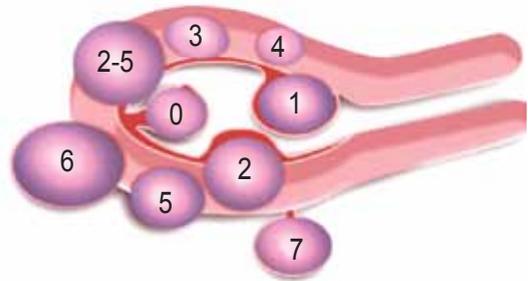
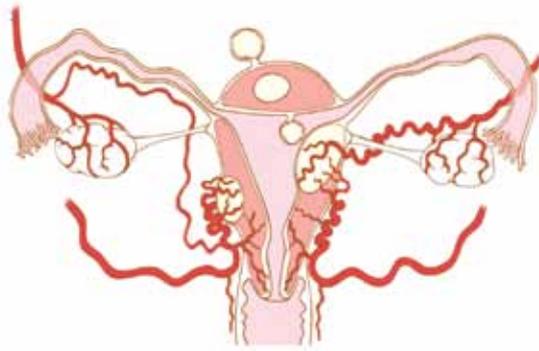


WOMEN'S HEALTH

Volume : 10, No. : 1 Jan - Jun 2017



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Editorial Note:

Dear Doctor,

It is our immense pleasure to inform you that we have published our newsletter, "Women's Health". In this issue we are focusing on "An Overview of the Aetiology, Epidemiology, Symptomatology and Management of Uterine Fibroids".

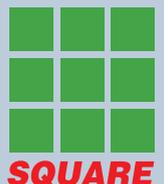
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An Overview of the Aetiology,
Epidemiology, Symptomatology and
Management of
Uterine Fibroids.



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An Overview of the Aetiology, Epidemiology, Symptomatology and Management of Uterine Fibroids

Uterine leiomyomas or fibroids are benign tumours arising from the smooth muscle cells of the myometrium. Clinically apparent in 25 % of women, they are the most common benign tumour affecting females. Whilst their exact prevalence is unknown, studies suggest that in women over the age of 50, fibroids are present in over 70 % of white women and up to 80 % of black women.

Historically, they were broadly classified as to their anatomical position, be it uterine (subserosal, intramural or sub-mucosal), cervical or in the broad ligament. More recently a tertiary classification has been developed, further categorizing lesions according to their specific intramural position and encroachment of the cavity. This is particularly helpful to clinical investigators and those planning surgical intervention.

Aetiology

The exact aetiology for the development of fibroids remains unknown; however, several studies have hypothesised that irrespective of size, fibroids develop following a mutation in a single smooth muscle cell, which then grows into a tumour via clonal expansion. It is well known that oestrogen and progesterone play an important role in the pathogenesis of fibroids; however, the exact mechanism by which they do so is unknown. There is some evidence that despite often normal serum levels of oestrogen and progesterone, levels of estradiol are higher in fibroids than in normal myometrial cells, thus leading to the up-regulation of both oestrogen and progesterone receptors with a consequent increase in mitotic activity. The overexpression of growth factors is also important, with factors including transforming growth factor B (TGFB), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) contributing.

Epidemiology

There are a variety of risk factors predisposing to the development of uterine leiomyomas, although caution must be exercised in the interpretation of the literature, much of which relates to Caucasian populations and some of which appears to be conflicting. The incidence of leiomyomas increases with age throughout the reproductive years, mimicking the physiological changes in reproductive hormones. Factors which increase lifetime exposure to oestrogen, such as obesity, early menarche and nulliparity have all been shown to increase the risk of developing fibroids, whereas factors such as high parity and early menopause, which decrease exposure to oestrogen, are protective. The role of the combined oral contraceptive pill (COCP) is controversial, with directly conflicting evidence available in the literature.

However, the progesterone only contraceptive depot medroxy-progesterone acetate has been shown to reduce the risk of fibroids and there is some evidence that the levonorgestrel bearing intra-uterine device (LNG-IUS) does the same.

