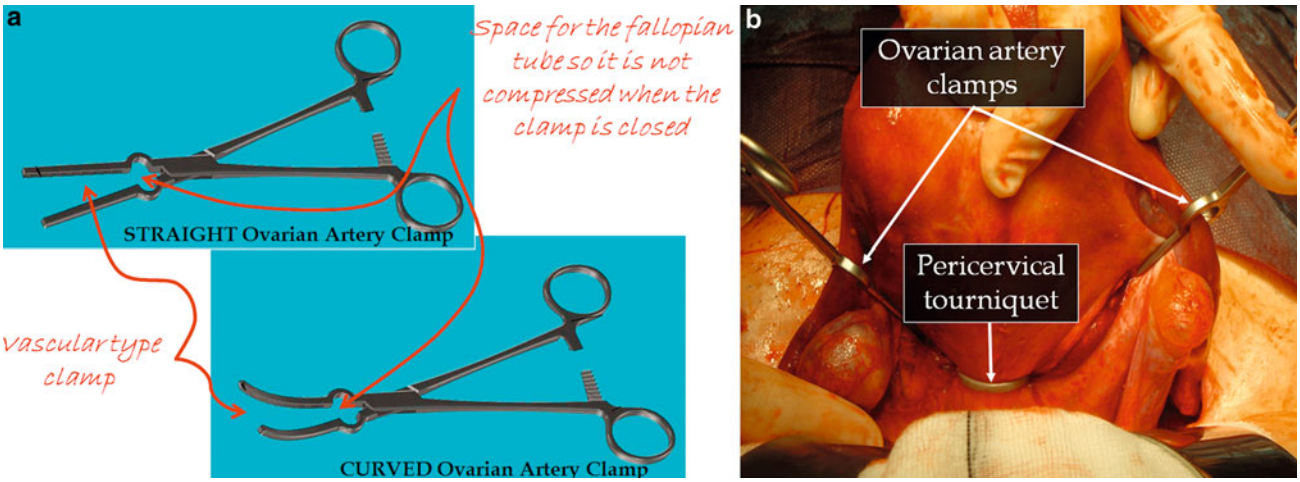


**Fig. 2** **a** Straight and curved ovarian artery clamps for use at open myomectomy. **b** Pericervical tourniquet and ovarian artery clamps in position at the start of open myomectomy

sepsis following repeat open myomectomy; in one case, over 100 fibroids were removed at surgery. This compares with rates of hysterectomy because of bleeding of 4 % in other published series (Olufowobi et al. 2004).

The other typical complications (e.g. wound, urinary tract and chest infections, venous thrombosis), occur as with any other open pelvic surgery. All patients are counseled regarding the theoretical risk of injury to bowel and bladder, but in reality, this rarely happens unless there are extensive adhesions around the uterus. We advise all our patients undergoing open myomectomy to delay trying for a pregnancy for at least 6 months to give time for the uterus to heal.

## 5 Hysteroscopic Myomectomy

To a gynaecologist, hysteroscopic myomectomy is the total opposite to open myomectomy. Whereas open myomectomy clearly represents major surgery with all its associated risks including haemorrhage, hysteroscopic myomectomy is an elegant and above all, relatively quick and atraumatic treatment for intracavitary and submucous fibroids. Bleeding is rarely an issue.

First described by the American Robert Neuwirth in 1976, when he used hysteroscopic scissors to cut the stalk of pedunculated intra-cavitary fibroids, two years later he introduced what arguably remains one of the most important development in modern gynaecology, the use of the resectoscope for excising submucous fibroids which are partially embedded in the myometrium (Neuwirth and Amin 1976; Neuwirth 1978). This includes most submucous myomas.

The instrumentation and techniques for hysteroscopic myomectomy have been developed further in the ensuing years with the introduction of the Versapoint device and more recently the intra-uterine morcellator (Di Spiezio et al. 2008). However, few would argue that the resectoscope remains the instrument par excellence for hysteroscopic myomectomy. It is both the most efficient instrument and the only one which can be used to remove fibroids which extend deep into the myometrium. The introduction of the miniresectoscope, a paediatric instrument which has been lengthened to make it suitable for use in adults, has meant that the benefits of resectoscopic surgery is now available in the outpatient/office setting (Papalampros et al. 2009).

### 5.1 Patient Selection

Whatever the instrumentation, patient selection is of paramount importance (Table 1). Hysteroscopic myomectomy should only be offered to women who have one or two relatively small ($\leq$5 cm for most gynaecologists) submucous fibroids (Fig. 3). Multiple submucous fibroids are rarely suitable for fear of inducing a surgical Asherman's syndrome with scarring and agglutination of the raw surfaces following surgery. Large fibroids are unsuitable as surgery is likely to be prolonged with a risk of fluid overload (see below). Subserous or transmural fibroids, even if they have an intra-cavitary component, are unsuitable as surgery will inevitably result in uterine perforation. Despite these restrictions, hysteroscopic myomectomy remains second only to open myomectomy at our Institution as surgical treatment for uterine fibroids, a situation no doubt explained by early diagnosis by ultrasound (Fig. 1).

### 5.2 Surgical Technique

The precise technique of hysteroscopic myomectomy depends on the instrumentation being used, but all share

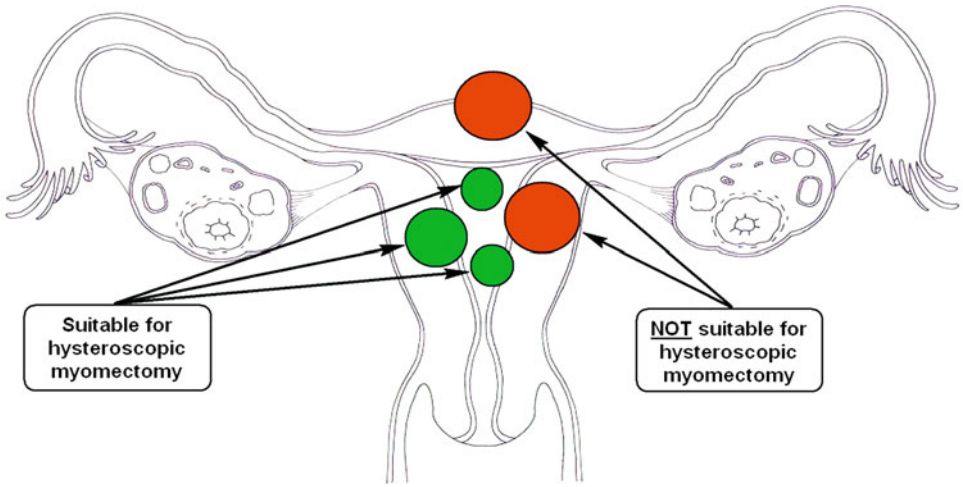


**Fig. 3** Not all fibroids are suitable for hysteroscopic myomectomy

some common principles. The cervix may have to be dilated to allow insertion of the operative hysteroscope; if this is necessary in the outpatient clinic, it is sometimes necessary to inject local anaesthetic into the cervix or paracervix. The uterine cavity has to be distended with a sterile low-viscosity irrigant at a relatively high pressure (100–150 mm Hg) to allow adequate separation of the uterine walls and visualisation of the fibroid(s). The choice of irrigant depends on the type of instrument being used, traditional fluids including 1.5 % glycine solution (for monopolar surgery) and normal saline (for mechanical or bipolar instruments).

Unless very small, the fibroid is then cut into pieces to aid removal, a process which is technically much easier with a resectoscope than the Versapoint because of the design and angle of the active electrode. Care has to be taken when resecting the intramural portion of any fibroid to avoid cutting too deeply and thereby perforating the uterus, and it is for this reason that fibroids which are <5 mm from the serosa are probably best not managed hysteroscopically. When there is a deep intramural component, we use a technique described by Mazzon (Italy) which involves dissecting out the fibroid using various cold knife (non-electrosurgical) electrodes (Casadio et al. 2011). Using this technique, performing partial myomectomy and leaving the deep part of the fibroid in situ can no longer be justified.

At the end of the surgery, most of the resected fibroid pieces are removed and sent for histological analysis. This is important as sarcomatous change is always a possibility, albeit a rare one.

## 5.3 Operative Complications

The major risks of operative hysteroscopy are listed in Table 4, of which uterine perforation and fluid overload are the classic complications (Aydeniz et al. 2002). In reality, all the complications listed are uncommon and largely avoidable by good technique.

Uterine perforation is arguably the major fear as it can result not only in uterine haemorrhage but injury to adjacent structures (e.g. bowel, bladder, major blood vessels). Perforation is avoided by ensuring that resection is not carried too deeply into the myometrium. If the uterus is perforated during myomectomy, the surgery must stop and a laparoscopy or laparotomy done both to control any uterine bleeding and to check for collateral damage.

Fluid overload and associated electrolyte derangement, which in extreme cases can be fatal and similar to the TURP syndrome seen in men, is avoided by continuous and careful monitoring of fluid balance throughout the procedure and stopping surgery if fluid balance reaches a pre-determined limit. We take the additional precaution in such cases of checking blood biochemistry, giving a small dose of furosemide (20–40 mg i.v.), and catheterising the bladder to monitor urine output with the expectation that there will be full metabolic return to normal within 12–24 h. The risk of serious sequelae has, anyway, been greatly reduced by the change from mono- to bi-polar electrosurgery and the use of more physiological electrolyte-containing uterine distension media.

Of the other risks, bleeding during surgery is uncommon for the simple fact that the intra-uterine distension pressure is usually above the mean arterial pressure. On occasions, heavy bleeding can occur at the end of the procedure when the uterus is deflated, particularly if a particularly large, deep fibroid has been excised, but this is usually simply managed by tamponade with an intra-uterine balloon for a few hours. Infection is generally very uncommon after hysteroscopy, but we do give prophylactic antibiotics during surgery. The authors have never seen gas embolism in their clinical practice.

**Table 4** Complications of operative hysteroscopy

| |
|---|
| Uterine perforation |
| Fluid overload |
| Haemorrhage |
| Gas embolism |
| Infection |
| Cervical trauma |
| Electrosurgical burn |

## 6 Laparoscopic Myomectomy

Laparoscopic myomectomy was first described towards the latter part of the 1970s at around the same time as hysteroscopic myomectomy. Kurt Semm, Professor of Obstetrics and Gynaecology in Kiel in Germany, considered by many to be the father of modern laparoscopic surgery, developed the instruments and techniques which made laparoscopic myomectomy as well as a long list of other procedures formerly done by laparotomy possible (Semm 1979). He introduced laparoscopic suturing techniques, large (10 mm) laparoscopic forceps, the Aqua-Purator for suction/irrigation, and relevant to myomectomy, a manual tissue morcellator to allow removal of the fibroid through a laparoscopic port. Although it took some time for his ideas to be widely accepted, laparoscopic myomectomy has become a standard gynaecological procedure, although one which is only undertaken by a minority of gynaecologists because of the need for an ability to suture laparoscopically to repair the uterus at the end of the procedure (Taylor et al. 2005a).

Technological advances since Semm's first description have meant the availability of larger and more efficient morcellators, morcellation always being relatively time consuming and greatly adding to the overall operating time. While Semm was looking directly through the laparoscope during surgery, which meant that his assistants were largely blind to the procedure and therefore of limited help, all laparoscopic surgery is now done under video monitoring, so the entire surgical team can play a role to make the procedure efficient and safe (Magos et al. 2011).

The earlier comments about pre-treatment with GnRH analogues apply equally to laparoscopic myomectomy as well, with the similar advantages and disadvantages.

### 6.1 Patient Selection

Laparoscopic myomectomy is principally indicated for patients who have a few small to medium-sized subserous and/or intramural fibroids associated with modest overall uterine enlargement (Table 1). Pedunculated subserous fibroids are particularly suited to a laparoscopic approach, whereas deep intramural fibroids are technically the most difficult to operate on. However, it would not be unfair to claim that no two gynaecologists have the same criteria for the procedure, and the upper limit for laparoscopic myomectomy in terms of number and size of fibroids to be removed is often a matter of personal preference. There is no doubt that the larger and more numerous the fibroids, the more difficult and time-consuming the procedure, and it is debatable whether spending over 7 h to remove a handful of myomas laparoscopically rather than taking 1–2 h by laparotomy can be justified (Hasson et al. 1992).

### 6.2 Surgical Technique

Many aspects of laparoscopic myomectomy are the same as for any laparoscopic procedure. It is not uncommon to use more ports than usual (say 4 instead of 3), to use larger ports (12–15 mm instead of 5 mm), and to place them higher in the anterior abdominal wall than usual so as not to be too close to the uterus. As noted above, for anything other than pedunculated subserous fibroids, uterine repair will be necessary so the gynaecologist must be able to suture laparoscopically.

Modifications of the classic laparoscopic procedure originally described by Semm have been developed to make the surgery easier. Hand-assisted laparoscopic myomectomy and laparoscopically assisted ultraminilaparotomy are two examples but have yet to be widely practised (Wen et al. 2010).

Intra-operative bleeding remains the major risk of surgery, just as with open myomectomy. As by definition only a few fibroids are to be removed, many gynaecologists use local dilute vasopressin infiltration to reduce blood loss during surgery. Great care has to be taken to ensure that the vasopressin is not injected directly into a blood vessel as this risks cardiovascular complications, and even death; it is for this reason that the use of vasopressin for this indication is banned in some countries (Hobo et al. 2009).

An arguably safer approach is to occlude the uterine vessels temporarily or permanently at the start of surgery using electrosurgery, sutures or clips (Dubuisson 2007). Again, care has to be taken to avoid inadvertently occluding the ureters which lie close. Our favoured technique is an adaptation of the triple tourniquets, we use at laparotomy which has the advantages that (a) blood flow from the ovarian vessels are also halted to provide total rather than partial haemostasis, and (b) there is less risk of injuring the ureter as there is no need for any pelvic side wall dissection (Taylor et al. 2005c).

Following excision of the fibroids, it is important to repair the uterus in layers. Not only does this provide haemostasis,

but importantly from the point of view of obstetric performance, reduces the risk of dehiscence in subsequent pregnancies.

On completion of the myomectomy, most gynaecologists use powered morcellators to remove the fibroid(s) through one of the ports, although fibroids can also be removed via a posterior colpotomy.

While the operating time tends to be considerably longer than with laparotomy, intra-operative blood loss, minor complications and patient recovery in terms of post-operative analgesia requirements, duration of hospitalisation and time taken for return to full activities are superior to open myomectomy (Jin et al. 2009).

### 6.3 Operative Complications

All the complications of open myomectomy apply to laparoscopic myomectomy but, as the fibroids which are removed tend to be smaller, the problems tend to be less frequent than with conventional surgery. Conversely, laparoscopic myomectomy has its own unique risks related to the surgical approach (Makai and Isaacson 2009). In essence, these can be summarised as (a) complications which occur at the time of laparoscopic entry (e.g. bowel or vascular injury), and (b) many injuries are not recognised at the time. While uncommon, undiagnosed injuries can have severe consequences quite apart from the need for reparative surgery, which tends to be by laparotomy and in the case of bowel injury, may involve a colostomy (usually temporary). It is important that patients contemplating laparoscopic myomectomy understand this and are also warned that the procedure may have to be converted to laparotomy should the need arise.

## 7 Robotic Myomectomy

Robotic surgery is a development of laparoscopic surgery which is becoming increasingly available. Rather than the surgeon directly holding and operating the instruments, the instruments are operated by the arms of a robot which in turn is controlled by the surgeon some distance away via a control panel. Currently, the only robot in clinical use is the da Vinci surgical system, and there have been a few favourable reports of its use for laparoscopic myomectomy (Chen and Falcone 2009).

The advantages claimed for robotic surgery over standard laparoscopic surgery include the availability of a three- rather than two-dimensional vision resulting in enhanced visualisation, wristed instrumentation which provides greater dexterity and control than hand-held devices, elimination of the fulcrum effect integral to conventional laparoscopy which means that the surgeon no longer moves their hand in the opposite direction to the intended path of the instrument, and not least for what is often a prolonged procedure, far greater comfort for the surgeon who, rather than having to strain over the patient sits comfortably at the robot console (Schreuder and Verheijen 2009).

On the negative side, the da Vinci system is very expensive in terms of capital and running costs. The setting-up time is considerably longer than with conventional laparoscopy. Due to its size, the operating room has to be relatively large. As a result, few units in the UK have a da Vinci surgical system. No doubt, their use will increase but whether robotic surgery ever becomes cost effective or even of benefit compared with conventional surgery remains to be seen (Liu et al. 2012).

## 8 Vaginal Myomectomy

Cost is certainly not an issue with vaginal myomectomy, which in contrast to hysteroscopic myomectomy, is a non-endoscopic method of removing fibroids via the vagina. Vaginal myomectomy for submucous fibroids which had prolapsed into the cervix and vagina was in fact the first myomectomy, practised in the 1840s by pioneers of gynaecological surgery such as Amussat in France and Atlee in the US. By the end of the nineteenth century, the technique had been expanded to include not only the removal of prolapsed fibroids, but submucous, intramural and even subserous fibroids. These techniques are well documented in textbooks, usually with beautiful drawings, such as “Operative Gynecology” by Harry Sturgeon Crossen published in 1917 (several of these books are available free for download from www.archives.org).

Today, apart from myomectomy for a fibroid which has prolapsed through to the cervix or vagina, vaginal myomectomy has largely been forgotten by most gynaecologists, and the technique is not even mentioned in some current textbooks. This is a pity as it is a very useful alternative to hysteroscopic and laparoscopic myomectomy in suitable cases. Compared with hysteroscopic myomectomy, this technique is suitable for fibroids larger than 5 cm in diameter, and there is no risk of uterine perforation, fluid overload or gas embolism to list but three risks. Compared with laparoscopic myomectomy, the surgery is considerably faster and the uterine repair stronger as conventional suturing can be used.

### 8.1 Patient Selection

As is evident from the above, a vaginal approach to myomectomy can be considered irrespective of the position of the fibroid, the sole exception being a dominant fundal

**Table 5** Proposed classification of vaginal myomectomy

| Type | |
|---|---|
| 1 | Avulsion of prolapsed pedunculated submucous fibroid |
| 2 | Non-incisional access to intracervical or intracavitary fibroid |
| 3a | Incisional access to intracavitary fibroid (Dührssen cervical incision) |
| 3b | Incisional access to intracavitary fibroid (incision continued as hysterotomy) |
| 4 | Colpotomy access to intramural and subserous fibroids |

fibroid which is better approached laparoscopically unless too large. Instead, the important considerations are, as in all vaginal procedures, adequate vaginal access and uterine mobility. Vaginal access is rarely an issue unless the patient is a virgo intacta, but obviously, surgery is easier in multiparous women who have delivered vaginally. Similarly, uterine mobility is not usually a problem unless the uterus is fixed by adhesions secondary to conditions such as severe endometriosis; it should be noted that adequate uterine mobility is not synonymous with utero-vaginal prolapse.

The main issue, then, is uterine and fibroid size. In the view of the authors, vaginal myomectomy for anything other than a prolapsed vaginal or cervical fibroid would be unduly difficult if the overall uterine size is ≥14–16 weeks gestation equivalent.

## 8.2 Surgical Technique

The various techniques of vaginal myomectomy are summarised in Table 5. The easiest technique is the Type 1 procedure, the one which Atlee described in 1845, and merely involves avulsing a fibroid which has prolapsed from the uterine cavity into the vagina. If the fibroid is lying in the cervix, removal may be aided by cutting the cervix longitudinally, the so-called Dührssen incision (Type 3a procedure). The incision can be extended into the uterus for the removal of fibroids which are in the uterine cavity or myometrium (Type 3b procedure). Finally, subserous fibroids can be accessed via an anterior or posterior colpotomy (Type 4 procedure) (Fig. 4).

If the cervix or uterus is to be incised, we inject vasoconstrictors into the cervix. It is in fact remarkable how relatively avascular the surgery is in most cases, probably explained by the fact that maneuvering.

Readers may be interested to learn that the original use for Dührssen incisions was to carry out vaginal Caesarean section. Yes, even a Caesarean section can be carried out vaginally!

Providing patient selection is appropriate, and vaginal myomectomy is not attempted in cases where the fibroids are obviously too large, our experience with all the various types of vaginal myomectomies is very positive. After a hiatus of 100 years or so, there is now particular interest in the Type 4 procedure not only in the West but as far afield as China (Yu et al. 2011). The technique has been favourable compared with laparoscopic myomectomy in randomised trials (Yi et al. 2011).

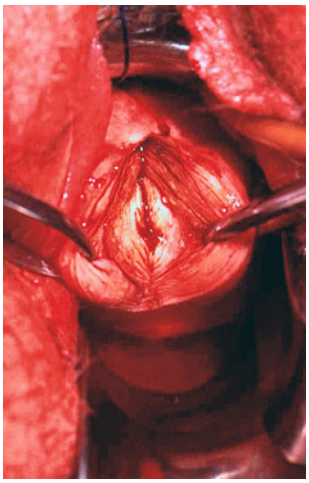

**Fig. 4** Type 4 vaginal myomectomy where an anterior intramural fibroid is being removed through an anterior colpotomy (an incision between the vagina and the peritoneal cavity)

## 8.3 Operative Complications

As with laparoscopic myomectomy, patients undergoing vaginal myomectomy should be warned about the risk of bleeding which may require blood transfusion, conversion to laparotomy, and hysterectomy. In reality, these complications are uncommon if patient selection correct. Despite operating though the vagina, infection is also infrequent in our experience, but we do give prophylactic antibiotics during surgery.

Perhaps, the commonest risk complication after the Type 4 procedure is formation of a pelvic haematoma, and it is for this reason that we sometimes leave a drain in the colpotomy incision (Davies et al. 1999).

# 9 Conclusion

Despite the passage of time, myomectomy remains an important treatment for uterine fibroids when uterine conservation is required. Myomectomy can be done in many ways, and many women can now avoid major open surgery. To what extent robotic surgery will change clinical practice remains to be seen, but we are encouraged by the renewed interest in the vaginal approach to myomectomy.

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# Myomectomy: Results and Complications

Ioannis Tsimpanakos and Adam Magos

## Contents




**Abstract**

Uterine fibroids are common hormone sensitive benign tumours of the uterus, with a reported incidence of up to 30–40 % in women of reproductive age with variations depending on the age group and ethnic background. Although they are asymptomatic in many cases, the presence and persistence of clinical symptoms warrants medical or surgical intervention. Myomectomy is advisable for symptomatic women who want to preserve their uterus. Myomectomy can be performed trans-abdominally, laparoscopically, vaginally or hysteroscopically. The aim of this intervention is to alleviate any menstrual symptoms and improve fertility. Whatever the route of surgery, however, myomectomy is classified as a major operation which is associated with both short- and long-term complications which, in many respects, depend on the size, location and number of fibroids. Apart from risks such as infection, bruising, deep vein thrombosis, which apply to any major surgical procedure, complications range from major intra-operative blood loss, occasionally necessitating hysterectomy, to longer term problems of post-operative adhesions and fibroid recurrence. There are also route-specific potential complications related to the type of myomectomy.


## 1 Introduction

Uterine fibroids are the most common benign lesion found in women of reproductive age, with over 25 % of women in this age group reporting clinical symptoms related to fibroids (Stewart 2001). These symptoms vary from anaemia to menorrhagia, dysmenorrhoea, pressure symptoms, urinary frequency, even infertility and recurrent miscarriage. The management of fibroids has been evolving over the last decades. In the United States, fibroids are the leading indication for hysterectomy with almost 240,000 hysterectomies performed annually for fibroid related problems

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(Chapman and Magos 2006). In the UK there has been a steady decrease in the number of hysterectomies and a gradual increase in the number of open myomectomies performed.

As discussed in the previous chapter, myomectomy may be performed abdominally, laparoscopically, hysteroscopically or vaginally. The approach depends on various factors including the site, size and number of fibroids, the experience of the surgeon and local resources and last but not least patient's choices and preferences (Chapman and Magos 2006). In this chapter we will present the main short- and long-term complications of myomectomy according to the type of procedure, as well as outcomes such as fibroid recurrence and fertility.

**Table 1** Complications of abdominal myomectomy

| | |
|---|---|
| *Short term* | |
| | Bleeding<br>Post-operative pyrexia<br>Wound infection<br>Haematoma<br>Thromboembolism<br>Paralytic ileus<br>Injury to adjacent structures (e.g. bowel, bladder)<br>Hysterectomy |
| *Long term* | |
| | Intraperitoneal adhesions<br>Small bowel obstruction<br>Incisional hernia<br>Nerve entrapment<br>Chronic abdominal pain |

## 2 Complications of Myomectomy

Whatever the route of surgery myomectomy is classified as a major operation not only in terms of surgical technique but also potential complications, both short- (peri-operative) and long-term. Short-term complications include those which are similar to those associated with any major surgical procedure (such as anaesthetic complications, infection, deep vein thrombosis) or can be specifically related to myomectomy and the route of surgery.

### 2.1 Open (Abdominal) Myomectomy

Abdominal myomectomy remains the only option in the case of large, multiple fibroids. However, this procedure has potentially considerable operative morbidity (Table 1), and a recurrence risk of between 23 and 51 % within 3–5 years of the operation, depending on the age of the woman at the time of myomectomy.

#### 2.1.1 Short-Term Complications

The most important complication is intra- and post-operative bleeding which may result in hypovolaemia necessitating blood transfusion in 20 % of cases, and in extreme cases, even hysterectomy. Based on some published series, the risk of haemorrhage is in the range of 2–8 % and varies with the size and number of fibroids as well as the intra-operative technique (Roth et al. 2003; West et al. 2006). One of the reasons for this is that although fibroids appear white and relatively avascular, they are surrounded by a plexus of often enlarged vessels in the adjacent myometrium. It is from these vessels that significant blood loss can occur during surgery and a number of techniques, including tourniquets and clamps, have been developed to occlude the uterine and ovarian arteries and minimize blood loss (Taylor et al. 2005). The risk of hysterectomy during myomectomy because of uncontrollable bleeding is, however, low (4 %) (Olufowobi et al. 2004), although higher at repeat myomectomy.

Peri-operative pyrexia is common and may occur in 10–30 % of cases, whilst wound infection may affect 2–5 % of women (Iverson et al. 1996). Myomectomy itself seems to be an independent predicting factor for the development of post-operative pyrexia in the first 48 h post procedure, as was demonstrated in the study by Iverson et al., who compared 101 women who had myomectomy with 160 who had undergone hysterectomy (Iverson et al. 1999). It is likely that the development of haematomas or the presence of necrotic tissue may contribute to the development of pyrexia rather than true infection. Therefore, meticulous haemostasis and the use of post-operative antibiotics may reduce this complication.

Other complications of abdominal myomectomy include those associated with laparotomy. These include thromboembolism, paralytic ileus, atelectasis, nerve damage especially when extending the incision more laterally, urinary tract complications or bowel injury (Mukhopadhaya et al. 2008). However, the risk of visceral injury is low when compared to hysterectomy (Iverson et al. 1996).

#### 2.1.2 Long-Term Complications

Long-term complications after major abdominal surgery such as open myomectomy, include the development of adhesions, incisional hernia and nerve entrapment.

The aetiology of abdominal adhesions is elusive but factors associated with their development post surgery include trauma, thermal injury, infection, presence of blood in the peritoneal cavity, ischaemia or tight suturing resulting in ischaemia (Liakakos et al. 2001; Duron 2007).

In case of open myomectomy, the type of uterine incision seems to have an effect on the development of adhesions. In an early study by Tulandi et al., the authors studied the incidence of adnexal adhesions within 6 weeks after myomectomy. Among women who had a posterior uterine

incision 93.7 % (15 out of 16) had adnexal adhesions compared to 55.5 % (5 out of 9) who had an anterior or fundal uterine incision (Tulandi et al. 1993).

Abdominal adhesions are considered to be associated with a range of complaints including infertility, small bowel obstruction, difficult repeat operations, increased risk for ectopic pregnancy or chronic abdominal pain (van der Wal et al. 2011; Swank et al. 2002).

Different pharmacological agents have been tried in order to prevent adhesion formation; however, a recent Cochrane systematic review showed that there is insufficient evidence for the use of steroids, icodextrin 4 %, SprayGel or dextran in reducing adhesion formation. Limited benefit was observed with hyaluronic acid but results were also inconclusive (Metwally et al. 2006). The risk of incisional hernia is about 10 % in patients undergoing major abdominal surgery and a risk factor for herniation is an incision more than 18 cm in length (Savage and Lamont 2000). In general Pfannenstiel incisions have a particularly low incidence of wound dehiscence and incisional herniation. With regard to the risk of nerve entrapment, it increases significantly when the incision extends laterally beyond the later edge of the rectus sheath. Nerve entrapment can result from transaction of the iliohypogastric and ileoinguinal nerves followed by formation of a neuroma, incorporation of the nerve by a suture in the closure of the fascial layers, or tethering or construction of the nerve in the scar tissue. It is important to recognise that symptoms may start early or manifest even years after surgery (Luijendijk et al. 1997).

## 2.2 Laparoscopic Myomectomy

Laparoscopic myomectomy is a less invasive alternative to laparotomy in cases of relatively small intramural or subserosal fibroids, when the number of fibroids is less than 3 and their size less than 8 cm (Dubuisson 2000). This procedure has also short- and long-term complications (Table 2).

### 2.2.1 Short-Term Complications

Short-term complications result reported by small randomized controlled trials show that laparoscopic myomectomy may be associated with reduced incidence of pyrexia, fewer blood transfusions and less post-operative pain than open myomectomy (Seracchioli et al. 2000). In addition there seem to be benefits in terms of faster post-operative recovery and reduced hospital stay (Mais et al. 1996).

Although laparoscopic myomectomy is generally done in patients with relatively small and/or few fibroids, intraoperative bleeding remains a major concern. One of the main reasons is because the repair of the uterine incision and the control of bleeding requires expert laparoscopic suturing skills. Mais et al. showed that blood loss was less at laparoscopic compared to abdominal myomectomy (200 ± 50 vs 230 ± 44 ml), but bleeding can be significant (Mais et al. 1996). In the more recent study by Landi et al., 14 of 368 women undergoing laparoscopic myomectomy had significant blood loss and required blood transfusion peri- or postoperatively (Landi et al. 2001).

**Table 2** Complications of laparoscopic myomectomy

| | |
|---|---|
| *Short term* | |
| | Bleeding<br>Injury to adjacent structures (e.g. bowel, bladder)<br>Specific risks associated with laparoscopy<br>Need to convert to laparotomy<br>Haematoma<br>Hysterectomy |
| *Long term* | |
| | Recurrence of fibroids |
| | Need for repeat procedure |
| | Adhesions<br>Uterine rupture in pregnancy |

Another significant complication is the risk for bowel injury which could require laparoscopic or even open repair, or worse, is not recognised at the time but only after the development of peritonitis. All patients undergoing laparoscopy are routinely warned that the procedure may have to be converted to laparotomy in case of bleeding or visceral injury.

### 2.2.2 Long-Term Complications

There are several studies suggesting that the risk of postoperative adhesions is reduced in cases of laparoscopic compared to abdominal myomectomy. It is estimated that after laparoscopic myomectomy 30.5 % of patients develop adnexal adhesions compared to 68.9 % of patients with abdominal myomectomy (Dubuisson 2000). This difference may be explained by differences in the size and number of fibroids, however, it is also possible that the laparoscopic route itself, the use of fine instruments, atraumatic manipulation and thorough washing may well contribute to this reduction. The clinical symptoms of the developing adhesions would be the same as in abdominal myomectomy.

Fibroid recurrence rate after laparoscopic myomectomy is in the range of 4–30 % with up to 10 % needs to have a repeat surgery (Buttram and Reiter 1981; Rossetti et al. 2001). In a randomised control trial by Rossetti et al., where patients were assigned to either abdominal or laparoscopic myomectomy, there was no significant difference in the recurrence of fibroids within 24 months from the procedure (23 vs 27 % respectively) (Rossetti et al. 2001). However, other studies state that the risk of recurrence is higher in laparoscopic than abdominal myomectomy (Seracchioli et al. 2000). One specific problem of the laparoscopic technique is that the loss of tactile sensation makes it

impossible to palpate the myometrium thoroughly and as a result, small intramural fibroids that do not deform the uterine serosa are easily missed and not excised. The pre-operative use of GnRH analogues is a controversial topic; some patients undergoing myomectomy may be treated with GnRH analogues with the aim to reduce the volume of fibroids and the vascularisation of the uterus. A randomised controlled trial by Fedele et al., looking at women who have been or not pre-treated with a GnRH analogue, showed that there was no difference in the duration of operation or intra-operative blood loss between the two groups. However, women who had been pre-treated with a GnRH analogue had a higher risk for recurrence of fibroids in the short term when they have been examined by transvaginal ultrasound within 6 months. These fibroids were intramural and less than 1.5 cm in diameter, which would have been difficult to identify with an abdominal ultrasound alone. The increased frequency of recurrence in these patients may be due to the fact that the GnRH analogue may induce a decrease in the volume and consistence of the fibroid making the smaller fibroids unidentifiable during the operation (Fedele et al. 1990). In a more recent study Rossetti et al., reported on 84 women who underwent laparoscopic myomectomy and were followed up for 36 months. In this study the only significant risk factor for recurrence of fibroids was the pre-operative use of a GnRH analogue. The authors also hypothesised that in these cases smaller intramural fibroids would have been difficult to visualise and, therefore, over-looked leaving fibroids in situ and so leading to higher recurrence rate (Rossetti et al. 2001).

## 2.3 Vaginal Myomectomy

As discussed in the previous chapter, the term 'vaginal myomectomy' encompasses four different technique types that can be used to remove fibroids depending on the position, size and number of fibroids to be removed, even in nulliparous women (Magos et al. 1994). Irrespective of the type of vaginal myomectomy, this route of surgery offers the possibility to remove greater fibroid mass with less operative time and postoperative pain, and better surgical repair of the uterus than, for instance, laparoscopic myomectomy (Thomas and Magos 2011). Depending on the experience of the surgeon, the procedure is also easier to perform compared to laparoscopic myomectomy while retaining the advantages of minimally invasive therapy. Nonetheless, it still represents potentially relatively major surgery and is not without short- and long-term risks.

### 2.3.1 Short-Term Complications

Vaginal myomectomy is associated with significantly lower incidence of postoperative pyrexia and shorter hospital stay compared with open surgery (Ben-Baruch et al. 1988; Plotti et al. 2008). The main complication is the risk of failure to complete the procedure vaginally and the need to convert to laparotomy. The rate of conversion to laparotomy is in the range of 8–9 % (Agostini et al. 2004; Birsan et al. 2003), but very much depends on patient selection. In the recent study by Agostini et al., 108 women had vaginal myomectomy by posterior colpotomy, 27 women had complications (25 %) including 17 (15.7 %) who were converted to laparotomy in order to complete the myomectomy. Complications included rectal injury (0.9 %) necessitating laparotomy, haemorrhage with Hb less than 6 g/dL (2.8 %), haematoma which drained spontaneously (0.9 %) and five cases of abscesses (4.7 %) treated conservatively or with vaginal surgical evacuation in two cases (Agostini et al. 2008).

### 2.3.2 Long-Term Complications

Studies regarding the long-term complications after vaginal myomectomy are still rare (Faivre et al. 2010). Post-operative development of adhesions may be a risk, although its incidence is unknown; in another study there no reported adhesions in the pouch of Douglas when patients were examined laparoscopically between 6 and 24 months after the procedure (Davies et al. 1999). The type of the incision used on vaginal hysterotomy may in theory compromise the integrity of the cervix and cause stenosis and cervical weakness in future pregnancies, but there is no evidence that this actually occurs. Uterine rupture during pregnancy or delivery may also be a potential complication, although there are no cases reported in the literature (Faivre et al. 2010; Rovio and Heinonen 2006). It is likely that the uterine repair performed vaginally is considerably stronger than when done by laparoscopic suturing.

