Fibroids: advice and treatment options

Fibroids occur in over 60 per cent of women and may be responsible for a number of symptoms. This article looks at their management and the advice pharmacists can give.

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FIBROIDS (also known as uterine leiomyomas, uterine myomas or fibromyomas) are benign fibrotic tumours that grow in and around the uterus walls. Fibroids start as microscopic groups of cells but can grow slowly to more than 20cm across. They occur in women of childbearing age, most commonly becoming symptomatic in those aged between 30 and 50 years. Incidence increases with age until the menopause, when fibroids usually stop growing or shrink. Women can have single or multiple fibroids of varying sizes. Fibroids occur in over 60 per cent of women, but only half will experience symptoms. They account for one in five gynaecological outpatient attendances.

Types

There are three main types of fibroid, classified according to growth site, which can affect symptoms and management options:

- **Intramural (growing inside the uterine wall)** Intramural fibroids are the most common and usually do not cause problems unless they are large. However, they can distort the uterine cavity and lead to fertility issues or problems inserting an intrauterine device.

- **Subserosal (growing outward from the uterus into the pelvis)** Subserosal fibroids can grow very large, putting pressure on surrounding organs. They are easiest to remove by laparoscopy (see later).

- **Submucosal (growing inside the uterus, under the endometrium — partially in the cavity and partially in the wall of the uterus)** Submucosal fibroids occur in only about 5 per cent of cases. If they grow long enough, they can protrude through the cervix. Many can be removed by hysteroscopic myomectomy (see later).

Submucosal and subserosal fibroids can also be pedunculated (ie, grow on a stalk; see Image).

Causes and risk factors

The cause of fibroids is not clear and is likely to be multifactorial; growth is stimulated by oestrogens and there is often a family history.

- **Birth control** Asian women tend to have a lower incidence of fibroids.2 Recent research has shown a dose-response correlation between lower serum vitamin D levels and increased severity of exposure. (Obesity leads to increases in extragonadal production of oestrogen. In addition, it is inversely related to serum levels of hormone-binding globulin, resulting in more active circulating oestrogens. There may also be alterations in metabolic control [eg, insulin receptors, insulin-like growth factors, etc] that stimulate fibroid growth.)

- **Other risk factors for fibroids include nulliparity, polycystic ovary syndrome, hypertension and diabetes.**

- The risk of fibroids is reduced by increased number of pregnancies and by the long-term use of progesterones (eg, progestogen-only pill or injection). Asian women tend to have a lower incidence of fibroids.

### Types of fibroid

- **Pedunculated subserosal fibroid**
- **Pedunculated submucosal fibroid**
- **Subserosal fibroid**
- **Submucosal fibroid**

### Causes and risk factors

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### Learning & development

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Reflect

Act

Plan

1 What are the common symptoms of fibroids?
2 What medicines are used to treat fibroids?
3 What self-care advice can be given to women with fibroids?

Before reading on, think about how this article may help you to do your job better.
uterine fibroids. When fibroid status was determined by ultrasound screening of 35- to 49-year-old premenopausal women (620 black, 416 white), it was also found that only 10 per cent of black and 50 per cent of white women had adequate vitamin D levels (ie, >20ng/ml). Women with sufficient vitamin D had an estimated 32 per cent lower odds of fibroids compared with those with vitamin D insufficiency. The association was independent of race.3

Symptoms and complications
Symptoms can be divided into three main classes:

- Menstrual complaints
- Mass effects
- Pregnancy complications

Menstrual complaints include heavy and prolonged periods (menorrhagia). This is mainly associated with submucosal fibroids — due to increased surface area of endometrium, reduced efficacy of uterine contractions to compress vessels and halt bleeding, and deranged vasculature surrounding fibroids. The increased blood loss can lead to anaemia.

Irregular bleeding may result from pedunculated submucosal fibroids.

Painful periods (ie, secondary dysmenorrhoea) can also occur because structural distortions affect uterine contractility.

Mass effects are related to the size and location of fibroids. They include pelvic or abdominal pressure, pain, heaviness, bloating and cramps, with subserosal fibroids often to blame.

The pain and bloating associated with fibroids tends to be constant. However, women often find pain (which may be present more as discomfort than pain for much of the month) is significantly worse during menstruation. Pain may also be experienced in the lower back and legs if a large fibroid is pressing on pelvic nerves. Acute and extreme pain can result from the torsion of a pedunculated fibroid, causing loss of its blood supply and degeneration. Torsion presents a surgical emergency.

