Nonsurgical Treatment of Uterine Fibroids

1. Introduction

Uterine fibroids are the most common pelvic tumours. Their incidence increases with age through the reproductive years, and they are more common in certain ethnic populations. The frequency of fibroids reported in the literature varies widely due to differences in diagnostic tests, populations studied and study design. The largest study to date, carried out in the USA, followed up on 95,061 female nurses aged 25–44 years prospectively, with questionnaires every 2 years to determine the incidence of fibroids among premenopausal women by age and race. The diagnosis of fibroids was self-reported and confirmed for a sample of cases. The crude incidence rate in this study was 12.8 per 1000 woman-years. The standardised rates were much higher in black than in white women; 30.6 and 8.9 per 1000 woman-years respectively. Even after adjusting for variables such as body mass index, infertility and contraception, the rates among black women were significantly higher than those among white women (relative risk [RR] 3.25; 95% CI 2.71–3.88). The prevalence of fibroids is lower in certain European countries. A Swedish study of 335 women, randomly selected from the Swedish population register, who underwent transvaginal ultrasonography showed a prevalence of 3% in women aged 25–32 years, and 8% in those aged 33–40 years. An Italian cohort study demonstrated an incidence of ultrasound-detected fibroids of 21% in a series of 341 unselected premenopausal women aged 30–60 years.

Nonsurgical treatment options for the management of fibroids are more popular of late; however their precise role in the overall management of uterine fibroids remains poorly defined, with some limited to facilitating the process of surgery and others seen as standalone treatments, potentially eliminating the need for surgery. This Scientific Impact Paper aims to clarify the potential place of nonsurgical interventions for uterine fibroids to aid clinicians and their patients.

2. Pathogenesis of uterine fibroids

The underlying pathogenesis and pathophysiology of fibroids is highly complex and far from completely understood. Ovarian steroids, oestrogen and progesterone are important in the pathogenesis of fibroids. It has been shown that fibroids have increased levels of oestrogen and progesterone receptors compared with normal myometrium, and an increased expression of the enzyme P450 aromatase, which allows the cells to synthesise their own endogenous estradiol, promoting growth by stimulating the proliferation of uterine smooth muscle cells. Progesterone on the other hand, through its production of the apoptosis inhibitor BCL-2 protein, increases fibroid bulk by inhibiting their programmed cell death.

Growth factors increase smooth muscle proliferation and act in a paracrine or autocrine manner. They are also responsible for the increase in the extracellular matrix (collagens, proteoglycans and fibronectin) associated with fibroids. The growth factors, transforming growth factor beta (TGF-β), heparin binding factor and insulin-like growth factor (IGF), have been identified in fibroids.

Cytogenetic examination of fibroids reveals that about 40% have chromosomal abnormalities, including translocations, trisomies, deletions and rearrangements. The remainder appear chromosomally normal, but exhibit mosaicism within the monoclonal tumour. These karyotype abnormalities correlate with fibroid size and site. The mechanisms that link the clinical phenotypes to their underlying genotypes vary. For example, translocations can either upregulate or downregulate...
a gene and its expressed protein, depending on where the gene sequence is spliced. Conversely, trisomies generally increase gene expression, through increased gene dosing. Cytogenic anomalies, mutations in mediator complex subunit 12, and aberrant DNA methylation/demethylation have been observed, and advances in epigenetics have implied a functional role of G protein-coupled receptor 10 overexpression and irregular microRNA expression in the pathobiology of fibroids; findings which require further investigation.\textsuperscript{10}

The familial inheritance of fibroids has also been examined. Twin studies\textsuperscript{11} have shown a strong susceptibility to fibroid development, with monozygotic twins twice as likely to develop fibroids compared with dizygotic. Familial clustering has been described\textsuperscript{12} and inherited disorders, such as cutaneous leiomyomatosis and inherited renal cell cancer are also associated with fibroids.\textsuperscript{13,14}

3. Classification of uterine fibroids

Fibroids are traditionally classified according to their anatomical location and divided into submucous, intramural (the commonest site) or subserous. Submucous fibroids are those that distort the uterine cavity and can be further divided into three subtypes: pedunculated (type 0); sessile with less than 50% intramural extension of the fibroid (type I); and sessile with 50% or greater intramural extension (type II). Intramural fibroids are those which do not distort the uterine cavity and leave less than 50% of the tumour protruding into the serosal surface of the uterus. Fibroids protruding 50% or more out of the serosal surface are considered subserosal, and are further divided into sessile or pedunculated.\textsuperscript{15} Fibroids contain multiple subtypes in two-thirds of cases.