It is well known that fibroids are more common in black women than in white women, although the reasons for such racial variance are poorly understood. Some studies report black women as between three to five times more likely to be affected. Additionally, black women are often younger at first presentation and tend to suffer with larger, more symptomatic fibroids. Despite the failure to identify specific genes as being directly involved in the development of fibroids, there is undoubtedly some heritability surrounding the condition, which often demonstrates familial clustering with first-degree relatives of sufferers 2.5 times more likely to be affected. In addition, twin studies demonstrated a higher risk of fibroids in monozygotic compared with dizygotic twins.

Presentation

Whilst the majority of fibroids are asymptomatic, those that do cause symptoms often result in significant morbidity. Symptoms commonly attributed to fibroids include abnormal bleeding, pelvic pain, pressure symptoms and infertility, with the location and size of the fibroids being important in determining which combination of symptoms, if any, occur. The bleeding pattern most commonly associated with fibroids is that of heavy menstrual bleeding or menorrhagia, which in many cases can result in iron deficiency anaemia. Submucous fibroids or those large enough to distort the endometrial cavity are most commonly associated with excessive bleeding; however, it may also occur in their absence on account of dilation of the endometrial venous plexuses caused by fibroid obstruction of myometrial veins. Whilst the size of fibroids does not necessarily correlate with the severity of symptoms, large fibroids may cause pressure symptoms which vary in accordance with the location of the fibroid and may sometimes be associated with pelvic pain. Anterior fibroids may cause urinary symptoms, whilst posterior fibroids may cause problems with defecation. Acute pain associated with fibroids is uncommon, however, may occur in the context of fibroid degeneration or in rare cases of torsion of pedunculated fibroids. The evidence surrounding fibroids and infertility is conflicting; however, there appears to be a general consensus that unless the fibroids are distorting the uterine cavity, they are unlikely to have a detrimental effect on fertility. Removal of fibroids distorting the cavity has, in some studies, been shown to improve conception rates; however, a recent Cochrane review was conflicting.

Diagnosis

The diagnosis of large fibroids is usually made clinically, based on the abdominal and bimanual findings of an irregularly enlarged, non-tender uterus. This is then confirmed on imaging, typically ultrasound. Smaller, asymptomatic fibroids are sometimes diagnosed incidentally, following imaging for other reasons. Ultrasound tends to be the first line of investigation, allowing assessment of the number, size and specific location of the fibroids, which appear as well defined hyper echoic and heterogeneous

masses. Submucosal fibroids, however, are harder to assess in this modality and may require additional imaging via hysteroscopy or saline infusion sonography, whereby saline is introduced into the endometrial cavity as a contrast medium to improve accuracy of assessment during conventional ultrasonography. MRI imaging, with its increased sensitivity and specificity, has been shown to provide a superior evaluation of fibroids and is frequently employed to help plan more invasive treatments such as uterine artery embolisation or myomectomy.

Classification

Numerous classifications of myomas can be found in the literature. All of them take into account the degree of intramural extension and/or uterine cavity distortion. The fibroid classification adopted by the ESGE (European Society for Gynecological Endoscopy) has the advantage of being very simple (G0 is a pedunculated intrauterine myoma, G1 has its largest part (>50%) in the uterine cavity, and G2 has its largest part (>50%) in the myometrium).

Fibroids can also be classified by their location: submucosal, intramural, and subserosal (Fig 1). Pedunculated fibroids can be intracavitary or exophytic and can undergo torsion or derive new

blood supply from adjacent structures (parasitize). Intramural fibroids are the most common type of fibroid, while submucosal fibroids are the least common type. However, a submucosal fibroid may be more symptomatic than a subserosal or small intramural fibroid, owing to its relationship with the endometrium. Bulk symptoms are more often seen with large intramural or subserosal fibroids.