Pressure on the bladder can result in urinary frequency or stress incontinence. Other mass effects include constipation or painful bowel movements and discomfort or pain during sexual intercourse. Obstructive renal impairment and renal failure are rare complications.

Fibroids can cause infertility or conception difficulties, and can increase the risk of miscarriage and preterm births. If fibroids growing in the uterine cavity (ie, intramural or submucosal) remain untreated, they can alter the shape of the uterus and position of the cervix so that the number of sperm able to enter the uterus and their ability to move around is reduced. Fibroids can block fallopian tubes and they can alter blood flow to the uterus so that the endometrium does not develop properly. Rarely, fibroids in the cervix can obstruct labour.

All these symptoms have been shown to diminish quality of life and may lead to anxiety or depression. An awareness of these problems will enable pharmacists to have meaningful conversations with women with fibroids.

Fibroids may also be asked about symptoms that require referral to a GP. These “red flag symptoms” are listed in Panel 1. Any women with extremely heavy bleeding (ie, requiring more than three sanitary pads per hour), severe or cyclical pain, dizziness, chest pain or shortness of breath should be sent to an accident and emergency department.

Pharmacists should also be aware that ovarian cancer symptoms can be vague and similar to fibroid symptoms. Any of the following three symptoms, if they occur on most days, require urgent referral.4

- Persistent pelvic and abdominal pain
- Increased abdominal size or persistent bloating
- Difficulty eating and feeling full quickly

Diagnosis
Because fibroids are commonly asymptomatic, they are often discovered during routine gynaecological examinations or scans. A variety of methods can be used to diagnose and assess fibroids including:

- Ultrasound scan (including use of a transvaginal probe to visualise smaller fibroids)
- Hysteroscopy (inspection of the uterine cavity with an endoscope via the cervix)
- Laparoscopy (inspection of the pelvic and external uterine structures with a laparoscope via an incision in the abdomen)
- Biopsy
- Other imaging (eg, magnetic resonance imaging)

Fibroids may be described in terms of the size the uterus has become and likened to the expected size at different weeks of pregnancy.

Management
Since fibroids are non-cancerous, treatment is reserved for those with symptoms, women with large asymptomatic fibroids or when fertility is affected. Women with mild symptoms or who are near menopause may prefer not to have any treatment. The aims of treatment include alleviating symptoms (eg, reducing bleeding or pain), shrinking the fibroid(s) and removing them. Sometimes medication is used to shrink fibroids before removal.

Treatment options are influenced by symptom severity, size and location of the fibroids, age and proximity to the menopause (on average 52 years in the UK), and the desire to maintain fertility. Some treatments can affect fertility temporarily or permanently. For example, the levonorgestrel intrauterine system (IUS) is contraceptive. Pregnancy is not advised after endometrial ablation.

Pharmacological treatment
About 30 per cent of women will request treatment for pain or heavy menstrual bleeding. The National Institute for Health and Care Excellence recommends in its clinical guideline for heavy menstrual bleeding that treatments should be considered in the following order:5

- Levonorgestrel-releasing intrauterine system (where at least 12 months’ treatment is expected)
- Combined oral contraceptives or, for women in whom hormonal treatments are not acceptable, tranexamic acid or non-steroidal anti-inflammatory drugs
- Norethisterone or injected progestogen

Intrauterine levonorgestrel The release of levonorgestrel from an intrauterine system (IUS; eg, Mirena) prevents endometrial proliferation so both the duration

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**PANEL 1: SYMPTOMS TO REFER TO A GP**

- Abnormal vaginal bleeding (irregular, intermenstrual, postcoital or post-menopausal)
- Abnormal vaginal discharge
- Secondary dysmenorrhoea (ie, new pain that occurs because of a medical condition [this tends to be in older women])
- Rather than primary dysmenorrhoea (pain which usually begins in the first year or so after periods start and is due to the normal process of menstruation)
- Severe intermenstrual pain and bleeding
- Pain or heavy bleeding uncontrolled by analgesics and tranexamic acid, respectively
- Pain with a late period (ectopic pregnancy possible)
- Fever or night sweats (could indicate malignancy or an urinary tract infection if fibroids affect bladder emptying)
- Pelvic mass or change in abdominal girth
- New pain after the menopause
- New bowel symptoms in patients over 50 years of age
- Excessive or unexplained weight loss

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and amount of menstrual bleeding are reduced. Blood loss can be reduced by over 90 per cent at three months, but irregular bleeding may occur for three to six months and women unable to tolerate this will request to have the device removed. Other side effects include acne, breast tenderness, weight gain and bloating.

