Modern management of fibroids

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Abstract
Uterine fibroids are common benign tumours that occur in women of reproductive age. They are frequently associated with symptoms that impact on quality of life and require treatment. Up until mid-1990s, this was usually surgical with either hysterectomy or myomectomy being performed. Although myomectomy conserves the uterus, it is associated with complications that might not enhance the chance of pregnancy and for those concerned about fertility, alternatives are being developed. The most widely used of these is uterine artery embolization (UAE), which is a very successful treatment in terms of treating symptoms such as heavy menstrual bleeding but the impact on fertility is, as yet, unclear. Other exciting developments are high intensity focussed ultrasound and MRI guided focussed ultrasound. These allow a more directed approach. However, these techniques require sophisticated equipment which is not yet generally available.

New medical treatments are being evaluated — the most popular currently are the progesterone receptor modulators that induce amenorrhea and a degree of fibroid shrinkage whilst having minimal effect on ovarian function. One has recently been licensed for short term use in the UK and Europe and it is hoped that longer term use will be possible in the future.

This review summarizes the information available on these techniques and also provides suggestions for further reading.

Keywords high intensity focussed ultrasound; progesterone receptor modulators; uterine artery embolization; uterine fibroids

Uterine fibroids are the commonest tumour of the female reproductive tract and occur in approximately 25% of women of reproductive age. They are frequently asymptomatic, but when they do cause symptoms, these are likely to be menstrual problems, sub-fertility or symptoms associated with the size of the fibroids. Traditionally, treatment has been surgical with hysterectomy for those who have completed their childbearing and myomectomy for those who wish to retain their uterus. Surgery is associated with operative mortality and morbidity. Myomectomy may also be associated with a risk of hysterectomy, post-operative adhesion formation and recurrence. Up until recently, many women have had a hysterectomy carried out although they would have preferred a treatment that allowed them to retain their uterus. It is for this reason that a number of options have developed in recent years and these options are outlined in Box 1.

Recent developments in the treatment of uterine fibroids

This review will focus on uterine artery embolization and progesterone receptor modulators as these are the most promising and well evaluated treatment modalities. Others such as high intensity focussed ultrasound (HIFU) are also discussed.

Diagnosis of fibroids
The only reason that fibroids can be treated conservatively without a tissue diagnosis is because malignancy is very unusual. It is almost impossible to determine an accurate incidence because the denominator is unknown. Since many women have asymptomatic fibroids, it is extremely difficult to determine what proportion will become malignant. In addition, leiomyosarcoma tends to occur in women in their 60s and 70s whereas uterine fibroids occur in women of reproductive age.

Diagnosis is made by imaging, either ultrasound or magnetic resonance imaging (MRI). The latter is particularly suitable for large fibroids and also allows the number to be determined more easily than with ultrasound. However ultrasound, particularly with modern equipment, is very accurate for those with fibroids below about 10 cm in size. However, MRI also facilitates visualization of the ovaries, which can be difficult in women with large fibroids using ultrasonography and MRI may also be able to diagnose adenomyosis more easily.

Fibroids and fertility
There are an increasing number of women over the age of 40 who wish to achieve a pregnancy having delayed childbearing and a significant proportion of these will have fibroids, since they are known to increase with age. It is unclear as to exactly what role of fibroids in sub-fertility is. A systematic review confirms that the evidence that fibroids cause sub-fertility is lacking. However, the best evidence comes from studies with assisted conception since fibroids are thought to decrease the success rate but whether this is confined to sub-mucous fibroids only is a matter of debate. There is no view among infertility specialists as to the most appropriate management for fibroids and further information in this area is very much needed.

Uterine artery embolization
Uterine artery embolization (UAE) has been carried out for the treatment of uterine fibroids since 1995. Prior to this it was used...
for massive obstetric haemorrhage and also bleeding from organs such as the liver, which is notoriously difficult to control. UAE is indicated for symptomatic fibroids and is an alternative to myomectomy since it allows conservation of the uterus and also only involves a short hospital stay. Follow-up data from randomized controlled trials has now been published that suggests it is a safe and effective treatment. UAE is particularly useful for indications such as heavy menstrual bleeding. It is also useful for other menstrual problems, pressure effects and pain. It is a good option for a majority of different fibroids regardless of their position within the uterus. The treatment is successful in a majority of patients depending on the indication although there is still some dubiety regarding impact on fertility and pregnancy as will be discussed below. Initial results came from case series of the pioneers and later, data from observational studies and RCTs have been added and will be discussed.