4. Clinical presentation of uterine fibroids

Symptoms associated with the presence of uterine fibroids include heavy and prolonged periods, pelvic pressure (from large fibroids), pain (resulting from torsion of a pedunculated fibroid or degeneration), urinary symptoms and constipation resulting from pressure by anterior and posterior fibroids. Whether fibroids cause infertility is the subject of considerable speculation. Although most women with fibroids are fertile, fibroids may interfere with fertility secondary to anatomical distortion and alterations to the uterine environment.\textsuperscript{16} For those women afflicted with fibroids the risk of miscarriage\textsuperscript{17} and pregnancy complications such as pain are also increased.

5. Treatment of uterine fibroids

Surgical treatment of fibroids was the mainstay of management prior to the introduction of nonsurgical options. Hysterectomy was the standard treatment for women troubled with fibroid-associated symptoms, prior to the advent of less invasive surgical options, especially for women not trying to conceive. Myomectomy, which involves removal of the fibroids while conserving the uterus, is the alternative surgical treatment and can be performed abdominally, laparoscopically or hysteroscopically depending on the fibroid location.

Several nonsurgical approaches for the treatment of fibroids have emerged over the last few decades, with medical therapies as well as radiological interventions being proposed. The medical therapies traditionally used are gonadotrophin-releasing hormone (GnRH) analogues and, more recently, selective progesterone receptor modulators (SPRMs), e.g. ulipristal acetate. Radiological interventions include uterine artery embolisation (UAE) and the use of magnetic resonance-guided high-intensity focused ultrasound (MRgFUS).

6. Nonsurgical treatment of uterine fibroids
6.1 Medical treatments

Gonadotrophin-releasing hormone (GnRH) analogues

GnRH analogues cause pituitary desensitisation resulting in a hypogonadotrophic and hypoestrogenic state. The oestrogen-deficient state causes shrinkage in fibroid volume and symptomatic improvement. GnRH analogues lead to a 40% reduction in fibroid volume after 6 months of treatment, and 97% of women reported improvement in their bleeding pattern. However, these drugs commonly have significant adverse effects, including hot flushes, insomnia, mood disorders, vaginal dryness, headaches and loss of bone mineral density. Given these adverse effects, they are preferred for short-term use prior to surgery to shrink the fibroids and reduce bleeding during surgery. Lethaby et al. suggested that use of GnRH analogues for 3–4 months prior to fibroid surgery corrected iron deficiency anaemia and reduced intraoperative blood loss. Add-back therapy with GnRH analogues, particularly for use beyond 6 months, is advocated to alleviate adverse effects, mainly bone loss, caused by the hypoestrogenic state. A Cochrane review concluded there was low or moderate quality evidence that tibolone, raloxifene, estriol and ipriflavone help to preserve bone density, and that medroxyprogesterone acetate and tibolone may reduce vasomotor symptoms. Moreover, women with a larger uterine volume demonstrated a lesser degree of fibroid shrinkage when some add-back therapies were used.

Selective progesterone receptor modulators (SPRMs)

SPRMs are thought to stimulate apoptosis and inhibit cell proliferation in fibroids. Ulipristal acetate is approved in the European Union as a preoperative treatment for moderate to severe symptoms associated with uterine fibroids and for intermittent treatment of fibroid symptoms in women of reproductive age. However, treatment beyond four courses of 3 months of therapy has not been formally studied, and it is noted in the assessment report for this product that unnecessary interventions for assessment of endometrial normality may be a consequence. Conversely, a diagnosis of endometrial abnormality may also be missed.