## 2.4 Hysteroscopic Myomectomy

Hysteroscopic myomectomy is the preferred technique for removing submucous fibroids, particularly those that are totally or mostly inside the uterine cavity. Fibroids extending deep into the myometrium can also be excised hysteroscopically although this requires greater surgical skill to avoid uterine perforation. The optimum instrument for removing submucous fibroids remains the resectoscope, and since the advent of the mini-resectoscope, the procedure can be carried out in the outpatient clinic or in office setting with no or minimal need for local anaesthesia (Chapman

**Table 3** Complications of hysteroscopic myomectomy

| | |
|---|---|
| *Short term* | |
| | Uterine perforation<br>Fluid overload<br>Electrolyte abnormalities<br>Haemorrhage<br>Cervical trauma<br>Injury to adjacent structures (e.g. bowel, bladder)<br>Infection<br>Hysterectomy |
| *Long term* | |
| | Intrauterine adhesions<br>Secondary amenorrhoea (Asherman's syndrome)<br>Uterine rupture during pregnancy |

and Magos 2006). This procedure is not void of complications, that are however uncommon and can be avoidable by good technique (Table 3).

### 2.4.1 Short-Term Complications

The reported rate of intra- or peri-operative complications varies widely between 0.3 and 28 % depending on the study. These complications include uterine perforation, which can be associated with damage to adjacent structures such as bowel, bladder and even blood vessels, cervical trauma, bleeding during surgery, infection, gas embolism and fluid overload (Di Spiezio et al. 2008). Uterine perforation may occur at any of these steps of the procedure: cervical dilation, insertion of hysteroscope or resection of fibroids. The risk seems to be higher in cases of deep fibroids within the myometrium (Murakami et al. 2005).

Fluid overload and the associated electrolyte imbalance is a serious complication, particularly if electrolyte-free uterine distension media are used as is necessary with monopolar electrosurgery. Fluid absorption occurs through the rich plexus of the vessels surrounding the fibroid and from transperitoneal absorption via the fallopian tubes. Severe fluids overload can cause hyponatremia, pulmonary oedema, heart failure, cerebral oedema and, in extreme cases, even death. Therefore careful monitoring of fluid balance is required during the procedure and if there is fluid overload, surgery should be stopped, U&Es checked, diuretics given and urine output monitored for diuresis. Deep intramural fibroids represent a higher risk for this complication mainly because of damage to larger size vessels. The size of the fibroid itself and the length of the procedure can also contribute to the risk of this complication (Murakami et al. 2005; Di Spiezio et al. 2008).

A complete resection is almost always achieved for submucous fibroids without intramural extension (type 0) or with those with intramural part of less than 50 % (type I). If the fibroid has an intramural part of 50 % or more (type II), there is the risk of incomplete resection and need for repeat surgery. This risk has been reported between 5 and 20 % depending on the study (Polena et al. 2007; Emanuel et al. 1999).

### 2.4.2 Long-Term Complications

Late complications of hysteroscopic myomectomy include intrauterine adhesions and uterine rupture during pregnancy, both of which are important problems for patients who want to have children. The incidence of the post-operative intrauterine adhesion has been reported between 1 and 13 % after hysteroscopic myomectomy (Murakami et al. 2005). However, in some studies this rises up to 45 % after resection of multiple fibroids (Taskin et al. 2000). The precise mechanism of the formation of post-myomectomy adhesions is not obvious in many cases; it would seem logical to assume that reducing trauma to healthy endometrium and the judicious use of electrosurgery during myomectomy, especially for deep intramural fibroids, could reduce the risk of this complication (Gambadauro et al. 2012). The association of endometrial trauma and formation of adhesions that may lead to secondary amenorrhoea has been described as Asherman's syndrome.

After hysteroscopic myomectomy, especially in cases of deep intramural fibroids, there is a risk of uterine rupture in pregnancy or during labour. We must note, however, that this is a rare complication, with only two reported cases to date (Di Spiezio et al. 2008). Although some surgeons believe that caesarean section should be preferred after removal of fibroids with intramural component (Cravello et al. 2004), there is lack of strong evidence to suggest that this would reduce the risk of uterine rupture.

## 3 Results of Myomectomy

### 3.1 Results on Fertility

Fibroids may cause reproductive dysfunction, although the relationship between fibroids and infertility is poorly established. Most studies estimate that uterine fibroids account for up to 5–10 % of cases of infertility; however, when all other causes of infertility are excluded fibroids may account for only 2–3 % of cases.

There are a number of isolated studies on the results of myomectomy on fertility, but the lack of large, randomised controlled trials makes it difficult to draw any firm conclusions. There is evidence that submucous fibroids impair fertility and their removal improves reproductive outcome (Connolly et al. 2000; Pritts et al. 2009). Intramural fibroids distorting the uterine cavity may also decrease fertility. But a recent meta-analysis has shown that their removal will not always improve fertility (Pritts et al. 2009). It is clear that subserosal fibroids do not seem to have an impact.

The rate of pregnancy after myomectomy in patients with unexplained infertility depends on the study and route of myomectomy. For abdominal myomectomy it has been reported between 65.3 and 66.7 % conceive after surgery (Ribeiro et al. 1999; Verkauf 1992). For laparoscopic myomectomy the rate of pregnancy ranges between 33 and 48 % (Dubuisson et al. 1996; Ribeiro et al. 1999). It is possible that the higher rates reported in some studies may be related to selection of groups of patients with a better prognosis. As for hysteroscopic myomectomy, Bernard et al. studied the outcome in 31 infertile women who had undergone hysteroscopic myomectomy with the number of removed fibroids being between 1 and 4. Pregnancy was achieved in 35.5 % and it was suggested that fertility after hysteroscopic myomectomy depends on the number of submucous fibroids resected and their association with intramural fibroids, but not on their size or location (Bernard et al. 2000). However, the results of myomectomy on fertility and pregnancy may be affected by confounding factors. For instance in some women with submucous/intramural fibroids distorting the cavity, other causes that might also impact on fertility were found during myomectomy (such as tubal disease, pelvic adhesions or endometriosis) (Olufowobi et al. 2004).

To assess and exclude the influence of these factors, in vitro fertilisation (IVF) provides a good model. A number of controlled studies have looked at the implantation rates in women with fibroids or those who had undergone myomectomy (Surrey et al. 2005). It seems that pregnancy rates in women with fibroids that distort the uterine cavity is about 9 % comparing to women without distortion of the uterine cavity (29 %) or women without fibroids (25 %) (Surrey et al. 2001). In addition, other studies found that women with fibroids less than 7 cm which do not distort the uterine cavity have similar implantation rates and pregnancy outcome to controls (31 vs 42 %) (Jun et al. 2001).

As is shown in a recent meta-analysis, despite the lack of solid evidence it seems reasonable to conclude that myomectomy for submucous or intramural fibroids which distort the cavity may improve implantation and pregnancy rates (Pritts et al. 2009).

## 3.2 Impact on Future Pregnancies

Pregnancy after myomectomy is generally considered "high risk" in terms of mode of delivery (vaginal versus caesarean section), risk of uterine rupture during pregnancy or delivery, and possible placental attachment to the scar area.

It has long been advocated that following myomectomy caesarean section is advisable in order to avoid uterine scar rupture. The risk of this complication is estimated to be 1.5 % following abdominal myomectomy and this percentage rises further when the uterine cavity is opened. Some authors also recommend caesarean section after laparoscopic myomectomy for cases of intramural or deep subserous fibroids, although uterine rupture has even been reported after removal of superficial subserous fibroids (Pelosi III and Pelosi 1997). However, there is no general consensus and in fact successful vaginal delivery has been reported after both procedures (Ismail and Bennett 2009; Nezhat et al. 1999; Sudik et al. 1996). The rate of complications during pregnancy, however, may be higher after second myomectomy (Frederick et al. 2002).

Seinera et al. followed up 202 patients who had laparoscopic myomectomy, 54 of whom became pregnant, and there were no cases of uterine rupture (Seinera et al. 2000). In a recent study Kelly et al., followed up 81 women post myomectomy (abdominal, laparoscopic or by hysteroscopy). There was no recorded case of ruptured uterus in women who delivered their first baby after abdominal myomectomy and a single case was reported at 36 weeks' gestation in a woman who had laparoscopic myomectomy. Although the authors concluded that laparoscopic myomectomy may be associated with a greater risk of scar rupture, the relatively small number of patients does not allow to draw firm conclusions (Kelly et al. 2008).

To address the risk of scar rupture, especially after laparoscopic myomectomy, Dubuisson et al., reported on 100 patients who delivered after laparoscopic myomectomy, of whom 58 delivered vaginally. There were three cases of spontaneous uterine rupture between 25 and 34 weeks of gestation, in none of the cases was the uterine cavity entered during the laparoscopic myomectomy, and only one of the ruptures occurred at the site of the myomectomy scar. The risk of uterine rupture after laparoscopic myomectomy was reported to be 1 % (95 % CI 0.0–5.5 %) (Dubuisson et al. 2000). This risk of scar rupture does not seem to be confirmed by more recent studies. In one of the largest series, Sizzi et al., reported on 269 pregnancies in women after laparoscopic myomectomy and there was only one spontaneous rupture at 33 weeks of gestation (0.26 %) (Sizzi et al. 2007).

There may be several factors affecting the risk of uterine rupture after laparoscopic myomectomy. For example, the difficulty in uterine repair and adequate suturing by laparoscopy rather than by laparotomy; however, this largely depends on the experience of the surgeon. (Dubuisson et al. 2000). Other possible causes are the inappropriate use of diathermy during laparoscopic myomectomy, the formation of haematoma, or the suturing technique that could have adverse effect on healing and scar formation (Pelosi III and Pelosi 1997; Dubuisson et al. 1995). There is not enough data to suggest that a short-time interval between the surgery and pregnancy could be another risk factor for incomplete healing of the uterine scar (Seinera et al. 2000).

It has been suggested that regular ultrasound scanning or post-operative MRI or MRI during pregnancy could be very useful for checking the thickness and quality of the hysterotomy scars and guide the need or timing of elective section (Ito et al. 1998).

### 3.3 Results on Recurrence of Fibroids

The reported incidence of recurrence of fibroids after myomectomy varies widely from 7 to 70 %, depending on the population studied, duration of follow-up or method of detecting recurring fibroids. In cases of abdominal myomectomy the cumulative risk of clinically significant recurrence was reported about 10 % at 5 years (Fauconnier et al. 2000). However, Hanafi et al., reported that the 5-year cumulative rate of fibroid recurrence diagnosed by transvaginal ultrasound was estimated as high as 62 %, with subsequent major surgery at 9 % (Hanafi 2005). The rate of hysterectomy for recurring fibroids after abdominal myomectomy varies from 4.3 to 16.8 % for studies with a maximum follow-up of over 5 years (Fauconnier et al. 2000).

The effect of age on the risk of recurrence of fibroids is controversial. In some studies the risk tends to increase with age, other studies show that it drops in women operated after the age of 35, while others report that the younger the woman undergoing myomectomy the higher the risk of recurrence. These seemingly opposite results could be explained by the fact that the incidence of fibroids increases with age and women who present with clinically significant fibroids at younger age are likely to have more aggressive "myometrial disease" (Fauconnier et al. 2000).

It seems that the position of the fibroids may influence the risk of recurrence. It has been recently reported that women without subserous fibroids were more likely to have a second operation compared with women with at least one subserous fibroid (odds ratio 4.1, 95 % CI 1.5–10.9). However, neither the size nor the number of myomas was predictive of subsequent surgery (Thompson et al. 2006). However, in another study the 5-year cumulative recurrence was lower where a single myoma was removed (11 %) compared to multiple myomas (74 %); subsequent pregnancy may also affect the risk of recurrence as women who conceived following myomectomy were less likely to have recurrence (26 %) compared to women without subsequent parity (76 %) (Hanafi 2005).

The hysterectomy rate after laparoscopic myomectomy varied form 6.1 to 13.8 % (Fauconnier et al. 2000), although in these studies the follow-up seems to be short. Rossetti et al., reported on the long-term follow-up of 81 patients randomised to abdominal or laparoscopic myomectomy and 84 nonrandomised patients. The recurrence rate between laparoscopic and abdominal myomectomy was comparable (23 and 27 % respectively), with most recurrences seen within 24 months of surgery (Rossetti et al. 2001).

### 3.4 Risk of Malignancy

Although fibroids are benign tumours, this should always be confirmed histologically to exclude the remote possibility of sarcomatous change. In the past, there have been reported cases of possible metastases from a histologically benign uterine leiomyoma. If this occurs it is usually on the background of a sarcomatous component within the leiomyoma or by finding evidence of intravenous leiomyomatosis or metastasis to the aortic lymph nodes. In cases of hysteroscopic myomectomy, the histopathologist should also look for any signs of endometrial pathology or metaplasia, although the type of specimen may not always be adequate to exclude the above (Amico et al. 2010).

### 3.5 Results on Menstrual/Uterine Bleeding

One of the main indications for the removal of submucous fibroids is the control of abnormal uterine bleeding and menstrual irregularities. In this context, resection of fibroids in pre-menopausal women results in improvement of symptoms in about 80 % of cases (Cravello et al. 1995). Incomplete resection or growth of pre-existing small fibroids are factors associated with failure to control symptoms or a recurrence of abnormal bleeding. The best menstrual outcome tends to in patients with normal uterine size preoperatively and small number of fibroids. Rarely submucous fibroids may be symptomatic in post-menopausal women causing abnormal uterine bleeding. In these cases, the hysteroscopic approach is a much more logical and less traumatic alternative to hysterectomy which can not only resolve symptoms but exclude the presence of underlying malignant pathology. In all reported series the resection of fibroids in post-menopausal patients results in resolution of symptoms with only rare cases needing hysterectomy (Cravello et al. 2004).

### 3.6 Results on Pelvic Pain and Bladder Symptoms

Fibroids do not usually cause abdominal pain. However, large degenerating or necrosed fibroids can lead to the development of this symptom. In addition, in pregnancy the rapid growth of the uterus and the subsequent growth of coexisting fibroids can be the cause of abdominal pain. Fibroids of the lower segment of the uterus applying pressure

on the bladder may cause symptoms such as frequency, dysuria or difficulty passing urine. Removal of these fibroids could improve symptoms; there are a number of case reports but long-term follow-up data are missing.

## 4 Conclusion

Myomectomy is a widely used technique that can be performed abdominally, laparoscopically, vaginally of hysteroscopically. The number, size and position of fibroids largely determines the type of approach. The complications of each procedure can be minimised by appropriate patient selection and correct surgical technique.

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# Myomectomy Following UAE

Bruce McLucas

## Contents




**Abstract**

Leiomyomas may be treated with UAE followed by myomectomy in a scheduled or unscheduled manner. UAE may be scheduled immediately prior to myomectomies if the patient has large fibroids or pedunculated or subserosal myomas, or wishes to maintain an intact uterus for the possibility of pregnancy within a short time window. UAE may be beneficial in these instances because it reduces blood loss in removal of large fibroids and prevents fibroid recurrence. Patients who benefit from the combination of these procedures include young patients with a high risk of recurrence and patients wanting to achieve pregnancy immediately after 6 months of the surgery. Unscheduled myomectomies occur if the UAE fails to relieve symptoms, if prolapsed of a submucous myoma occurs, or in the event of fibroid necrosis.


## 1 Introduction

This chapter will discuss myomectomy after uterine artery embolization [UAE]. We will cover two distinct groups of patients. First, patients who knew prior to myomectomy that they would have two procedures. Second, patients who underwent a myomectomy for treatment of a complication or failure after UAE. This distinction will be important. All too often, any surgery following UAE is considered a failure of the procedure. We will discuss the benefits of combination procedures to patients, and identify the patients who might benefit from this approach.

Other surgeries may take place after UAE. These include hysterectomy and cesarean section. These surgeries will not be covered in this chapter.


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## 2 Scheduled Myomectomy

### 2.1 Indications

UAE is suggested for women with symptomatic uterine leiomyomata, including menorrhagia, pelvic pain, and pelvic pressure among other bulk-related symptoms. In addition, many women seeking uterine preservation and fibroid treatment will choose UAE or myomectomy over hysterectomy. Generally, UAE is used as a pre-treatment method for myomectomy when fibroids are large or if the patient has a pedunculated subserous, or submucous myoma (Ngeh et al. 2004).

#### 2.1.1 Large Fibroids

Myomectomy to remove large fibroids may involve a more complicated surgery with increased blood loss and longer operative times. Ginsburg et al. has shown that patients with uteri larger than 600 mL resulting from large mass or multiple fibroids tend to fall in this category (Ginsburg et al. 1993).

Failure of UAE is more likely when the diameter of the myoma exceeds 8.7 cm (McLucas et al. 2001), however large fibroid size and uterine volume is not necessarily a contraindication to UAE. Large uterine myoma have been reported to be successfully embolized (Bradley et al. 1998). Treatment of large myoma with UAE followed by myomectomy (Fig. 1) has been shown to be a successful method of treatment (Paxton et al. 2006). Other guidelines include a uterus above the umbilicus. Even with a 50 % shrinkage of myomas, such patients may not experience symptom relief without a myomectomy to remove the bulk of tissue.

#### 2.1.2 Desire Fertility with Short Time Window

The combination of UAE and myomectomy for myoma is indicated for women who desire uterine preservation and fertility within a short time window. UAE can aid in treatment of myoma with subsequent myomectomy by ensuring no potential for regrowth given successful embolization. Myomectomy alone may not completely ensure uterine preservation because of the possibility of fibroid recurrence and subsequent myomectomy (Hanafi 2005) or surgical conversion from myomectomy to hysterectomy (Subramanian et al. 2001). UAE alone is not a contraindication for fertility. Pregnancy following UAE is not uncommon (McLucas 2013); however some complications of UAE may affect ability to achieve a viable pregnancy (Mara et al. 2012). Thus myomectomy combined with embolization may increase the likelihood of subsequent pregnancies (Nabeshima et al. 2003).

Our guidelines for UAE as a stand-alone procedure for women desiring fertility are as follows. The uterus should be less than the size of a 10-week gestation. The position of the myomas should be intramural to subserosal. The largest myoma should be less than 8 cm. Our percentage of patients who conceived without combination procedures was 48 % in women under 40 who stated a desire for fertility (McLucas 2013). We, however, are sensitive to the woman in her late 30s desiring fertility. We recommend that patients wait 6 months after UAE before conception (McLucas 2013). If patients feel that such a wait is too long, and with the possibility of additional wait time if the UAE is not successful, we will offer the patient the combination procedure. Patients need to be told that the combination procedure in this circumstance is optional.

**Fig. 1** Removal of large fibroids

UAE prior to myomectomy is an appropriate approach for treatment of fibroids in women who wish to achieve pregnancy shortly following treatment (Nabeshima et al. 2003). Generally women can begin to try to achieve pregnancy after 6 months after having UAE and myomectomy, the same amount of time for UAE alone. Concerning future pregnancies, UAE may be beneficial for women in whom extensive pelvic adhesions following myomectomy may result in a high possibility for hysterectomy. Such patients with extensive adhesions may require in vitro fertilization, and should be told such prior to any other procedure.

#### 2.1.3 Pedunculated Submucous or Subserous Myomas

Some authors have said that pedunculated submucous or subserous myomas are often considered a contraindication for UAE because of potential risks and complications, including ischaemic necrosis and separation from the uterus due to torsion at the stalk of the myoma (Levy 2008; Al-Fozan and Tulandi 2002). However in these cases, the only option may be a complicated myomectomy or hysterectomy. Women may opt for UAE if they do not want to undergo invasive surgery or wish to preserve their uterus. UAE has been suggested to be a viable and safe form of treatment for pedunculated subserous myomas with a

relatively small stalk diameter and these major complications may be rare (Katsumori et al. 2005). UAE may be useful prior to myomectomy for these types of fibroids because it facilitates easier removal of the fibroid. There is no need for gonadotropin-releasing-hormone agonists prior to myomectomy (Paxton et al. 2006). The outcome is better for patients with submucous and subserous myomas when undergoing myomectomy after uterine artery embolization as a pre-treatment (Butori et al. 2011).

First, hysteroscopic resection will have relatively decreased blood loss after embolization (Wamsteker et al. 1993; Walker and Barton-Smith 2006). The surgeon will have less worry about fluid absorption following embolization (Al-Mahrizi and Tulandi 2007). Thus, the hysteroscopic removal of pedunculated submucous myoma will be facilitated by prior embolization as well as allowing the surgeon to attack a larger myoma (Walker and Barton-Smith 2006). Pre-treatment with UAE decreases blood flow to a pedunculated subserous myoma, again allowing the surgeon the opportunity to remove a larger myoma that might be possible without prior embolization (Butori et al. 2011). A combination of UAE and myomectomy may be the optimum choice in these instances because it maximizes the benefits of both procedures for women choosing invasive but conservative treatment options.

Furthermore, a combination of UAE with either hysteroscopic or laparoscopic myomectomy will greatly diminish the incidence of necrosis following embolization (Al-Fozan and Tulandi 2002). The first reported death due to uterine sepsis was reported to have been found with a submucosal myoma (Vashisht et al. 1999) (Fig. 2).

**Fig. 2** Prolapsing submucous myoma

## 2.2 Benefits of UAE Prior

### 2.2.1 Decrease Blood Loss

UAE is beneficial prior to myomectomy in cases where periprocedural blood loss may be substantial (Ngeh et al. 2004). To reduce the possibility of excessive blood loss when removing fibroids, UAE has been successfully used prior to myomectomy (Butori et al. 2011; Serradilla et al. 2011). The advantages of using UAE for minimizing blood loss allow for more endoscopic approaches to complicated myomectomies. Surgery for multiple myomas may allow for tumor size reduction prior to surgery, which may decrease the possibility of conversion to hysterectomy. This is because tumor infarction occurs immediately following UAE. This combination procedure may also decrease hospital stay, as many potential postoperative complications may be avoided such as pyrexia due to hematoma (Dumousset et al. 2008). The technical removal of myomas may be easier with UAE prior. This includes removal of significantly reduced fibroid volume and ease of uterine suturing (Tixier et al. 2008).

Management of blood loss may also allow for laparoscopic removal of larger fibroids. To date, the largest fibroid reported to be removed by this method was larger than 20 cm (Madhuri et al. 2010). Generally, laparoscopic myomectomies are limited by myoma size because of the limited amount of space to manipulate the laparoscopic instruments. Laparoscopic myomectomy is the preferred method of myomectomy due to shorter hospital stay, less postoperative pain, and reduced risk of adhesions. Thus, by reducing potential blood loss through UAE larger myomas may be removed through this preferred method.

### 2.2.2 No Fibroid Recurrence

Although myomectomies seek to remove current fibroids and diffuse symptoms, fibroid recurrence remains a possibility. UAE prior to myomectomy prevents myoma regrowth because the tumors have been devascularized. Combining two procedures during one hospital admission has many advantages including those economically and logistically related. The recurrence rate following myomectomy has been reported to be as high as 75 % in some studies (Hanafi 2005). Because the surgery occurs immediately following the procedure, no time exists for collateral vessel formation.

### 2.2.3 Candidates

Some patients may benefit from myomectomy scheduled after UAE. This includes patients with large uterine fibroids with a high risk of excessive menorrhagia who wish to preserve their uterus or who do not wish to receive a blood transfusion. Young patients tend to fall in this category because they are farther from reaching menopause, in which fibroid growth generally ceases because the ovaries stop producing estrogen.

#### 2.2.3.1 Young Patients with High Risk of Recurrence

Studies have shown that younger patients who undergo myomectomy are at higher risk of fibroid recurrence and

subsequent surgery. Reed et al. found that 5 years after myomectomy, the age-specific cumulative incidence of a subsequent uterine surgery was greatest in women aged 30–34 years (38 %), which increased to 44 % at 7-year follow-up. The total incidence of repeat surgery is 20.2 %, which included repeat myomectomy and hysterectomy (Reed et al. 2006). This increased risk may also be related to whether the patient has completed childbearing at the time of consideration of a second surgery. The risk of recurrence may be diminished if the patient becomes pregnant following the initial procedure (Candiani et al. 1991).

#### 2.2.3.2 Patients Ready for Childbearing After 6 months

Myomectomy is suggested as the optimal fibroid treatment for women desiring future fertility (van der Kooij et al. 2012). Pregnancy is possible following myomectomy, but increased risk of uterine rupture due to adhesions and caesarian section may complicate childbirth (Goldberg and Pereira 2006; Lumsden 2002). UAE prior to myomectomy reduces the risk of adhesion formation. Adhesion formation is a known complication of abdominal or laparoscopic myomectomy (Butori et al. 2011). Although some adhesion formation have been reported following embolization, the incidence of this complication is unknown (Agdi et al. 2008). Furthermore, UAE and myomectomy in combination allows for removal of fibroids that may complicate pregnancy without the possibility of fibroid regrowth. Women may begin to try to conceive after 6 months of this combination procedure during the "golden period" because that is when myomas are less likely to recur (Candiani et al. 1991).

## 2.3 Surgical Technique

Myomectomy after UAE allows both the surgeon and the patient benefits compared to stand-alone myomectomy. We will address differences in laparotomy, laparoscopy, and hysteroscopy for myomectomy. Abdominal myomectomy is our preferred technique for multiple intramural myomata. We use this as the technique for large uteri as well. If the myomectomy is performed within 2 weeks of the UAE procedure, surgeons will be pleased by the almost bloodless field encountered. We have not had to convert any of our myomectomy patients to hysterectomy because of blood loss after embolization.

After 3 months, the amount of blood loss will increase, but not to the level of patients who have not undergone UAE. Myomectomy performed after 3 months is most commonly performed for a necrotic myoma. This condition is associated with malodorous discharge, and liquifications (Fig. 3). Cultures of the material within the myoma should be obtained, both aerobic and anaerobic. During the myomectomy, margins of the myoma and healthy myometrium

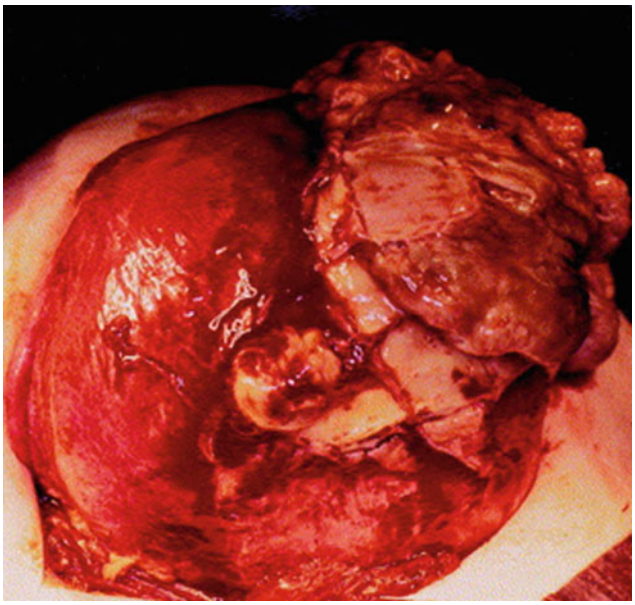

**Fig. 3** Necrotic myoma

may be blurred. Care should be taken to remove as much necrotic material as possible from the margins. We use manual pressure with lap sponges and gauze pads to aid in this process. A point of advise: the surrounding myometrium is invariably healthy, once the necrotic myoma is removed. We have only performed one hysterectomy (McLucas et al. 2001) on a patient post embolization with symptoms of necrosis. This was at the request of the patient.

During the post-operative myomectomy period when the procedure is performed for a necrotic myoma, we routinely continue broad spectrum antibiotic coverage for 7–10 days gram negative and anaerobic bacteria. This generally includes combination of antibiotics such as gentamycin and clindamycin (Spies et al. 2002). For patients with a penicillin allergy, vancomyocin is used (Weed 2003). No study has shown that the use of prophylactic antibiotics prevents infection after UAE, however it is suggested that prophylactic antibiotics reduce the risk of sepsis (Walker et al. 1999). Our patients often experience some febrile morbidity, and leukocytosis from bacteria at the margins of myomata. In spite of this, we have not had to perform a hysterectomy for post-operative infection. We counsel our patients prior to surgery of the likelihood of fever, and perhaps an extra day or two for antibiotic therapy.

### 2.3.1 Laparoscopic Myomectomy

If performed within the first 2 weeks post-operative after UAE, the surgeon will again benefit from a bloodless field. We offer patients with large pedunculated subserous myomata the option of a combination UAE followed by laparoscopic myomectomy for symptom relief. Patients are told about the risks of a second procedure performed under general

anesthesia. This is balanced by reports of pedunculated subserous myomata becoming necrotic post UAE (Katsumori et al. 2005). Also discussed is the relief of pain immediately after myomectomy, as opposed to waiting the 6 months for shrinkage after UAE. If on pelvic examination prior to UAE, the patient complains of pain when examining the area of pedunculated myoma, we will take this into consideration as well to offer patients a combination laparoscopic myomectomy and embolization (Dumousset et al. 2008). Late myomectomies tend to proceed generally after 3 months occurring laparoscopic myomectomy offers two additional challenges. First, filmy adhesions have been reported after UAE (Agdi et al. 2008). These may involve small bowel. We routinely perform a bowel prep on patients who are more than 3 months post embolization. We will discuss with the patient prior to surgery the option of abandoning the procedure if organized adhesions are encountered, or conversion to abdominal procedures. The second challenge is the myomectomy performed after the myomata have become calcified. These may pose a problem with some brands of morsellators.

#### 2.3.2 Hysteroscopic Myomectomy

Early performance of myomectomy using the resectoscope, within 2 weeks of UAE, will decrease risk of bleeding during the procedure. Also decreased are the risks of fluid overload when the blood supply to the myometrium is diminished. We will attempt to resect a pedunculated submucous myoma less than 5 cm in diameter after UAE. We have noted a high likelihood of prolapse in these myomata (McLucas et al. 2001). Larger myomata may be difficult to resect. We explain to the patient the options in treatment. Large myomata may require more than one procedure to safely resect (Lumsden 2002). Patients may wish to undergo abdominal myomectomy. We also discuss the possibility of intrauterine synechiae forming after hysteroscopic, or any myomectomy involving submucous myomata. Some patients prefer to pass a necrotic myoma, rather than undergo a hysteroscopic myomectomy. We discuss the risks of this alternative including risk of infection, a prolonged period cramp pain, and a malodorous discharge.

When performing hysteroscopic myomectomy more than 3 months after UAE, the calcified myoma may not be able to be removed using the resectoscope (McLucas 1991).

## 3 Unscheduled Myomectomy

### 3.1 Failure to Relieve Symptoms

UAE has been established as an effective means to treat symptomatic fibroids with many women opting for this less invasive procedure instead of hysterectomies. Although UAE has been shown to be successful in terms of symptom treatment in up to 90 % of patients, many women may go on to have additional procedures. In the literature women requiring subsequent, unplanned interventions has been reported to be 19–29 % (Gabriel-Cox et al. 2007; Volkers et al. 2007; Park et al. 2008). Unilateral UAE has been shown to be a risk factor for failure (Gabriel-Cox et al. 2007).

Clinical failure of UAE is assessed by patient survey of symptom relief because generally patients seek treatment for these benign tumors to alleviate the symptoms they cause. We assess symptom relief via self-report of bleeding, pain, and pressure on a three-point scale of mild, moderate and severe. We have reported symptom relief in 90 % of patients (McLucas et al. 1999). Poor symptom improvement may coincide with a smaller decrease in fibroid volume than in patients with complete symptom improvement (Toor et al. 2008). The majority of fibroid shrinkage occurs during the first 6 months post-treatment. Fibroids may continue to shrink for a year following UAE. If symptoms are not relieved within this time period, patients may opt to have another procedure. Clinical failure is assessed by patient surveys for symptomatic relief. All of the patients undergo a pelvic MRI with contrast after failure of embolization to assess the efficacy of UAE procedure (Walker and Barton-Smith 2006) Assuming no uptake of contrast on the myomata post embolization MRI, there is a possibility that patients may continue to complain of symptoms. Patients with enlarged uteri have been shown to have similar satisfaction rates as those with smaller uteri, thus uterine size may not be a predictor of failure.

Repeat UAE have been performed successfully (Chen et al. 2009) but subsequent myomectomy is the most common approach for subsequent fibroid treatment, particularly in women of childbearing age.

### 3.2 Prolapse of Submucous Myoma

When a submucous myomas has prolapsed into the vagina, UAE alone will not generally treat this patient's condition (Lumsden 2002). Generally, surgical removal of the submucous myoma will be indicated to reduce the chance of necrosis and possible infection (Dumousset et al. 2008). Surgical removal of prolapsed submucous myoma will be improved by prior UAE, which will block the blood supply to the pedicle of this submucous myoma (Dumousset et al. 2008; Liu et al. 2001) To reduce excessive blood loss when removing these fibroids, UAE may be necessary to block the arteries supplying the blood to the pedicle of the myoma. Management of prolapsed peduculated submucous myomas requires an ultrasound study to evaluate the characteristics (Hehenkamp et al. 2005) as treatment may be determined by

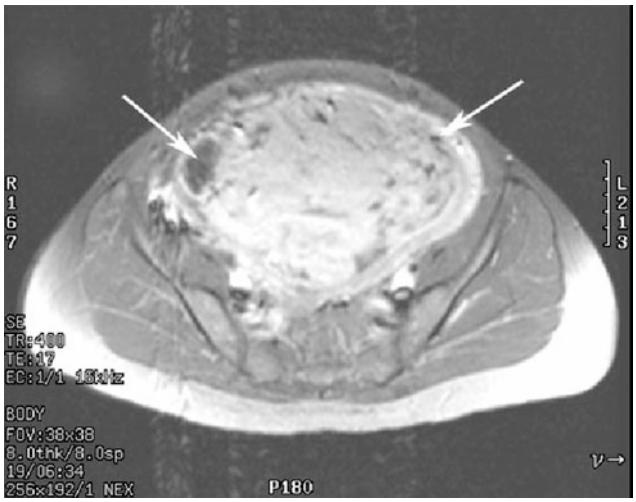


**Fig. 4** Air levels suggest abscess formation

size and location. Based on these characteristics, excision may be performed vaginally or abdominally.

Infective complications are more likely with submucosal myomas where exposure to intracavitary pathogens may occur (Golan et al. 2005; Rajan et al. 2004). In the event that these fibroids become prolapsed and infection occurs, hysteroscopic resection may be appropriate (Lumsden 2002).

### 3.3 Necrotic Fibroid

Complications following UAE include necrosis of myomas, particularly those that are submucous and pedunculated (Fig. 4) (Al-Fozan and Tulandi 2002). This condition may be potentially dangerous to the patient and, myomectomy may be undertaken to allow the patient to retain her uterus. A small submucous myoma as shown on MRI or ultrasound may be watched for the patient to complete the prolapse procedure without surgery (Wamsteker et al. 1993). The patient should be cultured and told to bring whatever tissue passes for pathological evaluation.

Laparoscopic myomectomy for necrotic fibroid may be necessary for signs of infection as well as temperature elevation and leukocytosis (Rajan et al. 2004; Seracchioli et al. 2003). Unlike a submucous myoma, a pedunculated subserous myoma suddenly presenting with pelvic pain will inevitably need surgical attention (Guarnaccia and Rein 2001). Intramural myoma often times require myomectomy by laparotomy to remove as much necrotic tissue as possible in order to preserve the uterus (Guarnaccia and Rein 2001; Seracchioli et al. 2000). All three of these conditions together account for less than 5 % (Walker and Barton-Smith 2006) of patients who undergo successful uterine artery embolization.