Although a high-quality ultrasonography (US) examination may be sufficient for evaluation in patients with straightforward cases of fibroids (for instance to estimate the size of a dominant fibroid), imaging evaluation is most reliably performed with magnetic resonance (MR) imaging to determine the characteristics, number, size, and location of fibroids and to assess for other pathologic conditions such as adenomyosis. The recognition of adenomyosis is important as it may alter the treatment approach, patient counseling and expectations. Adenomyosis is a diffuse or focal endometrial basal layer invasion of the myometrium that can cause symptoms similar to fibroids, and it is best seen on MR images as a thickened junctional zone (>12 mm), with scattered T1- and T2-hyperintense foci of endometrial glands (Fig 2).

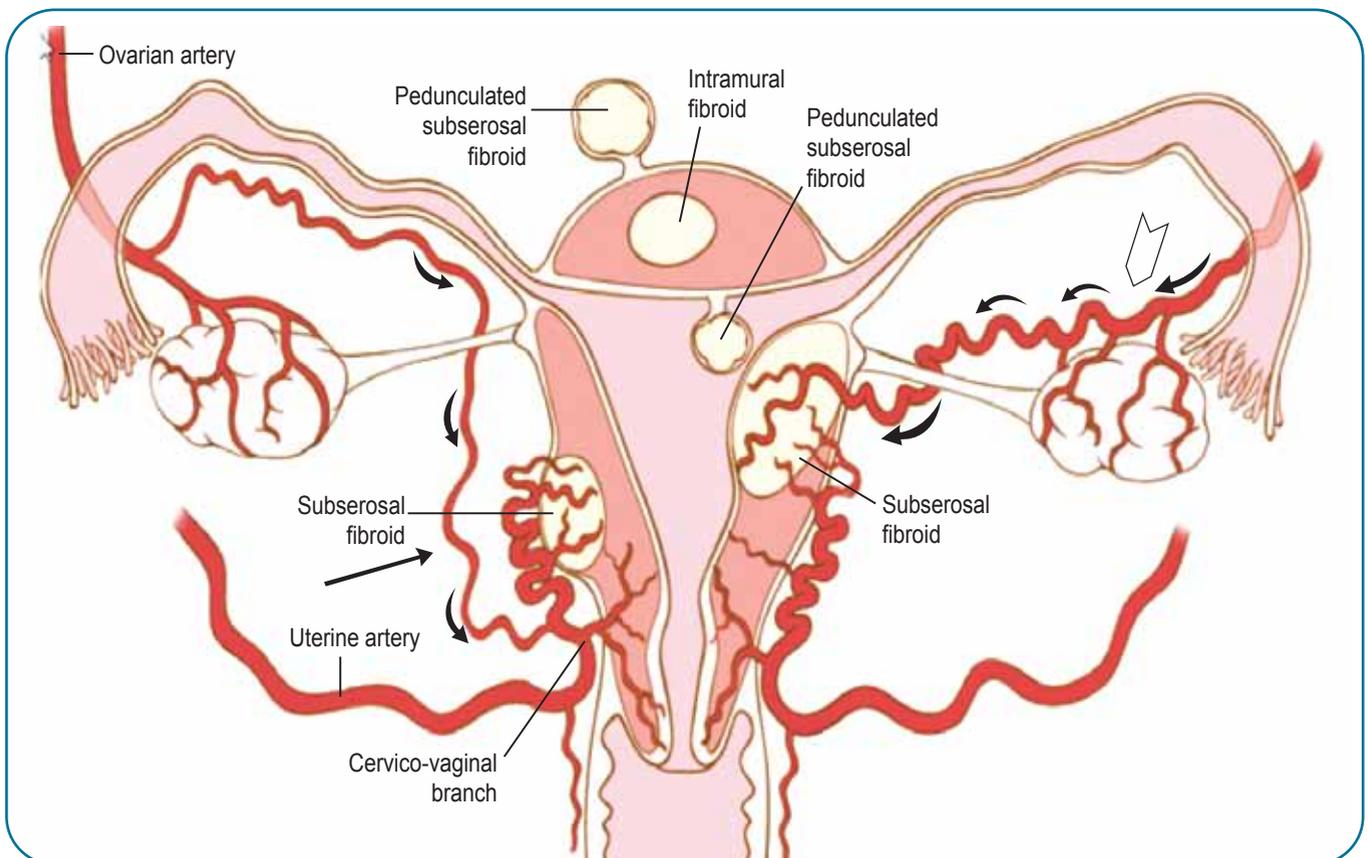


Figure 1: Illustration of fibroid location classification. A type I utero-ovarian anastomosis is depicted on the left of the figure (straight arrow) with flow from the ovarian artery toward the uterus in the tubo-ovarian segment feeding into the intramural portion of the uterine artery (curved arrowheads indicate direction of blood flow). A type II utero-ovarian anastomosis is