Fibroid volume
The median decrease in fibroid volume is about 40%, although some studies report a decrease in up to 70% This is similar to that achieved with administration of gonadotrophin-releasing hormone agonist (GnRH) agonist and is due to decrease in blood flow to the fibroid. However, unlike with GnRH agonist, the fibroid does not re-grow after treatment and also shrinkage may continue for many months rather than be confined to the first 3–6 months.

Menstrual symptoms
UAE is successful in decreasing menstrual blood loss as has been shown both subjectively and objectively in a number of studies. The mechanism for this decrease is unclear but may involve alterations in endometrial function.

The procedure
The objective of UAE is to completely infarct all the fibroid tissue while preserving both the uterus, ovaries and surrounding pelvic tissues and it is performed by an appropriately trained interventional radiologist. The vessels are visualized with angiography and the uterine artery identified (Figure 1). The femoral artery is cannulated at the groin and the catheter is fed through the femoral artery into the iliac artery, across the aortic bifurcation and into the uterine artery on the other side. If sufficient staff is available both arteries can be cannulated at the same time in order to decrease the length of time and thus the radiation burden, of the procedure. The variety of embolic agent varies from one operator to another but may affect the cost of the procedure as well as the determination of the embolic endpoint.

The procedure normally requires an overnight stay since pain after UAE is usual but responds well to analgesia. RCTs suggest that the pain is less severe than that experienced after a laparotomy.

Complications of the procedure
Data regarding complications are best obtained from the registries and large observational studies since the RCTs are not powered to show a difference in complication rates although conclusions are often erroneously drawn from them. Complications can be serious although this is rarely the case and can be divided as follows:

- immediate, i.e. those occurring during the procedure
- early, within the first 30 days
- late, beyond the first 30 days.

Immediate: there is a risk of local complications such as haematoma, thrombosis or pseudo-aneurism. However, these are most unusual as the catheter size is very small. Reaction to the contrast media is unusual. Failure to cannulate the uterine artery occurs in a very small percentage of cases and excessive embolization can cause infarction of other organs within the pelvis. As already mentioned, pain occurs in a majority of women although the severity does not seem to be related to the outcome in any way.

Early (30 days): post-embolization syndrome is common, although it is only severe in a minority of cases. It consists of pain, nausea, a flu-like illness, mild pyrexia and raised inflammatory markers. It probably occurs to some degree in virtually all
the patients who have UAE. If the symptoms are prolonged or the patient is becoming very ill then infection must be suspected.

Severe uterine infection which requires surgical intervention is less common than was originally predicted, which is fortunate as hysterectomy performed soon after uterine artery embolization tends to be a very difficult procedure. Vaginal discharge is common and usually settles down within a few days.

Many patients complain of pain that can be significant in the first 24 hours although it is less than after a laparotomy. It usually persists for several days but responds well to standard analgesia and recovery is rapid for a majority of women.

**Late (beyond 30 days):** unlike with surgical treatment, most of the complications of UAE occur beyond 30 days or start earlier and continue beyond this time.

Vaginal discharge can become chronic and in a small number of women it is foul-smelling and continues. On some occasions this is due to fibroid expulsion and evacuation of the uterus is required.

Fibroid expulsion probably occurs in 10% and is particularly common with sub-mucous fibroids. Occasionally operative intervention is required but usually if the patient is warned that this might occur then no further treatment is required. This can lead to a ‘cure’ when a single fibroid is passed in its entirety.

It is probable that the major complication rate is similar to surgery at around 3%, as has been documented in the HOPEFUL study and also the REST and EMMY trials. The rate of minor complications tends to vary with the classification and differ in type from that following surgery.

**Amenorrhoea**

Temporary amenorrhoea is common. The US Registry quotes 7.3% at 12 months, but the incidence is related to the age of the woman and is particularly common in those over 45. It is probably that UAE also affects the ovarian reserve. This is discussed further under ‘fertility’ below.

**Sexual function**

Adverse changes in sexual function have been reported in approximately 12% of women.