Often ischaemic necrosis and pelvic infection require hysterectomy (Godfrey and Zbella 2001). Unscheduled myomectomies may occur due to necrotic fibroid (Sabatini et al. 2003) following uterine artery embolization. UAE makes myomectomy rather than hysterectomy more manageable for necrotic fibroids, as the fibroid may be more easily removed without excessive bleeding.

In our experience, there have not been any cases of uterine necrosis (McLucas and Sostrin 2002), only necrotic myoma that need surgical intervention via myomectomy. Infection following UAE is possible, but rare (McLucas et al. 2001).

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# UAE is not Recommended for Women Wishing to Conceive

Mausumi Das and Togas Tulandi

## Contents




**Abstract**

Although considered a fertility saving option in women of reproductive age, current evidence suggests that uterine artery embolization can have an adverse effect on ovarian function as well as on future pregnancies. Uterine artery embolization is associated with a risk of premature ovarian failure, as well as occasional injury to the endometrium resulting in endometrial atrophy and adhesion formation. All of these including a subtle reduction in the ovarian reserve jeopardise fertility. Pregnancies following uterine artery embolization can be complicated by an increased rate of miscarriage, preterm delivery, intra-uterine growth restriction, malpresentation, abnormal placentation and post-partum hemorrhage. In view of the possibility of impaired ovarian function as well as increased pregnancy complications, women with fibroids who wish to conceive should not be treated with uterine artery embolization. Myomectomy should be recommended as the treatment of choice over uterine artery embolization in women desiring future fertility. The effect of uterine artery embolization for post-partum hemorrhage on future fertility is currently uncertain.


## 1 Introduction

Uterine artery embolization is a vascular radiological procedure, which in recent years has gained recognition as a treatment option in the management of uterine myomas and post-partum hemorrhage. Although it aims to keep the uterus intact and is often regarded as a fertility conserving option in women of reproductive age, evidence suggests that uterine artery embolization can have an adverse impact on fertility.

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## 2 Uterine Artery Embolization for Uterine Myomas

Uterine fibroids can cause menorrhagia, pelvic pain and symptoms of pelvic pressure. Several studies have shown that submucous and cavity-distorting intra-mural fibroids can impair implantation and placental development, leading to infertility and miscarriage (Bernard et al. 2000; Farhi et al. 1995; Pritts et al. 2009). In women with submucous myomas, hysteroscopic myomectomy resulted in a significant increase in the conception rate as compared to those in whom the myoma was not removed (Casini et al. 2006; Shokeir 2005; Somigliana et al. 2007). Casini et al. (2006) in their prospective randomized study involving 181 women affected by uterine fibroids, observed that in the group of women with submucosal fibroids, when surgery was not performed the pregnancy rate was 27.2 % with a miscarriage rate of 50.0 %, whereas the corresponding rates were 43.3 % and 38.5 % in women who underwent surgery ($p < 0.05$).

Uterine artery embolization (UAE) has been gaining in popularity in recent years as an alternative to hysterectomy in women with uterine fibroids. It is performed under local anaesthesia with intravenous conscious sedation. It has the advantage of being an out-patient procedure or overnight stay is required at most. The procedure is performed by passing a catheter through the femoral artery and advanced up to the distal part of the uterine artery followed by injection of the embolizing agent under angiographic guidance. It is then repeated on the opposite side.

Various embolic agents have been used, including tris-acryl microspheres, gelfoam and polyvinyl alcohol (PVA). It has been shown that larger trisacryl gelatin microspheres (700–900 micron) penetrate significantly deeper into myoma tissue compared with non-spherical PVA particles (355–500 micron) (Chua et al. 2005). Due to the irregular shape and size of the PVA particles and their tendency to aggregate, occlusion tends to be more proximal than required. Large microspheres may therefore have the advantage of specifically targeting the myoma tissue and minimising ischaemic injury to normal myometrium and reduce the possibility of entering the utero-ovarian collaterals (Chua et al. 2005). However, larger studies are required to substantiate these findings.

In a randomized study comparing the outcomes of UAE using tris-acryl gelatin microspheres versus PVA, those treated with tris-acryl gelatin microspheres were more likely to have complete infarction of all myomas and at least 90 % tumour infarction compared with patients treated with PVA. In this study, the authors used particles with 500–700 micron sizes followed by 700–900 microns (Spies et al. 2005a). Following occlusion, uterine ischaemia occurs and the myometrium becomes hypoxic. The myometrium is re-perfused by collateral arteries, and blood clots are lysed. The myoma undergoes infarction and ischaemic necrosis (Burbank and Hutchins 2000). Adverse events of UAE include infection, transcervical expulsion of a fibroid, non-purulent vaginal discharge, pelvic pain, delayed diagnosis of leiomyosarcoma, diminished ovarian reserve and premature ovarian failure.

In observational studies, UAE was followed by a decrease in excessive uterine bleeding in 90 % of women, 35–60 % reduction in uterine volume and a low rate of subsequent hysterectomy. In a randomized study of women with intramural myoma larger than 4 cm, UAE was reported to be as effective as myomectomy, but myomectomy was associated with more pregnancies and deliveries and fewer miscarriages (Mara et al. 2008). Yet, symptoms may persist in 20 % of women after UAE, necessitating other procedures, such as repeat embolization, hysterectomy or myomectomy (Spies et al. 2005b).

### 2.1 Fertility After Uterine Artery Embolization for Uterine Myomas

Several studies have highlighted the possibility of diminished ovarian function following UAE. In a randomized trial comparing UAE and hysterectomy, UAE was associated with decreased ovarian reserve, as demonstrated by a significant increase in FSH and fall in antimullerian hormone (Hehenkamp et al. 2007). Ovarian failure has been reported in up to 8 % of women following uterine artery embolization (Spies et al. 2005c). Decreased ovarian function after UAE is presumably due to embolization of the utero-ovarian collaterals decreasing the blood supply to the ovaries (Tulandi et al. 2002). The loss in ovarian function is age related and could be permanent or transient. Although the changes in menstrual function are usually transient, a particular concern is the possibility of decreased ovarian reserve reducing the chance to conceive. The incidence of premature menopause after UAE is 1–2 % in women younger than 45 years and 15–20 % in perimenopausal women over the age of 45 (Tulandi and Salamah 2010). On the contrary, myomectomy preserves ovarian function, making it the preferable intervention in women who wish to conceive.

Atrophic endometrium after fibroid embolization in woman with normal ovarian function has also been reported. Tropeano et al. (2003) reported a case of endometrial atrophy after uterine artery embolization with 150–250 μm polyvinyl alcohol microparticles for symptomatic fibroids. Post-treatment measurements of serum FSH, estradiol and ovarian imaging showed no change in ovarian function as compared with the baseline (Tropeano et al. 2003). Women should therefore be advised that uterine artery embolization may have a potential adverse effect on future fertility.

### 2.2 Pregnancy After Uterine Artery Embolization for Uterine Myomas

The safety of pregnancy after uterine artery embolization remains uncertain. Results from several studies suggest that pregnancies after UAE are complicated by an increased rate of miscarriage, preterm delivery, abnormal placentation, malpresentation and post-partum hemorrhage as compared to myomectomy (Goldberg et al. 2004; Pron et al. 2005; Tulandi 2007; Tulandi and Salamah 2010; Walker and McDowell 2006).

In a randomized trial comparing UAE versus myomectomy, there were significantly more pregnancies and fewer miscarriages following myomectomy than after UAE (Mara et al. 2008). In this study, in which 58 women were randomized to UAE and 63 to myomectomy, there were 33 pregnancies in 40 women after myomectomy as compared to 17 pregnancies among 26 women during the first 2 years of follow-up. The abortion rate was 64 % after UAE and 23 % after myomectomy (Mara et al. 2008).

Other studies have also demonstrated a high rate of miscarriage after UAE. In the Ontario multicenter prospective trial (Pron et al. 2005), the post-UAE spontaneous miscarriage rate was 16.7 % (24 pregnancies in 21 women of mean age 34 years), whereas the miscarriage rate was 27 % in the retrospective trial of Carpenter and Walker (26 pregnancies; mean age of patients, 37 years) (Carpenter and Walker 2005). Similarly, in a study comparing the pregnancy outcome after UAE versus laparoscopic myomectomy, there was an increased risk of miscarriage after UAE (24 %) as opposed to 15 % after laparoscopic myomectomy (Goldberg et al. 2004). In a retrospective analysis of 1,200 women who underwent UAE, 56 women conceived, but only 33 pregnancies had successful outcomes. There were 17 miscarriages, 2 stillbirths, 3 terminations and 1 ectopic pregnancy. There were 6 premature deliveries and 6 pregnancies were complicated by post-partum hemorrhage (Walker and McDowell 2006).

The increased rate of miscarriage after UAE was also illustrated in a prospective multi-centre study comparing laparoscopic uterine artery occlusion with UAE in women with symptomatic fibroids (Holub et al. 2008). Furthermore, hysteroscopic examination of the uterine cavity revealed that patients previously treated for intramural myomas by UAE had a significantly higher incidence of abnormal findings in the uterine cavity as compared to those after laparoscopic uterine artery occlusion (Kuzel et al. 2011). These included a necrotic defect of the endometrium, specifically, a fistula between the uterine cavity and intramural necrotic myoma.

In a recent metaanalysis involving 227 completed pregnancies after UAE, Homer and Saridogan (2010) found that miscarriage rates were higher in UAE pregnancies (35.2 %) compared to fibroid-containing pregnancies matched for age and fibroid location (16.5 %) (odds ratio [OR] 2.8; 95 % confidence interval [CI] 2.0–3.8). They also found that UAE pregnancies were more likely to be delivered by caesarean section (66 % vs. 48.5 %; OR 2.1; 95 % CI 1.4–2.9) and to experience post-partum hemorrhage (13.9 % vs. 2.5 %; OR 6.4; 95 % CI 3.5–11.7) (Homer and Saridogan 2010).

Pregnancies after UAE were also associated with higher rates of preterm delivery and malpresentation than pregnancies following laparoscopic myomectomy. In a study comparing data from 53 pregnancies after UAE and 139 pregnancies after laparoscopic myomectomy, a higher risk of preterm delivery and malpresentation was reported in the UAE group (Goldberg et al. 2004). An increased incidence of intra-abdominal adhesions probably due to coagulation necrosis of the leiomyoma following UAE has also been reported (Agdi et al. 2008).

Several studies have highlighted the increased frequency of post-partum hemorrhage following UAE (Goldberg et al. 2004; Pron et al. 2005). A multi-centre study involving 555 women with symptomatic leiomyoma, reported an increased incidence of abnormal placentation following UAE, which included placenta previa and placenta accreta resulting in caesarean hysterectomy. There was also an increased incidence of post-partum hemorrhage secondary to placental abnormalities (Pron et al. 2005). The primary embolic agent used in this study was 355–500 micron polyvinyl alcohol particles. Likewise, a retrospective analysis of 56 completed pregnancies after UAE showed that compared with the general obstetric population, there was a significant increase in post-partum hemorrhage in pregnancies after UAE (Walker and McDowell 2006).

In view of the above, women presenting with fibroids who wish to conceive are therefore not generally eligible for embolization (ACOG Committee Opinion 2004). Women with submucous fibroids should be treated by hysteroscopic myomectomy and they are not candidates for embolization (Lefebvre et al. 2003; Tulandi and Salamah 2010). Hence, although pregnancies following uterine artery embolization have been reported, myomectomy should be recommended as the treatment of choice over uterine artery embolization in women desiring future fertility.

## 3 Uterine Artery Embolization for Post-Partum Hemorrhage

Post-partum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality throughout the world, and its most common cause is uterine atony. UAE has emerged as an adjunct treatment to surgery for PPH that do not

respond to medical treatment (Deux et al. 2001; Merland et al. 1996; Mitty et al. 1993). UAE for PPH is performed for temporary embolotherapy using absorbable gelatin sponge. There are differences in UAE for the management of uterine fibroids and for PPH. While there are several options for conservative treatment of uterine fibroids, the options for PPH are limited. In addition, the blood vessels in the post-partum period are dilated.

### 3.1 Fertility After Uterine Artery Embolization for Post-Partum Hemorrhage

Whether UAE for PPH is also associated with impaired ovarian function is unclear. Instances of secondary amenorrhoea, intra-uterine synechia and atrophic endometrium have been reported (Gaia et al. 2009; Hardeman et al. 2010). However, this could be related to instrumentation of the uterine cavity, including manual removal of the placenta. Intra-uterine adhesions usually occur as a result of trauma to the uterine mucosa including curettage for miscarriage, postpartum curettage, post-abortion or post-partum endometritis and ischaemia following post-partum hemorrhage. Hysteroscopic resection of myomas or uterine septae as well as genital tuberculosis can also cause intrauterine adhesions.

Uterine necrosis following microparticle or coil embolization for obstetrical hemorrhage has been described (Cottier et al. 2002; Deux et al. 2000). Potential adverse effect on ovarian function includes ovarian exposure to radiation during fluoroscopy (Lee and Shepherd 2010) and decreased ovarian blood supply presumably due to embolization of the utero-ovarian collaterals. However, none of these concerns have been validated.

Most authors use absorbable gelatin, which is considered to be a temporary embolic material in contrast to permanent materials such as tris-acryl gelatine microspheres or polyvinyl alcohol particles (Lee and Shepherd 2010) and theoretically may better preserve fertility and the ability of the uterus to maintain a full-term gestation after UAE. In any event, a case of uterine necrosis after UAE using gelatin for PPH has been reported (Pirard et al. 2002).

Several studies have highlighted the increased incidence of synechia and placenta accreta after UAE. In a retrospective study, Gaia et al. (2009) found that of 107 women who underwent embolization with pledgets of absorbable gelatin sponge (Curaspon®), Curaspon powder or inert particles, 23 reported oligomenorrhoea and 6 amenorrhoea. They noted the occurrence of diffuse uterine synechia at the hysteroscopic examination; among them, 2 had been embolized with Curaspon powder and 1 with inert microparticles. Several attempts to remove the synechia by hysteroscopic resection were unsuccessful (Gaia et al. 2009). It is possible that endometrial ischaemia was the cause of diffuse uterine synechia in these cases.

The choice of material to embolize the arteries is of considerable importance. Non-resorbable microparticles can enter the endometrial arteries causing ischaemia with subsequent risk of amenorrhea, synechia or even ovarian failure if they pass into the utero-ovarian anastomoses (Hehenkamp et al. 2007; Spies et al. 2007; Tulandi et al. 2002). In contrast to embolization of fibroids, where non-resorbable microparticles are used, in the treatment of obstetrical hemorrhage, the material most commonly used is gelatin, which is usually absorbed within 1–3 weeks (Pelage et al. 1998; Yamashita et al. 1994). In the study by Gaia et al. (2009), out of 107 patients who underwent UAE, 66 reported regular menstruation, 33 reported subjective changes in the frequency and amount of menses, while 6 patients who developed secondary amenorrhoea were found to have uterine synechia, which could not be treated by hysteroscopic resection. Of 29 patients who attempted conception, there were 18 pregnancies leading to term deliveries, 3 of which were complicated by recurrent PPH due to abnormal placentation, requiring another UAE (Gaia et al. 2009).

### 3.2 Pregnancy Outcome After Uterine Artery Embolization for Post-Partum Hemorrhage

The most frequently reported complication in pregnancies after UAE for PPH is recurrent PPH. Cases of intra-uterine growth restriction have also been reported (Cordonnier et al. 2002). Endometrial impairment after UAE can adversely affect implantation and placentation and thereby have a negative impact on subsequent pregnancies. It has also been suggested that embolization can lead to placental insufficiency in subsequent pregnancies, with the risk of fetal growth restriction (Cordonnier et al. 2002).

In a retrospective review of 53 cases where embolization was used to treat patients with obstetric hemorrhage, no significant difference was noted in occurrence of pregnancy between the non-embolized and embolized groups. The authors also reported complications after UAE including post-partum hemorrhage, placenta accreta, secondary amenorrhoea, intra-uterine adhesions and atrophic endometrium in that group (Hardeman et al. 2010). Several studies have reported a significant increased risk of recurring obstetric hemorrhage following UAE (Picone et al. 2003; Salomon et al. 2003). This included an increased incidence of PPH due to placenta accreta (Salomon et al. 2003) requiring a hysterectomy. The high incidence of abnormal

placentation could be due to endometrial injury leading to abnormal trophoblastic invasion during the subsequent pregnancy (Salomon et al. 2003).

## 4 Alternative Radiological Techniques

Doppler-guided-uterine artery occlusion is a new non-invasive transvaginal technique, which employs a Doppler-guided device containing vascular clamp, Doppler receiver and Doppler ultrasound crystals to mechanically compress the uterine arteries bilaterally for 6 h. After the clamp is removed, normal myometrium reperfuses, while myomas do not, because of their inability to perform fibrinolysis. Though it has been suggested that it can decrease myoma volume by approximately 40–50 % (Tropeano et al. 2008), its effect on subsequent reproductive function has not yet been evaluated. This procedure could be complicated by occlusion of the ureter, leading to hydronephrosis requiring stenting (Vilos et al. 2006).

## 5 Conclusions

Although successful pregnancies after uterine artery embolization have been reported, current evidence suggests that UAE can have an adverse effect on ovarian function as well as on future pregnancies. UAE is associated with a risk of premature ovarian failure, as well as occasional injury to the endometrium resulting in endometrial atrophy and adhesion formation. All of these including a subtle reduction in the ovarian reserve jeopardize fertility. Technical improvement particularly in the size and shape of embolization particles may reduce these undesirable effects.

Current evidence suggests that pregnancies following uterine artery embolization can be complicated by an increased rate of miscarriage, preterm delivery, malpresentation, abnormal placentation and post-partum hemorrhage. Apart from intrauterine growth restriction, the long-term effects on children born after UAE are still unknown.

UAE for post-partum hemorrhage is different from that for uterine fibroids. If there are several conservative options to treat uterine fibroids, alternative treatment options for PPH are limited. The effect of UAE for PPH on fertility is still unclear.

In conclusion, because of the possibility of impaired ovarian function as well as increased pregnancy complications, women with fibroids who wish to conceive should not be treated with uterine artery embolization. Myomectomy should be recommended as the treatment of choice over uterine artery embolization in women desiring future fertility. As Hippocrates once said “Primum non nocere” or “First, do no harm.”

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# Costing Issues and UAE in the Developing World

Nigel Hacking

## Contents



**Abstract**

Uterine Artery Embolisation (UAE), first described in France in 1995, rapidly became commonplace in many countries, but has had poor uptake in the developing world. Since 1998, I, along with local contacts and colleagues in Radiology and Gynaecology have been able to set up large scale UAE services in the Caribbean, based out of Trinidad and from 2009 have added UAE to a comprehensive 'Fibroid centre' in Kenya at the Aga Khan University Hospital, Nairobi. In each situation this has required a close working relationship with medical, hospital and political personnel. Financial considerations, careful case load selection and planning with robust pre-procedural screening and imaging has been arranged as has very careful post-procedural care and follow-up. Over 1000 UAE cases have been performed in the Caribbean with very high success rates and no major complications nor deaths. Over 100 patients have now been treated in Kenya with a similar success rate and low complication rates. A mixture state-funded and private patients have been treated in both settings. The use of Gelfoam slurry as the embolic of choice in the majority and the avoidance of micro catheters wherever possible has led to an affordable procedure with costs equivalent to or less than hysterectomy in both settings.

## 1 Introduction

Uterine Artery Embolisation (UAE), first described in France in 1995 (Ravina et al. 1995), rapidly spread through USA (Goodwin et al. 1997), the UK (Bradley et al. 1998), much of Europe (Golfieri et al. 2000; Lohle et al. 2001; Zupi et al. 2001), Canada (Pron et al. 2003a, b), but has had patchy take up in many European countries, Australasia the Middle and Far East as well as countries in the Developing World.

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Initially lack of evidence, lack of Gynaecological support and worries over costs, both financial and radiation, concerns over complication rates (Vashisht et al. 1999; Lanocita et al. 1999; Godfrey and Zbella 2001) and uncertainty over the effect on fertility were all cited as reasons for poor take up of the UAE procedure.

In the UK the National Institute for Clinical Excellence (NICE), looked closely at UAE and issued guidance in 2004, 2007 and lastly in 2010 where they recommended UAE as one of the first line therapies in women with symptomatic fibroids wanting to avoid hysterectomy. The Royal Colleges of Obstetrics and Gynaecology and the Royal College of Radiology issued joint guidelines in 2000 (Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists 2000) and 2009 (RCOG and RCR 2009), as did the American College of Obstetrics and Gynaecology in 2008 (American College of Obstetricians and Gynaecologists (ACOG) 2008) and the American College of Radiology in 2009 (Burke et al. 2009). In Canada, the Society of Obstetricians and Gynaecologists along with the Canadian Association of Radiologists and Canadian Interventional Radiology Association issues guidelines in 2004 (Guidelines 2004). The Medical Services Advisory Committee of Australia provisionally approved UAE in 2006 (Application 1081).

A 2009 online survey assessing all members of the Cardiovascular and Interventional Radiologic Society of Europe was undertaken documenting the uptake of UAE across Europe (Voogt et al. 2011). 167 centres confirmed that they were performing UAE with UK, Germany and France having the highest number of centres with 24 countries having at least one UAE practicing hospital. A web-based survey undertaken by www.femisa.org.uk recorded 100 UK centres now offering UAE with over 20,000 procedures having been performed since its introduction.

UAE is, therefore, commonplace in Europe and the developed world. The UK-based HTA funded HOPEFUL study included a careful cost-effectiveness analysis (Hirst et al. 2008; Wu et al. 2007) and concluded that UAE was more cost-effective than hysterectomy even after taking account of complications seen after UAE.

Outside of Europe and North America the uptake of UAE has been patchy. Reports from Hungary (Szabo et al. 2001) and Hong Kong (Chiu et al. 2001) in 2001, India (Bapuraj et al. 2002), Brazil (Messina et al. 2002), Kuwait (Ahmad et al. 2002), Korea (Bai et al. 2002) and Taiwan (Chen et al. 2002) in 2002 and China (Hong 2004) and South Africa (Prollius et al. 2004) in 2004 were published.

Having started a UAE service in UK based in Southampton in 1998, I was keen to take this exciting new procedure out into the developing world. Clearly, the economic challenges and demands of setting up and maintaining a working UAE practice from afar would create many new obstacles and challenges.

## 2 UAE in the Caribbean

In 1998, because of the high prevalence of fibroids and the lack of a UAE service, I contacted the head of the Radiology Department at the University of West Indies in Trinidad. After visiting and discussions, it was obvious that they could not develop a UAE service on their own, Dr. Omar Khan, representing the University of WI in Trinidad felt that with hard work and good will on all sides it would be possible to setup such a service in Trinidad.

Following meetings with several Trinidad-based Gynaecologists and Anaesthetists a referral pattern and postoperative management strategy was agreed upon.

The plan was for me to visit several times a year. In each week-long visit, I would carry out UAE cases in the University Hospital Cardiac Catheter Laboratory. I would instruct, and train local clinicians, radiographic technicians in UAE techniques as well as teach medical students about the wider uses for Interventional Radiology. Permission was sought and granted by the hospital management and full medical registration with the Medical Board of Trinidad and Tobago was granted on application and interview.

Overall costing and funding this service was to be my responsibility. No monies were available from the hospital. Private patient fees could be levied in this partially state run, partially private medical institution. All-inclusive fees were calculated and charged to cover Radiological, Gynaecological, Anaesthetic, Hospital and Cath Lab charges as well as to cover the cost of all consumables and drugs.

Private Insurance companies were briefed and most agreed to provide cover for this procedure. After the first few cases there was press interest and newspaper and television companies invited us to discuss this exciting new noninvasive treatment. The word spread from patient to patient and a mixture of self-referral and Gynaecology-referral quickly evolved. Numbers grew from 20 per annum up to over 60 cases in 2004. By this stage the Ministry of Health (MOH) of the Government of Trinidad and Tobago were asking for expressions of interest to help the large waiting list of non-insured women awaiting surgical treatment for symptomatic fibroids. I was approached and successfully bid for some of these cases.

A new model for MOH patients was proposed and accepted. These women would be referred directly to 'Fibroid Caribbean' a company setup to manage this additional workload. An ultrasound and Gynaecological assessment then followed and suitable patients were scheduled to undergo UAE on one of my regular visits to Trinidad. Numbers quickly grew during 2004 and 2005 with over 30 and 80 cases in each year respectfully such that extra Interventional Radiologists (IRs) were required to provide this service. At that stage there were still no suitably trained local Trinidad or Caribbean-based IRs and trained UK-based

IRs were invited out and after a successful proctored week under my guidance they were employed to provide additional weeks of intensive UAE procedures. During 2006 and 2007, 115 and 215 MOH patients were treated by up to 4 UK-based IRs visiting up to seven times per year and performing up to 35 cases in a 5 day week. Additional private UAE procedures were accommodated and in Nov 2008 46 patients were treated by me during a 1-week visit.

An efficient, safe and well-supported service was established as numbers grew. All women would see a radiologist for a diagnostic US scan. If not already referred by a Gynaecologist they would be sent to see one prior to the UAE and the patient would then be seen again by the same Gynaecologist at 1–2 weeks after the procedure to ensure early recovery and then finally at 3 months after US scan to determine clinical and imaging response. MRI was available, but due to cost was not routinely utilised for either private or MOH cases. Possible Adenomyosis, suspected symptomatic fibroid slough and any persistent infections were investigated by contrast-enhanced MRI and this was provided within the package price for MOH patients or at additional cost for private patients. Additional Gynaecology appointments if required for any complications were also provided within the package price for MOH patients.

The aim was to keep all-inclusive prices for private and MOH patients as low as possible.

Major consumable costs included the choice of embolic and the use of microcatheters. Initially particulate PVA was utilised, but after several IRs reported excellent results with Gelfoam slurry, particularly in the Far East (Katsumori et al. 2006) dropping PVA in favour of Gelfoam slurry was adopted during 2001.

Excellent results were achieved, backed up by our own experience of Gelfoam embolisation in over 100 UK patients followed by contrast-enhanced MRI as well as symptom scores. Three and 12 month US follow-up performed for the first 100 cases performed in Trinidad indicated no deterioration in either volume loss in Uterus or dominant fibroid or in subjective symptomatic improvement. Microcatheters were used very sparingly and only in the cases of very small, tortuous uterine arteries or in the rare case of uterine artery rupture. Spasm was reduced by routine use of intra-arterial Nitronal.

An efficient ‘model was developed to allow the safe and personal treatment up to 40 patients in a 1 week period. All women were given patient information packs and encouraged to learn more about their procedure from the www.fibroidcaribbean.com website and its various links and references to well respected UK and US studies and clinical guidelines. Each patient filled out a medical questionnaire in advance and brought them to the hospital on the day of the procedure. This outlined the course of their condition. It assessed symptoms, previous treatments and future fertility wishes. All patients arrived together early on the morning of their UAE. After registration they were seen as a group in a good-sized meeting room. A 30–45 min face to face consultation with the IR was given. Their questionnaires and US scans were reviewed and all women were fully informed in the same group. The roles of the Radiologists, Anaesthetists and Gynaecologists were discussed as was the UAE procedure itself. Further written information was provided and the patients invited to ask pertinent questions regarding the procedure, their recovery and potential complications and their follow-up care. Each patient was given the opportunity to discuss individual and confidential concerns privately with the IR before the procedure and telephone and email contact addresses of all team members were distributed and each patient encouraged to contact the team if they had any concerns at any stage after the procedure.

After the discussion the women all signed consent forms together. This gave the IR a chance to repeat to the group the benefits and potential complications of the procedure. Instructions as to post-procedural pain management and Gynaecological and Radiological follow-up were given.

After consent the first two patients are taken into the preparation room, were changed and handed over to the Anaesthetic team. 1–2 Anaesthetists and operating department assistants (ODAs) then received the patients. They discussed further aspects of pre-, per- and post-operative sedation and pain management. They also stressed that any woman could phone them for further pain management advice after discharge.

The Cath lab nurses pre cut enough Gelfoam sponge into small 1–2 mm cubes for the day’s cases. After the first UAE procedure is completed, the 4Fr sheath is left in place until the patient is transferred back to recovery where a trained nurse removes it. The next patient is waiting outside the Cath lab and the turn around between each case is about 15 min. One anaesthetist looks after the previous patients both in recovery and when they are transferred back to the ward. The second anaesthetist supervises the patient undergoing the procedure to keep levels of sedation and intra-operative pain control well managed. The introduction of IV Buscopan by the Anaesthetic team appears to reduce post-procedural uterine spasm and seems to keep opiate requirements down to a minimum.

At maximum efficiency up to two patients per hour can be treated in this way. Once numbers had increased beyond 4 a day it became clear that keeping patients together with a dedicated team of nurses was the safest and most effective post op management strategy. A 6 bedded ‘ICU’ was utilised with two nurses and full patient monitoring. Morphine infusions with additional on demand Morphine PCA pumps would keep these patients pain free during the day and night after the procedure.

Post-UAE care and analgesia were dealt with by the anaesthetic team. All women were kept in overnight and discharged the following morning.

In just over 1,000 cases, only three required a second night in hospital and with IR and Anaesthetic telephone support only one has ever been readmitted for further IV pain management. All patients are also discharged on a 5-day course of antibiotics. They are given a 3 page discharge letter, detailing potential complications of UAE and are encouraged to visit their Gynaecologist after 1–2 weeks or sooner if there are clinical concerns. A copy of the same letter was given to them to hand over to their usual family doctor. They are given sick certificates for 2 weeks, and if requested information letters to their employers and insurance companies.

A change of government policy in Trinidad and Tobago in 2007 lead to stopping the MOH service after 2008. A total of 483 MOH patients had been treated between 2004 and 2008 and this as well as over 520 private patients adds up to over 1,000 cases treated in the Caribbean up to Sept 2013. Qualifying patients can still apply for UAE through the Trinidad and Tobago Social Welfare department and receive UAE free of any fee.

A telephone-based survey of 300 MOH patients was carried out in 2008. There was a 47 % response rate (143/300) with 88 % symptomatic improvement in responders. There had been no deaths or serious complications and 91 % of responders were satisfied with their treatment and outcome.

To date there are as yet no Interventional Radiologists in Trinidad trained or training to perform complex intervention. There are many diagnostic Radiologists who are very skilled at diagnosis of fibroids and their complications and have got excellent experience of ultrasound and MRI both pre- and post-UAE. There is local encouragement for Trinidad radiologists to travel to the UK or USA for training Fellowships.

## 3 UAE in East Africa

After hearing of the success of the Caribbean and particularly Trinidad UAE service Professor William Stones, Chair of Obstetrics and Gynaecology at the Aga Khan University Hospital in Nairobi, Kenya invited me out to his institution to set up a similar service. This took advantage of the Hospital's investment in a cardiac service that started with installation of a new Cardiac Cath lab in 2009. A team of local Gynaecologists, Anaesthetists and Diagnostic Radiologists was assembled to bring this together. Using the lessons learned in Trinidad, we were able to calculate the full costs for this service and we started up in December 2009. As in Trinidad this is primarily offered for insured and self- funding private patients. Qualifying women can apply to the hospital to meet their costs using the Kenya Social Welfare system and several women have received their treatment using this method.

Since 2009 numbers have built and 135 patients have been treated up to Oct 2013.

UFE is offered in the context of a gynaecological service at AKUH,N that serves Kenyan but also other East African women owing to the convenience of Nairobi as a regional transport hub and the profile of the hospital regionally. The service aims to be comprehensive with the University Faculty and private practitioners offering the full array of modern surgical options for women with fibroids. These include Open and Laparoscopic hysterectomy, open, laparoscopic and hysteroscopic myomectomy in addition to UAE so that advice can be individualised according to clinical indications and patient preference. UAE is used in combination with all these surgical options where deemed appropriate. Regular Continuing Medical Education (CME) meetings are held in Nairobi and many other Kenyan cities as well as in neighbouring Tanzania, Uganda, Rwanda, Burundi and Ethiopia so as to sensitise regional practitioners about the available options and the experience has been presented at speciality forums such as the Kenya Obstetrics & Gynaecological Society annual scientific conference. Whilst the majority of referrals are from Kenyan-based primary physicians and Gynaecologists there are increasing numbers of patients visiting from surrounding African countries.

The service has been setup along Trinidad lines except we have been able to build into the overall package price both pre and follow-up MRI scans when deemed necessary into this service. In addition, we hold an annual reception at the hospital inviting all previous patients to attend along with any prospective patients. This has attracted press interest, which in turn has increased awareness of the range of available options for fibroid treatment, whether by surgery or UAE.

AKUH,N provides services on a private not-for-profit basis. Many patients are funded through their medical insurance cover while those covering their own costs are offered an inclusive package. The hospital also has a substantial Patient Welfare Programme where the costs of care can be subsidised based on an individual needs assessment. Increasing numbers of patients have been treated using this Welfare programme over the past 3 years.

As visiting faculty, I am invited to work at the Aga Khan University Hospital for 2 weeks a year. As in Trinidad I regularly lecture, teach and build local capacity through hands on training in the context of Aga Khan University's 4 year residency programme leading to an MMed degree. Two local Radiologists have become keen on IR and have both pursued IR Fellowships in the USA. Both these two as

well as a third, who has had an IR Fellowship in Israel have had hands on experience in UAE and I am hopeful will be able to take over this service in the next few years.

## 4 UAE in the Developing World

Evidence for UAE services elsewhere in the developing world is scanty. From my own enquiries and help from the companies supplying embolic materials I have discovered that the majority of UAE's performed in South America are in Brazil and Argentina. At present, this seems to be exclusively performed by IRs although Cardiologists in Mexico also perform UAE. The high cost of consumables in Brazil has limited the uptake of UAE.

All current services are performed in the private sector although an exciting philanthropic venture to provide UAE for free to low income women in Brazil was introduced by an IR team in 2008. It is estimated by them that over 200,000 low income women are having hysterectomy each year in their country with the majority being for fibroids. The 'Angiomovel', a truck equipped with a mobile C-Arm Cath Lab was used to treat 25 women from each of 4 Sao Paulo Hospitals (Angiomovel 2011).

## 5 Conclusion

Whilst UAE is now commonplace in Europe, North America and other developed world areas its uptake in the developing world has been slower. Economic factors have been important, but in Trinidad and Sao Paulo government and philanthropic involvement has shown that it is feasible to perform UAE safely and to high standard. In Trinidad and Kenya Social Welfare cases can now be performed for qualifying cases and the UAE performed for no or minimal cost to the patient. Economies of scale allow Cath Lab and Hospital costs to be kept to a minimum and the use of Gelfoam as the embolic and avoidance of routine micro-catheters allows consumable costs to be kept to a minimum without sacrificing much in terms of efficacy.

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# Who Can and Should do Uterine Artery Embolisation

John F. Reidy

## Contents



## 1 Introduction

The first report of uterine artery embolisation (UAE) as a primary treatment for uterine fibroids was in 1996 (Ravina et al. 1995). The leading author in this seminal paper was a gynaecologist and the radiological input was by neuroradiologists. Radiologists, particularly interventional radiologists (IRs) who had been embolising in great variety of clinical situations since the 1980s, seized on this new application with enthusiasm—here was an elective procedure for a common condition that was minimally invasive compared with the standard treatment which for most women was a major surgery and a hysterectomy.