depicted on the right of the figure (open arrowhead) with at least partial direct supply of the fibroid by the ovarian artery without prior connection to the uterine artery. Note that less common extrauterine locations, such as cervical or broad ligament fibroids, are not included (the incidences of which have not been well studied).

Studies reveal that pretreatment MR imaging evaluation may alter therapy in about 20% of patients with fibroids.

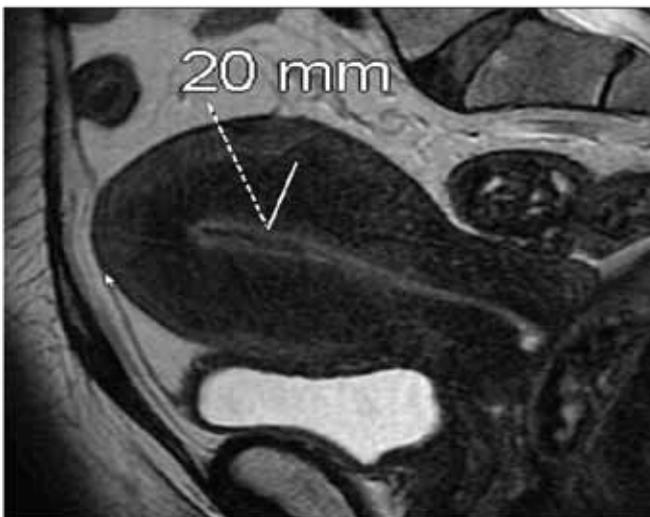


Figure 2: Sagittal T2-weighted MR image of a uterus with adenomyosis, indicated by junctional zone thickening greater than 12 mm (T2- and T1-hyperintense foci of myometrial glandular tissue support the diagnosis, not depicted here).

More recently, the FIGO classification was published, describing eight types of fibroids as well as a hybrid class (association of two types of myomas) (Fig. 3). As different types of fibroids are often present at the same time (depending on the site), this classification offers a more representative 'map' of fibroid distribution and will be used further for the establishment of new algorithms.

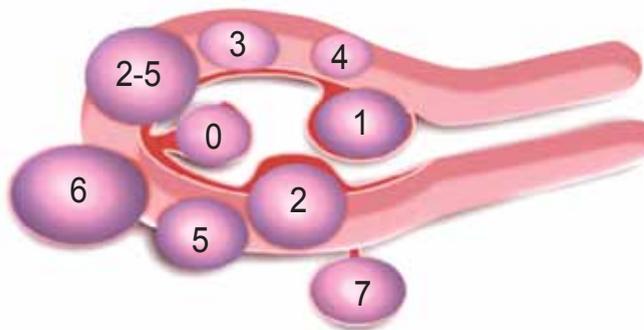


Figure 3: FIGO classification of uterine fibroids.

Fibroid types range from 0 to 8.

