Uterine fibroids
an update for GPs

Uterine fibroids are very common in our community and GPs will be required to assess and manage women with this condition. This update describes recent scientific and clinical advances in this area, together with pointers to possible future therapies.

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Fibroids, or leiomyomas of the uterus, are common but their true incidence is unknown because they develop in more than 45% of women by the fifth decade without coming to clinical attention. They are rare before puberty and normally atrophy after the menopause. Fibroids may be single or multiple and may be located in any part of the uterus, causing variable symptoms that depend on their location within the uterus.

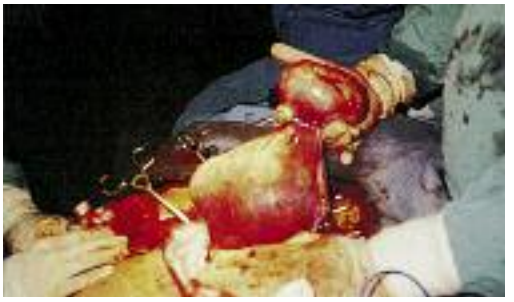


Figure 1. A pedunculated serosal fibroid as seen at caesarean section.

Aetiology

The aetiology of fibroids is uncertain but recent work is shedding more light in this area.

Risk factors for fibroids

The earlier a woman has her menarche the greater her chance of developing fibroids (Table 1). Obesity is another risk factor, the rate of developing fibroids increasing with increasing body mass index (BMI). A family history of fibroids has also been shown to increase a woman's risk of a developing fibroids. Age-adjusted rates for the presence of uterine fibroids among women of African origin are two to three times those of Caucasian women. Pregnancy and hormone therapy may induce growth in fibroids but the chance of such growth is less than 30% (Figure 1).

IN SUMMARY

- **Risk factors for the development of uterine fibroids include an early menarche, obesity, nulliparity and being of African origin.**
- **The incidence and severity of a woman's symptoms depend on the size, number and anatomical location of the fibroids in the uterus.**
- **Diagnosis of uterine fibroids is by clinical examination, pelvic ultrasound examination (including vaginal ultrasound with or without saline infusion sonography), MRI and CT scan.**
- **Beware the postmenopausal fibroid – it may be an ovarian tumour.**
- **Management options for symptomatic fibroids include hysteroscopic submucous fibroid resection, laparoscopic and open myomectomy, laparoscopic or open hysterectomy and in some cases uterine artery embolisation.**
- **The use of GnRH agonists to shrink the size of fibroids before surgery has made both open and endoscopic treatment easier and safer.**

Table 1. Factors affecting fibroid development

Increased risk
Early menarche
Obesity
Family history
African origin

Reduced risk
Live-born children
Cigarette smoking

Unknown effects
Oral contraceptives
Injectable contraceptives
Hormone therapy

It has been shown that women who have had live-born children are at a 20 to 50% reduced risk of fibroids. Cigarette smoking also reduces the risk of developing fibroids.

The effect of exogenous ovarian steroids such as oral contraceptives, injectable contraceptives and hormone replacement therapy on the development of fibroids has also been studied. The results from these areas of study are conflicting and no definitive statements can be made at this stage.

Recent findings

Hormones

Although the initiating factors for the development of fibroids are unknown there is considerable evidence showing that the ovarian steroids oestrogen and progesterone are important factors for tumour growth. Biochemical and molecular studies have shown that fibroids have significantly increased levels of both oestrogen and progesterone receptors when compared with normal myometrium.