Mirena is inserted into the uterine cavity within seven days of the onset of menstruation and should be replaced after five years if continued treatment is necessary. This treatment is not suitable for women who are trying to conceive, although fertility is restored on removal. The IUS is occasionally expelled spontaneously and this may be a greater risk with submucosal fibroids or large intramural fibroids disturbing the uterine cavity. Women should be advised to feel for the threads monthly.

Tranexamic acid

Tranexamic acid is an antifibrinolytic which is a potent competitive inhibitor of the activation of plasmogen to plasmin. It should be initiated when menstrual bleeding has started. It has been shown to reduce menstrual loss by up to 58 per cent. The recommended dosage is 1g orally tds for up to four days. If the bleeding is heavy, the dosage may be increased to 4g daily. Gastrointestinal discomfort is the most common side effect.

Tranexamic acid may be sold for use by women aged 18 years or over to reduce heavy menstrual bleeding over several cycles. Cycles must be regular (21–35 days) with no more than three days’ variability in duration. Women who have taken tranexamic acid for three menstrual cycles without a reduction in bleeding should be referred to their GP.6

NSAIDs

Non-steroidal anti-inflammatory drugs are the treatment of choice for women who also have dysmenorrhea because their inhibition of prostaglandins means that they reduce blood loss by 20–50 per cent as well as reducing pain. Over-the-counter options include ibuprofen, naproxen and diclofenac. (Note, however, that OTC naproxen is licensed for primary dysmenorrhoea only.) On prescription, mefenamic acid is licensed for heavy menstrual bleeding. Aspirin is not recommended because it is less effective at reducing menstrual bleeding and has a higher risk of side effects.

To maximise analgesic efficacy women can be advised to take NSAIDs from the start of their pain or bleeding (or from the day before a period is due) and to take them regularly for two to three days. Ensure women are taking effective dosage (eg, 200–400mg ibuprofen tds). For pain relief in women who cannot take NSAIDs or who experience gastrointestinal upset, paracetamol is an alternative but it lacks prostaglandin inhibition.

Other hormonal treatments

Combined oral contraceptives (COCs) are second-line after levonorgestrel-releasing IUSs for heavy menstrual bleeding associated with fibroids.7 COCs regulate the menstrual cycle and decrease endometrial growth, giving symptomatic improvement including reduction in blood loss. Although fibroid growth is partly hormone dependent, COCs or progestogens used to manage symptoms do not appear clinically to increase fibroid volume.

The third-line alternative oral norethisterone may be used at a dose of 15mg daily from days 5–26 of the menstrual cycle to give significant reduction of bleeding. (Note there is limited trial evidence for “long-course” use [unlicensed] compared with shorter-course licensed use from day 19 to 26).8 If the other third-line option, long-acting injectable progestogen (Depo-Provera), is used for over two years, bone mineral density should be reviewed.

Drugs used to shrink fibroids or used pre-operatively include GnRH analogues and ulipristal.

GnRH receptor agonists

GnRH receptor agonists reduce fibroid volume through inhibiting oestrogen. Initial stimulation of pituitary gonadotrophins causes an increase in luteinising hormone and follicle-stimulating hormone and initial rise in oestrogen levels but continuous or repeated administration inhibits the pituitary-gonadal axis and induces a hypo-oestrogenic state. Menorrhagia is improved and some patients may become amenorrhoiec.

The GnRH agonists licensed in the UK for treating fibroids are goserelin (3.6mg by injection every 28 days, maximum three doses), leuprorelin (3.75mg by injection every month, maximum six months) and triptorelin (3mg by injection every four weeks, minimum three and maximum six months’ treatment).

Treatment duration is limited by side effects. Regression is not permanent and on stopping treatment fibroids may return to their original size or may also become larger. Half of patients given leuprorelin had up to six months’ sustained symptomatic benefit even though the uterus had returned to pre-treatment size. GnRH agonists are most often used to shrink fibroids pre-operatively to reduce bleeding complications and allow use of less invasive techniques.