0=Pedunculated, intracavitary; 1=Submucosal, <50% intramural; 2=Submucosal, ≥50% intramural; 3=Contact with endometrium, 100% intramural; 4=Intramural; 5=Subserosal, ≥50% intramural; 6=Subserosal, <50% intramural; 7=Subserosal, pedunculated; 8=Other (e.g. cervical, parasitic). Where two numbers are given (e.g. 2-5), the first number refers to the relationship with the endometrium, while the second number refers to the relationship with the serosa; e.g. 2-5= Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities respectively.

Principles of Management

As previously stated, the majority of fibroids are asymptomatic and so may be managed expectantly, without the need for any intervention. For those causing symptoms, treatment is tailored to

the individual, based on the symptoms, size and location of the fibroids, age and desire for future fertility and is broadly classified into medical or surgical management.

Medical options for fibroids and bleeding

Leuprolide Acetate (GnRH agonists/antagonists)

- Controls bleeding
- Shrinks fibroids

Ulipristal Acetate (Selective progesterone-receptor modulator)

- Controls bleeding in >90% of women
- Shrinks fibroids

Ulipristal Acetate 5 mg is the US FDA approved only oral medication to treat uterine fibroids without surgery.

Ulipristal Acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Ulipristal Acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Dosage Guideline

The treatment consists of one tablet of 5 mg to be taken once daily for treatment courses of up to 3 months each.

Tablets may be taken with or without food. Treatments should only be initiated when menstruation has occurred.

The first treatment course should start during the first week of menstruation. Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion. The treating physician should explain to the patient the requirement for treatment free intervals.

Repeated intermittent treatment has been studied up to 4 intermittent courses.

If a patient misses a dose, the patient should take Ulipristal Acetate as soon as possible. If the dose was missed by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

Surgical Management

Whilst hysterectomy has always been the most effective treatment for symptomatic fibroids, it constitutes major and definitive surgery and is not always appropriate or indeed preferable, for all patients. As women are choosing to have their families later, there is increasing demand for fertility sparing procedures, of which myomectomy is the most popular. This involves resection of the fibroids whilst preserving the uterus and is increasingly performed via laparoscopic and hysteroscopic techniques. Whilst seemingly a less invasive procedure than hysterectomy, the morbidity rates are comparable, with haemorrhage and infection the most commonly occurring complications and post-operative adhesion formation frequent. Laparoscopic myomectomy, whilst boasting a significantly shortened recovery time and reduced postoperative pain compared with open procedures, often takes longer and is technically more complex. Even with the most expert of operators, laparoscopic.

UtalTM

Ulipristal Acetate INN 5 mg

Tablet



*The only medication to treat Uterine Fibroids
without surgery*

Dosage Guideline

- Once daily for 3 months
- The dose can be repeated with a gap of 4 weeks



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myomectomy still carries an 11.3 % chance of necessitating conversion to open myomectomy. Additionally, laparoscopic procedures are associated with a much higher recurrence rate when compared with open myomectomy, the figures quoted at 51 % and 10 %, respectively, after 5 years. There have also been concerns that the uterine scar following laparoscopic myomectomy may not be as resilient as that of an abdominal procedure and may therefore be more likely to rupture during a subsequent pregnancy, although this is not well supported in the literature. For submucosal fibroids, there is the option of hysteroscopic resection, which may be undertaken as a daycase procedure, often under local anaesthetic or mild sedation. The risk of complication is low and satisfaction rates are high. Despite evidence to suggest that myomectomy, irrespective of route, increased the risk of uterine rupture and the need for operative delivery in subsequent pregnancies, a further study did not show any increased risk of adverse outcome in the fetus.