**Infection**

This occurs in 0.5% of cases and is associated with fibroid necrosis and possibly, expulsion. It usually responds to antibiotics but occasionally can cause a chronic problem. In some instances, post-embolization syndrome arises de novo after many months and consequently new onset of pain in a woman who has had embolization means that this must be considered.

**Further intervention**

UAE does not always work and about 25% of women will need further treatment by 5 years. About half of these will have a hysterectomy and the remainder a further UAE, medical treatment or endometrial ablation.

**Evaluation of UAE**

Since this is a relatively new intervention, it has been thoroughly evaluated. There have been a number of randomized controlled trials usually with hysterectomy or myomectomy as a comparator. In addition, there have been large observational studies, including the HOPEFUL trial and also the American Registry. The HOPEFUL trial is an audit comparing the results of UAE carried out in large units throughout the UK and hysterecomy. Data on the latter was obtained from the VALUE audit of 32,000 hysterectomies with data being extracted from women who had the procedure for uterine fibroids. A Cochrane review that originally reported in 2006 has recently been updated.

The best information on safety and major complications can be obtained from the Registry and from the HOPEFUL trial since the RCTs are not powered to demonstrate a difference in complications. The major complication rate is reported at between 3% and 5% which compares favourably with hysterectomy for fibroids. The incidence of minor complications is high. UAE appears to be at least as safe as surgical treatment.

UAE has been shown to be cost-effective since the hospital stay is consistently shorter and normal milestones are reached rapid. HOPEFUL reports a 23% chance of further intervention following UAE at a mean follow-up of 4.6 years, a figure that has been confirmed by the REST and EMMY trials reporting at 5 years.

UAE is a very useful proven uterine sparing procedure but (rather like endometrial ablation and the treatment of heavy menstrual bleeding) spares the majority of women a hysterectomy although success cannot be guaranteed. It is associated with a short recovery time and most patients are very satisfied.

Comparison has been made with myomectomy but studies are small. There are significant issues surrounding myomectomy as will be discussed in more detail in the section on fertility. A small RCT randomized 120 patients and 43 of the myomectomies were laparoscopic. At two years re-intervention after UAE exceeds that after myomectomy. There was also a trend to a higher FSH level in the UAE group. However, there were more pregnancies and fewer miscarriages in the myomectomy arm, although the study is too small for these figures to be conclusive. Further studies of UAE versus myomectomy are underway.

**Fertility issues**

Information regarding fertility after UAE has been derived from small studies since, up until recently, the intention to conceive was considered a contraindication to the procedure by some gynaecologists and radiologists. However, now it is felt that it can be used in women wishing to have a pregnancy in the future. Pregnancies in women who have had UAE have been carefully followed up and more information is available than following other treatments such as myomectomy where data collection is incomplete. However, as some reports have suggested an increase in complications of pregnancy, careful counselling is required.

UAE is associated with ovarian failure as has been mentioned above. However, this is most unusual in younger women but all women must be warned that there is the potential for this to occur, which is obviously unfortunate for somebody wishing to conceive. The studies that have been carried out that include pregnancy as an endpoint suggest that there may be an increase in the likelihood of pre-term delivery, miscarriage, abnormal placentation and postpartum haemorrhage and that these complications occur more frequently than after myomectomy. Uterine rupture has also been reported. However, until a randomized
controlled trial is carried out, this cannot be stated with certainty as the women having myomectomy are often younger and the comparison must be made with other women of the same age who have uterine fibroids and not the population of pregnant women as a whole. Information collection after myomectomy in general is also far from complete.

In addition, the problem with the trials is that sub-fertility often has a multiple causes and many women included are over 35 years of age when fertility tends to decrease naturally. Many women who have uterine fibroids do conceive and it is unclear as to how much impact the position of the fibroids has on outcome as mentioned above.

**Cost-effectiveness**

UAE is thought to be a cost-effective procedure when compared with surgery although the failure rate reflected in the requirement for further surgery of up to 25% may impact on this.

**Levonorgestrel secreting intrauterine system**

This is a very effective method of treating heavy menstrual bleeding in women with a normal uterine cavity or where there are small fibroids. Evidence suggests that it is unlikely to be of value with those who have an enlarged uterus and is often expelled during the menses. It has little or no impact on fibroid size and works by making the endometrium very thin. Many women complain of irregular bleeding, particularly in the early months of use. It is an extremely effective contraceptive and therefore not suitable for women wishing to conceive.