Gynaecologists were generally less enthusiastic in their uptake and acceptance of this new procedure, but as the experience of UAE has increased and national medical societies and bodies representing both radiologists and gynaecologists gave it their cautious approval, it has become more generally accepted.

Most commonly, IR procedures are undertaken at the request of a specialist referring clinician but in some situations this may not be necessary. The guidelines for UAE have all recognised that women should be referred by a gynaecologist who has made a full clinical evaluation and has discussed the other and alternative treatments for fibroid disease. If it has been accepted that gynaecologists are essential in the workup for UAE, similarly IRs have assumed they are the only operators capable of offering an UAE service. Although these divisions of clinical practice and responsibility generally apply, they have been questioned.

There are a number of aspects of UAE that will be addressed here that should be addressed in the establishment of UAE service.

Each will be separately considered:

1 Is it necessary for all women to be seen and assessed by a specialised gynaecologist prior to UAE?
2 Should clinicians other than IRs carry out uterine artery embolisation?

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3 If other clinicians, e.g. gynaecologists and cardiologists are to do UAE, what credentialing is necessary? Of course the same checks should apply to IRs.
4 Who should look after women immediately after UAE and be responsible for their in-hospital treatment?
5 In the event of early concerns or complications (<1 month), who should be responsible for their care?
6 Who should see women for their routine follow-up?

## 2 Is it Necessary for All Women to be Seen and Assessed by a Specialist Gynaecologist?

When a woman is referred to a gynaecologist by her family doctor, he will assess the clinical symptoms and signs, and will commonly make a clinical diagnosis of uterine fibroids backed up by some imaging, most commonly initial ultrasound. Many will now routinely request an MRI scan with contrast and there is a tendency for more MRIs to be requested even when there are cost considerations in the local clinical practice. When symptoms are considered to be significant and related to fibroids, the possible treatments of hysterectomy, myomectomy and UAE should be considered and discussed. If women are then referred for UAE, this can mean two hospital specialists are involved which may have financial implications.

It has been suggested that the family doctor can assess and refer directly to the IR without the need for the hospital gynaecologist to be involved. This assumes that the family doctor is fully competent to make a gynaecological assessment. Obviously, if there are any clinical or imaging concerns, referral to a more specialised gynaecologist would then be necessary. When an IR sees a woman to discuss UAE, he is not in a position to discuss the alternative treatments of hysterectomy and myomectomy with detailed knowledge but he can give reasonable discussion as the gynaecologist is able to, regarding UAE. The radiologist will then assess the woman for UAE and if based on the clinical and imaging findings she was considered suitable would make the arrangements to proceed with the procedure. In this situation where a woman is referred directly to an IR for UAE, it would be essential for the family doctor to be credentialed for the gynaecological assessment and to have close links to a more specialised hospital gynaecology service. A recent survey of UAE practice in Europe found that 76 % were referred for UAE by their gynaecologist with only 4 % via the family doctor but that 20 % were direct self-referrals to the radiologist! (Voogt et al. 2011).

## 3 Should Clinicians Other than IRs Carryout Uterine Artery Embolisation Procedure?

One of the problems of vascular and interventional radiology is that following the development of new procedures, clinicians then take up a procedure related to their clinical practice and make it their own. This is usually the case where there is potentially a large volume of activity and cardiac angiography and intervention is a very good example. Unlike many procedures pioneered by IRs, the great majority of UAE has been carried out by IRs. Most gynaecologists have shown little interest in developing catheter skills and taking on these cases. It has, however, spurred gynaecologists to look at other uterus-conserving techniques, particularly myomectomy. If gynaecologists do not start with any catheter skills, the same cannot be said for cardiologists, and in some parts of the world interventional cardiologists have taken on UAE with no difficulty. This situation, as in other vascular procedures, is often aided by the fact that many radiologists have so much clinical work with general radiology and cross-sectional imaging. A recent Internet search identified a number of cardiology websites mainly in the USA detailing UAE procedures. It is not clear whether the procedures would be done by cardiologists or IRs. A few gynaecologists have seriously taken up UAE and if they become skilled, they are then in a very good position to deal with the clinical aspects of the case and to discuss the various treatment options. One point regarding uterine artery embolisation which applies to radiologists as much as to gynaecologists is that many cases may be fairly straightforward but occasionally cases may be very difficult so that without a lot of catheterisation embolisation experience and techniques such as coaxial embolization, a higher technical failure rate would be expected. Some early work has shown that with IRs in training greater experience equates with greater technical success and shorter procedure times.

## 4 If Other Clinicians, e.g. Gynaecologists and Cardiologists are to do UAE, What Credentialing is Necessary?

Whoever undertakes UAE, there are three aspects of the technique that need to be considered in the credentialing process:

1. Percutaneous arteriographic technique.
2. Selective arteriography and catheterisation.
3. Embolisation techniques.

Interventional radiologists (IRs) will have a large experience of percutaneous catheterisation and selective arteriography and almost certainly some experience of embolisation, although some radiologists are wary of it as they feel embolisation can be associated with significant complications. If then an IR wants to establish a UAE practice, it would then be important to have a detailed knowledge of the vascular anatomy and the variations that occur; but this should not present problems. It is important to establish protocols for the aftercare management and aspects such as post-procedure analgesia. Though it can be argued that IRs are best equipped to carry out UAE in some centres, radiologists have so much work with intervention as well as with imaging that there is no manpower available to run effectively a UAE programme. This situation may be even more marked in less developed countries where radiologists may be better paid doing cross-sectional radiology and are not attracted to interventional radiology that can involve emergency on-call work.

For an interventional cardiologist, percutaneous catheterisation and selective arteriography would present no problems. Also they are very familiar with coaxial catheterisation techniques, which may be necessary and many feel are important in UAE. There is evidence that in some countries already cardiologist are taking on UAE where radiologists are not willing to get involved. They will, however, have no experience of embolisation so that it would be necessary for them to familiarise themselves with all the technical details as well as gaining an understanding of anatomy and the other practical issues associated with UAE. Before doing cases on their own, they should spend time with IRs doing UAE or arrange to be proctored for a number of cases if doing them in their own units.

It is unusual for gynaecologists to want to take on fibroid embolisation cases. Most are happy to be involved in the assessment and selection of women for UAE and in their aftercare. They have no background or experience on the three aspects of the technique needed for UAE, so that if they do decide they would like to carry out these procedures, they would then need significant endovascular training.

McLucas has championed the case for gynaecologists carrying out UAE. Whilst accepting that they have no catheterisation background, he believes that they have an advantage with an intimate knowledge of pelvic anatomy as well as vascular anatomy. He also makes the point that with some hospitals interventional radiologists are not available or not interested in taking up UAE and that if a gynaecologist does UAE, he is able to deal with all aspects of fibroid management and that he is best placed to discuss the alternative treatments and to assist the woman in making the best treatment of choice. He has argued the case for gynaecologists doing UAE and has made recommendations for credentialing (McLucas et al. 2003).

There are of course a number of precedents where radiologists have established catheter-guided therapies but which have been largely taken over by nonradiologist clinicians who have developed the skills to further and dominate these techniques. Cardiologists took over coronary arteriography and coronary intervention many years ago and more recently vascular surgeons have developed from being exclusively open surgical operators to becoming predominantly endovascular specialists. The trend started in the early 1990s following earlier guidelines the Society of Vascular Surgeons published recommendations on training and credentionaling in 2009 (White et al. 1999). The senior and well-established vascular surgeons had difficulty in making this conversion from open to endovascular but the newer breed with training programmes and simulation models are now achieving 'technical parity' with their IRs as well as dominating the clinical practice. Probably the most important consideration is that whoever does the procedure, they should have a significant commitment and that they do a regular volume of cases.

For a gynaecologist to become a fully established sole operator for UAE, a range of technical knowledge as well as catheter skills need to be established. If a comparison is made with junior radiologists undergoing training in arteriography it is essential that they gain a lot of practical experience in the lab, doing arterial punctures and arteriography, so that they become confident in the performance of these procedures. This should involve assisting radiologists in UAE procedures and gradually undertaking more of the technique so that they can confidently become the sole operator. Taking the model of the junior radiologists in training, it would be necessary to have say two sessions a week for 3 months or so to develop the necessary skills and confidence.

Catheterisation of the uterine arteries can be a straightforward procedure when the anatomy is fairly regular and the arteries are of good size. However, there are difficult cases with variant anatomy and arteries that can prove very difficult to selectively catheterise. Less experienced operators, be they IRs, cardiologists or gynaecologists, are then going to have a higher technical failure rate than the more experienced Interventional Radiologist. In addition, screening times and X-ray doses will be higher in the less experienced and especially for difficult cases. It has been observed that screening times decrease with IRs in training as their exposure to UAE increases. In view of the above, it is difficult to come up with clear-cut credentialing guidelines although the Society of Interventional Radiology in the USA made recommendations back in 2000 (Spies et al. 2001).

One suggestion is that they should be able to complete 50 UAE cases on their own or with very little assistance. Such advices would have to be tempered by the local situation. For example, if UAE was the only reasonable option and there was limited local UAE expertise available, it would be reasonable to proceed with lesser expertise if no other treatment was on offer.

## 5 Who Should Look After Women Immediately After UAE and be Responsible for Their in-Hospital Treatment?

Most operators following UAE will keep women in overnight to have best control of the pain that is part of the post-embolisation syndrome. Clearly, the person carrying out the UAE must be responsible for this in-hospital care. Whether they go on a gynaecological ward or on a more general service does not matter but it is important that the nursing staff looking after these women are familiar with their management and particularly regarding the analgesia and the post-embolisation syndrome. Apart from the post-embolisation syndrome, significant complications following UAE are rare and invariably unrelated to the procedure and due to other medical conditions. In well over a 1,000 women, I have never had to consult a gynaecologist for any problems during their hospital stay.

## 6 In the Event of Early Concerns or Complications (Less than 1 month), Who Shall be Responsible for Their Care?

In the aftercare, after women leave the hospital, it is important that IRs (or Cardiologists) work closely with gynaecological colleagues and that clear-cut responsibilities are established. Soon after women leave the hospital, the most common problem is related to post-procedure pain. Again the IR or other operator is the best position to deal with these issues. When problems occur later on, there are concerns that there could be infection or fibroid expulsion. IRs and cardiologists can give general advice but these women will need clinical/gynaecological assessment, so either they should go direct to the gynaecologist, or the IR should direct them and organise for them to be seen. Generally speaking, as it is rare for gynaecologists to undertake UAE, it is equally rare for IRs to involve themselves in clinical assessment of women; but if they have organised themselves to do this, there is no reason why they should not take full responsibility.

## 7 Who Should See Women for Their Routine Follow-up?

Local conditions and staffing levels will again determine how much routine follow-up is undertaken and who will do it. A minimalist approach as practised with a number of surgical procedures now would be that once a woman has recovered from the procedure she would be only seen in the event of problems or recurrence. The other extreme would be for all women to be routinely seen in a clinic and to have a follow-up MRI study. It can be argued that the doctor who referred the woman for the UAE, be their gynaecologist or a general physician with gynaecological skills is the best person to see women for routine follow-up but this is countered strongly by many IRs and their representative bodies who believe that IRs are not just technicians but clinicians as well. The logistic problem that IRs running clinics present is that unless an IR has very focussed IR activity or there are high IR staffing levels, this presents problems if they want to have clinical involvement in the great range of other IR activity that now exists. An alternative would be to have specialised nurses dealing with these patients so that the gynaecologist/IR would only see cases that presented problems. This effectively would be a multidisciplinary team approach. Most units will not do routine MRI in women post-UAE and will reserve its use for women with no improvement or when complications are considered.

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# Is There a Place for UAE in Adenomyosis?

Paul N. M. Lohle

## Contents




**Abstract**

Adenomyosis is a benign invasion of endometrium into the myometrium that results in a diffusely enlarged uterus that microscopically exhibits ectopic non-neoplastic endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium. This benign disease has either a focal or diffuse distribution in the uterine wall. Between 60 and 80 % of women with adenomyosis have coexisting pelvic localisations of the disease. Adenomyosis may occur alone, but is more frequently accompanied by fibroids in up to 55 % of cases.


## 1 Introduction

Adenomyosis is a benign invasion of endometrium into the myometrium that results in a diffusely enlarged uterus that microscopically exhibits ectopic non-neoplastic endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium (Fig. 1) (Bird et al. 1972; Benagiano and Brosens 2006). This benign disease has either a focal or diffuse distribution in the uterine wall. Between 60 and 80 % of women with adenomyosis have coexisting pelvic localisations of the disease. Adenomyosis may occur alone, but is more frequently accompanied by fibroids in up to 55 % of cases (Fig. 2) (Ferenczy 1998; Vercellini et al. 1993; Siskin et al. 2001).

The clinical diagnosis is challenging, as the presenting symptoms overlap with common uterine disorders such as fibroids of the uterus (Azziz 1989; Vercellini et al. 1993). Adenomyosis is often underdiagnosed and is responsible for disabling symptoms such as in particular heavy menstrual bleeding and pain, with or without bulk related symptoms and fertility issues in premenopausal women (Valentini et al. 2011).

The reported occurrence of adenomyosis varies significantly. The prevalence of adenomyosis in tissues obtained from hysterectomy is reported between 8.8 and 31 % (Benson and Sneeden 1958; Owolabi and Strickler 1977). With broad criteria for the diagnosis of adenomyosis, a


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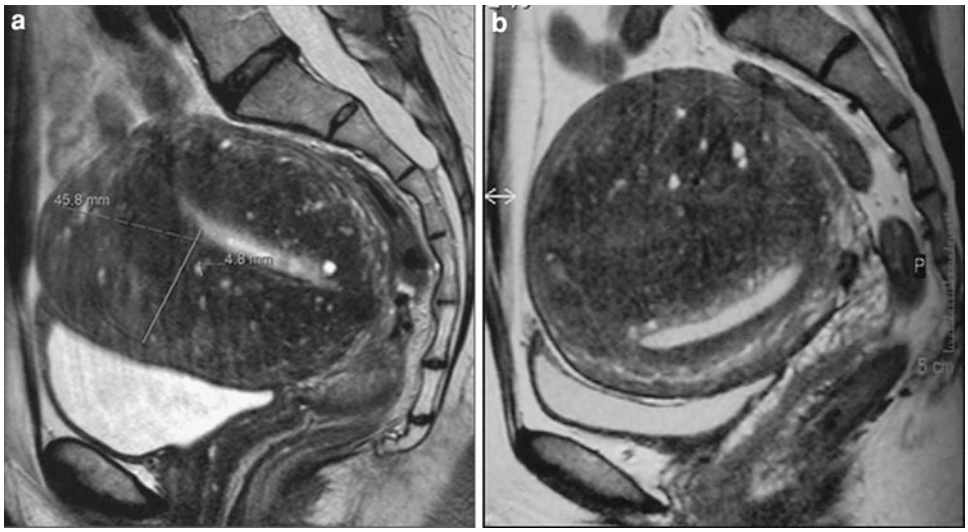


**Fig. 1** Sagittal T2-weighted MRI of diffuse (**a**) and focal (**b**) adenomyosis

prevalence as high as 70 % in women between 40 and 50 years of age is suggested (Azziz 1989). The incidence of adenomyosis in the population at risk is between 8.1 and 16.7 % with clinical manifestations in about two-thirds of women. Of women with clinical manifestations of adenomyosis, about one-fifth are under 40, but the vast majority are between 40 and 50 years. (Utsunomiya et al. 2004; Bergeron et al. 2006; Peric and Fraser 2006). Risk factors for adenomyosis are presumed to be related to reproductive activity (with an increased risk in multiparity, miscarriage, and endometriosis), smoking, Caesarean section, induced abortion or curettage (Vercellini et al. 2006).

## 2 Diagnostic Imaging and Fundamental Radiological Signs

In women with suspected adenomyosis, the first-line imaging technique is usually transvaginal ultrasound (TVUS). TVUS is inexpensive and readily available. Fundamental TVUS signs are (1) increased myometrial echogenicity or linear hyperechoic bands extending deep into the myometrium, indicating the presence of islets of ectopic endometrial tissue, (2) hypoechoic areas in the myometrium compatible with hyperplasia of the muscle tissue surrounding the ectopic tissue, (3) anechoic areas due to glandular dilatation or myometrial cysts, (4) poor definition of the junction zone, and (5) enlargement of the uterus with asymmetrical thickening of one of the walls. The presence of at least three of these signs is highly suggestive of adenomyosis (Dueholm 2006). Sensitivity, specificity and accuracy of TVUS for adenomyosis vary among 80–86, 50–96 and 68–86 %, respectively (Reinhold et al. 1999).

Magnetic resonance imaging (MRI) is particularly useful both in doubtful TVUS cases and in providing a complete evaluation of the disease with its panoramic views. With T2-weighted images and contrast enhanced T1-weighted MRI, the thickness of the junction zone can reliably be measured; a thickness over 12 mm is considered diagnostic for adenomyosis. The presence of foci of high signal intensity within the myometrium constitutes an additional, but not a mandatory criterion (Figs. 1, 3). MRI is a reliable modality for diagnosing adenomyosis, with a sensitivity varying in the literature between 78 and 88 % versus 53 and 89 % for TVUS and a specificity of 67–100 % versus 67–98 % for TVUS (Reinhold et al. 1999; Tamai et al. 2005). MRI can categorise adenomyosis as focal or diffuse and can be repeated in time to evaluate the effect of treatment.

Three different groups of uterine adenomyosis are easily identified with MRI: (1) pure adenomyosis, (2) adenomyosis with fibroid predominance, and (3) uterine fibroids with adenomyosis predominance (Fig. 2). Adenomyosis may be subdivided in diffuse or focal. Focal adenomyosis is also known as adenomyoma. From personal experience, maybe around 80 % of these women have adenomyosis mixed with fibroids, 15 % pure diffuse adenomyosis and 5 % pure focal adenomyosis (adenomyoma).

Adenomyosis with fibroid predominance is defined when fibroids are larger than 5 cm with extensive contact with the uterine cavity (two-thirds of the cavital surface area) and patients presented with dominant bulk symptoms in the presence of adenomyosis. If the combined fibroids were smaller than 5 cm in size and/or covered less than two-thirds of the cavital surface area, these cases were defined as combined disease of predominant adenomyosis (Froeling et al. 2011).

Regarding follow-up after uterine artery embolisation (UAE) for adenomyosis, evolution of symptoms is the most important parameter. In patients with improvement of symptoms and satisfaction with treatment, MRI follow-up may not be necessary as a routine procedure. However, in patients with insufficient clinical response after UAE, MRI can be helpful to compare thickness of the junction zone,

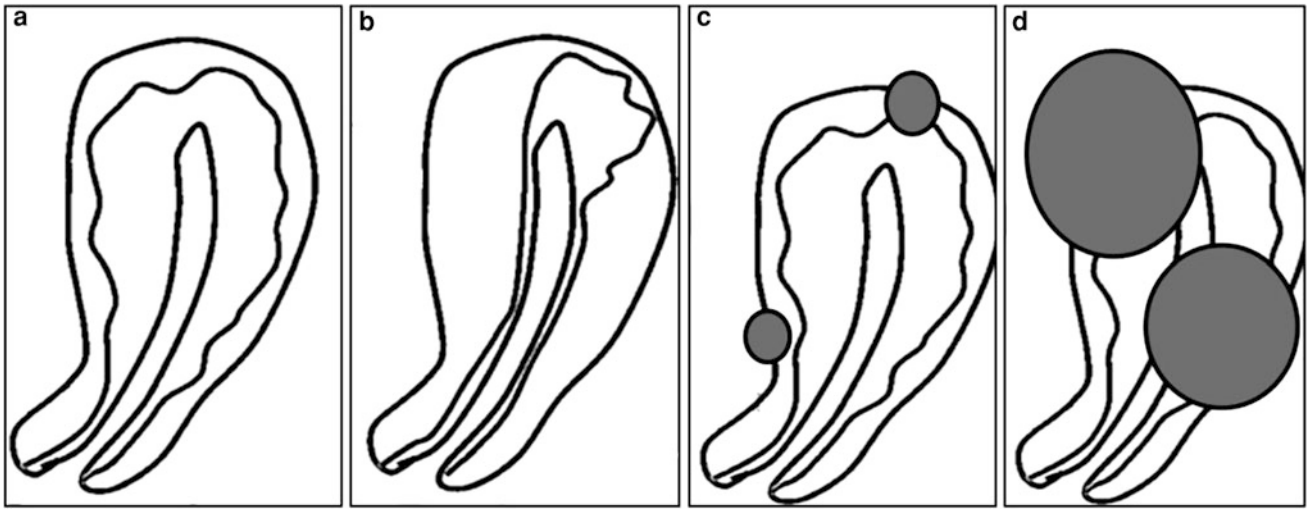


**Fig. 2** Different types of adenomyosis with or without fibroids. **a** Diffuse pure adenomyosis; **b** focal pure adenomyosis (adenomyoma); **c** diffuse adenomyosis dominance with fibroids; **d** diffuse adenomyosis with fibroid dominance

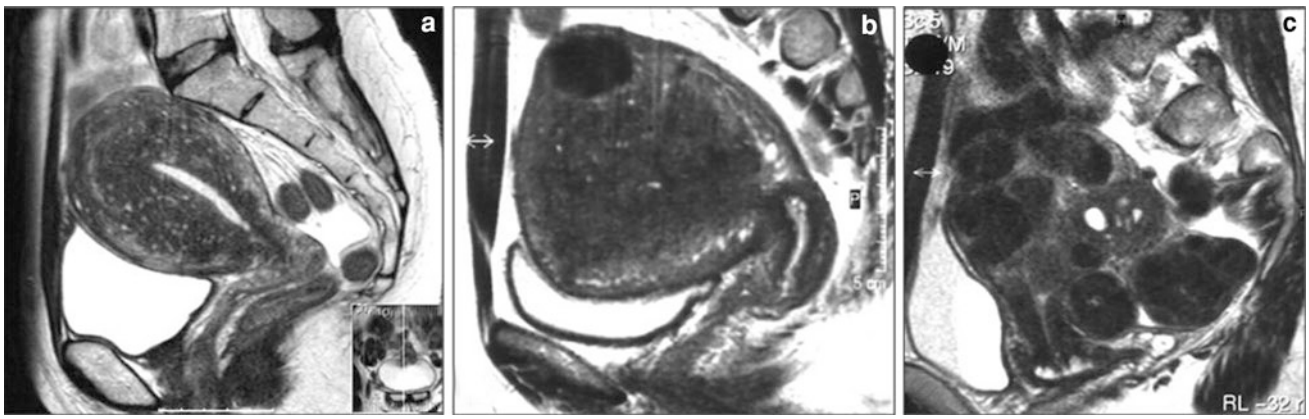


**Fig. 3** Sagittal T2-weighted MRI of different types of adenomyosis. **a** Diffuse pure adenomyosis; **b** adenomyosis dominance with fibroid; **c** adenomyosis with fibroid dominance

the infarction rate, the uterine volume, and other parameters with baseline findings and thus MRI follow-up may guide clinical decision making.

## 3 Treatment Options

### 3.1 Medical Treatment

Medical treatment of adenomyosis ranges from local treatment with the release of medications by a intrauterine device (IUD) to systemically administered treatment.

IUD-released progestogens are used to reduce heavy menstrual bleedings in women with adenomyosis**.** These medications cause the decidualisation of the endometrium and consequently atrophic changes to reduce the amount of bleeding as in women with symptomatic adenomyosis (Fedele et al. 1997).

Medications available for systemic administration include gonadotropin-releasing hormone (GnRH) agonists. Adenomyosis is an oestrogen-dependent disease. GnRH agonists induce menopause by reducing the release of pituitary gonadotropins. The levels of oestrogen are lowered, producing atrophy and reduced volume of the uterus. If the therapy is interrupted, the effect is reversible (Faquhar and Brosens 2006).

### 3.2 Surgery

Excision or enucleation is usually the preferred surgical approach for focal adenomyosis, but the type of treatment is heavily dependent on the type of lesion and the extent of myometrial involvement (Faquhar and Brosens 2006). Hysterectomy is the preferred surgical option for women with

symptomatic adenomyosis if there is deep involvement of the myometrium. In cases of diffuse adenomyosis in which hysterectomy is considered, trans-vaginal access is preferable to trans-abdominal access due to the lower morbidity and shorter hospital stay of the former. Regarding the complications of trans-vaginal hysterectomy, a study on two groups of patients, one with fibroids and the other with adenomyosis reported a higher risk of lesions to the urinary bladder in patients from the latter group (Furuhashy et al. 1998). The reason is probably the greater complexity in identifying the vesico-vaginal septum due to the presence of adhesions. This is explained by the fact that adenomyosis and endometriosis may coexist in the same patient with pelvic adherences very frequently present in the latter (Valentini et al. 2011).

Hysterectomy is usually indicated as a definitive treatment. Rates of complication after hysterectomy range between 1.5 and 29.3 %. Hysterectomy is associated with complications such as blood loss, bowel and general uro-genital injury, pain, and infection. Recovery time is reported to range between 6 and 8 weeks (Faquhar and Brosens 2006; Meyers and Steege 1998; Dembek et al. 2007), and health care-related expenses and lost time at work (Volkers et al. 2008) render hysterectomy an option associated with high costs.

### 3.3 MRI-Guided 'High-Intensity Focused Ultrasound'

MR-HIFU is a new, image-guided, non-invasive technique which enables treatment of tumours by thermoablation by ultrasound waves. The treatment is completely guided by MRI, which offers advantages for therapy planning, monitoring and visualisation of the treatment result. MR-HIFU has a broad spectrum of applications, including ablation of uterine fibroids (Voogt et al. 2011). Most of these applications are still under research. The advantage of the non-invasive character of the treatment is that it can be performed on an outpatient basis and that recovery is fast. MR-HIFU has been used in adenomyosis with varying results. Therefore, although the technique seems to be a useful alternative, further studies are needed to clarify its effective role (Rabinovici and Stewart 2006).

### 3.4 Embolization

In 1995, Ravina published the first report of women treated by uterine artery embolization (UAE) for symptomatic uterine fibroids (Ravina et al. 1995). UAE has emerged as an effective therapy in the treatment of uterine fibroids. The clinical success rate of UAE for uterine fibroids with respect to symptomatic improvement of associated menorrhagia and pelvic pain ranges from 85–95 % to 80–90 % (Katsumori et al. 2007; Goodwin and Spies 2009). There is about 25 % chance of failure of symptom control or recurrence after UAE for uterine fibroids at a 5 year follow-up (Spies et al. 2005a, b; Lohle et al. 2008). This minimally invasive therapeutic alternative to surgery has been reported to be associated with high patient satisfaction rates (Goodwin et al. 1997; Worthington-Kirsch et al. 1998; Spies et al. 2002; Goodwin et al. 2008; Hehenkamp et al. 2008; Hirst et al. 2008).

Based on the similarity of symptoms caused by uterine fibroids and adenomyosis and the positive results after UAE for fibroids, this interventional procedure has been investigated as a possible option to treat adenomyosis. Successful infarction of symptomatic fibroids with UAE may also be achievable in women suffering from focal or diffuse adenomyosis with or without fibroids.

## 4 Embolization in Adenomyosis

Although clinical manifestations of uterine fibroids and uterine adenomyosis are similar, their treatment may differ. In addition to medical treatment, radical, or conservative surgery is well-established treatment options for symptomatic fibroids (Dumousset et al. 2008). Adversely, uterine adenomyosis usually requires hysterectomy because of poor results of hormone treatment or endometrial ablation (McCausland and McCausland 1998).

Embolization of the uterine artery is a therapeutic approach adopted for treating fibroids. Adenomyosis and uterine fibroids may coexist and symptoms can be similar. The interventional treatment accepted for fibroids might therefore be applicable to adenomyosis. Several studies have documented treatment of adenomyosis with UAE (Smith et al. 1999; Goodwin et al. 1999; Spies et al. 1999; Wood 2001; Siskin et al. 2001; Chen et al. 2002; Jha et al. 2003; Toh et al. 2003; Kim et al. 2004; Pelage et al. 2005; Kitamura et al. 2006; Kim et al. 2007; Lohle et al. 2007; Duan et al. 2008; Bratby and Walker 2009; Froeling et al. 2011). Although the first results of UAE for adenomyosis were disappointing, later studies showed substantial clinical improvement in the majority of treated women with adenomyosis. Similar to UAE in fibroids, the targeted embolization with occlusion of uterine artery vessel branches with embolic material will induce cessation of arterial blood flow to the adenomatous tissue. Intentional infarction will eventually result in complete or partial elimination of adenomyotic foci and subsequently relief of symptoms.

### 4.1 Uterine Artery Embolization Procedure

In 1995, the first report was published of women treated by UAE for symptomatic uterine fibroids (Ravina et al. 1995).

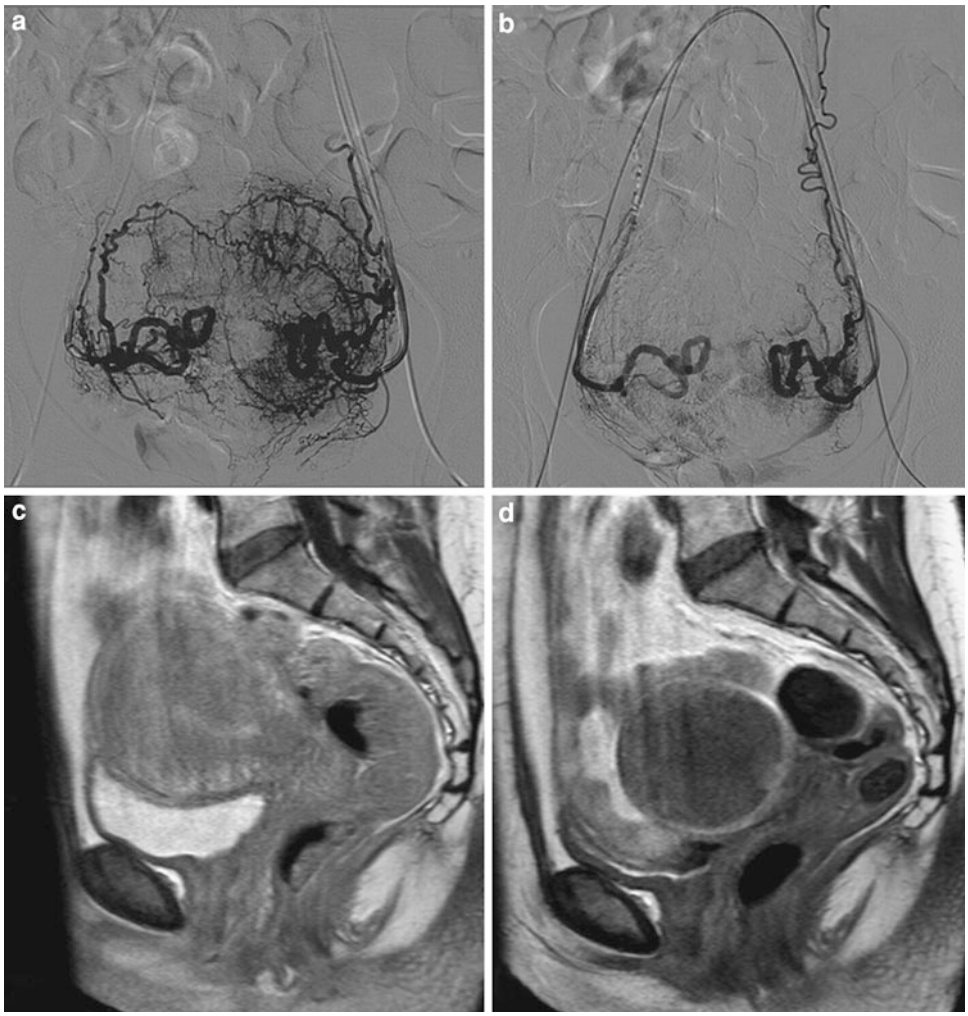


**Fig. 4** UAE in a woman with pure adenomyosis. **a** Frontal angiogram with contrast injection of both uterine arteries demonstrating the vascularization of adenomyosis with deep penetrating parallel arterioles; **b** Frontal angiogram after UAE with the proper embolization end-point; **c** Sagittal contrast enhanced T1 weighted MRI of pure adenomyosis before UAE; **d** Sagittal contrast enhanced T1 weighted MRI 3 months after UAE demonstrating complete infarction of pure adenomyosis with uterine volume reduction

The UAE catheterisation technique for symptomatic adenomyosis is no different from the technique for symptomatic fibroids, apart may be from the angiographic embolization endpoint and maybe the embolic agent particle size. It is reported by some authors that the angiographic embolization endpoint should be when there is complete stasis at the level of the ascending distal part of both uterine arteries in case of adenomyosis (Lohle et al. 2007; Smeets et al. 2011). Embolization is performed by using a particulate embolic agent. The most widely used embolic agent is non-spherical polyvinyl alcohol particles ranging from 255 to 900 microns in size (Popovic et al. 2011). Others prefer the use of spherical embolics, calibrated microspheres, ranged in size from 500 to 700 microns, in order to facilitate deep penetration into the small afferent arterioles of adenomyosis. In contrast to the perifibroid vascularization pattern of uterine fibroids, adenomyosis has a deep and more diffuse distribution of parallel afferent arterioles throughout the myometrium (Dundr et al. 2006). The difference in vascularisation might explain the reported higher failure rate after UAE in women with adenomyosis compared with UAE for fibroids. The currently available data do not seem to indicate a preferred embolic agent for use in women with symptomatic adenomyosis. Although in part based on speculation, to my experience, deep penetration with the embolic agent seems to be needed for optimal infarction of areas with adenomyosis. Calibrated microspheres are able to selectively occlude the tiny arterial branches of the adenomatous tissue deep in the uterine stroma and thus create adequate tissue infarction (Fig. 4). It has been demonstrated that calibrated microspheres have a predictable behaviour. Their uniform size and shape, their constant compressibility and elasticity results in deeper penetration into the small arterioles than non-spherical polyvinyl alcohol particles (Chua et al. 2005; Lohle et al. 2007; Smeets et al. 2011).

My preferred angiographic end-point of embolization in adenomyosis is when there is complete stasis of flow of contrast in the ascending segment of both uterine arteries. The stability of the end-point is regularly checked after 5 min and

additional particles injected if the end-point is not reached. In my experience, the more aggressive way of embolizing until complete stasis in case of adenomyosis (as opposed to fibroids) provides better infarction rates and clinical results. The angiographic end-point of embolization until near stasis seems to be sufficient for symptomatic fibroids (Spies et al. 2005a, b). During and after embolization, intravenous narcotics and non-steroidal anti-inflammatory drugs are administered for adequate pain control (Froeling et al. 2011).

Regarding timing of the UAE procedure, Chen et al. evaluated UAE during the menstrual cycle in terms of differences in treatment efficacy. Patients were scheduled for UAE during the proliferative or luteal phase of menstruation. Their data showed that the difference in timing of UAE did not have a significant effect on efficacy in the treatment of adenomyosis (Chen et al. 2008).

### 4.2 Results of Embolization in Adenomyosis

There are no randomized controlled trials assessing the efficacy of UAE comparing with surgery or other treatment options as a treatment for adenomyosis. A complete and detailed meta-analysis on UAE for the treatment of adenomyosis is published including 15 studies with a total of 511 patients, published between 1999 and 2010 (Popovic et al. 2011). Clinical improvement of bleeding, pain, and bulk-related symptoms were reported by three quarters of included women. The median follow-up was 26.9 months. In this review, a distinction was made between pure adenomyosis and adenomyosis with uterine fibroids and short-, mid- and long term results were described.