Whilst the concept of uterine artery embolisation (UAE) is not new to gynaecologists, its role in the treatment of fibroids is evolving. The procedure involves the percutaneous insertion of polyvinyl alcohol particles, via a femoral artery catheter, into the ipsilateral or contralateral uterine artery, interrupting the blood supply to the uterus, resulting in ischaemic degeneration of the fibroids. Whilst many women suffer with pain and nausea in the immediate post operative period, it is a generally well tolerated and safe procedure. Other rarer complications include hot flushes and mood swings, fibroid expulsion and necrotic fibroid infection. Premature ovarian failure is documented in approximately 1 %; however, this tends to be limited to women over the age of 45. Following UAE, 80–90 % of patients report either an improvement or complete cessation of their symptoms within the year, with an associated 40–70 % reduction in fibroid volume. Studies comparing outcome with hysterectomy are similar, with symptom control and satisfaction nearly identical. Recovery rates for UAE are significantly shorter, with most women discharged home the following day. Complication rates are also similar; however, those related to UAE often occur much later than those of hysterectomy. Re-intervention rates are significantly higher in women who have undergone UAE and are quoted as up to 32 % at 5 years. The evidence comparing UAE with myomectomy is less substantiated; however, again symptom control and satisfaction rates are similar. Recovery time was shorter in UAE; however, again re-intervention rates were higher.

Despite being offered to women wishing to retain their fertility, the impact of UAE and myomectomy on fertility and subsequent pregnancy outcomes remains relatively unknown. Evidence is sparse and attempts at direct comparisons blighted by multiple confounding factors. Given the current lack of evidence based-recommendation regarding the best fertility sparing treatment for women with fibroids, the Royal College of Obstetricians and Gynaecologists (RCOG) whilst supporting the role of both UAE and myomectomy, recommends a careful discussion of the pros and cons of this with a clinician who has an interest in assisted reproduction and fertility.

For women who have completed their family and are looking for a permanent and definitive treatment, hysterectomy remains the only treatment to guarantee complete resolution of symptoms and eliminate any chance of recurrence. Historically, this would routinely be performed as an abdominal procedure; however, as surgical technique advances, this is increasingly undertaken laparoscopically or indeed vaginally, thus reducing intraoperative blood loss, recovery time and hospital stays. The ability of ultrasound to interact with tissues is well recognised, with high intensity ultrasound having the potential to heat tissues to a temperature sufficient to cause cell death. Historically, its therapeutic use has been limited by an inability to appropriately target the energy; however, with advances in imaging techniques, this is now achievable with the concurrent use of MRI.

In the treatment of fibroids, patients are positioned prone on a specially integrated bed, whereby the ultrasound is delivered through a phased array transducer via a gel pad and waterbath. Simultaneous MRI imaging allows ultrasonic energy to be targeted to a specific point within the fibroid to facilitate focal tissue necrosis. It also provides quantitative temperature feedback to assess outcome and post treatment imaging to evaluate results. Small-scale trials confirm an excellent safety profile and good short term efficacy, with improvement in symptoms and a concurrent decrease in the size of the fibroid. That said more research is needed to establish longer-term efficacy and outcome. In 2004, the FDA approved the use of magnetic-resonance-guided focused ultrasound surgery (MRgFUS) in women with a uterine size less than 24 weeks and in whom childbearing was complete. This was updated in 2015 to allow consideration of women who wished to maintain their fertility. Although limited, the evidence available reports maintained fertility with most subsequent pregnancies being carried to term without complication.

Conclusion

Fibroids are the most common benign tumour to affect women and although many are asymptomatic, those that do cause symptoms often do so with significant morbidity. With women choosing to start their families later in life, there is an increasing demand for fertility sparing treatments, thus excluding many of the current management options. Of those available, there is relatively limited research regarding subsequent fertility and pregnancy outcomes, necessitating further, more robust, research. For women seeking a more definitive treatment, the recent controversy regarding the use of morcellators in laparoscopic hysterectomy has restricted their use, thus limiting access to minimally invasive surgical treatment. As with any proposed management, women should be fully counselled regarding all of their available options and the potential risks involved with each. Treatment should be tailored to the individual patient and planned according to the presentation, size and location of the fibroids. Where appropriate the need for future fertility should be considered and options presented based on the best available evidence.

- References :** 1. Curr Obstet Gynecol Rep (2016) 5:65–72
2. www.fda.gov



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