**Progesterone receptor modulators**

Over recent years evidence has grown that progesterone and its receptor play a key role in fibroid growth and development. Initially, it was thought that oestrogen was more important of the two hormones but now this view has been challenged. Some clinical studies have shown that synthetic progestins reverse the effect of gonadotrophin-releasing hormone agonists (GnRH ag) although this is not a consistent finding with all. In addition, although the progesterone receptor antagonists, cause some reduction in mean leiomyoma volume, the presence of intrauterine progestogen does not seem to consistently increase fibroid size suggesting the role of progesterone is less clear cut than that of oestrogen. Studies have been carried out with mifepristone, asoprisnil and ulipristal although only the latter has a license for use in women with fibroids.

**Heavy menstrual bleeding**

Asoprisnil, a novel, orally active and selective progesterone receptor modulator exhibiting partial and mixed agonist/antagonist effects on various progesterone target tissues in animals and humans, has been shown to be effective in decreasing menstrual blood loss.

Asoprisnil has been studied in women with uterine fibroids over a three-month treatment period. It has a dose dependent effect and at higher dosages decreases blood loss in up to 83% of women. It also decreases uterine artery blood flow. Similar studies have now been performed with ulipristal that has received a license for a limited period only prior to hysterectomy or myomectomy. The decrease in menstrual blood loss is highly significant with shorter duration and lighter flow. Progesterone receptor modulators also act very quickly and bleeding is lessened within the first week of use.

**Endometrial effects**

The progesterone receptor modulators induce an unusual appearance of the endometrium. It is associated with an endometrial antiproliferative effect in non-human primates in the presence of follicular phase oestradiol levels. Hyperplasia does not appear to occur with short term use in spite of follicular phase oestrogen levels. Endometrial morphology is described in a way that differs from the normal menstrual cycle. There are profound changes and this may be associated with the efficacy since blood vessels appear to be thickened rather than thin walled and friable as occurs with progestagens when administered alone. The changes are described as the progesterone receptor modulator associated endometrial changes (PAEC) and histopathologists are being trained to identify them and determine the significance. Currently it limits the use to the short term as it is possible that, like oestrogen, the development of abnormal changes increases with duration of use. Development of asoprisnil was suspended for this reason although that of ulipristal is ongoing.

**Fibroid size**

Progesterone receptor modulators have a modest effect on size with a decrease of up to 26%. This means it is unlikely to be effective where fibroid size is the principal presenting complaint. The decrease in uterine artery blood flow documented following the use of asoprisnil is a mechanism that may contribute to the efficacy of other treatments for fibroid-related symptoms such as GnRH agonists as well as the decrease in fibroid size.

Assessment of symptoms associated with fibroids reveals that progesterone receptor modulators are effective and the improvement in the menstrual problems is associated with improved quality of life. Adverse events are most unusual, the drug being extremely well tolerated. Clinical trials have recently been reported and given widespread publicity and it is likely their use will increase.

No major side effects have been documented. When developed further, ulipristal and others like it are likely to be very popular agents for use by women who wish to have conservative treatment for their uterine fibroids.

**High intensity focused ultrasound**

**Mechanism of action**

This is a thermo-ablative technique that has been studied for over 60 years. In the past it has been used to treat tumours of prostate, breast and liver and uses either ultrasound or MRI guidance. The use of MRI guided focused ultrasound surgery (MRgfs) for uterine fibroids, has recently been pioneered and clinical trials are ongoing. It is a non-invasive thermo-ablative technique as in diagnostic ultrasound the waves pass through the anterior abdominal wall and significant heating occurs only where the waves converge at the focus. It provides continuous imaging, not only of the fibroid but also of other surrounding vital structures such as bowel, bladder and sacral nerves. It also allows the temperature of every treatment point to be monitored. Each therapeutic sonication is preceded by imaging of the treatment area and followed by temperature feedback in order that a
surgeon can increase power if necessary to optimize effective
calculation of the tissues. There is also the potential to prevent
damage to other surrounding normal tissues. Early evaluation
studies are being carried out looking at quality of life and the
presenting symptoms of the fibroids. Data are promising,
although the decrease in the size of the uterine fibroids seems to
be modest compared with other treatment modalities.