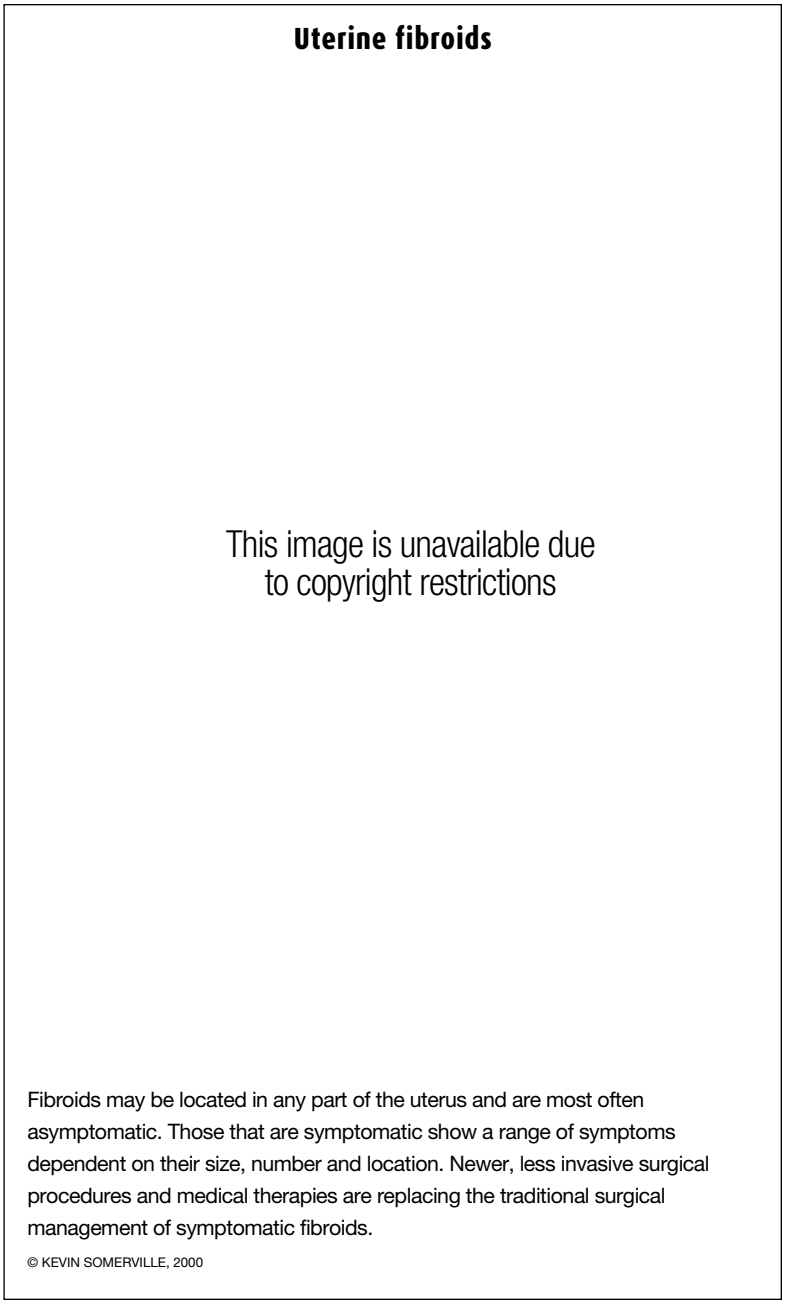
Fibroids also show an increased expression of aromatase P450, which allows cells to synthesise endogenous oestradiol. Oestradiol has been shown to stimulate the proliferation of uterine smooth muscle cells, these cells showing increased mitotic activity and decreased apoptosis.

Increased levels of the bcl-2 protein, a protein that has been shown to prevent the normal course of apoptosis, are also found in fibroids. Production of bcl-2 protein by fibroid cells is significantly increased by progesterone. Thus progesterone may influence the rate of cell proliferation by delaying or inhibiting apoptosis in fibroids.

Growth factors

Many of the growth factors abnormally expressed in fibroids are also abnormally expressed in other mesenchymally derived pathological conditions,

Uterine fibroids



Fibroids may be located in any part of the uterus and are most often asymptomatic. Those that are symptomatic show a range of symptoms dependent on their size, number and location. Newer, less invasive surgical procedures and medical therapies are replacing the traditional surgical management of symptomatic fibroids.

including the formation of keloid scars. A growth factor shown to be involved in wound repair and implicated in a variety of fibrotic diseases is transforming growth factor B (TGF-B). The increased amount of some subtypes of TGF-B found in fibroids is thought to be responsible for the loss of the antiproliferative response of fibroids.

A second group of growth factors found in fibroids are the heparin-binding growth factors. Several of these growth factors are angiogenic in that they stimulate the proliferation of vascular endothelial cells. Fibroids are well-vascularised growths and, like many other tumours, require an adequate blood supply for their continued growth.

The role that insulin-like growth factors play in the growth of fibroids is also being studied, but at present the significance of these results is not clear. Knowledge of what makes fibroids grow will allow the development of treatments that reverse such growth patterns and may provide nonsurgical treatment options in the future.