A phase III trial of ulipristal acetate, involving 209 women with symptomatic fibroids and heavy menstrual bleeding, investigated the efficacy and safety of long-term treatment for symptomatic uterine fibroids. Women received up to four 3-month courses of ulipristal acetate 10 mg daily. After the first course of ulipristal acetate, amenorrhoea, which was defined as lack of bleeding for at least 35 days, occurred in 79% of women with median onset of 4 days and a median fibroid volume reduction of 45%. After two, three and four treatment courses of ulipristal acetate, amenorrhoea rates were 89%, 88% and 90% and mean fibroid volume reductions were 63%, 67% and 72%, respectively. All endometrial biopsies showed benign histology without hyperplasia. The study concluded that repeated 3-month courses of ulipristal acetate effectively controlled symptoms and decreased fibroid size in women with symptomatic fibroids. Another study by the same group of authors investigated the efficacy and safety of two 12-week courses of 5 mg or 10 mg daily of ulipristal acetate in 451 women with symptomatic fibroids and heavy bleeding. In the 5 mg and 10 mg treatment groups, 62% and 73% of women, respectively achieved amenorrhoea during both treatment courses. The proportion of women achieving controlled bleeding, defined as no episode of heavy bleeding and a maximum of 8 days of bleeding during at least 56 days of a treatment course, during two treatment courses was greater than 80%. Menstruation resumed after each treatment course and was diminished compared with baseline. After the second treatment course, median reductions from baseline in fibroid volume were 54% and 58% for the women receiving 5 mg and 10 mg of ulipristal acetate, respectively. Three cases of endometrial hyperplasia were reported in this study, including one simple atypical hyperplasia which resolved into benign secretory endometrium by the end of treatment. A few cases of spontaneous pregnancies without surgery, and a number of pregnancies following myomectomy after
pretreatment with ulipristal acetate have been reported. Long-term reproductive outcomes following repeated intermittent ulipristal acetate are not known.

6.2 Radiological interventions

Uterine artery embolisation (UAE)

UAE was introduced in 1995 as an alternative technique for treating fibroids and provides effective short-term treatment of heavy menstrual bleeding, pressure symptoms and pelvic pain. The updated Cochrane review included seven randomised controlled trials comparing UAE with hysterectomy/myomectomy with a total of 793 women. There was moderate quality evidence to suggest similar patient satisfaction rates following UAE compared to surgical modality at 2- and 5-year follow-up. UAE was associated with a higher rate of surgical intervention (between 15% and 32%) after 2 years. The review emphasised the need for careful patient selection and counselling because of the higher risk for further surgical intervention. Overall, the data suggest less encouraging reproductive outcomes following UAE compared with surgery. A study included 121 women with fibroids larger than 4 cm who were randomised to UAE or myomectomy and followed for 24 months. Compared with the surgical group, the pregnancy (50% versus 78%) and delivery rates (19% versus 48%) following UAE were significantly lower. The miscarriage rate was also significantly higher in the UAE group (64% versus 23%). A systematic review and meta-analysis showed significantly higher miscarriage rates after UAE compared with control women with untreated fibroids (35.2% versus 16.5%). Significant adverse effects of UAE on endometrium and fertility have been reported. In one study, approximately 60% of women showed abnormalities at routine hysteroscopic examination 3–9 months after UAE, including intrauterine adhesions, protruding myomas, myometrial fistula and necrotic tissue. A follow-up study involving 61 women after UAE found a low monthly fecundability rate of 0.1% (95% CI 0–0.3%) and no reduction in ovarian reserve. The study concluded that UAE might have an adverse effect on fertility and should not be routinely offered to women of childbearing age.

In a retrospective analysis of pregnancy outcomes following UAE, out of 56 (58.9%) pregnancies had successful outcomes, of which six (18.2%) were premature. There were 17 (30.4%) miscarriages, three terminations, two stillbirths and one ectopic pregnancy. Of the 33 successful deliveries, 24 (72.7%) were delivered by caesarean section. There were 13 elective sections and the indication for nine was fibroids. There were six cases of postpartum haemorrhage (18.2%). The study concluded that there was a significant increase in delivery by caesarean section and an increase in preterm delivery, postpartum haemorrhage, miscarriage and lower pregnancy rates following UAE compared with the general obstetric population.

Magnetic resonance-guided high-intensity focused ultrasound (MRgFUS)

MRgFUS provides an alternative to surgery for the treatment of uterine fibroids. This therapeutic option causes thermal coagulation of the target fibroid by methodically sonicating multiple locations to reduce volume and provide symptom relief.