Safety
It appears to be a safe intervention. The early studies have been
designed to demonstrate safety and only a small proportion of
the total volume has been treated. This has limited the success of
it as it has been documented that the success in providing
symptom relief is proportion to the volume treated. It is also a
very time consuming procedure and a fibroid of about 7 cm in
diameter may take 2 or 3 hours to treat.

Symptom improvement has been demonstrated in many of
the women. Selection criteria to establish which women are
suitable for this procedure are being developed but currently the
technique is limited by the fact that only a small number of fi-
broids can be treated at a session, and consequently those with
multiple fibroids are either unsuitable or need to have multiple
treatment sessions. At the moment the risk of recurrence is un-
clear and only long term studies will be able to determine this.

Effect on size
Although the volume reduction is small, symptom resolution can
occur in its absence, possibly because of its alteration in the
production of angiogenic growth factors from the myomas. It is
also thought to be cost-effective.

Fertility following MRg HIFU
As with UAE the initial clinical trials excluded women desiring
pregnancy although a study designed for women trying to
conceive was commenced but has been abandoned. The mean
age of the women was 37 with 40% over 40. Unlike with many
studies involving women with fibroids, the women were of
normal body weight. Forty one per cent were delivered with 26%
experiencing a miscarriage. Complications were common but it is
difficult to be sure whether the rate is higher in a cohort of
similar women not having the treatment.

Outcome
Data are available at 12 and 24 months. Outcome is directly
related to the non-perfused volume of the fibroid as might be
expected, which impacts on the number of women requiring a
repeat treatment. It is probable that as experience of the tech-
nique grows, that success will increase as more of the fibroid will
be ‘treated’. Long term efficacy does not seem to be associated
with a greater likelihood of adverse events. Sacral neuropathy
has occurred and also skin burns.

Currently it is not readily available as the equipment is only
found in a few centres around the world. However, this is a
modality that is likely to develop and become important in the
treatment of uterine fibroids.

Uterine artery occlusion
Gynaecologists expert in laparoscopic surgery might wish to
carry out uterine artery occlusion to achieve relief of fibroid-
related symptoms. The underlying mechanism is similar to that of
UAE but utilizes external rather than internal occlusion. A
Czech study compares 38 women achieving pregnancy after LUAO
with 20 having UAE. The women included in the study were
younger than those in many similar studies with mean ages of 34
and 32 years for the LUAO and UAE groups respectively. They
were also slender with a mean BMI of only 22 in the LUAO
group. The presenting symptoms are not recorded. The rate of
miscarriage was less in women having LUAO but otherwise
pregnancy outcome appeared similar.

Uterine artery occlusion has been compared with UAE in a
randomized study performed in Egypt. The difference in the
resumption of symptoms (heavy menses) was 2.2% which
although statistically significant, may not be clinically significant.
However, if patients are hysteroscoped 4 months post-treatment,
nearly half of those having UAE have abnormalities of the
endometrium compared with only 3% in those having uterine
treatment although a vast majority are minor.

Conclusion
It will be important to consider position, size and number of the
fibroids when making any comparison between treatment mo-
dalities. UAE and possibly LUAO are likely to be more suitable
for women with multiple fibroids than HIFU. Also, the popula-
tion in the study comparing LUAO and UAE is unclear and if
significant numbers of women have asymptomatic fibroids
associated with some difficulty in conceiving, this may impact on
the results. None of these treatments are likely to be of value in
women with large fibroids as the mean decrease in fibroid vol-
ume is less than 50% in most studies.

If the endometrial changes following administration of pro-
gesterone receptor modulators can be confirmed as being
harmless and insignificant, then it is likely that their use will
develop further as being a safe and effective treatment of
fibroids.

FURTHER READING
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**Practice points**

- Uterine sparing treatments for symptoms associated with uterine fibroids are being developed and thoroughly evaluated
- UAE has been the most extensively studied method and has been shown to be safe and effective
- Progesterone receptor modulators are a very important addition to the treatment choices although they are only advocated currently for short term use
- HIFU is also promising although it is only suitable for women with a small number of fibroids that are not excessively large
- Other treatments are being trialled by those with particular skills such as LUAO
- The impact of these treatments on pregnancy outcome is still uncertain and patients must be carefully counselled.
- These treatments are cost-effective when compared with hysterectomy and myomectomy but further treatment will be required in at least 25% of women
- Recovery time post procedure compares well with surgery