Cytogenetics

Cytogenetic analysis of fibroids has revealed consistent results: about 40% of fibroids have nonrandom chromosomal abnormalities, including translocation between chromosomes 12 and 14, trisomy 12, rearrangements of the short arm of chromosome 6 and the long arm of chromosome 10, and deletions of chromosomes 3 and 7. These chromosomal abnormalities may represent secondary somatic changes in genetically susceptible cells.

About 60% of fibroids, however, are chromosomally normal and, therefore, further work in this area is required.

Symptoms

As mentioned earlier, the symptoms associated with fibroids are quite variable and depend on the location of the fibroid within the uterus (Figure 2). They include:

- abnormal uterine bleeding
- pelvic pain or pressure
- reduced bladder capacity, with resultant urinary frequency
- constipation
- reproductive dysfunction.

Pressure caused by uterine fibroids on veins and lymphatic channels within the pelvis can also cause lower limb oedema.

Mechanisms by which fibroids cause abnormal uterine bleeding include:

- an increase in the size of the endometrial surface area
- an increase in the vascularity and vascular blood flow in the uterus
- interference with normal uterine contractility
- endometrial ulceration over a submucous fibroid
- compression of the venous drainage within the myometrium.

Pain may be caused by a pedunculated fibroid (submucous or subserosous) twisting on its pedicle and becoming ischaemic. A submucous fibroid may cause a bloody vaginal discharge and uterine cramping pain as the uterus attempts to expel the fibroid from the uterine cavity through the cervix and into the vagina.

Diagnosis

Evaluation of uterine fibroids should include both clinical and ultrasonographic examination to determine their number, size and position (Figure 3). The diagnosis may be obvious on clinical examination but caution is necessary because it is not always easy to distinguish between a uterine fibroid and an ovarian mass clinically. The appearance of a necrotic submucous fibroid coming through the cervix may be mistaken for a cervical cancer, while a pedunculated subserosal fibroid can be difficult to distinguish from an ovarian tumour because clinically it appears to be

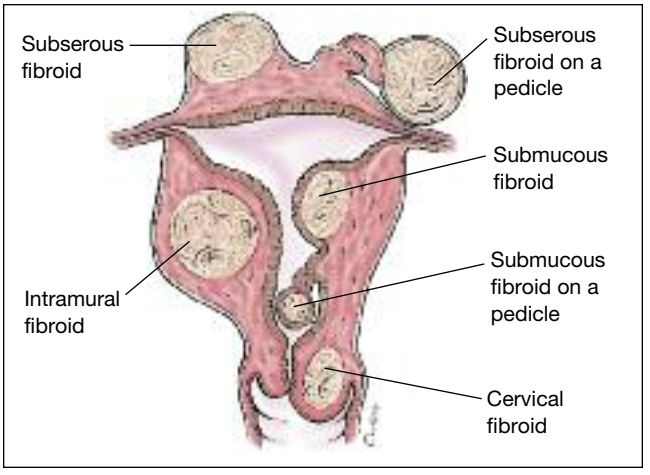


Figure 2. Locations of fibroids within the uterus and cervix. Pedunculated fibroids may twist and cause pain.

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Figure 3. Ultrasound showing a uterine fibroid. Sagittal section; F = fibroid and B = bladder.

separate from the uterus due to its pedicle. The co-existence of an intrauterine pregnancy and fibroids should also be remembered in a woman of reproductive age.

Pelvic ultrasonography, including vaginal ultrasound, and CT scanning (Figure 4) are recommended aids in distinguishing between the above conditions, although even with ultrasonographic assessment it may be difficult to distinguish a solid ovarian tumour from a pedunculated subserosal fibroid. Vaginal ultrasound together with the introduction of saline into the uterine cavity is helpful in distinguishing intrauterine polyps, submucous fibroids and intramural fibroids that indent the uterine cavity. Other causes of distortion to the uterine cavity (such as congenital anomalies) can also be diagnosed by saline infusion ultrasound. X-ray hysterosalpingography, magnetic resonance imaging (MRI), laparoscopy and hysteroscopy can also be of help in making a correct diagnosis, provided that pregnancy has been ruled out beforehand.

Degenerative changes may occur within fibroids, usually because of compromised vascularity. Such changes include hyaline or cystic degeneration, necrosis, red degeneration and calcification.

