

Advances in the management of uterine fibroids

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Abstract

Uterine fibroids are extremely common, with major surgery the current main management option; uterine artery embolisation is an alternative, but risks to fertility are unclear. Minimally invasive procedures are becoming more commonly performed via both the hysteroscope and laparoscope, minimising recovery time for patients. Recently, small doses of progesterone receptor modulators (mifepristone and asoprisnil) have been shown to be effective in reducing menstrual blood loss and fibroid size. Progress from here should include the development of a well-tolerated oral preparation that will maintain fertility.

Introduction and context

Fibroids are present in up to 70% of women of reproductive age [1]. Although many women with fibroids are asymptomatic, others find they cause a major disruption to daily life. There is evidence to implicate a genetic predisposition; monozygotic female twins are twice as likely to be concordant for hysterectomy and/or hospitalization for fibroids as dizygotic twins [2]. In a recent genetic study with sister-pairs with fibroids, the embryonic proliferation modulator *HMGA2* gene was identified as a potential gene associated with a predisposition for fibroids [3].

The mechanism(s) for fibroid growth is an area of much research interest. Matsuo *et al.* [4] reported greater cellular levels of the anti-apoptotic protein Bcl-2 in leiomyoma cells than in normal myometrium. The sex steroids oestrogen and progesterone have a role in fibroid growth during the reproductive years, with fibroids regressing after menopause. There is biochemical, clinical, and pharmacological evidence to support a role for progesterone in the pathogenesis of fibroids. Fibroids have increased concentrations of both isoforms of the progesterone receptor (PR-A and PR-B) [5].

The main associated symptoms are often problematic; heavy menstrual bleeding [5,6] may result in severe anaemia and social embarrassment and the presence of a pelvic mass may lead to marked discomfort, abdominal distension, and pressure-related bladder symptoms [7]. Additionally, distortion of the uterine cavity may result in subfertility. Submucosal fibroids have been shown to decrease pregnancy rates and so removal of such fibroids where subfertility is an issue may be considered [8], however, subserosal fibroids do not appear to be related to fertility. Intramural fibroids are thought to decrease fertility: although there is a lack of randomised trials, it has been shown that, with *in vitro* fertilisation, there is a reduced delivery rate in patients with untreated fibroids but no change to delivery rate in those having had a myomectomy [9].

The mainstay of present management for large symptomatic fibroids is surgery – hysterectomy or myomectomy. These are both major abdominal operations with associated risks and prolonged recovery time. Uterine artery embolisation (UAE) carries a risk of pelvic infection and there is limited evidence regarding the risks for future pregnancies [10-12].

The levonorgestrel-releasing intrauterine system [LNG-IUS, Mirena® (Bayer Schering Pharma)], although highly effective as a treatment for heavy menstrual bleeding, often fails if the uterine cavity is markedly enlarged or distorted by fibroids. There is no evidence to show that a LNG-IUS reduces fibroid size [13]. Gonadotrophin-releasing hormone analogues can reduce the size of fibroids by around 30%, but this should be regarded as a short-term or pre-operative mode of management as the resulting hypo-oestrogenic state can result in osteoporosis if prolonged use occurs. In addition, the fibroids tend to re-grow when such treatment is ceased [14].

Recent advances

The randomised clinical 'EMMY' (Embolisation versus Hysterectomy) multi-centre randomised control trial prospectively looked at health-related quality of life outcomes for hysterectomy and UAE at intervals up to 24 months, with regards to mental and physical health, urinary function, and overall patient satisfaction. The only significant difference between the groups was that patients who underwent hysterectomy were more satisfied with the received treatment than women who underwent UAE [15].

The 'HOPEFUL' (Hysterectomy Or Percutaneous Embolisation For Uterine Leiomyomata) study, a retrospective multi-centre cohort study, assessed the treatment of symptomatic uterine fibroids with either hysterectomy or UAE and compared efficacy, safety, and cost-effectiveness. Complications and cost were less in the UAE group, even when retreatment (with uterine preservation) was taken into consideration [16].

Women undergoing UAE (compared to hysterectomy for symptomatic uterine fibroids in a randomised trial) have been reported to have a faster recovery time but were at risk of treatment failure in 9-20% of cases [12]. Ovarian reserve may be affected by both hysterectomy and UAE. Although permanent loss of ovarian function after UAE usually affects those aged over 45, there may be impaired ovarian function in younger patients [17]. This issue needs to be considered as some women wishing to maintain their fertility opt for UAE.

A recent prospective observational study evaluating long-term efficacy and complications of UAE after 5-7 years has shown that this is a beneficial treatment for women wishing to avoid hysterectomy (satisfaction rate of 88%) [18,19].