### 4.3 UAE Results in Pure Adenomyosis

Short term follow-up after UAE in pure adenomyosis resulted in improvement of symptoms in 83 % of women with a median follow-up of 9.4 months. The uterine volumes decreased by 25–32 %. Mid- and long term results, after a median follow-up of 40.6 months, showed sustained improvement in the vast majority.

### 4.4 UAE Results in Adenomyosis with Fibroids

Short term results in patients with adenomyosis with fibroids demonstrated clinical improvement in 93 % of women with a median follow-up of 10.7 months. Long-term follow-up (34.2 months) showed that 82.4 % of women reported sustained significant improvement of symptoms after UAE.

### 4.5 Additional Therapy and Complications after Embolization

In this meta-analysis, hysterectomy after UAE was needed in 13 % of women with adenomyosis, mostly around 12 months after UAE (Popovic et al. 2011). The risk of permanent amenorrhoea was around 21 %, occurring 3–6 months after UAE. However, permanent amenorrhoea only occurred in women older than 45 years of age at the time of UAE. Most patients experienced some form of mild post-embolization syndrome. There were no deaths or serious adverse events related to UAE for adenomyosis reported. (Siskin et al. 2001; Lohle et al. 2007; Bratby and Walker 2009).

### 4.6 Imaging Findings after UAE in Adenomyosis with or Without Fibroids

MR imaging showed considerable changes after UAE. Uterine volumes and junction zone thickness demonstrated reductions of 27–54 % and 12–24 %, respectively (Siskin et al. 2001; Jha et al. 2003; Kim et al. 2004; Pelage et al. 2005; Kitamura et al. 2006; Lohle et al. 2007; Kim et al. 2007; Bratby and Walker 2009).

Several studies have tried to identify follow-up MRI predictors for good long-term clinical outcome of UAE in patients with symptomatic adenomyosis. Decrease of junction zone thickness, volume decrease of the uterus, and presence of areas of infarction after UAE were inconsistently observed in women both with and without improvement of symptoms (Siskin et al. 2001; Jha et al. 2003; Kitamura et al. 2006; Kim et al. 2007). In one study of 40 patients, the only predictor for hysterectomy during follow-up after UAE was the initial thickness of the junction zone. The women with hysterectomy during follow-up had significantly thicker junction zones compared with the women having clinical improvement both at baseline (mean 23 vs. 16 mm, $P = 0.028$) and at a 3 month follow-up (mean 15 vs. 9 mm, $P = 0.034$). Patients with an initial thick junction zone may be informed about the lower chance of clinical success. The presence or absence of fibroids additional to the adenomyosis had no relation with clinical outcome (Smeets et al. 2011). Interestingly, in another study there was no significant correlation of clinical outcome after UAE and the depth of uterine adenomyosis measured by the junction zone thickness or with respect to the different patterns of uterine adenomyosis such as focal or diffuse at baseline MRI (Froeling et al. 2011). This is partially in line with a third study where no difference in clinical and imaging outcome after UAE was found with respect to the pattern of uterine adenomyosis (Kitamura et al. 2006).

## 5 To conclude

There are many therapeutic options for symptomatic adenomyosis. When medical therapy or endometrial ablation is not sufficient and hysterectomy is not being considered, UAE is an effective and safe alternative for hysterectomy.

During the last decade, the UAE technique has undergone several refinements and extended its application beyond the embolization of fibroids. Now, also patients with pure adenomyosis or adenomyosis with fibroids, are potential candidates for UAE. Clinical and symptomatic improvements have been reported by many studies regarding UAE for adenomyosis. Short-term outcomes for pure adenomyosis and adenomyosis with fibroids range from 83 to 93 %. In the long term, patients report significant improvement in 65 % of pure adenomyosis and in 82 % of adenomyosis with fibroids. UAE has minimal side effects, is cost-effective and preserves fertility. Therefore, UAE is an attractive treatment option, and a valuable alternative to hysterectomy.

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# The Role of Magnetic Resonance Guided Focused Ultrasound for Uterine Fibroids

Anne Roberts

## Contents




**Abstract**

Uterine fibroids are the most common pelvic tumor in women. Fibroids can cause significant bleeding during menses, as well as causing pelvic pressure and pain, urinary frequency, urinary incontinence, constipation, obstetrical complications, and infertility. It has been estimated that 30 % of women with fibroids have significant symptoms. (Flynn et al. 2006) The treatment for fibroids includes: medical therapy (oral contraceptives, GRNH agonists), myomectomy (hysteroscopic, laparoscopic, and open), hysterectomy (laparoscopic/robotic and open), and uterine artery embolization (UAE). Magnetic Resonance Guided Focused Ultrasound (MRgFUS) is being increasingly used for the treatment of uterine fibroids. Combining MR imaging to define the target and to control and monitor the ablation, and an ultrasound transducer that controls and delivers the focused ultrasound beam, MRgFUS allows a non-invasive approach to the treatment of uterine fibroids.


## 1 Introduction

Uterine fibroids are the most common pelvic tumor in women. Fibroids can cause significant bleeding during menses, as well as causing pelvic pressure and pain, urinary frequency, urinary incontinence, constipation, obstetrical complications, and infertility. It has been estimated that 30 % of women with fibroids have significant symptoms (Flynn et al. 2006). The treatment for fibroids includes: medical therapy (oral contraceptives, GRNH agonists), myomectomy (hysteroscopic, laparoscopic, and open), hysterectomy (laparoscopic/robotic and open), and uterine artery embolization (UAE). Magnetic Resonance Guided Focused Ultrasound (MRgFUS) is being increasingly used for the treatment of uterine fibroids. The ExAblate® 2000, (InSightec, Haifa, Israel) received a CE mark in 2002 and


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was approved by the FDA in 2004. A second system, the Sonalleve MR-HIFU system (Philips Medical Systems, Vantaa, Finland), received a CE mark in 2011 and is being marketed in Europe and Asia. It is now in FDA trials in the US for the treatment of uterine fibroids. There is a new ExAblate 2100 system (InSightec, Haifa, Israel) that received a CE mark in 2012. Combining MR imaging to define the target and to control and monitor the ablation, and an ultrasound transducer that controls and delivers the focused ultrasound beam, MRgFUS allows a non-invasive approach to the treatment of uterine fibroids. Given the various alternatives, what is the role of MRgFUS for uterine fibroids?

## 2 Physics Principles of MRgFUS

An understanding of the basic principles of MRgFUS will help in understanding which patients may be candidates for the procedure, and which patients may not be good candidates.

### 2.1 Ultrasound Principles

The goal of MRgFUS is to deliver focused high-energy ultrasound into tissue in order to cause thermal coagulation of the targeted tissue. The ultrasound waves are focused into a beam and multiple beams from the phased array elements are then focused on a particular target. The sound waves pass through the skin and non-target tissue to focus on the designated target and to deliver the energy to that target (Tempany 2007). The principle is similar to focusing the sun's rays by a magnifying glass in order to burn a hole in a piece of paper. In the ExAblate system there is a phased array transducer with 208 array elements that are individually controlled. There is a computer-controlled positioning system, a multichannel radiofrequency amplifier system, and a user interface. These components are integrated with an MR imaging system (standard is 1.5 T, but the system can also be used with a 3 T machine) (McDannold et al. 2006) (Figs. 1 and 2). The volume of ablation after an individual sonication pulse is small; approximately 6 mm × 25 mm, and so multiple consecutive sonications are required to produce a treatment effect (Smart et al. 2006).

The relatively small size of the individual focal points and the cooling intervals required between sonications means that long treatment times are needed to treat fibroids. The Sonalleve system has a phased array 256 channel transducer and the focus of the HIFU beam is electronically steered along a trajectory that comprises multiple outward-moving concentric circles (Kim et al. 2012a, b). This creates a volumetric ablation in which the system can provide four differently sized ellipsoidal treatment cells that are 4, 8, 12, or 16 mm in the axial dimension and 10, 20, 30, or 40 mm in the longitudinal dimension, respectively (Kim et al. 2012a, b). This allows treatment volumes of 0.08, 0.67, 2.26, and 5.36 mL, respectively (Kim et al. 2012a, b). The larger volume of ablated tissue should potentially reduce treatment time. The ExAblate 2100 system allows the transducer to come closer to the abdominal wall, decreasing the energy density on the patient's skin (Trumm et al. 2013). Larger sonication spots (up to 70 mm; previously 45 mm) allow ablation of larger fibroid volumes (Trumm et al. 2013). The maximum energy level of the sonications has also been increased to 7,200 J (Trumm et al. 2013). There is also 3D treatment planning software that helps to reduce total treatment time (Trumm et al. 2013). All of these changes are attempts to increase the speed and effectiveness of the ablation.

The application of high intensity focused ultrasound causes an increase in the temperature of the tissue in the focal area. When the temperature elevation is large enough and maintained for an adequate period, tissue damage will result (Hynynen 2008). To create thermal damage, the exposure of the tissue to a given temperature has to exceed a threshold time. If the temperature/time does not exceed the threshold, the tissue may recover. When the temperature in the target is raised to an appropriate level, protein denaturation occurs, resulting in cell death and creation of a coagulation necrosis. The tissue in the path of the ultrasound beam, away from the focus, is warmed, but only to sub-lethal temperatures (Catane et al. 2007). Although a certain measured energy may be put into a tissue, the temperature elevation is not necessarily the same in all tissues. The type of tissue, the presence of large blood vessels that act as a heat sink, the size, and shape of the ultrasound field all influence the temperature elevation achieved (Hynynen 2008).

### 2.2 MRI Temperature Measurement Principles

MRI has important properties for monitoring the focused ultrasound procedure. MRI has excellent soft-tissue contrast and the ability to provide fast, quantitative temperature imaging in a variety of tissues (Stafford and Hazle 2008). The proton resonance frequency shift (PRF) of water changes in response to changes in temperature (Tempany 2007). For both the ExAblate and Sonalleve equipment, real-time thermal mapping at the target site is achieved using phase imaging on the basis of the shift in PRF caused by temperature rise (Catane et al. 2007; Voogt et al. 2012a, b). Phase-difference fast-spoiled gradient-echo MR imaging, or "phase map" imaging, is performed at the targeted


**Fig. 1** *ExAblate* MRI table. The table will dock with the MRI scanner. The ultrasound transducer can be seen in the *middle* of the table. (Image courtesy of InSightec)

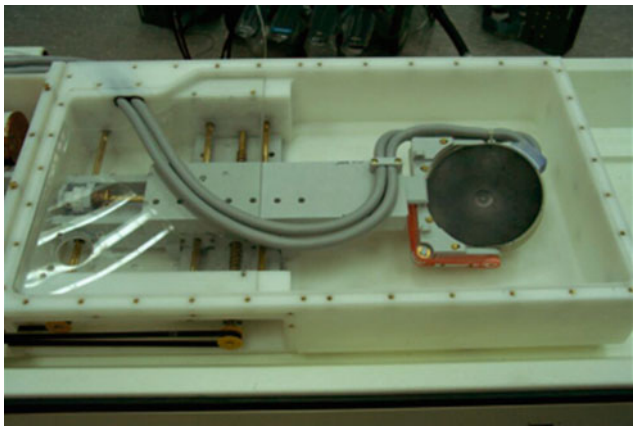

**Fig. 2** The inner workings of the ExAblate equipment that shows the ultrasound transducer connected to cables that help control the positioning of the transducer, (Image courtesy of InSightec)

region before, during, and immediately after sonication (Tempany 2007). These images are used to construct the temperature images acquired during the sonications (McDannold et al. 2006). Those images are automatically compared with a reference image obtained immediately before the sonications to create a real-time thermal map (Catane et al. 2007). The benefit of combining MR with the focused ultrasound treatment is real-time monitoring of the localization of the individual sonications, enabling the measurement of energy deposition and the temperature changes in the region being treated, and feedback on the effectiveness of the sonications (Tempany 2007). The Sonalleve system provides the option of using the online acquired temperature information for automatically controlling the sonication using a thermal feedback method which stops the sonication when the measured thermal ablation and temperature profile match with that intended for the chosen treatment cell (Voogt et al. 2012a, b; Venkatesan et al. 2012).

## 3 Candidates for MR Guided Focused Ultrasound

The patient should have symptoms referable to fibroids and should be prescreened with an MRI. The prescreening MRI should be performed in the prone position, which gives a better idea of the positioning of the uterus/fibroids when the patient is in the treatment position. There should be a limited number of fibroids preferably 1–4 since each of the fibroids will require treatment and large numbers of fibroids will make the time of treatment prohibitive. The size of a single fibroid should usually be under 10 cm and usually more than 900 ml of total fibroid volume is an exclusion. Fibroids that are homogeneous and hypointense (dark) on T2 seem to respond better than fibroids that are heterogeneous and hyperintense (bright) on T2 (Funaki et al. 2007; Tempany 2007). Fibroids should be enhancing since if they have degenerated/infarcted (lost their blood supply) there is no reason to treat them.

Patients cannot have contraindications to MR imaging such as cardiac pacemakers, sensitivity to MR contrast agents, severe claustrophobia, or patients who exceed the size limitation of the MRI scanner. Abdominal scarring (Fig. 3) or bowel loops in the path of the ultrasound beam are contraindications, unless they can be displaced from the beam path; (Yoon et al. 2011) patients with intrauterine device in place should have the IUD removed. The presence of IUDs has been an exclusion criteria. Potentially if the IUD is completely out of the path of the ultrasound beam, it might be possible to treat

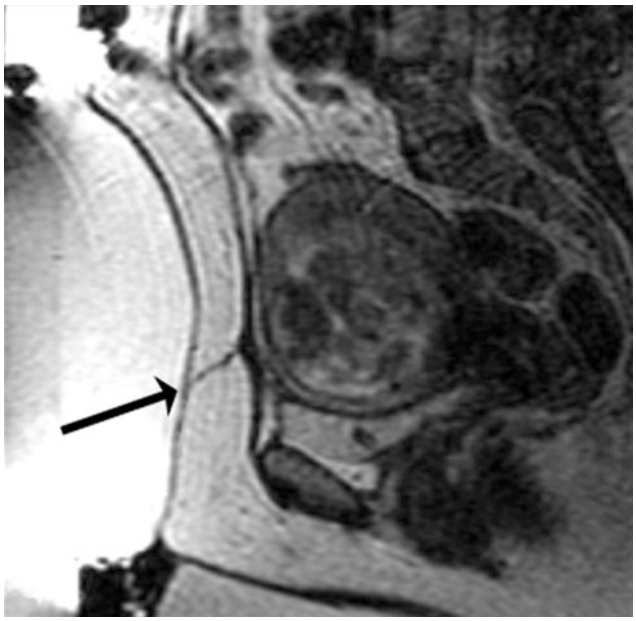

**Fig. 3** Screening MRI demonstrates a scar (*arrow*) from a previous Caesarian section. This scar is directly in the path of the ultrasound beam. Treating in the vicinity of a scar may lead to severe burns and is a contraindication for MRgFUS treatment

the patient. Patients with diffuse adenomyosis and no fibroids probably should not be treated, although treatment of focal adenomyosis/adenomyomas has been described (Rabinovici et al. 2006; Fan et al. 2012; Polina et al. 2012). Patients with both adenomyosis and fibroids should be counseled that although their fibroids may be able to be treated, the adenomyosis may be the cause of symptoms. Obese patients may have so much subcutaneous tissue that the fibroid is largely out of the range of the ultrasound beam. If the fibroid or the majority of the fibroid is beyond the ultrasound's focal distance then an adequate treatment will not be possible.

Patients cannot be pregnant, and should not have any other pelvic pathology (active pelvic inflammatory disease, pelvic carcinoma, undiagnosed vaginal bleeding, etc.) that requires treatment or further investigation. Patients with a history of a prior UAE should be assessed with caution because of concern that interaction between the ultrasound beam and the particles used for UAE may lead to a poor result or potentially cause complications if the beam is scattered by the particles.

Determining the patients who might be candidates for the procedure is somewhat difficult. A number of patients (37 %) who were symptomatic with uterine were excluded because they did not meet the clinical criteria for entrance into a study (Arleo et al. 2007). However, if there are no study criteria to be fulfilled then potentially 100 % of patients could be candidates (Zaher et al. 2009). Not all women, even if they are clinically candidates for the MRgFUS procedure are anatomically suitable for the procedure. Approximately 25 % (Zaher et al. 2009) to 75 % (Stewart et al. 2006; Arleo et al. 2007) of patients clinically eligible are not anatomically eligible. The reasons for exclusion include a high fibroid volume, bowel in the path of the beam, significant adenomyosis, pedunculated fibroids, small or nonexistent fibroids, degenerative or infarcted fibroids, bright T2 weighted fibroids, or arteriovenous malformations, or calcified fibroids (Arleo et al. 2007; Zaher et al. 2009).

## 4 MR Guided Focused Ultrasound Procedure

The MRgFUS procedure is an outpatient procedure. Patients come in early in the morning, and have the procedure and are discharged once they have recovered from their sedation, usually about 30 min after having finished the procedure.

The patient is asked to fast over night, and in some cases when the position of the bowel is considered problematic, the patient maybe asked to follow a low residue diet for a few days prior to the procedure. The skin on the lower abdominal wall from the umbilicus to the pubic symphysis is shaved to prevent any air bubbles being trapped in the hair, which would interfere with the ultrasound beam and potentially increase the risk of skin burns. The skin is cleaned with alcohol to remove any lotion, oils, or powder on the skin that might put the patient at risk for burns. An intravenous catheter is placed so that the patient can be given moderate sedation and any other medications that might be required. A Foley catheter is placed since the patient will be undergoing the procedure for up to 4 h and it is important to be able to keep the bladder empty since filling of the bladder will displace the uterus and change the positioning of the fibroids.

The procedure is performed with the patient lying in a prone position on the treatment table with her pelvis positioned over the transducer. Her abdomen is in a water bath, with degassed deionized water, in contact with an acoustic gel pad (Fig. 4). The patient is positioned with her feet toward the MRI chamber allowing her to look out into the room, which has the benefit of reducing claustrophobia. The patient is usually given conscious sedation to help her relax during the procedure.

The treatment planning begins by obtaining localizer images to determine if the patient is properly positioned with the uterus over the transducer (Fig. 5). The treatment area is defined by the radiologist, and the target volume is analyzed with superimposition of ultrasound beam paths in all three planes (Fig. 6). The energy beam pathway is evaluated to avoid any structures that would be in the path such as bowel, pubic bone, bladder, or nerves. No sonication should be performed within 4 cm of a bony structure in the far field of the beam. The path is also examined to make

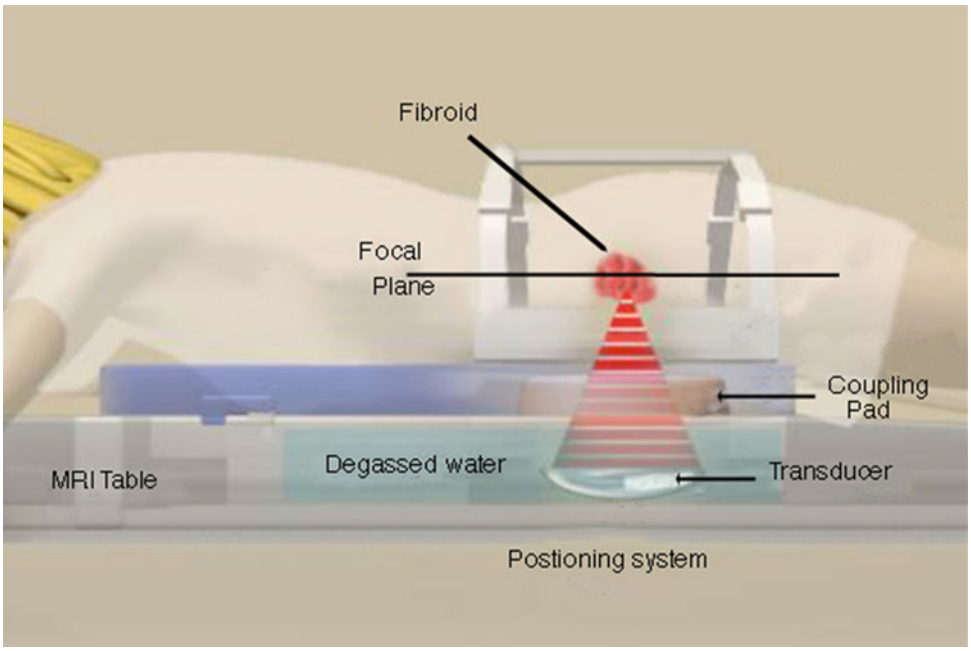


**Fig. 4** Patient in position on the MRgFUS table. She is lying in the water bath on top of an acoustic gel pad that allows good contact between the transducer and the body

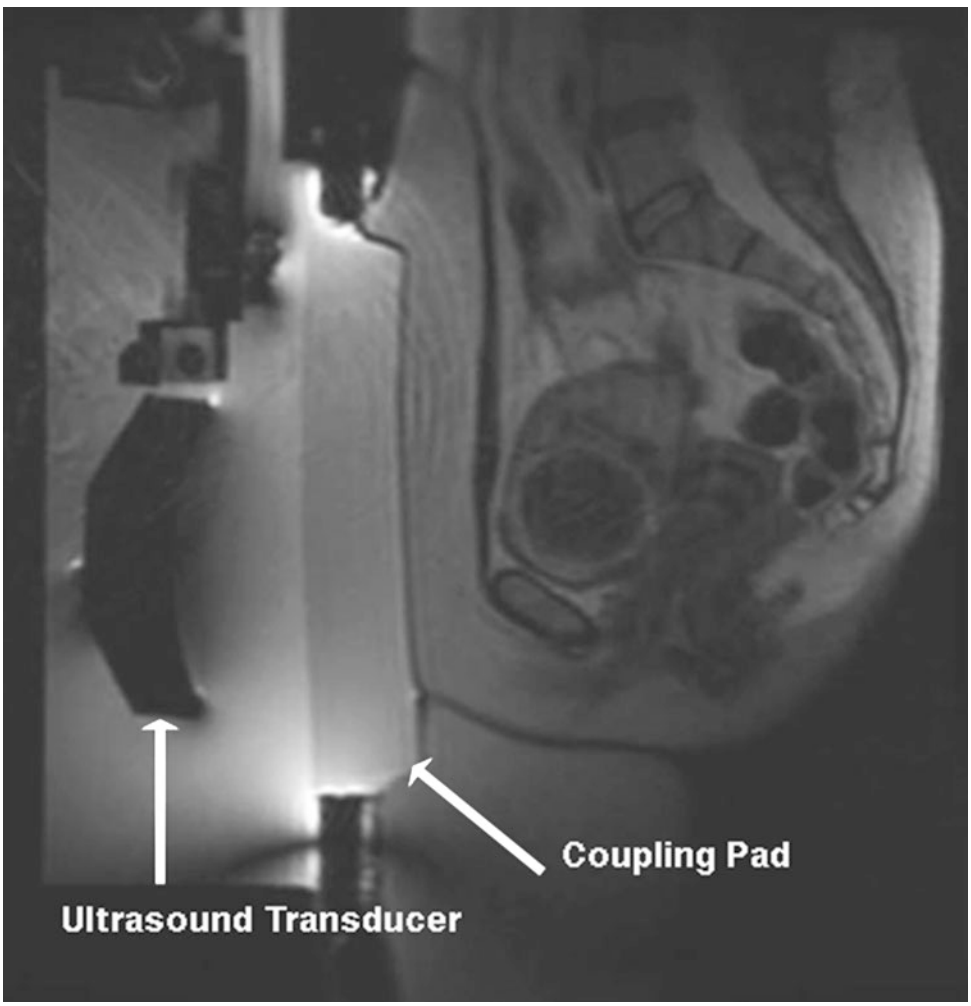


**Fig. 5** A preliminary scan that demonstrates the ultrasound transducer, and the coupling pad. Ideally, the fibroid should be directly opposite the concave portion of the transducer. This positioning is very good

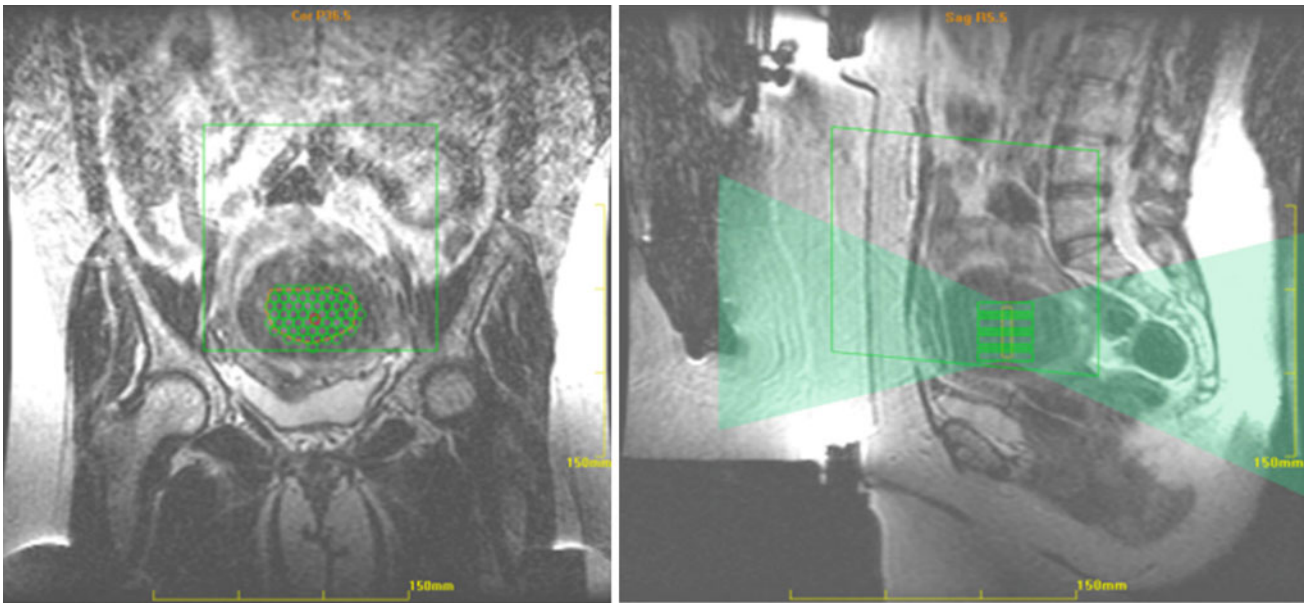


**Fig. 6** The treatment area has been drawn in the center of the fibroid. The small *green circles* within the treatment area define the number and position of proposed sonications. On the sagittal image, the fan of *green* shows the planned sonication beam path. Note that the patient is positioned somewhat below the transducer, ideally she should be moved up slightly to get the fibroid opposite the transducer

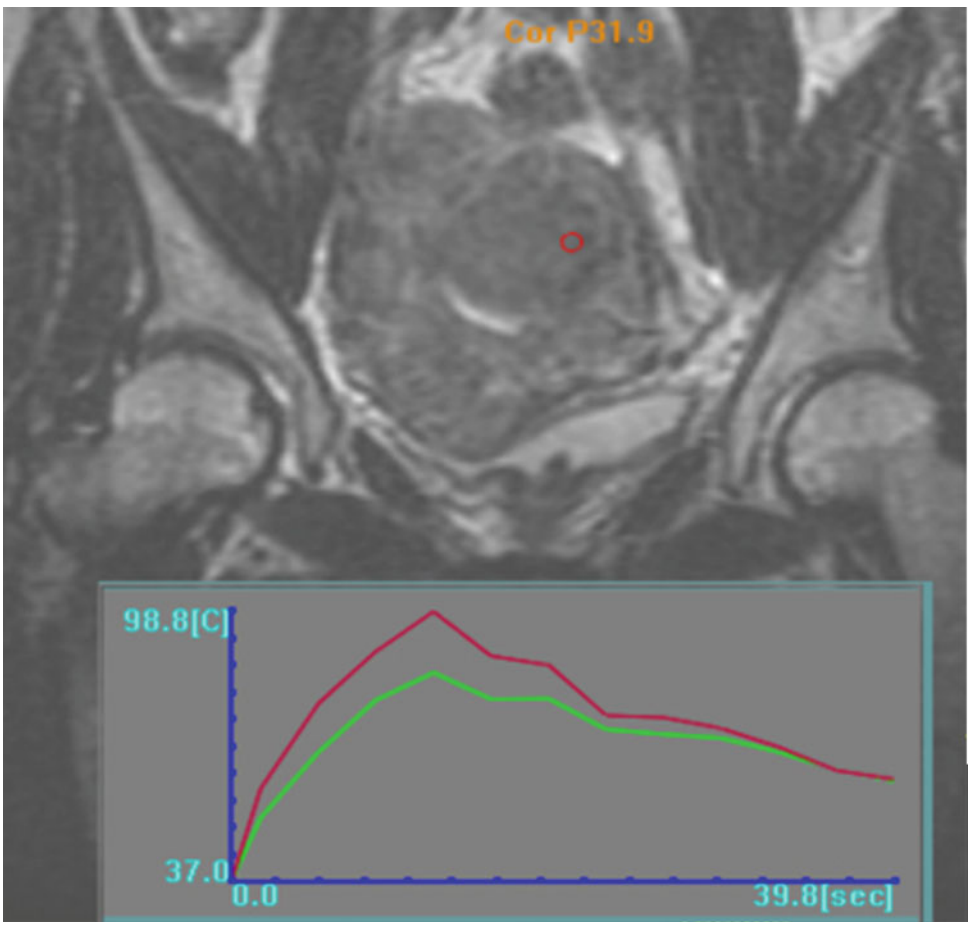


**Fig. 7** The temperature graph of a sonication. The sonication spot is shown as a *red circle* on the fibroid. The superimposed graph show that there was a 40 s sonication that reached a maximum temperature of 98.8 °C. This temperature is somewhat high; ideally the temperature would peak at 70–80 °C

sure that there are no scars, surgical clips, or air bubbles that might cause ultrasound aberrations. The number and position of sonications are planned to encompass the entire target volume. With the Sonalleve equipment the location, size, and number of treatment cells are chosen and positioned on the 3D planning images (Kim et al. 2012a, b). The ultrasound transducer beam can be tilted in multiple directions in order to avoid bowel, pubic bone, or sacrum.

If the fibroid is at the serosal surface of the uterus, a 0.5 cm margin of non-targeted tissue should be maintained. This is to prevent the possibility of thermal damage of tissues in close proximity to the serosal surface of the uterus. If there is bowel anterior to the uterus, positioned between the abdominal wall and the uterus, the bladder can be filled using the Foley catheter, and this will elevate the uterus and may displace the bowel. Depending on the depth of the fibroid, it may be possible to treat through the distended bladder. Otherwise the bladder is emptied, and in some cases the bowel may remain displaced above the uterus allowing the treatment to proceed. If the bowel again moves into a position anterior to the uterus, a rectal tube (barium enema equipment) can be placed and after the bladder is again distended, the colon can be filled with water, which causes the uterus to be shifted anteriorly. Then when the bladder is emptied, the pressure on the uterus by the recto-sigmoid may allow the uterus to push the bowel out of the way.

The patient is given a "panic button" to hold during the treatment that allows her to stop the equipment if she experiences severe pain or heating during the procedure. She is asked to be particularly aware of burning sensation on the abdominal wall, or of pain radiating down her legs. The patient is also made aware that the procedure is not painless. Most patients experience a cramping sensation during each sonication. Some patients have described the sensation as "back labor". Some sonications have more discomfort than others, depending on the area of the fibroid being treated, and depending on the energy, power, spot size, and other parameters (Fig. 7).

Procedure time is variable depending on the size, and number of the fibroids being treated, and also depending on the amount of time needed to position the patient, and potentially to mitigate the position of bowel or scar. Most patients do not tolerate more than about 4 h in the scanner which was the maximum allowed in the clinical trials in the US. Variable times have been reported with procedure times ranging from about 2–7 h with a mean of about 4 h in some recent studies (Trumm et al. 2013; Kim et al. 2012a, b).

Following the treatment, fat-saturated, T1-weighted contrast enhanced images are obtained in the sagittal, coronal, and axial planes to evaluate the extent of the ablated area. The volume of ablated tissue can then be calculated, and a percentage of treated versus non-treated fibroid tissue can be determined (Fig. 8). If there remains a substantial amount of perfused (non-treated) tissue, the patient may undergo a second treatment to try and ablate the remaining viable fibroid tissue.

## 5 Complications

Skin burns may occur from air being trapped between the transducer and the patient's skin, and images should be evaluated carefully for any evidence of bubbles. Such burns are more likely to be small and superficial. Skin burns seem to be most common and most serious when there is an abdominal scar, usually from prior Caesarian section or from laparotomy. Full-thickness skin burns may result and may require excision and closure, or a skin graft. In some cases, the patient may not report pain during the procedure and the lack of pain may be due to denervation of the skin adjacent to the scar (Smart et al. 2006).

Burns of bowel are a serious complication, which would require laparotomy and resection of bowel. It is extremely important to evaluate the space between the abdominal wall and the uterus to make sure that no bowel is trapped in front of the uterus. The bowel lying on top of the uterus is less of a problem since it is visible and the treatment zone can be drawn to avoid the beam traversing this area. During the procedure it is important to evaluate the images to make sure there is no evidence of bowel moving into the field. Particularly in patients who are fidgeting in the scanner, the bowel may shift. If there is any indication of a change in bowel position it may be necessary to rescan the patient to make sure that the treatment path is clear of bowel.

Sciatic nerve damage caused by heating of the bone close to the nerves has been reported and may take months to resolve. One case of DVT in the lower extremity has been reported. Edema in the tissues of the anterior abdominal wall may occur. It can be recognized on the post sonication MRI examination and the patient can be told that she will probably experience a small, tender bump in the soft tissues that will resolve over the next 7–10 days.

## 6 Results

Pelvic pain and pressure symptoms seem to resolve most quickly with most women commenting that the fibroid feels softer and the pressure particularly on the bladder seems decreased. Improvement in menstrual bleeding seems to take longer commonly taking three menstrual cycles before noticing improvement (Hesley et al. 2006). Measurable fibroid shrinkage does not occur immediately and it may be 3–4 months before the patient notices any change in the size of the fibroid.