Fibroids tend to be slow growing benign tumours and are most often asymptomatic, but if growth becomes rapid then conversion to a leiomyosarcoma should be considered. This, however, is rare (one to two cases per 1000 fibroids).

Treatment

Asymptomatic fibroids generally do not require treatment but should be checked annually and scanned every one to two years. Symptoms that necessitate treatment include excessive bleeding, pain, infertility and pressure symptoms. Concerns about the possibility of malignant change in a fibroid warrant surgical treatment.

The traditional management of fibroids has been surgical. Now, with less invasive surgical procedures available, plus the development of medical options and uterine artery embolisation, women have many more treatment options available to them (Table 2). Combinations of medical and surgical treatments are also widely used. Management, however, still involves careful assessment and knowledge of the benefits and risks of each treatment option. Referral for a gynaecological assessment before making a final recommendation for treatment is advisable to ensure that the correct diagnosis has been made. Appropriate counselling of the woman is recommended if the best results are to be obtained.

Table 2. Management options for symptomatic uterine fibroids

Surgical procedures

Hysteroscopic fibroid resection
Laparoscopic myomectomy
Open myomectomy
Laparoscopic hysterectomy
Open hysterectomy
Uterine arterial embolisation (not yet proven)

Medical treatments

GnRH agonists

Surgical treatments

Hysterectomy and myomectomy

Surgical treatment options include hysterectomy and myomectomy. The endoscopic surgical approach includes

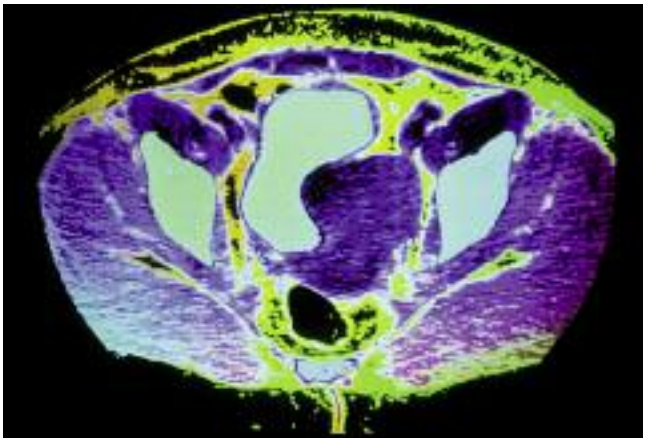

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Figure 4. Coloured CT scan through a woman's lower abdomen showing a large fibroid (centre, dark blue) pressing against the bladder (top centre, light blue). To the left and right of the fibroid are the pelvic bones (also light blue) and below it is the lumen of the uterus (black circle). The yellow areas are uterine wall.

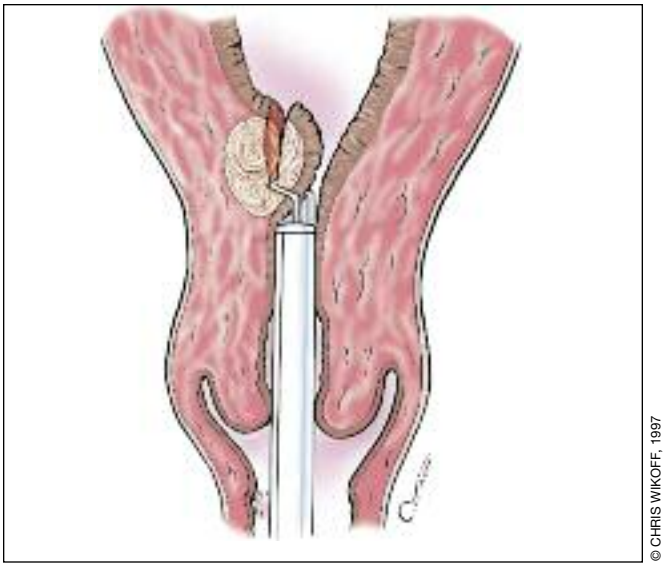

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Figure 5. Hysteroscopic resection of a submucous fibroid.

hysteroscopic and laparoscopic resection or ablation of the fibroids (Figure 5). Destruction of the fibroids can be with myolysis (coagulation) or cryomyolysis using specially designed liquid nitrogen laparoscopic probes to freeze the fibroid tissue. Only experienced laparoscopists should perform laparoscopic myomectomy, and the safety of the procedure for women planning pregnancy requires further evaluation.