A long-term study involving 77 women with symptomatic fibroids comparing outcomes following MRgFUS (median follow-up 60.7 months) and UAE (median follow-up 61.9 months) found the intervention rate to be significantly higher for MRgFUS compared with UAE (66.7% versus 12.2%; \( P < 0.001 \)). The health-related quality-of-life scores were significantly better in the UAE group compared with the MRgFUS group. Although this modality is mainly offered to premenopausal women with symptomatic fibroids who do not wish to become pregnant, there have been several reports of successful pregnancies following MRgFUS. Rabinovici et al., in their preliminary study of 51 women who conceived after undergoing MRgFUS for fibroids, found live birth, ongoing pregnancy, and miscarriage rates of 41%, 20%, and 28%, respectively. A systematic review of reproductive outcomes...
following fibroid treatment with MRgFUS found a vaginal delivery rate of 53% (19/35). The authors concluded that the MRgFUS may become the treatment of choice for women who desire fertility, but further larger trials are needed to validate the findings.

Some minor complications have been reported following MRgFUS, including skin burns, abdominal wall oedema, febrile morbidity; major complications, such as deep vein thrombosis, bowel injury, persistent neuropathies; and the need for emergency hysterectomies. In a 5-year follow-up study of 162 women who underwent MRgFUS for symptomatic fibroids, the investigators found a high reintervention rate of 58.64%. The minor complication rate was 3.9% and serious complication rate (e.g. persistent neuropathy, fibroid expulsion) was around 1.1%. The major limitation of MRgFUS is that many women are not eligible for the procedure because of the bowel interposition between ultrasound beam and fibroid, or as the presence of more than five fibroids, their size or shape, or the presence of adenomyosis. Fröling et al. found that of 783 premenopausal women, with a mean age of 44.2 years, only about 40% were eligible for MRgFUS compared with 99.2% for UAE.

7. Areas of research

7.1 Radiofrequency ablation (RFA)

RFA has been advocated as a minimally invasive method to treat fibroids. RFA energy uses volumetric ablation to destroy tissue resulting in a more controlled zone of thermal injury. Treatment of fibroids with RFA requires very accurate localisation or targeting of the placement of the operative device. Currently, a variety of approaches are available for localising the device, including laparoscopic ultrasound guidance, transcervical, intrauterine ultrasound guidance and transvaginal ultrasound guidance. Initial studies have reported encouraging results in terms of symptom improvement and shrinkage of fibroid size. However, there is much to be learned about this technique, such as its long-term success rates, how to identify the appropriate surgical candidates, and its impact on subsequent fertility and pregnancy outcomes.

7.2 Gene therapy

Fibroids have become a target for gene therapy in recent years. Gene therapy involves the introduction of genetic material into a patient’s cells to achieve a therapeutic benefit. Strategies include: mutation compensation of dysregulated genes; replacement of defective tumour-suppressor genes; inactivation of oncogenes; introduction of suicide genes; immunogenic therapy and antiangiogenesis-based approaches. Preclinical studies of gene therapy have shown promising results in uterine fibroids and the researchers involved are of the view that this approach is not far from becoming a medical reality.

8. Conclusion

For a woman with symptomatic fibroids who wishes to retain her uterus, a variety of nonsurgical options are available. However, patient selection is important and women should be counselled regarding the potential benefits and adverse effects of current options. In women seeking to remain fertile, medical treatments are not a long-term option, and the place of ulipristal acetate for women with fibroids prior to fertility treatment has yet to be fully explored. Current data suggest reduced fecundity and higher risk of pregnancy complications following UAE administration, and long-term data are needed to validate the safety and reproductive and obstetric outcomes of MRgFUS.

9. Opinion
The development of effective nonsurgical therapeutic options for treatment of symptomatic uterine fibroids has significantly progressed over the past two decades providing women with greater choice. However, surgical removal of fibroids remains the mainstay of treatment for the majority of women who wish to maintain their fertility, although the adjunct use of medical therapies to shrink fibroids and reduce patient morbidity prior to surgery has significant merit. Further research is required to examine the use of nonsurgical therapies for women with fibroids prior to commencing fertility treatment, and to develop effective nonsurgical therapies that help reduce fibroid symptoms without impacting negatively on reproductive outcomes.

**References**


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