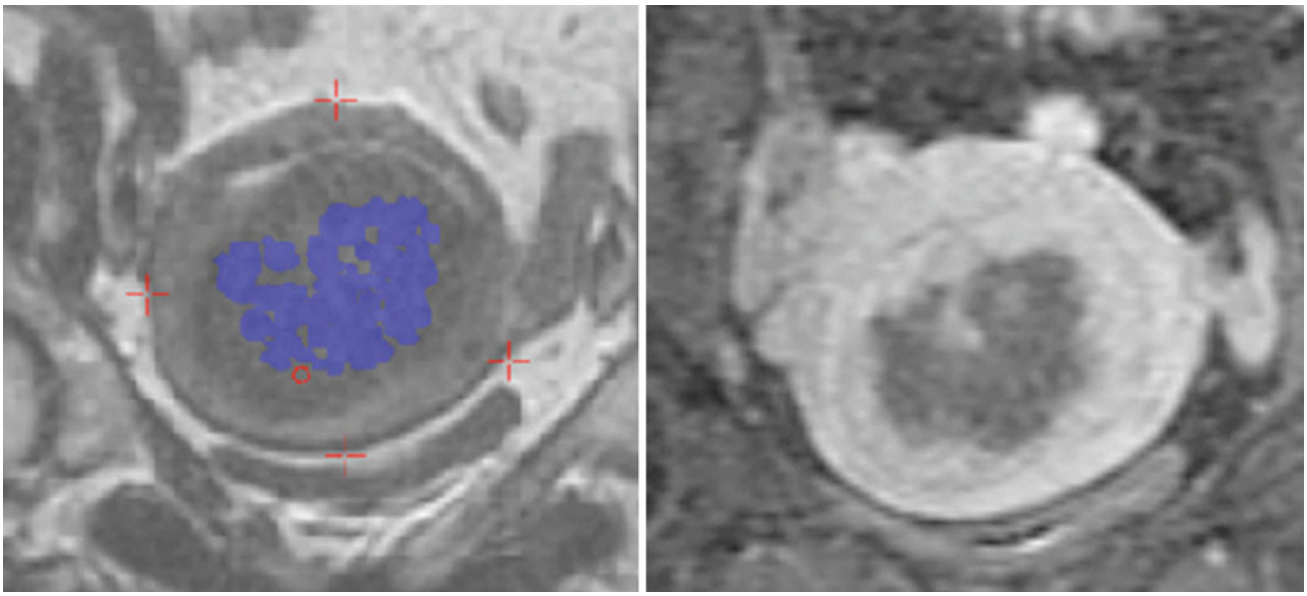

**Fig. 8** The image on the *left* demonstrates the accumulated thermal dose seen represented by the *blue dots*. Ideally these *blue dots* would all be confluent and would cover all of the fibroid. The *red cross marks* represent fiducials that are placed at the beginning to the planning session to help determine if the patient moves. The image on the *right* demonstrates the nonperfused region of treatment effect. The *center* of the fibroid is *dark*, indicating there is no blood flow into this region. The outer area of the fibroid is *white*, indicating continued perfusion

In most treatments, contiguous nonperfused areas are observed. In some cases, the outline of the nonperfused areas match the thermal dose distribution provided by the MR thermal calculations (McDannold et al. 2006). In other cases, the nonperfused area is larger than what is calculated by the thermal dose distribution. The nonperfused area is always within the fibroid (McDannold et al. 2006). The explanation for the increased area of nonperfusion may be related to damage of blood vessels supplying the fibroid. If a large blood vessel carrying blood to the fibroid becomes occluded, then more of the fibroid would be nonperfusing than would be predicted by the thermal dose distribution. A potential treatment strategy is to target the area where vessels enter the fibroid. However, this requires visualizing the blood vessels, which may not always be possible (Voogt et al. 2012a, b).

There is a definite correlation between the volume of thermal ablation created at the time of the treatment and the clinical outcome. The nonperfused tissue volume (NPV) should be as high as possible (>60 %), as there is a close relationship between the NPV and outcomes (Tempany 2007). If patients are stratified by percentage of NPV, there is a marked increase in patients requiring alternative treatment for their fibroids (Olive 2008). If the NPV is greater than 40 %, the percentage of patients having an alternative therapy is 17 %. If the NPV is between 20 and 30 % then 35 % will have alternative therapies, 10–20 % NPV then 44 % had alternative therapies, and if 0–10 % of the fibroid was nonperfused at the end of the treatment then 48 % had alternative therapies (Olive 2008). A mean percent ablation volume of 54 and 51 % for menstrual and bulk-related symptoms seemed to allow alleviation of those symptoms at 12 months, but if only 37 % mean ablation volume reduction was obtained then symptoms were not alleviated at 12 months (Mikami et al. 2008) (Fig. 9).

A study by Funaki et al. (2007) evaluated the signal intensity of the T2-weighted images and the therapeutic results. They categorized the fibroids on the basis of signal intensity as: Type 1, low signal intensity on T2; type 2, intermediate intensity; and type 3, high intensity. The intensities were measured in relationship to the intensity skeletal muscle (type 1), or myometrium with type 2 having an intensity higher than skeletal muscle but lower than the myometrium, and type 3 with a signal intensity equal to or greater than the myometrium (Fig. 10). The type I fibroids had the best results. They also found that the panic button was pushed more frequently in patients with type 3 fibroids than type 1 or type 2. A study by Mikami et al. (2008) also demonstrated a higher technical success (treatment of the planned target zone) in patients with low intensity fibroids when compared to high intensity fibroids (Fig. 11). They also found patients with low intensity fibroids who were technical failures, and all of these women were obese with a subcutaneous and visceral fat tissue thickness of >2 cm.

Studies have primarily been done using the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire. This questionnaire was developed to address menorrhagia, non-bleeding symptoms of fibroids, and to assess the quality of life impact by fibroids (Spies et al. 2002). The average symptom severity score at 24 months

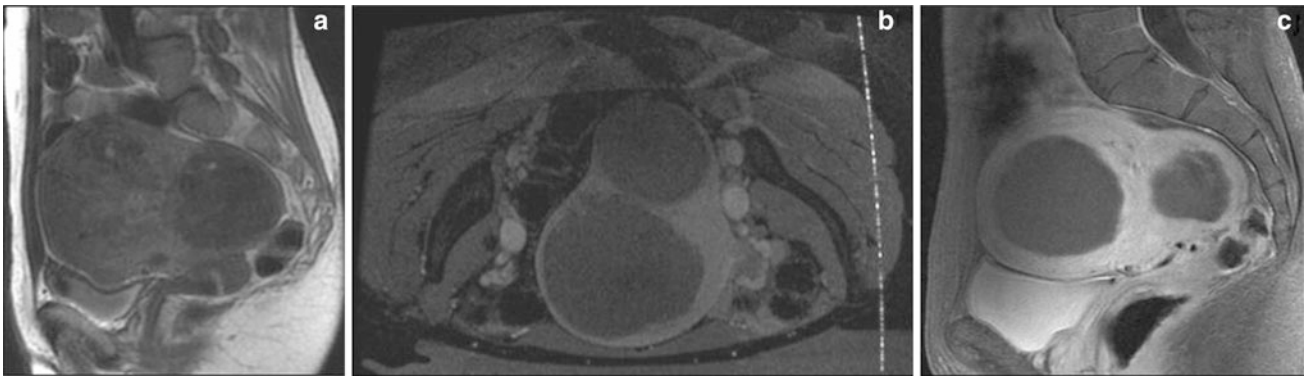


**Fig. 9** **a** Patient with two very large fibroids. The posterior one is hypointense (type 1), the anterior one is slightly more hyperintense (type 2). The total length of the uterus at this point was 14 cm that makes it unlikely that the far portion of the posterior fibroid will be treated since the beam is limited to about 12 cm, **b** fibroids immediately following procedure following the administration of gadolinium. The hypointense posterior fibroid is completely treated and there is almost complete treatment of the anterior fibroid with perhaps some wisps of enhancing tissue along the borders. The patient was treated with 65 sonications and the estimated nonperfused volume was 93 %. This may represent an effect on the fibroid vasculature. **c** At 6-month follow-up there has been a decrease in the size of the fibroids. The patient's bulk symptoms have resolved

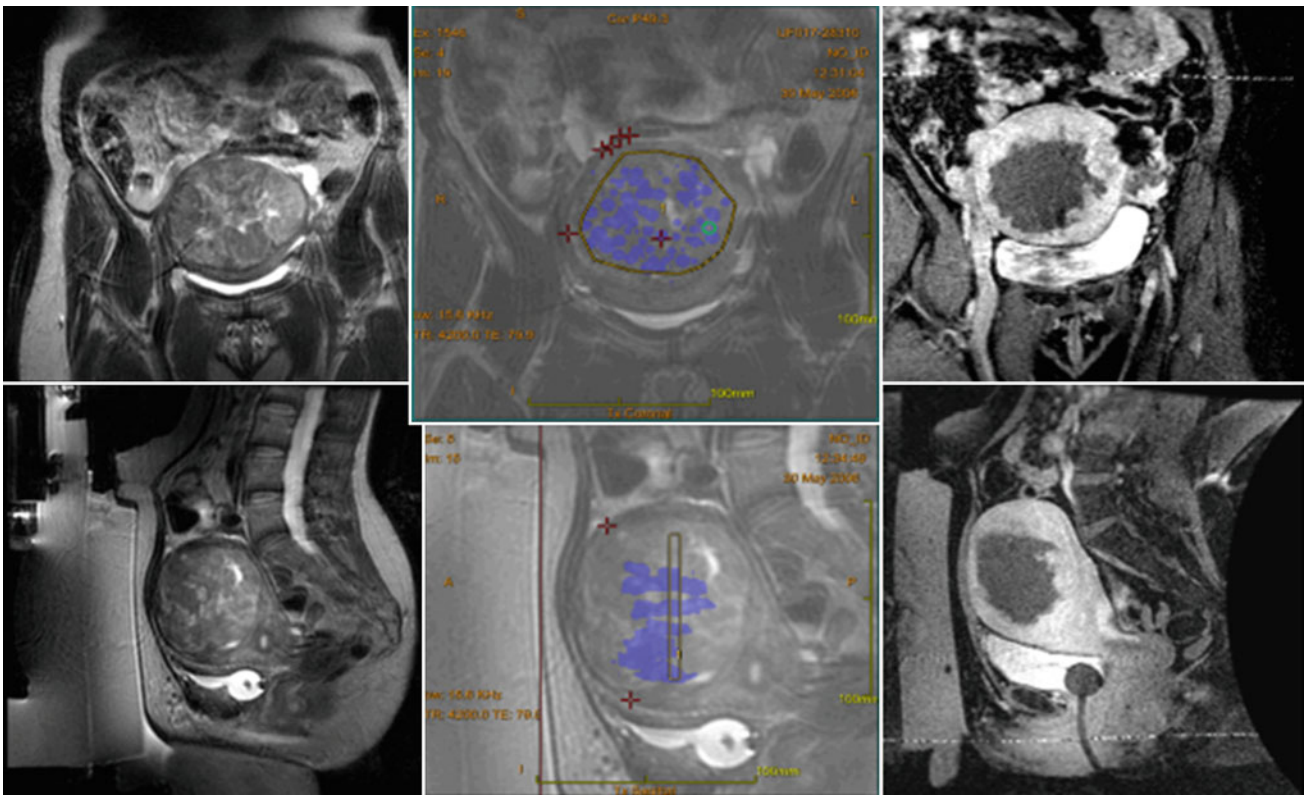

**Fig. 10** A hyperintense fibroid (type 3). The fibroid was treated with 105 sonications. The thermal accumulated dose appears somewhat spotty, although the fibroid appears to have a more homogenous response. The estimated NPV was 70 %

was 31.5 in the >40 % NPV, while it was 57.6 in the group with 0–10 % NPV. The average change in symptom severity score was 31.9 in the >40 % NPV group and 21.4 in the 0–10 % NPV (Spies 2007). This is slightly less favorable than the UAE long-term follow-up from the Fibroid Registry (Goodwin et al. 2008). In that report, the symptom severity score mean was 16.54 and there was a mean improvement at 3 years of 41.41 points in comparison to baseline.

One of the most important concerns regarding MRgFUS is what will happen with areas of the fibroid that continue to have perfusion. It seems clear that few of the treated fibroids are completely infarcted following even a successful

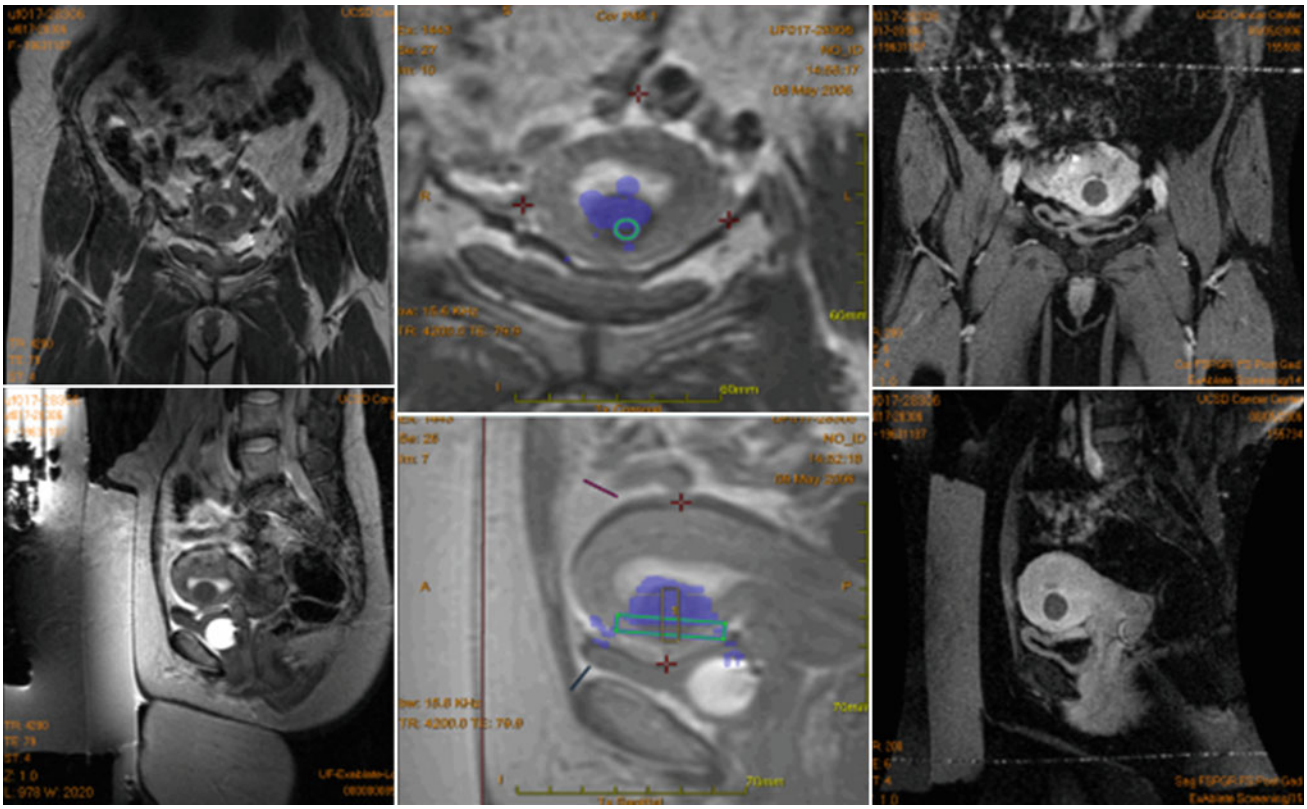

**Fig. 11** A very small submucosal fibroid that was causing a large amount of bleeding. Patient did not want to undergo a hysteroscopic resection although that would probably have been very appropriate. Fibroid was treated with 44 sonications with a complete response. The patient's symptoms completely resolved

procedure. From follow-up studies in the UAE literature it appears that change in volume is not as important over the long term as a change in the perfusion (Pelage et al. 2004). Volume reduction may mask residual viable tissue that is growing, and so the percentage of volume reduction maybe less useful than assessing the perfusion outcome of the fibroids (Pelage et al. 2004). This may lead over time to recurrent fibroid symptoms. One study of patients 3 years after MRgFUS showed a sharp decline in the nonperfused volume during 6 months after MRGFUS and a continued gradual decline over the remaining 3 years (Kim et al. 2011). This would suggest that regrowth of fibroids maybe occurring and this can potentially lead to a recurrence of symptoms. Comprehensive data is still lacking on the long-term durability results for MRgFUS.

## 7 Where Does MRgFUS Fit into the Treatment of Fibroids?

Women with symptomatic fibroids that are few (1–4) in number, and accessible to the ultrasound beam would be potential candidates. The fibroids cannot be too posterior, nor can there be bowel in front of the uterus that cannot be displaced. Ideally, the fibroids would be homogeneously low signal intensity on T2 imaging. The fibroids should not be large (<10 cm) or if large then potentially pretreatment with gonadotrophin-releasing hormone (GnRH) agonists might be attempted. GnRH agonists appear to affect the uterus and myoma volume by the result of decreased levels of estrogen and progesterone, but other mechanisms may be involved, including induction of myoma degeneration and hyaline necrosis, a decrease in the size or number of leiomyoma cells, a reduction in extracellular matrix, or a decrease in blood flow to the uterus (Parker 2007). In a study evaluating GnRH agonists prior to MRgFUS, the GnRH agonist was given as 3 doses, one every 28 days and the MRgFUS was performed 14–21 days following the third injection. This study reported that symptom severity scores markedly decreased (by approximately 65 %) after patients were given GnRH agonists (Smart et al. 2006). Following treatment with MRgFUS, the median symptom severity score at 6 and 12 months was significantly reduced by 45 % and 48 %, respectively (Smart et al. 2006). After three doses of the GnRH agonist the uterine volume had decreased approximately 39 %; after treatment follow-up MRI at 6 and 12 months demonstrated a reduction in volume of the target leiomyoma of 21 % at 6 months, and

37 % at 12 months in comparison to the pre-GnRH fibroid volume (Smart et al. 2006). The GnRH agonists reduce the fibroid size, which decreases the time required to treat the fibroid and may allow more patients to be eligible for the procedure. There may be an additional benefit as the fibroids have decreased blood flow, and this may allow higher temperatures to be produced due to diminished heat conductivity (Smart et al. 2006).

Patients who are interested in future fertility may be candidates for MRgFUS. Insightec has a CE mark for treatment of patients who desire future fertility although with a warning that this should be discussed with their physician. In the US, the FDA instructions to providers states: "Women who are pregnant or desire to become pregnant in the future should not have the ExAblate treatment. Pregnancies following ExAblate could be dangerous for both mother and fetus" (Health 2004). There have been a number of pregnancies reported following MRgFUS. A group of 51 patients with 54 pregnancies demonstrated 41 % of pregnancies resulted in deliveries and ongoing pregnancies in 20 %. Elective pregnancy terminations were 13 % and miscarriages were 26 % (Rabinovici et al. 2010). There have been concerns that UAE might have an effect on the normal myometrium (Rabinovici et al. 2010) and that patients undergoing UAE may have decreased fertility compared to those undergoing myomectomy (Maro et al. 2008).

Although uterine artery embolization procedures are usually very successful, there are a small number of patients who have part of a fibroid, or one of several fibroids that is not completely embolized and continues to demonstrate enhancement. Such fibroids will continue to grow, even as the devascularized portion disappears, the vascularized portion will gradually reconstitute the fibroid (Pelage et al. 2004). Usually, the residual areas of perfusion are relatively small and if in an area where focused ultrasound could be performed then a relatively short procedure might allow for complete infarction of the fibroid. The primary question that is unanswered is what effect focused ultrasound might have on the embolic particles, and conversely what effect the particles might have on the ultrasound energy. These interactions should be studied in an animal model, and then if there seems to be minimal effect, a study on human patients should be performed.

The cost of the MRgFUS is a difficult calculation. It is largely determined by the cost of the MRgFUS machine (about 1 million US dollars) and then the cost of the MRI room time. The use of MRI room time has been a considerable drawback to the widespread acceptance of MRgFUS. Tying up an MRI scanner for 4–5 h is a problem for many centers. If one considers how many brain, spines, knee, etc. scans can be done in 4–5 h and calculates the income lost by using the equipment for MRgFUS, the potential room charges for the procedure are very high. This is very dependent on individual practices since the MR capacity maybe highly variable by region. There is no hospitalization following the procedure, and there is a rapid return to normal activities which helps to decrease the overall costs of treatment.

MRgFUS is now approved in the US for treatment of pain from metastatic bone lesions. It is also being developed for use in other organ systems such as the brain—for treatment of tumors and essential tremor, prostate, breast, liver, and renal tumors.

It seems reasonable now that MRgFUS has progressed and the technique is more standardized that control trials between various treatments for uterine fibroids would be appropriate. This would certainly help answer the question of where MRgFUS fits in the minimally invasive treatment of fibroids. One of the most critical is a randomized comparison with UAE. Such a trial, *Fibroid Interventions: Reducing Symptoms Today and Tomorrow* (FIRSTT) has been proposed and is enrolling patients at the Mayo Clinic and Duke University (Bouwsma et al. 2011). More trials of this type should be performed.

MRgFUS is an evolving technique and is likely to continue to play an increasing role in the treatment of fibroid disease.

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# Part II

# Bleeding in Obstetrics

# Obstetric Management of Postpartum Haemorrhage

Millicent Nwandison and Susan Bewley

## Contents




**Abstract**

Obstetric haemorrhage remains the leading cause of maternal mortality and morbidity worldwide, but deaths are rare in developed countries. The use of interventional radiology over the last 30 years has changed from a novel technique in specialised centres to become a viable management option in the control of massive haemorrhage both before and after hysterectomy. This chapter covers the management of postpartum haemorrhage and the role of interventional radiology.


## 1 Introduction

Worldwide it has been estimated that 358,000 maternal deaths occurred in 2008 (WHO, UNICEF, UNFPA and The World Bank publication 2012, http://whqlibdoc.who.int/publications/2010/9789241500265_eng.pdf; http://www.childinfo.org/maternal_mortality.html), with developing countries accounting for 99 % of cases. Haemorrhage remains the leading cause of maternal mortality, accounting for approximately one-third of deaths. The presence of skilled birth personnel with appropriate training and skills has continued to be identified as key to preventing and reducing maternal deaths worldwide.

Haemorrhage itself is common in both the developed and developing countries, it is the success in saving lives that varies. In the United Kingdom, obstetric haemorrhage was identified as the sixth most common cause of direct maternal death in the most recent Confidential Enquiry into Maternal Deaths (CMACE 2011). In the triennium 2006–2008, 261 women in the UK died directly or indirectly related to pregnancy. Nine out of the total of 107 direct deaths (8.4 %) were attributable to haemorrhage. Six of the nine women (67 %) received substandard care in their management and four of the nine women (44 %) had received major substandard care contributing significantly


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to the death. Even though this was a reduction since the previous triennium, when haemorrhage was the third commonest direct cause of maternal death, the conclusions drawn from both reports highlight that substandard care remains a significant contributor to the fatalities which could have been avoided. It is a condition with a very high number of 'near-misses' per death, with one maternal death occurring out of 150 estimated yearly performed peripartum hysterectomies (Knight 2007).

The stark contrast between countries such as the UK where death is largely successfully avoided to developing countries where little or no skilled care contributes to maternal death from haemorrhage should prompt all clinicians involved in maternity care to strive to eradicate death from haemorrhage in all countries.

## 2 Physiological Changes in Pregnancy

Maternal plasma volume increases from about 2.6 L when non-pregnant to 3.8 L at birth. This increase is achieved in early pregnancy and remains constant. The red cell mass increases steadily throughout the pregnancy, however, with the disproportionate increase in plasma volume compared to red cell mass a relative 'physiological anaemia' results. Iron supplementation can increase the red cell mass and correct anaemia. Anaemia is undesirable at delivery as it is thought to be a risk factor for haemorrhage and certainly compromises the maternal response.

Cardiac output increases in early pregnancy by about 40 % from about 4.5 to 6 L/min and this is maintained until birth. By term, this results in blood flow of about 500 mL/min to the expanding uterus. The lumen of the spiral arteries expands to accommodate this increased blood flow and the result is a reduced pressure in the arterial blood flow to the placenta. After birth and placental separation, this increased blood flow has to be cut off within seconds or else haemorrhage ensues. Blood loss up to 500 mL after delivery is regarded as physiologically normal. It is part of the normal mechanism that returns the mother's blood and circulatory parameters to their normal non pregnant levels. Healthy pregnant women can cope with this loss without difficulty.

Myometrial contraction is the main driving force, both for placental separation and haemostasis through constriction of the spiral arteries. The physiological increase in the clotting factors VII, VIII, X and fibrinogen in pregnancy and during labour promotes deposition of a fibrin matrix over the placental bed vasculature which promotes haemostasis after placental separation.

**Table 1** Risk factors for post-partum haemorrhage (Adapted from Royal College of Obstetricians and Gynaecologists 2009)

| | |
|---|---|
| Antenatal factors | Previous PPH |
| | Previous caesarean delivery |
| | Age > 40 years |
| | Obesity BMI > 30 |
| | Multiple pregnancy |
| | Fibroid uterus |
| | Anaemia (Hb < 9 g/dl) |
| | Antepartum haemorrhage |
| | Polyhydramnios |
| | Preeclampsia/eclampsia |
| | Pregnancy induced hypertension |
| | Abnormal placental localisation (praevia and accreta) |
| | Baby > 4 kg in current pregnancy |
| Intrapartum factors | Induction of labour |
| | Pyrexia in labour |
| | Preeclampsia/eclampsia |
| | Prolonged first stage of labour >12 h |
| | Uterine hyperstimulation |
| | Prolonged second stage of labour (>2 h in a primpara and >1 h in a multipara) |
| | Episiotomy |
| | Instrumental delivery |
| | Caesarean delivery |

## 3 Postpartum Haemorrhage

Primary postpartum haemorrhage (PPH) is defined as bleeding of 500 mL or more from the genital tract in the first 24 h after birth. Secondary postpartum haemorrhage is the loss of blood between 24 h and 12 weeks post delivery.

Primary and secondary PPHs can further be defined by severity, i.e. minor or major though no formal internationally recognised definitions exist. Larger PPHs have been variously called moderate, major, severe or massive. Different publications use different thresholds for these haemorrhages depending on purpose (e.g. >1.5 L, >2 L, >2.5 L, etc.). In practice, however, whether primary or secondary, the volume of blood loss that causes cardiovascular instability or morbidity in a woman is variable.

The majority of PPHs are unpredictable but the presence of risk factors increases the likelihood (Table 1). Preventive measures should be implemented to minimise maternal morbidity and avoidance of a fatality. These measures may include correction of anaemia in the antenatal period,

advising delivery in a consultant-led unit, active third stage management (Begley et al. 2011), additional use of oxytocinon infusion and multidisciplinary team delivery (Mousa and Alfirevic 2007).

## 4 Management of Postpartum Haemorrhage

Once excessive bleeding is recognised, management of the woman involves several parallel components: stopping the bleeding (depending on cause), fluid resuscitation and communication with relevant senior obstetric, anaesthetic and haematological teams as well as the patient and her family. Resuscitation of the patient with fluids, blood and blood products is indicated primarily on clinical signs and symptoms as well as on coagulation results. This takes place simultaneously with trying to identify and arrest the cause of the bleeding (Table 2). The most common cause of primary PPH is uterine atony, but other causes such as retained placental tissue, uterine rupture, uterine inversion, vaginal or cervical lacerations, abnormal placentation or haematomas or extra-genital bleeding must also be considered and excluded. So traditionally, the causes for postpartum haemorrhage usually relate to one of the 'four Ts': Tone, Tissue, Trauma and Thrombin.

When haemorrhage continues then second-line therapies must be initiated as simultaneous resuscitation of the patient continues. Second-line therapies encompass a number of surgical measures as outlined in Table 2.

At laparotomy, surgical interventions include compression sutures, ligation of the internal iliac vessels and hysterectomy. The recourse to emergency hysterectomy is not a decision that is made lightly as it removes future childbearing possibility. However, it must not be delayed; this is a common criticism in mortalities. The decision is usually made as a life-saving measure and in conjunction with another senior obstetric or gynecological colleague and the procedure is often performed jointly.

**Table 2** Management of primary PPH (Adapted from Royal College of Obstetricians and Gynaecologists 2009)

| | |
|---|---|
| Mechanical measures | Rub up a contraction |
| | Empty the bladder by insertion of urinary catheter |
| | Examine the vagina to exclude vaginal and cervical lacerations |
| | Bimanual uterine compression |
| | Evacuation of the uterus (manual removal of placenta, examination under anaesthetic or evacuation of retained products) |
| Pharmacological measures | Oxytocinon 5 units by slow i.v. injection |
| | Ergometrine 0.5 mg by slow i.v. or i.m. injection (contra indicated in women with hypertension unless exsanguinating) |
| | Oxytocinon infusion |
| | Carboprost 0.25 mg by i.m. injection repeated at 15 min intervals up to eight doses (contraindicated in women with asthma unless exsanguinating) |
| | Misoprostol 1000 mcg rectally |
| | Tranexamic acid |
| | Recombinant factor VIIa |
| Surgical measures | Repair of perineal or vaginal trauma |
| | Control of surgical bleeding at caesarean |
| | Intrauterine balloon tamponade |
| | Haemostatic brace sutures |
| | Bilateral ligation of uterine arteries |
| | Bilateral ligation of internal (hypogastric) arteries |
| | Selective arterial embolisation |
| | Hysterectomy—must be considered early once surgical measures started |

*i.v.* intravenous, *i.m.* intramuscular

### 4.1 Tamponade Techniques

One of the first, and technically easiest, second-line measures to control bleeding from an atonic uterus is insertion of a hydrostatic uterine balloon catheter into the uterine cavity followed by inflation of the balloon with 300–500 mL of saline to exert a tamponade effect on the uteroplacental vessels. In modern obstetric practice, this has superseded the previous method of packing the uterus with large gauze swabs. Various catheter devices exist e.g. Sengstaken–Blakemore oesophageal catheter, Rusch and Bakri balloon catheters. Various authors have reported success in stopping PPH and thus averting a hysterectomy. The general success rate is around 78 % (Royal College of Obstetricians and Gynaecologists 2009).

### 4.2 Uterine Compression Sutures

Figures 1, 2 and 3 show various compression sutures. The brace compression suture was first described by B-Lynch et al. (1997). The technique requires laparotomy and a bimanual compression test performed prior to its insertion. If the compression test is ineffective in reducing bleeding then the B-Lynch suture is unlikely to be successful. The principle of action is that the suture exerts a direct compression effect on the myometrium to promote uterine tone without interfering with the uterine blood supply. Since 2007, several other variations of uterine compression suture techniques have been described such as the Cho square

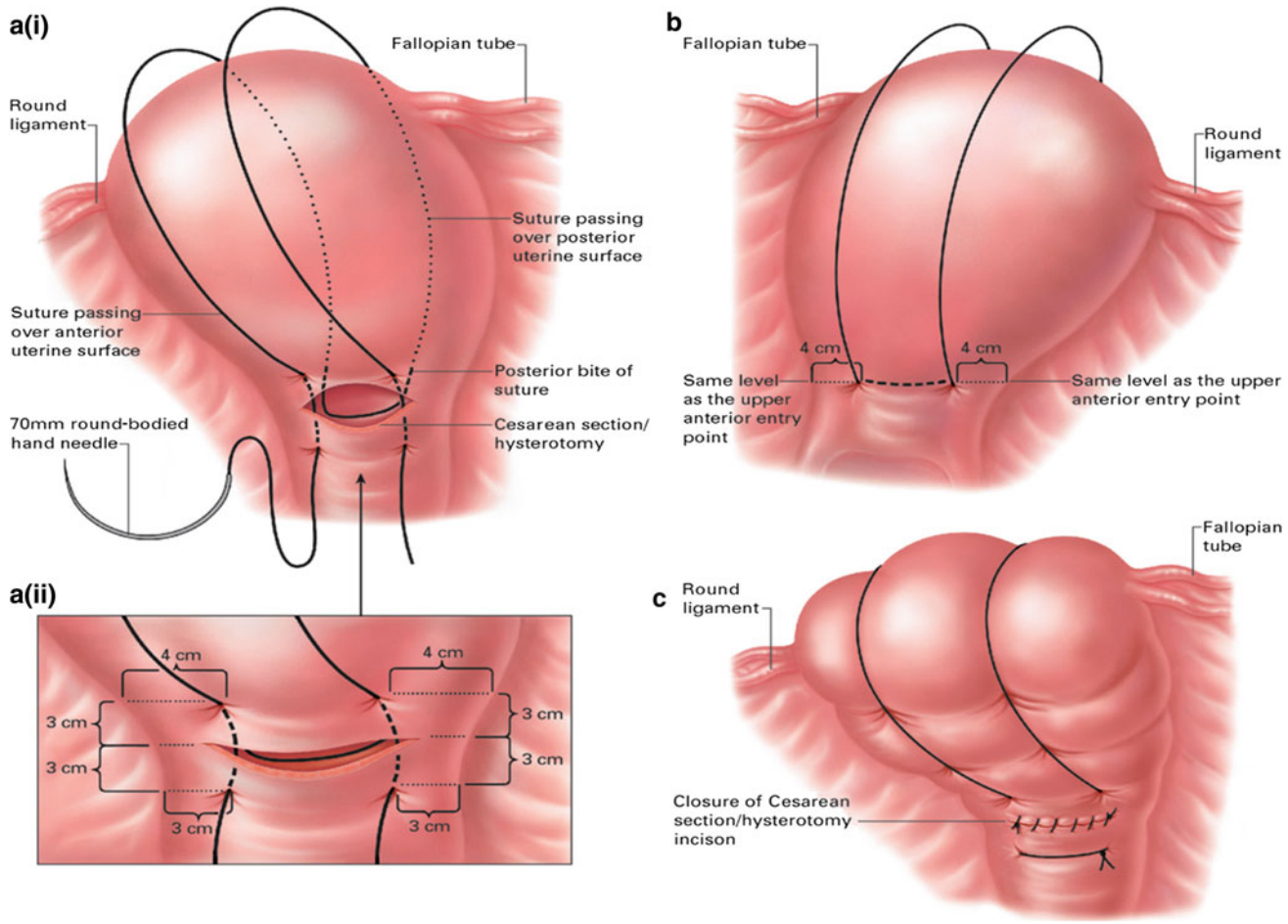


**Fig. 1** The B-Lynch Suture. Figure reproduced from A Textbook of Postpartum Haemorrhage, a comprehensive guide to evaluation, management and surgical intervention. Edited by Christopher B-Lynch FRCS, FRCOG, D. Univ., Louis Keith MD, PhD Andre Lalonde MD, FRCSC, FRCOG and Mahantesh Karoshi MBBS, MD. www.glowm.com/pdf/PPH_2nd_edn_Chap-51.pdf

sutures, the Hayman suture and the Pereira suture (Cho et al. 2000; Hayman et al. 2002; Bhal et al. 2005; Pereira et al. 2005; Nelson and Birch 2006; Ouahba et al. 2007). A 91.7 % cumulative success rate in controlling PPH has been reported for a combination of the various techniques (Doumouchtsis et al. 2007).

Advantages of uterine compression sutures include simplicity in application, short operating time (5–15 min), but importantly preserving the uterus and the possibility of a future pregnancy. Complications are few, but may arise immediately postoperatively or up to 2 years. There have been no reported deaths arising from complications, but case reports included pyometra, ischaemic uterine necrosis, uterine suture erosion and uterine synechiae, with acute or chronic inflammation and uterine necrosis being the most widely reported complications. Cases of successful pregnancies without any significant complications for mother and baby have been reported in the literature. The time of subsequent conception varies from 3 months to 3 years. No cases of subfertility requiring assisted conception have been reported (Fotopoulou and Dudenhausen 2010; Mallappa Saaroja et al. 2010).

## 4.3 Internal Iliac Artery Ligation

The traditional surgical means of uterine conservation is step-wise devascularisation of the blood supply to the uterus. The uterine vessels and/or the ovarian vessels may be ligated if the operator is confident that ligating that branch alone will stop the haemorrhage, but this is unlikely given the substantial collateral pelvic circulation. Thus, bilateral ligation of the internal iliac arteries is performed, as it has been shown to significantly reduce the pelvic pulse pressure and facilitate haemostasis. Substantial collateral pelvic circulation means that blood supply to the pelvic viscera is not compromised.