The creation of an artificial meno - pause by presurgical treatment with gonadotropin-releasing hormone (GnRH) agonists corrects anaemia, reduces the risk of bloodborne infections (from blood transfusions) and allows what used to be emergency surgery to now be elective surgery. GnRH agonists can also reduce the size of fibroids by up to 50%, thereby making surgery technically easier and therefore safer.

Uterine artery embolisation

Uterine artery embolisation has been used to treat a number of haemorrhagic obstetric and gynaecological conditions including bleeding in cancer, postpartum and postsurgical patients. This newer treatment method is not universally available and, until greater experience with the technique has been documented, is generally considered to still be in its infancy.

The advantages of uterine artery embolisation include:

- ease of bleeder detection
- ability to achieve rapid control of bleeding with or without identification of the exact bleeding site
- ability to assess easily the results of treatment and to reinstitute further embolic therapy in the same or collateral vessels if necessary.

Technical success rates for uterine artery embolisation have been put at 98 to 100%. Complete resolution of the treated fibroid-related symptoms and correction of menorrhagia are above 85%. The complication rate of the procedure is low but complications include severe ischaemic necrosis pain and continuing haemorrhage, both requiring a surgical solution. A recent US study, however, has reported that 29% of women who underwent embolisation for treatment of symptomatic fibroids needed further invasive treatment in the three to five-year period after the procedure, compared with 3% of women treated with abdominal myomectomy.[1] This study emphasises that uterine artery embolisation is still on trial and not yet a proven alternative to surgery.

Currently available medical treatment

GnRH agonists

GnRH agonists such as goserelin (Zoladex 3.6 mg Implant) stop the release of follicle stimulating hormone and luteinising hormone from the anterior pituitary, thereby inducing a medical menopause. This in turn causes fibroids to shrink.

Adverse side effects of treatment include the development of troublesome hot flushes and, if the treatment extends for more than six months, osteoporosis. Treatment is, therefore, restricted to two to three months, and the hot flushes can be managed by the use of very low dose oestrogens without undoing the benefits of reducing the size of the fibroids and stopping menstruation. Suitable oestrogens are oral oestriol 1 mg (Ovestin Tablets) and oestradiol 1 mg (Progynova) and transdermal oestradiol patches 75 µg (Menorest 75). This regimen is called 'oestrogen add back'. If the treatment is stopped, the uterus and fibroids rapidly return to their pretreatment volume and menses return within four to 10 weeks.

Medical therapies under assessment

Mifepristone (RU 486)

Mifepristone is a derivative of norethisterone that has antiprogesterone and antiglucocorticoid activities. Its primary action on fibroids is as an antiprogestin. Studies show that mifepristone effectively treats symptomatic fibroids, and that it has fewer side effects than the GnRH agonists. Unfortunately, mifepristone is currently not generally available for this purpose in Australia.

Interferons

Treatment of fibroids with interferons is being studied overseas. These compounds act by reducing the amount of basic fibroblast growth factor, which has angiogenic activity, or by preventing its action. Interferons may, therefore, be clinically useful in the treatment of fibroid-related bleeding.

Selective oestrogen receptor modulators

Tamoxifen and raloxifene bind to oestrogen receptors and exhibit tissue specific agonist or antagonist activity. Although neither drug has been studied in regard to fibroid treatment in women, preclinical studies in rats caused a 40 to 60% reduction in tumour incidence.

Cytotoxic gene therapy

Cytotoxic gene therapy has been shown to inhibit both tumour growth and benign cellular proliferation in laboratory animals. Further studies are needed before such therapy can be applied to the management of fibroids in humans.

Conclusion

The clinical detection of uterine fibroids is often easy but beware the postmenopausal fibroid because it may be an ovarian cancer. The management options for symptomatic fibroids continue to increase and GPs should be fully informed about methods for investigation and treatment, with their attendant benefits and risks, when advising their patients. MT

Reference

1. Broder MS, Goodwin S, Chen G, et al. Comparison of long-term outcomes of myomectomy and uterine artery embolization. Obstet Gynecol 2002; 100: 864-868.