Side effects include menopause-like symptoms of oestrogen deficiency (eg, hot flushes, increased sweating, muscle stiffness, vaginal dryness) and decreased bone mineral density. Hormone replacement therapy may be prescribed to prevent these without compromising the efficacy of treatment. Examples include Tibolon, raloxifene (benefit on bone loss only), oestrogens and progestogens (either separately or combined).

Ulipristal

An oral, selective progesterone receptor modulator (SPRM) with a partial progesterone antagonist effect, ulipristal (Esmya®) was licensed in 2012 for the pre-operative treatment of uterine fibroids. Uterine bleeding, pain and fibroid volume are reduced by approximately 20 per cent and quality of life improved without the side effects of other treatments such as the GnRH agonists. Median time to amenorrhoea at the licensed dose in clinical trials (PEARL I and PEARL II) was seven days. In the PEARL I study, 73 per cent of
patients were amenorrhoeic by week 13.7,8

Anecdotal evidence suggests that the beneficial effects are maintained for some time after stopping treatment. There is, as yet, no long-term data on effects on the endometrium, general health or fertility. Benign endometrial histological changes have been detected during treatment, although these returned to normal within six months of stopping treatment in most patients. The licence has recently been revised so that the initial three-month course may be repeated once.

Daily oral dosing may be preferred by many women to monthly injections of a GnRH agonist and will reduce clinic workload. The dose is 5mg daily, starting during the first week of the menstrual cycle for up to three months.

Drug interactions include CYP450 inhibitors and inducers, hormonal contraceptives and drugs affecting gastric pH. Patients should be advised to avoid grapefruit juice and St John’s wort.

A number of other drug treatments for fibroids have been investigated and examples are given in Panel 2.

Medical procedures
Other management options for fibroids include surgery, endometrial ablation and interventional radiology. Symptoms can be reduced by removing the fibroids (laparoscopic or hysteroscopic myomectomy) or the whole uterus (hysterectomy). About 30,000 women each year have a hysterectomy in the UK because of fibroids.

Endometrial ablation, including radiofrequency, thermal balloon, microwave or MRI-guided percutaneous laser ablation will reduce bleeding. Some ablation methods will remove small fibroids. Interventional radiologists use uterine artery ablation (UAE) to shrink the fibroids, with 60 per cent shrinkage at six months and further improvement possible up to a year. There are currently no long-term data on recurrence rates but 20–25 per cent of patients having UAE may need further treatment within five years. UAE may increase the risk of requiring a caesarean section and there is the possibility of other pregnancy complications. The implications of all the treatment options must be discussed fully with the woman before a decision is made, including the likelihood of success of any desired pregnancy.

Self-care advice
There is plenty of advice that pharmacists can give on self-management of fibroid symptoms. For pain, in addition to offering an NSAID or other analgesic, the following can be recommended:

- Applying local heat (eg, use a hot water bottle or heat pad, or take a warm bath)
- Trying transcutaneous electrical nerve stimulation
- Exercising (may help ease pain as well as aiding weight loss)

For menorrhagia, tranexamic acid may be offered with the advice to see a GP if the bleeding does not improve after taking it for three periods in a row or if new symptoms develop. Tranexamic acid may be used in combination with NSAIDS.

Patients concerned about bleeding may have a symptom diary recording pain, cycle length and the number of sanitary towels or tampons used, which will be useful for their doctor.

Pharmacists can also give advice on supplements (see Panel 3). They can look out for signs of anaemia and be aware of women at risk of vitamin D deficiency (eg, those with dark skin or little sun exposure) so that information on dietary vitamin D intake and safe sun exposure can be offered.

For patients with constipation related to fibroids, pharmacists can ensure that the use of opioid analgesics is minimised. They can also advise on maximising fluid and fibre intake and exercise, as well as recommending a suitable OTC laxative (eg, lactulose, ispaghula husk, senna and docusate).

Pharmacists can also signpost patients to support groups such as the British Fibroid Trust and the Pelvic Pain Support Network.

Further reading
- The National Institute for Health and Care Excellence has developed a clinical guideline on heavy menstrual bleeding (CG44, 2007)
- The Royal Pharmaceutical Society has produced a quick reference guide on ovarian cancer that includes key signs and symptoms for use by pharmacists and pharmacy staff.
- There is also a Royal Pharmaceutical Society quick reference guide related to the OTC supply of tranexamic acid.