The technique of internal iliac artery ligation involves identifying the bifurcation of the common iliac artery, where it is crossed by the ureter. A longitudinal 4–5 cm

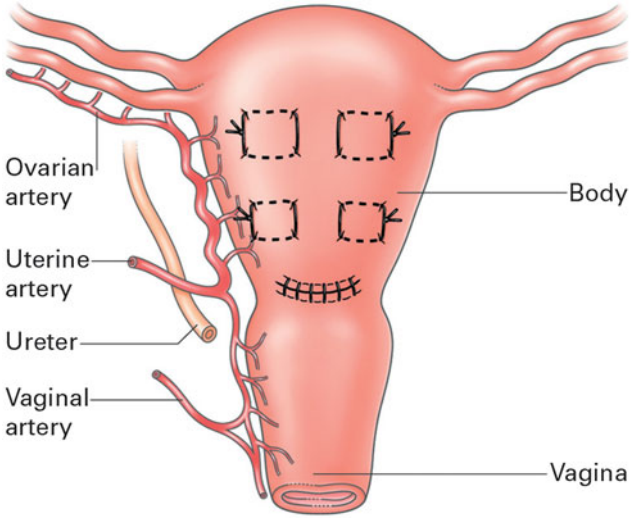


**Fig. 2** The Cho multiple square sutures—compressing anterior to posterior uterine walls. Figure reproduced from A Textbook of Postpartum Haemorrhage, a comprehensive guide to evaluation, management and surgical intervention. Edited by Christopher B-Lynch FRCS, FRCOG, D. Univ., Louis Keith MD, PhD Andre Lalonde MD, FRCSC, FRCOG and Mahantesh Karoshi MBBS, MD. www.glowm.com/pdf/PPH_2nd_edn_Chap-51.pdf

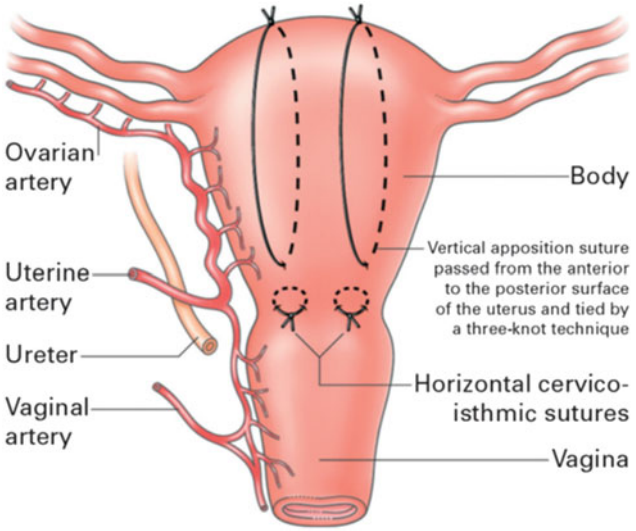


**Fig. 3** The Hayman uterine compression suture. Figure reproduced from A Textbook of Postpartum Haemorrhage, a comprehensive guide to evaluation, management and surgical intervention. Edited by Christopher B-Lynch FRCS, FRCOG, D. Univ., Louis Keith MD, PhD Andre Lalonde MD, FRCSC, FRCOG and Mahantesh Karoshi MBBS, MD. www.glowm.com/pdf/PPH_2nd_edn_Chap-51.pdf

incision is made in the pelvic peritoneum at the level of the bifurcation of the common iliac artery, inferior and lateral to the ureter. The internal iliac artery is ligated 2.5 cm distal to the bifurcation of the internal and external iliac artery. This brief description of the procedure illustrates the potential risks associated with this technique especially to the unfamiliar operator. The procedure carries risk of traumatising the internal iliac veins and worsening bleeding, injury to the ureters, misidentification of the internal iliac artery for the external iliac artery and prolonged operating time due to the attention in separating tissue planes. Obstetricians are becoming unfamiliar with this technique due to reductions in major gynaecological operating and subspecialisation, so the assistance of an experienced colleague, gynaecologist, gynaeoncologist or vascular surgeon should be readily sought.

To date Palacios-Jaraquemdad's (2011) paper is one of the few that compares bilateral uterine artery ligation against other uterine compression sutures. This single author review describes a decade of 539 personal cases of bilateral uterine artery ligation (BUAL), B-Lynch, Cho, Hayman or Pereira sutures in 13 hospitals in Buenos Aires with a success rate of 93 %. In stopping haemorrhage secondary to uterine atony, the author demonstrated the efficacy of BUAL was 84 %, but 95 % in combination with the other compression sutures. The author comments on the low to mid difficulty of performing BUAL, which is in keeping with other reports by experienced operators. Regardless, the additional information that compression sutures are significantly more efficacious supports the literature suggesting that this should be the first line surgical intervention when medical management has failed. Few complications have been reported from BUAL and there have been reports of successful pregnancies afterwards (Joshi et al. 2007; Nizard et al. 2003). However, BUAL also largely precludes subsequent radiological intervention and this is also why it is falling out of favour in the modern era.

## 5 Role of Interventional Radiology in Postpartum Haemorrhage

Table 3 shows the range of uses of interventional radiology in PPH, either as an emergency or electively.

The 2006 Health Care Commission report on the 10 maternal deaths at Northwick Park Hospital, United Kingdom (Healthcare Commission 2006) recommended the involvement of interventional radiology in the optimal management of postpartum haemorrhage. The 2007 RCOG Good Practice Guideline (Royal College of Obstetricians and Gynaecologists 2007) on the emerging role of interventional radiology set more clear guidelines where interventional radiology should be considered and echoes this recommendation.

What is evident from these reports is that all units should have a jointly agreed guideline for the management of massive PPH. In addition, clear and early communication must be established between the lead obstetrician and the interventional radiologist. Both clinicians should have an

**Table 3** The use of interventional radiology in postpartum haemorrhage either as an emergency or elective procedure (Adapted from Reference Royal College of Obstetricians and Gynaecologists 2007)

| | |
|---|---|
| Emergency role | Atonic uterus |
| | Surgical complications or uterine tears at time of caesarean section |
| | Vaginal or cervical tears at time of instrumental delivery |
| | Bleeding while on recovery unit or postnatal ward regardless of mode of delivery |
| | Bleeding following hysterectomy |
| Elective role | Placenta praevia |
| | Known or suspected placenta accreta or percreta |
| | Known or suspected uterine arterio-venous malformations |

early dialogue regarding when interventional radiology would be best timed in the management of the woman. This is obviously easiest in planned cases where interventional radiology may be needed e.g. planned elective caesarean section for placenta praevia, accreta or percreta. In the more common, unexpected and 'out of hours' scenario of PPH, the agreed guideline should state when the interventional radiologist should be called (e.g. when the estimated blood loss has reached 1500 mL and haemostasis has not been achieved, or that the obstetrician has identified that radiological intervention would be most appropriate—such as inability to access the bleeding vessel, for example with bleeding from a vessel high up in the vaginal wall secondary to perineal trauma following delivery).

Interventional radiologists become conversant with pelvic arterial anatomy due to experience in pelvic trauma, and more relevantly in performing uterine artery embolisation for uterine fibroids and can take additional specific training.

The procedure of embolisation for PPH does not differ in the route used. The right common femoral artery is cannulated under local anaesthesia and the internal iliac angiograms obtained. Either the uterine artery or the anterior divisions are then occluded.

In an elective setting prior to surgery, balloon catheters can be placed in the uterine arteries bilaterally ready to be inflated if PPH should ensue or removed if it does not. This type of multi-disciplinary pre-planning in the context of a known major placenta praevia, accreta or percreta, is vital. In the case of emergency intervention, extravasation of the contrast medium may direct targeted vessel embolisation. If this is not evident, then bilateral uterine artery embolisation is performed using tiny particles of polyvinyl alcohol, or other agents such as Gel foam. This takes a few minutes to do and the Gel foam is degraded within 6 weeks allowing for recanalisation of the uterine artery blood flow. The radiation exposure is present but is not a valid objection in the face of life-threatening haemorrhage. It is reported to be similar to radiation exposure of an abdominal CT scan (Nikolic et al. 2000).

The success of interventional radiology is higher when the patient is well resuscitated and stable despite active bleeding. Practical considerations include transfer of the patient to the radiology suite, the rate of bleeding and resuscitation as all this takes some time.

Case series have reported successful pregnancies and outcomes for women who had uterine artery embolisation. The associated complications reported in case series are few, but can be serious. Complications reported include: puncture site false aneurysm and haematomas; lower limb paresthesia; femoral vein thrombosis; ischaemia of the buttock, leg or foot; uterus, bladder and vaginal necrosis; small bowel ischaemia. There has not been shown to be an increase in the recurrence of PPH in subsequent pregnancies but there is an association with fetal intrauterine growth restriction (Pelage et al. 1999; Vegas et al. 2006; Josephs 2008; Lee and Shepherd 2010; Maassen et al. 2009; Shim et al. 2006; Sukhbir et al. 2007).

There are no randomised controlled trials to answer the question of whether interventional radiology is superior to traditional surgical techniques in stopping major PPH and averting the associated maternal complications, morbidity and mortality, primarily due to the unpredictable nature of PPH.

Doumouchtsis et al. (2007) reviewed the literature for arterial embolisation, uterine balloon tamponade, uterine compression sutures and pelvic devascularisation in the management of PPH. No randomised controlled trials were found. Forty-six observational studies were identified in their review and the outcomes are similar to previous reports. These studies suffer from bias in terms of the setting and choice of treatment. The primary success outcome was stopping PPH after failure of medical therapy. Primary success rates were 90.7 % for arterial embolisation, 91.7 % for B-Lynch and other compression techniques, 84.6 % for arterial ligation/pelvic devascularisation and 84 % for uterine balloon tamponade. They concluded that no method for the management of PPH is clearly superior. The choice a clinician might make would then depend on the cause of PPH and condition of the patient, facilities, familiarity with technique and the judgement about need and risk of transfer, risk of failure or delay of life-saving hysterectomy.

Most recently, the best comparative study to date is by Kayem et al. (2011) using the UK Obstetric Surveillance System, a national system for studying rare obstetric events (see Tables 4 and 5). This prospective population-based study looked at the use of second-line therapies for managing PPH and is the first study to compare the effectiveness of surgical measures and interventional radiology. Second-line therapies were uterine compression sutures, pelvic vessel ligation, interventional radiology techniques and

**Table 4** Outcomes of specific second-line therapies after uterotonics alone. Shown as proportion of women successfully treated and numbers undergoing hysterectomy (Reproduced from Kayem et al. 2011)

| Treatment used | PPH treated successfully *n* (%, 95 % CI) | Hysterectomy *n* (%, 95 % CI) |
|---|---|---|
| Uterine compression sutures | 120 (75 %, 67–81) | 32 (20 %, 14–27) |
| Interventional radiology | 12 (86 %, 57–98) | 2 (14 %, 0–43) |
| Pelvic vessel ligation | 5 (36 %, 13–65) | 6 (43 %, 18–71) |
| rFVIIa | 5 (31 %, 11–59) | 7 (44 %, 20–70) |

**Table 5** Outcomes of specific second-line therapies after failure of intrauterine tamponade. Shown as proportion of women successfully treated and numbers undergoing hysterectomy (Reproduced from Kayem et al. 2011)

| Treatment used | PPH treated successfully *n* (%, 95 % CI) | Hysterectomy *n* (%, 95 % CI) |
|---|---|---|
| Uterine compression sutures | 20 (53 %, 36–69) | 14 (37 %, 22–54) |
| Interventional radiology | 7 (87 %, 47–100) | 0 (0 %, 0–37) |
| Pelvic vessel ligation | 1 (17 %, 0–64) | 3 (50 %, 12–88) |
| rFVIIa | 4 (27 %, 8–55) | 7 (47 %, 21–73) |

recombinant factor VIIa. Successful outcome was not requiring a hysterectomy. Of interest to note is that if intrauterine tamponade failed then there was a higher rate of success in cases where clinicians chose interventional radiology rather than applying uterine compression sutures (although there may have been biases in those choices).

The management of PPH is an obstetric emergency that, if managed promptly, appropriately and with multidisciplinary involvement, has a successful outcome for the mother. The majority of PPHs are secondary to atony which is largely treatable with uterotonic drugs. As a relatively new and welcome addition to the armamentarium, the routine place and use of interventional radiology, where facilities exist, should be developed, audited and subject to review.

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# The Role of Interventional Radiology in the Management of Abnormal Placentation

Christopher Hay and Ian Gillespie

## Contents




**Abstract**

The prevalence of placenta previa and morbidly placenta accreta is increasing as a result of the increased rate of caesarean sections. Major placenta previa and placenta previa accreta mandate delivery by caesarean section and carry the risk of massive haemorrhage and hysterectomy. Women with placenta accreta are at particular risk of major haemorrhage and its complications. The insertion of prophylactic Internal Iliac Occlusion Balloon Catheters (IIOBCs) is to be carefully considered in cases of placenta accreta and placenta previa accreta and is supported in recent published guidelines. Where IIOBCs are ineffective in controlling haemorrhage, additional gelatine foam embolisation should be considered. Prophylactic internal iliac balloon occlusion with or without embolisation has not however been demonstrated in the literature to reduce the complications of massive haemorrhage or to reduce the need for hysterectomy in placenta accreta. Complications as a result of IIOBCs are not uncommon. Many of these are related to long dwell times and displacement of the balloon catheters and may be minimised by scrupulous technique. Advances in technique, operator experience, the use of closure devices and IR suites fit for obstetric delivery may improve the efficacy and safety of the use of prophylactic IIOBCs with and without embolisation.


## 1 Introduction

The prevalence of low-lying placental insertion (placenta previa) and morbidly adherent placenta (placenta accreta) is increasing as a result of the increased rate of caesarean sections (CS). Placenta accreta and previa frequently coexist as placenta previa accreta.

Radiology has a central role in patient management of these conditions. Antenatal ultrasound (US) allows for identification of low-lying placentas from 20 weeks and

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transvaginal US may characterise and classify placental position and morphology. Where abnormal placentation is suspected, a 32 week scan may be performed to further check placental morphology and penetration. Non-contrast MRI, though not demonstrated to be more sensitive than US, may have a role to play where US is inconclusive both in diagnosis and of accreta and placental mapping for caesarean section. These modalities thus help develop strategies for delivery.

Major placenta previa and placenta previa accreta mandate delivery by caesarean section and carry the risk of massive haemorrhage and hysterectomy. Women with placenta accreta are at particular risk of major haemorrhage and its complications and in these cases, Interventional Radiology may have a role to play in delivery. In centres where Interventional Radiology (IR) is available it can offer the Obstetrician both prophylactic balloon occlusion and, where necessary, arterial embolisation. This chapter aims to discuss the role of IR in abnormal placentation and the life threatening haemorrhage associated with it.

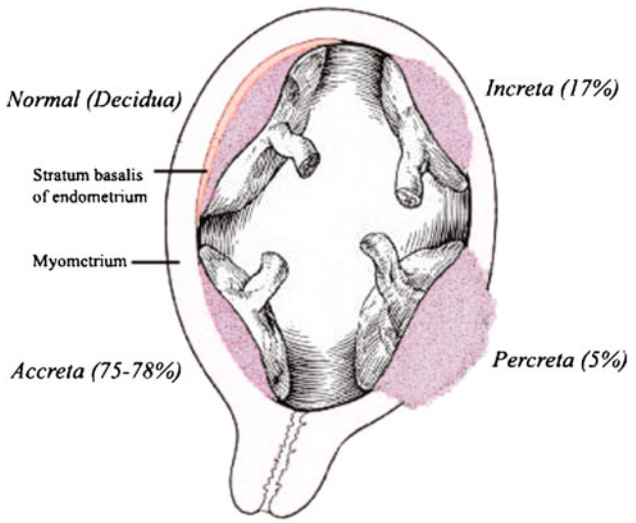


**Fig. 1** Diagram demonstrating the classification of abnormal placentation dependant on the depth of penetration into the myometrium

## 2 Placenta Previa, Placenta Accreta and Placenta Previa Accreta

### 2.1 Definitions

#### 2.1.1 Placental Previa

In placenta previa, the placenta is inserted in the lower segment of the uterus. The clinical classification aided by US findings can be divided into major, where the placenta lies over the cervical os and minor/partial where the leading edge of the placenta encroaches upon, but does not cover the cervical os.

#### 2.1.2 Placenta Accreta

This morbid condition of abnormal placental invasion of the uterine wall may be divided up into accreta, increta and percreta depending on the depth of penetration of the placenta (Fig. 1). In placenta accreta (78 %), the placenta penetrates into the decidua basalis; in placenta increta (17 %), the placenta penetrates into the myometrium and if through the myometrium is termed placenta percreta (5 %). In this chapter, the term placenta accreta will be used for all conditions unless specified.

#### 2.1.3 Placenta Previa Accreta

The two above conditions may co exist where the placenta is inserted low and is morbidly adherent.

### 2.2 Incidence

The incidence of abnormal placentation is on the rise and is associated with the increased caesarean section rate (Clark 1985, 1986; To 1995; Wu 2005; Usta 2005; Silver 2006; Solheim 2011). In addition, the chance that the placenta is not only previa but also accreta also increases with the number of caesarean sections. It follows that percentage of women requiring hysterectomy as a result of this condition will also increase. A study from the US following a cohort of over 30,000 women who delivered by caesarean section demonstrated placenta accreta to complicate 0.24 % of first pregnancies, 0.42 % of second, and rising incrementally to reach an incidence of 8.99 % for sixth or more caesarean section deliveries. In the cohort with placenta previa, the risk of placenta also being accreta was 3, 11, 40, 61 and 67 % for first, second, third, fourth and fifth or more caesarean sections (Silver 2006). Forecasts from the US where caesarean section rates reached 32.9 % in 2009 predicts that the rate of caesarean sections will rise to 56.2 % by 2020 and will be associated with many more previas, accretas and likely maternal deaths (Solheim 2011).

### 2.3 Diagnosis

#### 2.3.1 Ultrasound

Vaginal bleeding after 20 weeks should raise the suspicion of placenta previa. Routine transabdominal US at 20 weeks will also allow for identification of previa. If detected, then transvaginal imaging may be indicated to further investigate/reclassify the diagnosis (Smith 1997; Lauria 1996). In high risk patients with a major previa or accreta at the 20 week scan repeat imaging with US is recommenced at 32 weeks to clarify the diagnosis and plan multidisciplinary strategies for delivery (Royal College of Obstetricians and Gynaecologists 2011).

### 2.3.2 MRI

Two recent studies comparing the sensitivity and specificity of US versus non-contrast MRI showed no difference in their abilities to detect placenta accreta (Dwyer 2008; Masselli 2008) though one of these studies demonstrated that MRI was better at demonstrating the depth of penetration of the placenta (Masselli 2008). Thus, MRI may provide a useful tool for problem solving in difficult cases.

## 3 Preparations for Delivery in Placenta Previa/Previa Accreta

The most recent RCOG guidelines concerning the diagnosis and management of placenta previa/previa accreta recommend that "all women with placenta previa and their partners should have a discussion regarding delivery, indications for blood transfusion and hysterectomy" recognising the serious nature of the condition and potential devastating complications. The mode of delivery is based on the clinical judgment and US findings but any woman with a placenta less than 2 cm from the cervical os is likely to require caesarean section. Elective caesarean section is recommended with uncomplicated placenta previa planned for 38–39 weeks and for women with placenta accreta at 36–37 weeks (Royal College of Obstetricians and Gynaecologists 2011).

In the UK, a six point care bundle has been developed by the National Patient Safety Agency, Royal College of Obstetrics and Gynaecology, and Royal College of Midwives for the treatment of placenta accreta (Paterson-Brown and Singh 2010). This involves: 1. a consultant obstetrician supervising the delivery, 2. a consultant anaesthetist supervising the anaesthetic, 3. the availability of blood and blood products 4. multidisciplinary pre-operative planning 5. the local availability of a level 2 critical care beds and 6. discussion and consent concerning possible interventions (including interventional radiology).

### 3.1 Management of Placenta Previa/Accreta

Placenta previa where uncomplicated is unlikely to require input from interventional radiology as planned caesarean section is less likely to result in massive haemorrhage or emergency hysterectomy. Some major previa cases may require IR input if post partum haemorrhage occurs and internal iliac arterial embolisation is desired. Accurate antenatal scanning of placental position and depth of involvement is essential in forewarning the clinician to the appropriate preparations, but even then not all cases of placenta accreta can be diagnosed antenatally. Placenta previa and a history of caesarean sections should lead to a high index of suspicion.

Placenta accreta is associated with a higher incidence of complications morbidity and mortality and various strategies for conservative and operative management have been recommended. The abnormal penetration of the placenta complicates placental detachment at caesarean section and in all but those patients with focal accreta then hysterectomy without attempting to separate the placenta is recommended (Oyelese 2006). Conservative management in the form of leaving the placenta in situ has been attempted in selected cases but may be associated with complications such as infection, delayed haemorrhage and reoperation requiring hysterectomy (Timmermans 2007). Even where hysterectomy is planned control of haemorrhage may be challenging and expert Obstetric surgery is mandated. It is in these cases that transcatheter techniques may have an important role to play in prophylactic and emergency control of haemorrhage. Placenta percreta involving the bladder is of particular concern as torrential haemorrhage, bladder injury and urethral damage are not uncommon when attempting hysterectomy (Abbas 2000).

### 3.2 Interventional Radiology and Transcatheter Techniques in the Management of Abnormal Placentation

The routine 20 and 32 week US scanning (with the aid of MRI in some selective cases) will select the deliveries that may require the support of Interventional Radiology.

Intra arterial balloon occlusion for control of bleeding was described as far back as the Korean war (Edwards 1953; Hughes 1954) and transcatheter embolisation techniques in the treatment of obstetric and gynaecological emergencies have been reported since 1979 (Brown 1979).

Transcatheter techniques in the context of abnormal placentation have included:

- Prophylactic internal iliac occlusion balloon catheters (IIOBC).
- Prophylactic (internal iliac) arterial catheterisation, balloon occlusion and embolisation (PACBOE).
- Emergency transcatheter arterial embolisation.
- Occlusive balloon catheters in other sites e.g., aortic or common iliac.

### 3.3 Evidence for Transcatheter Techniques in Abnormal Placentation

There are no randomised controlled trials to help support the use of transcatheter techniques in abnormal placentation. The published literature concerning transcatheter techniques in abnormal placentation consists of uncontrolled case reports and a few small case-controlled studies.

### 3.3.1 Prophylactic Internal Iliac Occlusion Balloon Catheters

In one of the earliest series in the literature, (Levene 1999) followed five patients with placental accreta prospectively who delivered with the aid of prophylactic balloon occlusion and compared them to a control group numbering four patients. Balloon positioning was inconsistent amongst this study group (internal iliac $n = 7$, anterior division $n = 1$ and uterine $n = 2$). This study demonstrated no significant reduction in estimated blood loss (mean 5,025 ml vs. 4,653 ml), transfusion requirements (5.5 units vs. 4 units) or hospital stay (7 days vs. 5 days). Given the small size of the study it is difficult to extrapolate much from the conclusion that no significant differences were found in their outcome measures.

The largest single retrospective case series study (Shrivastava 2007) looked at blood loss, transfusion requirements, operative time and hospital stay for 69 women who underwent hysterectomy for placenta accreta. Of these women, 19 had internal iliac artery balloon occlusion at delivery. No difference in the primary outcomes was demonstrated. The balloon occlusion group demonstrated significant complications in three patients who were directly related to balloon placement. Two patients required bypass surgery and thus the authors concluded that it was difficult to support the use to IIOBCs where there was no perceived benefit and significant attendant risks to their placement.

There is also support for the use of IIOBCs in the literature, one of the earliest being a retrospective study of five women with potential accreta who underwent caesarean section and hysterectomy with the aid of prophylactic IIA balloon occlusion catheters (Kidney 2001). Placenta accreta was present in three patients; the remaining two patients having previa alone. Blood loss was estimated at between 1,100 and 4,000 ml and two patients required no blood products implying the usefulness of the technique though no control group was included for comparison.

More recently, a retrospective case-controlled study reviewed the cases of 25 women with placenta accreta who underwent elective caesarean section (Tan 2007). Eleven women had preoperative balloon occlusion compared to a 14 patient control group. This demonstrated a significantly lower intra operative blood loss, transfusion requirement and operative caesarean section time in the balloon occlusion group. No significant complications were recorded with respect to the placement of the balloon catheters and vascular access in this series.

Another retrospective case series is also supportive (Carnavale 2011), they looked at 21 patients with placenta accreta diagnosed antenatally by US and MRI. All had inflation of IIOBC at the time of cord clamping and CS followed by hysterectomy. Estimated blood loss was between 200 and 4,000 ml, a blood loss similar to other studies utilising the same IIOBC techniques. However, they also reported two patients requiring surgical thrombectomy for lower limb embolic complications related to balloon placement.

The importance of accurate prenatal diagnosis cannot be overstressed as demonstrated in a retrospective study of 2008 (Mok 2008). In this study of 13 patients (12 of which had prophylactic IIA occlusion balloons placed prior to caesarean section for suspected previa accrete) blood loss varied between 300 and 14,000 ml. Of note, six women did not require balloon inflation as previa only was encountered at operation and two patients had balloons inflated though previa only was encountered. The sensitivity and specificity of the prenatal diagnosis was poor in this study at 38 and 33 %, respectively. It may be argued that this may expose some women unnecessarily to the risk of complications from the placement of IIOBCs.

Another retrospective case series (Thon 2011) assessed the success of prophylactic balloon occlusion in suspected placenta previa accreta by chart review and retrospective questionnaire. Of the 14 women, 7 were found to have previa alone at CS. Uncomplicated separation of the placenta occurred in three of the seven placenta previa group, thus the IIOBCs were not necessary. The remaining 11 patients had IIOBCs inflated, in six cases it was deemed efficacious, deemed unnecessary in one further case and did not help in other four instances. Blood loss in this group varied between 700 and 15,000 ml and nine patients required hysterectomy. This case series recorded a number of complications, including groin haematoma, IIOBC migration and lower limb arterial insufficiency.

There are also a number of single case reports supportive of prophylactic IIOBC (Weeks 2000; Shih 2005; Yi et al. 2010) all describing balloon occlusion without embolisation in placenta accreta. Low blood losses 800–1,500 ml were recorded in these reports. Two cases were of the increta type (Weeks and Yi) and one percreta (Shih). Interestingly, the reported success of the placenta percreta case was achieved with the use of common iliac balloon occlusion.

### 3.3.2 Prophylactic Arterial Catheterisation, Balloon Occlusion and Embolisation

Additional embolisation with gelatine sponge is a further option in the treatment of placenta accreta. The rationale for additional embolisation has been intimated from the apparent failure of surgical IIA ligation observed in some surgical series (Clarke et al. 1985; Evans and Mcshane 1985) due to extensive pelvic collateralisation.

One of the earliest reports in the literature (Dubios 1997) concerned two cases of placenta percreta. The axillary arteries were used for access and balloon occlusion was followed with gelatine sponge embolisation. They described

good outcomes with blood loss between 1,500 and 2,000 ml.

A case-controlled series (Bodner 2006) of 28 patients with placenta accreta included six patients who underwent IIOBC insertion, caesarean section and transcatheter gelatine foam embolisation prior to either hysterectomy ($n = 5$) or uterine curettage ($n = 1$). This group was compared to 22 patients who underwent caesarean hysterectomy alone. The authors admit that there were significant differences in pre-delivery hospitalisation in the embolisation group and that the embolisation group were also delivered at an earlier gestational age. The two groups also differed in size thus it is difficult to extrapolate much from the findings that there was no difference in estimated blood loss, volume of replaced blood products, fluid replacement needs, operating time or post-operative recovery time.

Another retrospective case series in the literature reviewed 22 patients treated for obstetric haemorrhage of a variety of causes with transcatheter techniques (Ojala 2005). A subset of seven patients had prophylactic IIA catheterisation and arterial embolisation for placenta previa. These seven patients had a prenatal diagnosis of placenta previa (two with concomitant accreta one with percreta). One of the accreta patients and the percreta case required hysterectomy and encountered large blood losses 4,000–10,000 ml despite balloon occlusion and embolisation.

A further small retrospective series of six patients with obstetric haemorrhage (Hansch 1999) contained two patients with placenta previa accreta. In one patient, despite the IIOBC and gelatine foam embolisation, haemostasis could not be obtained and hysterectomy was preformed (with an estimated blood loss of 4,000 ml). The second previa accreta case and IIOBCs was reported as being effective in reducing blood loss at CS. Bleeding, however, resumed 10–15 min later presumably as the result of collaterals and gelatine foam embolisation was performed of the internal iliac arteries, this patient avoided hysterectomy but had an estimated blood loss of 3,300 ml. The other four patients in this study demonstrated a variety of other obstetric haemorrhagic conditions that responded variably to IIOBC and embolisation.

The term prophylactic pelvic artery catheterisation, balloon occlusion and embolisation (PACBOE) was coined in 2010 (Sivan 2010). They retrospectively reviewed 30 cases with suspected placenta accreta, 25 were demonstrated to be placenta accreta at CS. In eight cases, catheterisation was transbrachial and transfemoral in 22. The balloons were inflated at delivery and where bleeding was deemed to be massive then gelatine foam embolisation was additionally performed. The median blood loss in this study was 2,000 ml (500–9,000 ml) but no control group was included for comparison. The transbrachial group had a higher estimated blood loss and operative time compared to the transfemoral group. This report demonstrated a low rate of hysterectomy (8 %) compared to other studies and attributed this to experience acquired in single centre multidisciplinary approach.

PACBOE has been linked to positive outcome in a case report (Faranesh 2007) concerning the treatment the of the feared placenta percreta with bladder involvement. After balloon occlusion and subtotal hysterectomy, the patient was transferred to IR suite for the embolisation (part of the adherent placenta invading the bladder had been left in situ). A four unit transfusion of red cells was required but patient was discharged well at 9 days.

#### 3.3.3 Emergency Transcatheter Embolisation

Most of the literature above describes prophylactic measures where all possible arrangements have been made to pre-empt the particular dangers of abnormal placentation. This is reliant on the clinical and radiological suspicion and work up. Where the need for IR becomes apparent or desirable during post partum haemorrhage, it may be possible to insert IIOBC or other angiographic catheters and embolise the IIA in the emergency setting whether this is related to undetected abnormal placentation or not. The 24 h availability of IR has been recognised as highly desirable and successful outcome often reliant on early recognition of the severity of the haemorrhage.

The Ojala study (Ojala 2005) mentioned above included 15 patients with PPH treated in the angiography suite with embolisation of both IIAs with gelatine foam. This emergency embolisation group contained four patients with placenta previa/accreta, one patient in this group was treated with embolisation alone as a primary procedure and avoided hysterectomy, the three others required hysterectomy followed by embolisation.

#### 3.3.4 Aortic Balloon Occlusion

Though most cases of IIOBC described are of IIA or anterior division of the IIA, balloon occlusion of the aorta has been described by of placenta percreta (Paull 1995; Bell Thomas 2003; Masamoto 2009) for the elective or emergency treatment of massive haemorrhage.

## 4 Technique

### 4.1 Technical Variations from the Literature

- The choice of sheath size varied in the literature from 6 to 8 F and was not mentioned in other studies.
- Most authors have described a contralateral approach to the IIA over the iliac bifurcation the exception being axillary (Dubois 1997) brachial (Sivan 2010) approaches and an ipsilateral approach (Shih 2005) for CIA occlusion.

- The most often cited balloon catheter used was the Boston Scientific five or seven French occlusion balloons catheters (Boston Scientific, Natick, MA, USA) which may be inflated to 8.5 or 11.5 mm.
- Occlusion balloon catheter position is most often been described in the internal iliac artery or anterior division of IIA. Common iliac (Shih 2005) and uterine arterial positions have also been described (Levine 1999).
- The use of continuous flush via sheath side arm has been described in only a few studies but may be more common than stated. Anything short of scrupulous attention to flush may potentiate arterial complications.
- Almost without exception access and balloon positioning was performed in IR suite prior to patient transport to theatre. Two more recent publications have highlighted the effective use of the IR suite as delivery suite and operating room (Kodali 2010; O'Rourke 2007).
- Most authors report that a test injection was performed to determine the volume necessary for occlusion with only a few authors performing check fluoroscopy in theatre to ensure balloon position had not changed.
- Additional embolisation with gelatine sponge was routinely used in a number of studies (PACBOE). Otherwise, it was used in selected cases with difficult to control haemorrhage.
- Fluoroscopy time for the placement of occlusion balloon catheters varied from 60 s to 7 min 30 s.
- The use of closure devices is not reported in any of the literature. This may be as a result of the historical nature of much of the literature prior to the widespread introduction of these devices into clinical practice.

## 4.2 Complications Attributed to IIOBC

There is a great variability in the reporting of complications. Most series and case reports describe an excellent safety and a low morbidity. Others describe multiple complications. Shrivasta et al. described iliac artery thrombosis and haematoma in one patient, internal artery dissection in a second and femoral arterial occlusion in a third (the later two patients requiring bypass surgery).

Carnevale et al. also described two significant complications in their group of 21, both patients had long operations and dwell times for the IIOCBs, one had femoral and the other iliac arterial thrombosis both treated by embolectomy.

There are case reports dealing specifically with the complications of IIOCBs. One case report (Sewell 2006) describes a popliteal thrombosis requiring embolectomy despite the use of prophylactic intravenous heparin. Another (Bishop 2011) described multiple complications in the same patient of balloon puncture, leaking pseudo aneurysms of the IIA requiring covered stent insertion which went on to thrombose and a second late pseudo aneurysm on the contralateral sided at the site of the arterial sheath insertion.

These cases emphasise the need for scrupulous technique with regard to femoral sheath to avoid thromboembolism and the complications of balloon catheters.

### 4.2.1 The IR Suite as the New Obstetric Theatre

Many new IR suites have been developed with the potential for safe surgical practice, a process often driven with the development of complex endovascular procedures such as stent graft insertion. With respect to standards for obstetric surgery laminar air flow, medical gases, suction, gas scavenging systems, appropriate flooring, modern anaesthetic equipment and surgical lighting should all be considered (Kodali 2010). The potential exists for performing the entire case, from IIOBC insertion to CS, hysterectomy and any necessary IR procedure to ensure stasis in the IR suite where the appropriate provisions have been made. A small case series published the successful delivery of three patients with abnormal placentation in IR suite (O'Rourke 2007). There are obvious advantages in this, most intuitively that there is no need for patent transfer thus reducing the likelihood of balloon displacement. In addition, high quality fluoroscopy is then available to assist in any re-imaging, repositioning or embolisation. Not all IR suits are in close proximity to the rest of the operating or obstetric departments, thus complicating the task by transferring the appropriate instruments and expertise required in emergency surgery.

### 4.2.2 A Practical Algorithm for the Insertion of Prophylactic IIOBCs

- Informed consent by the interventional radiologist performing the case should be obtained covering the risks of access site complications, failure of access, balloon displacement, arterial rupture, lower limb arterial embolism, emergency surgery and the potential need for gelatine foam embolisation (and any complications secondary to this, e.g. non target embolisation/pelvic ischaemia/pain).
- If epidural anaesthesia is to be considered then this should be inserted prior to IIOBC placement.
- The patent should have a urinary catheter placed prior to placing the occlusion balloons.
- If practicable and safe, the whole procedure should be performed in the IR suite. The ability to achieve a precise balloon placement with no subsequent patient transfer must have significant advantages. The position of the IIOBCs is then likely to remain optimal. Further to this position checks, movement and subsequent embolisation is much more easily achieved.
- Where this is not possible (as in the literature described above) the traditional method by which the IIOBCs are inserted in IR suite may have to suffice.