Hysteroscopic myomectomy is now the standard minimally invasive surgical procedure for treating submucosal fibroids. It is safe and effective and avoids opening

the uterine cavity [20]. Hysteroscopic removal of submucosal fibroids appears to be of benefit where infertility is an issue [8]. A recent prospective randomised matched control trial found that hysteroscopic myomectomy for submucous fibroids in women with unexplained primary infertility improved pregnancy rates [21]. The use of smaller diameter hysteroscopes with working channels and bipolar technology may remove the need for any anaesthetic and give the option of such procedures being conducted in the outpatient setting when the fibroids are small. The vaginoscopic, 'no touch' approach removes the need for cervical dilatation, a tenaculum, or even a speculum. Where the theatre setting with general anaesthetic is indicated, pre-operative vaginal misoprostol has been shown to reduce the need for cervical dilation, and to minimise operative difficulties and cervical complications [22].

Minimally invasive abdominal procedures offer many advantages over open techniques. A randomised trial [23] comparing laparotomy, mini-laparotomy, and laparoscopic-assisted mini-laparotomy for myomectomy has shown similar operating times. Laparoscopic-assisted mini-laparotomy, however, offered a reduced time of paralytic ileus and quicker discharge from hospital [23]. Laparoscopic myomectomy has also been shown to result in reduced post-operative pain and requirements for analgesia compared with laparotomy in the first 3 days after surgery [24]. However, open myomectomy is sometimes the procedure of choice where the fibroid uterus is large and fertility is desired [25]. A recent prospective randomised control trial [26] has shown that the triple tourniquet technique (applied to the uterine and ovarian vessels) to temporarily occlude uterine blood supply, thereby keeping intra-operative blood loss to a minimum and reducing morbidity for the patient, is more effective than pre-operative gonadotrophin-releasing hormone analogues [26].

Progesterone receptor modulators have been demonstrated to be effective in the management of symptomatic uterine fibroids [27]. Eisinger *et al.* [28] found low dose (both 5 mg and 10 mg) mifepristone administered daily for 6 months resulted in comparable fibroid regression. A recent randomised controlled trial supports this finding [29]; 100 women were randomised to either 5 mg or 10 mg of daily mifepristone for 3 months. Trans-abdominal ultrasound scan was performed pre-treatment, at 45 days, and at 3 months to assess uterine and fibroid volume, the latter reducing by around 50% in both groups [29].

The selective progesterone receptor modulator asoprisnil (10 and 25 mg daily for 3 months) has been studied in

women with symptomatic fibroids scheduled for hysterectomy. Uterine blood flow (determined by resistance index and pulsatility index) and volumes of the largest fibroid and the uterus were assessed. The intensity and frequency of menstrual bleeding were recorded on a menstrual pictogram. The increased pulsatility index and the significantly increased resistance index observed indicated a decrease in uterine artery blood flow. Analysis of menstrual pictogram scores showed a significant decrease in frequency and intensity of bleeding compared with placebo. Further studies are required to evaluate safety and efficacy of asoprisnil when administered for a longer term [30].

Implications for clinical practice

There is an unmet need for a pharmacological agent that would result in fibroid shrinkage and reduce menstrual blood loss whilst maintaining fertility and oestrogenic state. The ideal treatment would be minimally invasive, cost-effective, efficacious, tolerable with minimal side effects, and have a low incidence of fibroid recurrence. This would significantly reduce the number of major abdominal surgical procedures required for this common gynaecological complaint.

Until such time, minimally invasive procedures offer a number of advantages over open abdominal surgery; with hysteroscopic resection, anaesthetic can often be avoided, and with laparoscopic myomectomy recovery time is quicker and post-operative pain is reduced.

The decision regarding optimal management for the patient is based on a number of factors: fertility desire, past medical and surgical history, the size of the fibroids and the patient's preference and lifestyle (occupation and family; can she afford the time spent in hospital associated with hysterectomy and the recovery time at home thereafter?). Risks and benefits of each option must be carefully explained. A recent study has shown that symptoms, particularly of pain and bleeding, determine the choice for intervention rather than the size and number of fibroids [18].

Abbreviations

EMMY, Embolisation versus Hysterectomy; HOPEFUL, Hysterectomy Or Percutaneous Embolisation For Uterine Leiomyomata; LNG-IUS, levonorgestrel-releasing intrauterine system; PR, progesterone receptor; UAE, uterine artery embolisation.

Competing interests

KIM declares that she has no competing interests. HODC has received support for research staff and for laboratory consumables from TAP Pharmaceutical Products, Inc.

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