**Fig. 2** A compliant occlusion balloon catheter is seen here inflated in the Internal Iliac Artery proximal to its bifurcation into anterior and posterior divisions. A check injection of contrast via the catheter lumen confirms stasis of flow distal to the balloon

- Ultrasound-guided Seldinger technique with local anaesthetic infiltration should be used for bilateral retrograde common femoral arterial sheath placement.
- Sheath size sufficient for the occlusion balloon catheters to be used in the IIA should be selected (The Boston Scientific occlusion catheters most often cited in the literature require a 8F sheath, there are reports of use with 7F sheaths for this balloon though this is off label).
- The contralateral IIA may be obtained with an angled 4 or 5F Cobra catheter and guide wire with fluoroscopic assistance, sub-selective catheterisation of the internal iliac artery or the anterior division of the IIA can be made at this point. The authors would advise against catheterising the uterine artery due to the perceived risk of causing foetal hypoxia.
- Exchange can be made at this point for the IIOBC of choice.
- An infusion on heparinised saline should be started via the side arm of the sheath for the duration of the case.
- Test inflations with 50:50 contrast:saline mix can then be made so as to result in arterial occlusion, this may be checked with injection of contrast via the catheter lumen (Fig. 2). Care should be taken in determining the volume required as over inflation of compliant balloons may result in arterial rupture. The balloons should be inflated only briefly and one at a time to avoid the risk of foetal hypoxia.
- The arterial sheaths may be sutured into position and the balloon catheter shafts secured in position with copious adhesive tape.
- The patient may then be transferred to the obstetric theatre for caesarean section. Meticulous attention should be given to minimising the movement of the balloon catheters and the continuous infusion of heparinised saline via the arterial sheath sidearm's.
- Ensure a radiolucent operating table has been used.
- Following CS and clamping of the umbilical cord obstetric assessment of placental position, separation and degree of haemorrhage may prompt the inflation of the balloons to the predetermined volumes. This may be done blind so as not to impede the emergent actions of the operators.
- The resultant reduction in haemorrhage may or may not be perceived by the operators. The communication between surgeon, anaesthetist and radiologist must remain fluid and adaptive.
- Continued haemorrhage may prompt gelatine foam embolisation of the anterior division internal iliac arteries. This is best achieved with the aid of the attendant mobile

fluoroscopy unit. This will mandate surgeons desisting at least briefly in their efforts at surgical haemostasis.
- Should this fail then whole internal iliac arteries may be embolised to near stasis with gelatine foam in a life threatening situation.
- Should the situation become desperate as a result of pelvic collateralisation then the balloon catheters may be moved to occlude common iliacs. Alternatively, an aortic occlusion balloon may be utilised though this will require sheath upsizing.
- Post procedure the balloon catheters and sheathes may be removed, alternatively the sheaths may be left in situ with the heparinised saline running via side arm so as to assist in rapid re-intervention for any delayed haemorrhage. The use of closure devices has not been mentioned in the examined literature and may potentially be of significant benefit as many of the complications relate to prolonged dwell times of these sheaths. Closure devices should not preclude emergent arterial reaccess if required.

### 4.3 Anatomic Considerations for the Failure of IIOBC in Arresting Haemorrhage

The pelvis has a very extensive collateral arterial circulation, even discounting the invasive nature of the placenta itself. The haemodynamics of IIA's ligation were investigated in the 1960s (Burchell 1964) where flow and pressure measurements were made before and after ligation of the IIAs. With bilateral ligation, pulse pressure was seen to diminish by 85 %, the mean pressure by 24 % and the blood flow by 48 %; with unilateral ligation, pulse pressure decreased by 77 %, mean pressure by 22 % and blood flow by 48 %. Angiographic studies from the 1960s (Burchell 1966; Chait 1968) where imaging was acquired shortly after surgical ligation of the internal iliac arteries as a means of controlling haemorrhage demonstrated collaterals supplying the pelvis almost immediately. Some of the arteries named in contributing to the anastamoses that maintained pelvic arterial supply included the medial femoral circumflex, last lumbar, lateral sacral and superior haemorrhoidal amongst others. Surgical series concerning ligation of the IIAs have been published as a means of controlling obstetric haemorrhage (Usta 2005; Evans and Mcshane 1985; Clark 1985); however, there persisted a substantial risk of failure of haemostatic control. This may be more likely to fail in the presence of placenta accreta. It should be remembered that any subsequent embolisation will be more difficult following arterial ligation.

The lessons from the above studies would indicate that embolisation at best can hope to reduce blood flow as complete cessation cannot in all probability be accomplished, especially in the severest forms of placenta previa accreta.

### 4.4 Techniques for Preserving Fertility

Major placenta previa alone, though requiring CS, may allow for normal placental separation and thus hysterectomy may be avoided. The prognosis for patients with placenta accreta in all but its partial form is more likely to involve hysterectomy. Where there is partial accreta, adherent portions may be left in place as trying to separate them may result in severe haemorrhage. These women are at risk of delayed haemorrhage and preparations for failure of conservative management should be made. Where the placenta dose not separate (true full accreta), it is recommended that the placenta is left in place, the uterus closed and hysterectomy then performed (RCOG Green top guidelines 2011). In an effort to avoid hysterectomy and preserve fertility, some authors have suggested that placenta may be left in situ and allowed to reabsorb (Timmermanns 2007; Bretelle 2007). Regular clinical and US follow-up is required to ensure that placenta is safely resorbed. This technique is associated with septic and haemorrhagic complications resulting in hysterectomy.

Interventional radiology has been promoted with the intention of helping to preserve fertility. Tan et al. in their retrospective study of 11 patients utilising IIOBC, described 5 patients in whom the placenta was to be retained, these patients had additional gelatine foam embolisation. Two patients had the placenta successfully delivered implying that they were not true percreta. Two patients went on to develop severe post partum haemorrhage resulting in hysterectomy with a four unit transfusion in one and endometritis in the other. A third patient with a retained placenta developed disseminated intravascular coagulopathy.

Ojala et al. (2005) described a similar technique in their retrospective study for a subgroup that had prophylactic IIOBCs placed for abnormal placentation (mainly placenta previa but two casesof PA). Of these seven patients, five underwent additional embolisation with gelatine sponge and three of these patients avoided hysterectomy.

As discussed above, Sivan et al. in 2010 used PACBOE for 31 cases with suspected placenta accreta reported a low rate of hysterectomy (8 %) compared to other studies. As mentioned they attributed this to the experience acquired in single centre multidisciplinary approach.

## 5 Conclusions

- The incidence of abnormal placentation is increasing. Multidisciplinary strategies for planned delivery are strongly recommended.
- High quality ultrasound will help select cases that will benefit from IR support. MRI may further clarify placental anatomy and depth of penetration.

- Placenta previa is less likely to require the support of interventional radiology; however, selected cases may still benefit from the use prophylactic IIABOCs.
- Placenta accreta and placenta previa accreta usually mandate hysterectomy and are associated with the complications of massive haemorrhage. The in house availability of 24 h interventional radiology is strongly recommended.
- The insertion of prophylactic IIAOBS is to be carefully considered in cases of placenta accreta and placenta previa accreta and is supported in recent published guidelines.
- Where IIOBCs are ineffective in controlling haemorrhage, then additional gelatine foam embolisation should be considered.
- Prophylactic internal iliac balloon occlusion with or without embolisation has not, however, been demonstrated in the literature to reduce the complications of massive haemorrhage. The literature largely comprises case reports and small retrospective case studies with variable techniques and equipment.
- Prophylactic internal iliac balloon occlusion with or without embolisation has not been demonstrated to reduce the need for hysterectomy in placenta accreta.
- Complications as a result of IIAOBCs are not uncommon. Many of these are related to long dwell times and displacement of the balloon catheters and may be minimised by scrupulous technique.
- Some series and case reports support the role of IIOBC and PACBOE in helping to slow haemorrhage and allow for positive outcomes in this potentially fatal condition.
- There is a need for further studies, ideally multicenter trials to further evaluate these potentially life and fertility preserving techniques.
- Advances in technique, operator experience, the use of closure devices and IR suites fit for obstetric delivery may improve the efficacy and safety of the use of prophylactic IIAOBCs and PACBOE.

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# Part III

# Pelvic Congestion Syndrome

# Pelvic Venous Congestion

William Stones

## Contents



**Abstract**

Pelvic congestion is a diagnosis now infrequently made by gynecologists as a cause of chronic pelvic pain. Recent literature has been almost exclusively from radiological practice and does not always relate the diagnosis to pain. In this context the concept of pelvic congestion is reviewed from an historical perspective, clinical correlates identified, the pathophysiology discussed, and the place of this diagnosis in modern practice considered.

## 1 Pelvic Congestion: History of the Concept

Taylor proposed the concept of venous congestion as a cause of chronic pain in the mid-twentieth century (Taylor 1949). Congestion referred to dilatation and sluggish flow in the utero-ovarian veins, but this was not a commonly accepted concept in clinical diagnosis. Using a transcervical approach with injection of contrast medium into the myometrium, Beard and colleagues reported a comparison of radiological appearances of the pelvic veins in women with a range of clinical presentations (Beard et al. 1984). In the radiological literature, pelvic congestion was not exclusively linked to symptoms of pain, but a range of other conditions. In further work, a vasoconstrictor was used to provide evidence for a causal relationship between congestion and pain symptoms. Vasoconstriction in the pelvic veins was associated with symptom relief (Reginald et al. 1987).

**Pelvic congestion syndrome** is probably best considered in terms of a symptom complex primarily presenting in women in the reproductive age group, whereas endometriosis (at least its symptomatic presentation) is more common in nulliparous women, and childbearing does not appear to afford protection from pelvic congestion, probably the latter condition does not have a hormone-dependent inflammatory basis. However, parity is not a risk factor as has been thought in some literature studies. Typical complaints include a shifting location of pain, deep dyspareunia and

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postcoital pain, and exacerbation of pain after prolonged standing (Beard et al. 1988). Taylor's original observations included abnormal ovarian morphology in the presence of venous congestion and it is possible that a basis in ovarian endocrine dysfunction may exist: associated ovarian morphology is characterized by predominantly atretic follicles scattered throughout the stroma, while in contrast to polycystic ovary syndrome the volume of the ovary is normal. The thecal androstenedione response to LH was increased as in polycystic ovarian syndrome, but granulosa cell estradiol production was reduced compared to normal tissue (Gilling-Smith et al. 2000).

Imaging features of pelvic congestion are dilated uterine and ovarian veins with reduced venous clearance of contrast medium. Ovarian vein reflux seen during transuterine venography was not included as a necessary condition for this diagnosis in the original scoring system, which includes the diameter of the ovarian veins, the distribution of vessels, and delay in clearance of contrast medium. In pregnancy, massively dilated ovarian pelvic veins are seen on ultrasound or visualized at Cesarean section: these are not normally associated with pain probably because these dilated vessels are characterized by high rates of flow.

There is evidence for therapeutic benefit in these patients of reassurance based on the concept of pelvic congestion, thus explanation of their pain in terms of a functional condition similar to cerebral migraine may be appropriate rather than explanations in terms of an anatomical abnormality or progressive pathological condition. Other approaches to therapy have included stress reduction and hormonal therapy with progestogens. Medroxyprogesterone acetate 50 mg as daily dosage has been shown to be effective, (Farquhar et al. 1989) and GnRH agonists with or without estrogen "add-back" are increasingly used in this indication, with some RCT evidence for benefit (Soysal et al. 2001). Hysterectomy and bilateral salpingo-oophorectomy followed by long-term estrogen replacement therapy is an option for those who have extreme symptoms partially or temporarily relieved by hormonal therapy, but this is naturally a treatment of a last resort.

Patients presenting with vulval varices outside of pregnancy, especially those with other sites of peripheral venous disease represent a different clinical entity to "pelvic congestion syndrome" and the underlying disorder may be nonfunctionality of valves in the pelvic veins together with more prominent anastomoses to the ovarian veins. A surgical approach involving extraperitoneal dissection of the ovarian veins has been described for this condition (Hobbs 1976), although details of patient outcomes are lacking in the literature. This is the group of patients that has been evaluated using interventional radiology techniques for vein occlusion in the last 10–15 years. Using percutaneous selective catheterization of the ovarian veins the presence of reflux has been considered diagnostic and to represent an indication for embolotherapy. Selective catheterization studies do not always evaluate the uterine veins and do not include venous clearance of contrast medium in the assessment of congestion, and unfortunately have not always included detailed clinical information. The term "pelvic venous incompetence" has been seen in the literature, emphasizing the presence of "varices" meaning dilated veins, but making no specification regarding reflux or venous clearance (Venbrux et al. 2002). For research and for clinical assessment purposes, it is therefore important to strive for clarity about two possibly distinct conditions as follows:

1. Women presenting with significant symptoms of pelvic pain and who are found to have 'pelvic congestion' including dilated vessels with reduced clearance, but not necessarily ovarian vein reflux. This clinical presentation can be classified as 'pelvic congestion syndrome'.
2. Women presenting with vulval varicosities or varices (outside pregnancy) and ovarian vein reflux, with or without pelvic pain.

It is also necessary to consider individuals who are asymptomatic but have either "pelvic congestion" or ovarian vein reflux at venography, MR imaging, or ultrasonography: in this context the imaging findings are likely to be coincidental. Unfortunately, even current reports tend to confuse the diagnostic categories and give incomplete clinical data about the patients included. Van der Vleuten and colleagues report positive outcomes for embolization in "pelvic congestion syndrome" with statistically significant change in summed symptom scores from mean of 26 (on a scale of 10–50) before embolization to 21 two months after the first embolization and to 19 at the time the survey was completed, but do not report detailed symptomatic information, such as presence of dyspareunia or pain scores (van der Vleuten et al. 2012).

Below, evidence from anatomic, physiologic, and imaging studies that might underpin an understanding of the clinical spectrum of pelvic congestion and ovarian vein reflux is reviewed.

## 2 Anatomy

Consistent with the embryologic origin of the uterus and ovaries, the ovarian arteries in humans arise from the aorta at a level below the origin of the renal arteries, with a variant course arching over the renal veins in some cases. Other anatomic studies confirm that the left ovarian vein consistently joins the left renal vein. On the right, the ovarian vein usually joined the inferior vena cava directly, but joined the right renal vein in 8.8 % of cases. With regard to valves, these have been described as either usually absent, or present in up to 90 % of cases; in the latter study valves were more

likely to be absent in parous women. Taken together, the cadaver studies suggest that where present, reflux down the ovarian vein is a functional rather than anatomic phenomenon. Valves are sometimes encountered during ovarian venography, but their absence should not be considered abnormal. The spermatic vein is rather longer than the ovarian vein, and the need for valves in the male and their failure leading to varicocele is not an appropriate analogy for pelvic congestion in the female. While ovarian vein reflux may be more demonstrable on the left than the right, there is no evidence for any predominance of left sided symptoms, whether of pain, dyspareunia, or vulvar varicosity, in contrast to varicocele. Valves are identified in branches of the internal and external iliac veins in around 10 % of male and female cadavers, indicating that venous return in iliac vessels also is nondependent on competent valves (Lepage et al. 1991).

A number of authors have drawn attention to the complex structural relations of the uterine and ovarian arteries and veins. In some species, local hormonal influences apparently transmitted through veno-arterial shunts are important in the regulation of the corpus luteum but this is not thought to be a factor in human luteal function. However, the concept of countercurrent exchange between human utero-ovarian veins and arteries has received some experimental support. The human ovarian circulation undergoes changes at the menarche, during the menstrual cycle, in pregnancy, and at the menopause, both in large vessels and at the level of the capillary network. The different phases of reproductive life are associated with changes both in size and volume flow in the uterine and ovarian arteries and veins. In pregnancy, although the ovaries are inactive, markedly dilated ovarian veins contribute to the venous drainage of the uterus. Thrombosis of massively dilated ovarian veins is a rare cause of acute abdominal pain in the puerperium (Savader et al. 1988).

Some of the changes in the uterine and ovarian veins may be a consequence of fluctuating levels of ovarian steroid hormones. During the normal menstrual cycle, the ovarian veins are exposed to 100-fold higher concentrations of estrone and estradiol compared to peripheral plasma (Baird and Fraser 1975). Although data are not available for human vessels, in oophorectomized mice the uterine and ovarian veins, but not the femoral or iliac veins or inferior vena cava, enlarged in response to estradiol or testosterone administration. This suggests that uterine and ovarian vessels have a special sensitivity to ovarian steroid hormones.

## 3 Vascular Physiology

Venoconstriction has a homeostatic role in maintaining cardiac output in response to changes of posture, and is under sympathetic control. Veins may also respond to local pressure changes with myogenic activity sufficiently coordinated to result in a peristalsis-like movement of blood back to the heart. In the absence of tissue supports and the variable presence of valves, venous return in the utero-ovarian circulation is likely to be aided by spontaneous contractility. This has been observed in vitro and in vivo (Stones et al. 1990). The full range of endothelial and perivascular autonomic innervation is present in the human ovarian vein, and has been demonstrated experimentally the release of vasoactive agents from the isolated perfused human ovary. Many of these agents are mediators of inflammation and pain sensation, providing a link between vascular phenomena and pain. Relevant mechanisms have been reviewed (Stones 2000). It may be that pelvic congestion reflects a systemic disturbance of vasomotor regulation.

## 4 Ultrasound Imaging

Dilated pelvic veins can be seen using transabdominal or transvaginal sonography. However, the use of ultrasound to replace venography has proved problematic, especially because reflux at the origin of the ovarian vein is difficult to visualize, and flow rates are typically very low making it difficult to obtain a satisfactory spectral display using Doppler. Thus, the venous clearance element of pelvic congestion, well seen using transuterine venography, is difficult to reproduce. Comparing the two modalities, the technical limitation of conventional Doppler was overcome using transvaginal power Doppler, which has much greater sensitivity to low rates of flow. However, in a comparison with transuterine venography the correlation between findings in 42 women was poor. Thus, venography may continue to have a place (Campbell et al. 2003). More recently, dynamic MRI may have come to represent the "gold standard".

## 5 Imaging Studies with Renal Transplant Donors

Healthy kidney donors are evaluated using angiography, CT, and/or MRI before surgery to assure normal anatomy. Observations in donors have been reported in three studies. A total of 27/273 women had evidence of left ovarian venous reflux of whom 22 completed a questionnaire about symptoms. Of these, 13 reported pelvic pain and 10 had reduced or absent symptoms after left nephrectomy (Belenky et al. 2002). By contrast, in two other studies in this group involving 8 and 16 women, while the ovarian vein diameters of donors with evidence of reflux were greater than those without, none had symptoms of pelvic

pain. A possible explanation for the discrepant findings is the lack of prospective symptom data collection from the donors, with or without venous reflux, which makes the true significance of reflux difficult to assess.

## 6 Clinical Outcomes

In considering the outcomes of treatment, it is important to keep in mind the diverse uses of the diagnostic label of "pelvic congestion" as discussed earlier. The available evidence for the benefit of interventions for pelvic congestion based on randomized clinical trials is limited and hormonal interventions predominate: other interventions are supported only by observational studies (Stones et al. 2005). A recent report of symptomatic improvement with Implanon, a contraceptive implant, is of interest because of its wide availability internationally, the long duration of action and a good adverse effect profile (Shokeir et al. 2009). In interventional radiology studies, symptom improvement is noted in between half and 90 % of patients. As a group these studies are difficult to interpret because of variable entry criteria, incomplete documentation of clinical symptoms, and the duration and completeness of follow-up (Maleux et al. 2000; Venbrux et al. 2002). One report emphasized the presence of dyspareunia as indicating a poor outcome following embolotherapy (Capasso et al. 1997), while others have reported improvement in this symptom after treatment. Laparoscopic surgical experience of ovarian vein ligation is anecdotal. An early report (Takeuchi et al. 1996) described two successful cases although as in the radiologic literature clinical details are sparse.

## 7 Conclusion

More than half a century after Taylor put forward the concept of pelvic congestion, how much further forward are we? Clearly, understanding of basic mechanisms of vascular control and pain has progressed considerably, but specific pharmacotherapy directed toward a possible systemic vascular abnormality remains elusive. However, we have randomized clinical trial evidence of benefit for medical treatments of pelvic congestion. The challenge is for gynecologists and radiologists to work together to agree diagnostic criteria and to present carefully documented studies of the clinical outcomes of radiologic interventions. As noted in a recent systematic review, "controlled trials comparing medical and interventional treatments are urgently needed for pelvic congestion syndrome (PCS)-associated pelvic pain" (Tu et al. 2010).

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# Embolization in Pelvic Congestion Syndrome

Lindsay Machan

## Contents




**Abstract**

Pelvic congestion syndrome remains a poorly understood entity whose existence, let alone appropriate methods of investigation and treatment, are still under legitimate question. It is important that any endovascular therapist contemplating ovarian vein embolization *works* closely with a gynecologist, not only to ensure that other causes of pelvic pain are excluded, but to share in the considerable post procedure needs of these patients. Pelvic congestion syndrome is increasingly being diagnosed both clinically and by imaging in patients with pelvic pain. Referral patterns are changing to include women being screened for lower extremity venous insufficiency. Although there is a striking consistency to the clinical improvement achieved by ovarian vein embolization by multiple authors, it is necessary that any physician undertaking this procedure convey the controversial nature of the syndrome to the patient. Improvement in pain symptoms should be expected in 80–90 % of patients with significant improvement in 60 %. Treatment appears durable at 5-year follow-up. There remains considerable variation in the endovascular approach, and the optimum approach remains to be proven.


## 1 Introduction

Embolization of the gonadal vein is one of the simplest procedures in endovascular medicine. Conversely, in clinical medicine, management of chronic pelvic pain is among the most difficult tasks. This is due to the difficulties with diagnosis and treatment detailed in the prior chapter. It is critical to reiterate that although varicosities in the pelvis secondary to ovarian vein reflux are a recognized cause of chronic pelvic pain (Cheong and Stones 2006), they are frequently seen incidentally on imaging studies in asymptomatic women. Without associated symptoms, dilated pelvic veins are not abnormal. As is the case with symptomatic

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male varicoceles (a well accepted clinical entity), it is not clear why some patients with gonadal venous reflux have pain when the majority don't. Further complicating the situation, it is common for pelvic venous ectasia to develop after pregnancy (Hodgkinson 1953). However in "physiologic" venous ectasia blood flow is typically antegrade and there may not be sluggish flow or bulbous varicose venous dilation.

## 2 Clinical Presentation

There are four ways pelvic varicosities may come to the attention of a physician.

i. Pelvic Congestion Syndrome. The features of the syndrome have been described in the previous chapter.
ii. Labial or lower extremity varicose veins. For both surgical and endovascular treatments of venous reflux, the basic principle is to treat the highest point of reflux first. Vulvoperineal varicosities can be found in 4–8.6 % of patients with lower extremity venous insufficiency and may accompany ovarian vein insufficiency (Jung et al. 2009). Labial and perineal varicosities, lower extremity varicosities in unusual distributions, or lower extremity varicosities which recur after appropriate treatment can signal the presence of ovarian vein reflux. With increased patient demand and greater breadth of available therapies for varicose veins, this has become an increasingly frequent indication for investigation and treatment.
iii. Acute ovarian vein thrombosis. This is an uncommon cause of acute abdominal or pelvic pain (Harris et al. 2012).
iv. Incidental finding on cross-sectional imaging. On CT-dilated ovarian, veins can be seen in up to 63 % of parous women without symptoms of pelvic congestion and in 10 % of nonparous women (Rozenblit et al. 2001).

## 3 Preprocedure Workup

All patients with chronic pelvic pain should have the benefit of clinical evaluation by, and shared peri-procedural care with a clinician with expertise in chronic pelvic pain. Pelvic varices can be demonstrated by multiple imaging modalities, however, the author's routine is to ensure the patient has had laparoscopy and pelvic ultrasound or MRI prior to pelvic venography. This is to exclude other disorders which might cause pelvic pain, not to make the diagnosis of pelvic congestion.

If the patient suffers from lower extremity varicosities, the workup before pelvic venography includes a detailed clinical assessment by a specialist physician expert in venous disease and a lower extremity duplex ultrasound assessment for venous reflux. Laparoscopy is not necessary in these patients unless there is suspicion of pelvic pathology.

### 3.1 Laparoscopy

Laparoscopy is the most effective means of diagnosing other causes of chronic pelvic pain and virtually all women with chronic pelvic pain should undergo this procedure. In particular, minimal lesion endometriosis, the most common cause of chronic pelvic pain will not be detected by ultrasound and may only be detected by an expert laparoscopist. Dilated veins may not be visible because of their retroperitoneal location, the increased intra-abdominal pressure with peritoneal insufflation, and increased venous drainage with Trendelenberg positioning that are part of laparoscopic examination. Thus, a negative laparoscopy in a woman with chronic pelvic pain does not exclude the diagnosis of pelvic congestion.

### 3.2 Cross-Sectional Imaging

Although imaging can demonstrate pelvic varicose veins, direct visualization of tortuous and dilated ovarian veins with venography is still felt to be the gold standard for accurate diagnosis of pelvic congestion. The author does not view a normal noninvasive imaging study as a contraindication to ovarian venography when there are symptoms which might be due to pelvic congestion.

#### 3.2.1 Ultrasound

Ovarian and pelvic varices can be seen as multiple dilated tubular structures with venous doppler signal around the uterus and ovary on both transabdominal or transvaginal US with color Doppler. Sonographic diagnostic criteria for pelvic congestion have been published (Kuligowska et al. 2005). These include: (a) tortuous pelvic veins with a diameter greater than 4 mm (b) slow blood flow (about 3 cm/s), and (c) a dilated arcuate vein in the myometrium that communicates between bilateral pelvic varicose veins. The author prefers to rely on abnormal accentuation of blood flow with Valsalva maneuver rather than utilizing strict size criteria. Veins can vary considerably with body position, nervousness or hydration, or may be dilated from physiologic ectasia from prior pregnancies.

### 3.2.2 CT and MRI

On CT and MRI pelvic varices are seen as dilated tortuous paraovarian or parauterine tubular structures, frequently extending to the broad ligament and pelvic sidewall or paravaginal venous plexus (Coakley et al. 1999). On T1-weighted MR images, pelvic varices have no signal intensity because of flow-void artifact; on gradient-echo MR images the varices have high signal intensity. After the intravenous administration of gadolinium, T1 gradient-echo sequences demonstrate blood flow in pelvic varices with high signal intensity. On T2-weighted MR images they usually appear as an area of low signal intensity; however, possibly because of the relatively slow flow through the vessels, hyperintensity or mixed signal intensity may also be seen.

## 4 Ovarian Venography and Embolization

The clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum recommend retrograde ovarian and internal iliac venography as the test of choice for the diagnosis of pelvic venous disorders, but suggest it be most often reserved for patients in whom intervention is planned (Gloviczki et al. 2011).

### 4.1 Indications

i. Unexplained chronic pelvic pain.
ii. Pelvic varicosities seen at laparoscopy, ultrasound, or open operation in a patient with appropriate symptoms.
iii. Lower extremity varicose veins immediately recurrent after adequate surgical treatment, or lower extremity varicosities in an unusual distribution such as the posterior thigh.
iv. Severe labial, perineal or buttock varicosities. These are difficult to treat, and conservative therapy should always be contemplated. If intervention is undertaken, these will recur immediately after sclerosis unless the ovarian vein "pressure column" is interrupted beforehand.

### 4.2 Contraindications

I. Contraindications to angiography
   (a) Severe anaphylactoid reactions to radiographic contrast media
   (b) Uncorrectable coagulopathy
   (c) Severe renal insufficiency.
II. Phobia to medical implants.
III. Patient has other cause of pelvic pain not adequately treated.

### 4.3 Patient Preparation

Timing of the procedure in relation to menstrual or pain cycle is unimportant. The patient should be restricted to clear fluids after midnight for a morning appointment, clear fluids after breakfast for an afternoon appointment. The patient should be admitted to a day care bed as considerable sedation may be required.

As important as technical excellence during the procedure is the manner in which the interventional team interacts with these patients and their clinician. This implies awareness of, and appropriate response to, the emotional overlay that often accompanies any chronic pain syndrome. These patients may require considerable time for consultation and reassurance before and after the procedure, and more analgesia during it. Clinical management includes encouragement and frequent explanations that symptom resolution in chronic pain syndromes may take several months after treatment of the cause. It is important to remember that one person's ache is another's agony.

### 4.4 Technique of Ovarian Venography and Embolization

A tilting table can be helpful but is not essential. The transjugular approach is preferred by the author as it is a more straight-line access to the pelvic veins and the right ovarian cannulation can be performed with no catheter exchange required. However, many experienced practitioners perform ovarian venography via femoral access with high technical success rates.

#### 4.4.1 Transjugular Route

1. After ultrasound-guided puncture, a sheath is introduced into the right internal jugular vein. Through this a catheter, usually a multipurpose shape, is directed into the peripheral portion of the left renal vein and a diagnostic renal venogram performed. with the patient performing a Valsalva maneuvre. Published venographic criteria for the diagnosis of pelvic venous insufficiency include reflux in the ovarian vein with valvular incompetence, dilation of the ovarian vein to greater than 5 mm, abnormal opacification of the uterine and utero-ovarian arcade, reflux across the midline into contralateral veins; demonstration of vulvar or thigh varices, and stagnation of contrast in the pelvic veins (Beard et al. 1984). If there is no reflux into the ovarian vein after left renal vein injection and the left ovarian vein clearly arises from the renal vein, this is considered a negative study. Selective ovarian venography to detect reflux in nondilated veins is not necessary in the author's experience.

If there is ovarian venous insufficiency, the catheter is advanced into the distal left ovarian vein and forceful injection is performed to identify all collateral channels. Depending on the size of the branches and extent of the varicosities the catheter is either directed into each of the 2 or 3 largest branches, or immediately above them. Occlusion of the ovarian vein is performed from this level back to the pxoximal vein. The author's preferred method is to infuse 3 % tetradecyl sulfate (each 2 cc opacified with 0.5 cc of contrast) as the patient performs a valsalva maneuver until there is stasis of flow at the catheter tip. The volume ranges from 2.5 to 12.5 cc per ovarian vein. Manufacturer's recommended doses vary widely and are generally made for varicosities in the extremities Published maximums for pelvic injection are not available to the author's knowledge. The remainder of the vein is occluded with intermittent long coils "laid out." This method of coil deployment involves holding the guidewire in place as the catheter is withdrawn, thus the coil is uncovered and deployed in elongated form. Various sclerosants, glue, or Gianturco coils (alone or with liquid agents) have all been used.

The same multipurpose shape catheter is then directed into the right renal vein. Rarely the ovarian vein will arise from the renal vein. Most often the purpose is to define the right renal vein origin as the ovarian vein typically arises from the vena cava immediately inferior and anterior to the renal vein orifice. Right ovarian venography and, if appropriate, embolization are performed in the same fashion as described for the left. After embolization, or if ovarian venography is negative, bilateral internal iliac venograms are then performed. Rarely internal iliac branch venous reflux will cause symptomatic pelvic varicosities. We do not routinely embolize the internal iliac veins, however, other interventionists do this routinely, even when reflux is not seen (Venbrux et al.). The author uses the same multipurpose catheter to perform internal iliac venous occlusion by infusion of tetradecyl sulfate as the patient performs valsalva maneuver, capping the occluded segment with a coil. Other interventionists use a balloon occlusion catheter.

### 4.4.2 Transfemoral Route

A catheter is introduced into the right femoral vein and directed into the peripheral left renal vein. This can be any preshaped catheter such as a Cobra catheter. Renal venography and selective left ovarian venography and embolization are performed using the same diagnostic criteria and methods as described for the transfemoral route.

The catheter is then exchanged for shepherd's crook-shaped catheter such as a Simmons or equivalent, and a right ovarian venogram, and if needed, embolization are performed in the same fashion as described for the left. The right ovarian vein can be difficult to locate or catheterize. The author's favored suggestion is to abandon attempts from the femoral route and achieve access from the jugular route. Selective catheterization of each internal iliac vein is then performed, usually after reintroduction of a Cobra catheter.

## 5 Results of Embolization

Edwards reported the first published case of ovarian vein embolisation for pelvic congestion syndrome (Edwards et al. 1993). Since then the treatment of pelvic congestion syndrome by embolization has been reported using coils alone or various combinations of embolic agents. As well, variable combinations of occlusion of single or both ovarian veins and pelvic veins have ALSO been described.

Kwon et al. reported a series of 67 patients treated with coil embolization alone, of whom 64 had left ovarian vein occlusion, 1 right ovarian vein occlusion, and 2 bilateral ovarian vein occlusion (Kwon et al. 2007). Clinical improvement was seen in 82 %.

The largest published series of patients with pelvic congestion syndrome treated by endovascular therapy includes 202 patients with pelvic pain selected from a population of patients with lower extremity venous insufficiency (Laborda et al. 2013). These authors utilized coil occlusion alone, with the intention to treat all refluxing veins including both ovarian and appropriate branches of both iliac veins. Nearly all patients had at least three of four veins treated. Clinical benefit was seen in 94 % of patients utilizing a visual analog scale (VAS) pain questionnaire. After treatment the clinical response continued to improve for most of the first year. Lasting and significant benefit was documented with VAS pain scores decreasing from 7.3 to 0.78 (on a ten point scale) in the 89 % of patients who were followed for 5 years.

The addition of pelvic vein sclerosis to ovarian vein embolization was introduced in a publication of 56 patients in 2002 (Venbrux et al. 2002). Sodium morrhuate 5 % mixed with gelfoam was injected into the pelvic veins from the ovarian vein prior to its occlusion with stainless-steel or platinum coils. At a separate procedure appropriate branches of the internal iliac vein were then embolized in the majority of patients by injecting sclerosant through an occlusion balloon. Significant and partial response was seen in 96 % in this report. Pain assessed by a VAS questionnaire showed a decrease in pain level from 7.8 to 2.7 at 12 months. The series was later updated to include 127 patients (Kim et al. 2006). At a mean follow-up of 45 months 83 % of patients experienced durable clinical improvement. The recurrence rate of pelvic pain was 5 %.

Other sclerosants have been described for the treatment of pelvic congestion syndrome. Gandini reported the use of 3 % sodium tetradecyl sulfate (STS) foam to treat 38 patients with pelvic venous insufficiency (Gandini et al. 2008). Foam was injected until pelvic venous stasis was demonstrated and did not subsequently place coils. Clinical improvement was reported in 100 % of treated patients. Injection volumes were typically 30 ml on the left and 20 ml on the right. The right side was treated only when varices did not cross the midline from left to right.

Carpasso treated 19 women with pelvic congestion syndrome by embolization with enbucrylate and coils (Carpasso et al. 1997). Thirteen patients required unilateral embolization and 6 bilateral. Five patients developed recurrence treated successfully by embolisation. Initial technical success rate was 96.7 %, and there were no complications. At mean follow-up of 15.4 months 73.7 % of patients' symptoms were improved, completely in 57.9 %. The authors noted that the 8 patients who had only partial or no relief suffered from dyspareunia.

A prospective comparison of percutaneous endovascular versus surgical therapies has been published (Chung and Huh 2003). One hundred and six women diagnosed with pelvic congestion syndrome after laparoscopy and venography were randomized to ovarian vein embolization, hysterectomy with bilateral oophorectomy, or hysterectomy with unilateral oophorectomy. Pain assessment scores using a VAS pain scale and standardized stress questionnaire were compared at presentation and 3, 6, and 12 months following treatment. Embolization was found to be significantly more effective at reducing pelvic pain compared to surgery, except for those patients with the highest stress scores. In those patients the benefit over surgery was lost at 1 year. Embolization was completed with coils alone—unilateral left ovarian vein in 90, unilateral right ovarian vein in 8, and bilateral in 8 patients. Single oophorectomy had the least effective results, supporting the need for complete hormonal suppression in order for surgery to be beneficial.

## 6 Complications

Eighty to 90 % of patients suffer a postembolization syndrome characterized by pain, fever, and nausea and vomiting. This can occur irrespective of embolic method, with coils alone or when liquid agents are used. The severity varies tremendously from patient to patient and can last from a few hours to several days. Other significant toxicities are rare. To the author's knowledge there have been no reports of clinically significant non-target embolization.

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