



A FOGSI President's Initiative

**KEY
PRACTICE
POINTS** 
2019
INDIAN PERSPECTIVE
By Dr. Nandita Palshetkar

**KEY PRACTICE POINTS ON
FIBROIDS**

New

Elata[®] 5mg Tablets

Ulipristal Acetate

First Line Management in Uterine Fibroids

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DCGI | Health Canada | EMEA

- Significant and Sustained Fibroid Volume Reduction
- Rapidly controls Heavy Bleeding
- Reduces Surgical Complication





Dear FOGSIANS,

In this era of evidence-based medicine, Gynaecologists often must make decisions where neither evidence nor consensus exists. Fortunately, there is a growing body of evidence to assist in managing Endometriosis, Fibroids and OAB. With Key Practice Points, the idea is to regularly create evidence and consensus based practical approach to the diagnosis and management of indications, thereby ensuring a higher quality of care to patients.

Key Practice Points (KPP) from FOGSI supported in science through Science Integra will be an annual affair to bring the best talent across the country and get them to discuss, deliberate and create easy point of reference to practice better.

Hope you all will maximise from the KPP outputs and pass on further for the betterment of the community and the STREE in all. Our sincere gratitude to Alembic Pharmaceuticals for their educational grant for the Key Practice Points.

Best wishes!

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KEY PRACTICE POINTS ON FIBROIDS

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From left to right: **Sitting** – Dr. Ritu Joshi, Dr. Aswath Kumar, Dr. Apoorva Pallam Reddy, Dr. Fessy Louis
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Uterine Fibroids: Recommendations for Diagnosis and Management

Introduction

Uterine fibroids (myomas or leiomyomas) are the most common benign tumours in women of reproductive age and may be asymptomatic, but they are also a major source of clinical morbidity.^{1,2} Fibroids originate from the smooth muscle of the myometrium and consist of large amounts of extracellular matrix that contain collagen, fibronectin, and proteoglycan.^{1,3}

Depending on study populations and diagnostic methods, the prevalence of fibroids ranges from 4.5% – 68.6%. In the reproductive age group, fibroids may become clinically apparent and can cause significant symptoms in approximately 25% of women.⁴ In India the prevalence of fibroids is reported to be 37.65% in rural populations and 24% in the urban populations.⁵

Risk factors for uterine fibroids

The etiology of fibroids is multifactorial and not yet clearly understood. The rare occurrence of fibroids before menarche and their regression after menopause suggests that their growth is dependent on estrogen and progesterone.^{1,3}

A study was conducted to identify the risk factors associated with uterine fibroids. The prevalence of fibroids was significantly lower in the younger group (25–35 years) (6.7%) versus the groups aged 36–45 years (prevalence of 33.3%, $\chi^2 < 34.4$, $p < 0.00010$ and 46–56 years (prevalence of 60%, $\chi^2 < 53.7$, $p < 0.0001$).⁶

EXPERT OPINION

Risk factors of fibroids include early menarche (younger than 10 years), increasing age (before onset of menopause), family history of uterine fibroids, nulliparity and high BMI.

Classification of uterine fibroids

Fibroids are heterogeneous in their size and location. The FIGO (International Federation of Gynaecology and Obstetrics) classification system (Figure 1) and the European Society of Gynaecological Endoscopy (ESGE) (Table 1) for uterine fibroids are simple and provide a frame work for both clinical and research practice.

The FIGO classification is the more detailed classification based on location and type while the ESGE classification specifically relates to submucous fibroids.^{2,7}

Leiomyoma subclassification system

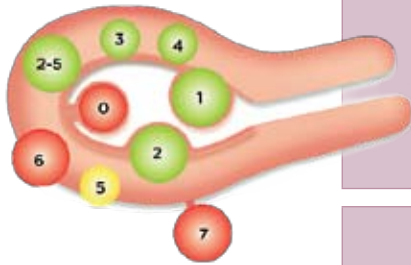


Figure 1. FIGO classification of uterine fibroids

SM-Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	>50% intramural
O-other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal >50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify eg, cervical, parasitic)
Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium, while the second refers to the relationship to the serosa. One example is given below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively

Table 1. ESGE classification of submucous myomas

Type 0	Entirely within endometrial cavity No myometrial extension (Pedunculated)
Type I	<50% myometrial extension (Sessile) <90 degree angle of myoma surface to uterine wall.
Type II	≥50% myometrial extension (Sessile) ≥90-degree angle of myoma surface to uterine wall.

EXPERT OPINION

The FIGO and ESGE systems should be used for the classification of fibroids and pre-surgical classification should be considered for selected clinical situations.

Pathophysiology of uterine fibroids

Uterine fibroids arise from the myometrium and are composed of disordered 'myofibroblasts' buried in an extracellular matrix that accounts for a substantial portion of tumour volume. Steroid hormones are an important influence in leiomyoma pathogenesis. While traditional teaching has highlighted the role of estrogen, recent opinion has shifted to progesterone which appears to be the more important hormone. Progesterone receptors are upregulated in leiomyomas compared with normal myometrium. Other influences include genetic factors, vascular factors, fibrotic factors, and stem cells.⁸

EXPERT OPINION

Since the pathophysiology of fibroid development is influenced by hormones, progesterone and progesterone receptors along with genetic factors and disturbance of aromatase function are now acknowledged as the most significant factor. Progesterone and its receptors hence represent potential targets for inhibiting growth of myomas.

Diagnosis of uterine fibroids

Clinical diagnosis

Most fibroids are asymptomatic, with an incidental diagnosis at the time of routine investigation or tests for unrelated conditions.⁹ Symptomatic fibroids may present with abnormal uterine bleeding, pressure symptoms, pain, fertility issues, and obstetric complications.¹⁰

There are various factors which obfuscate the diagnosis of fibroids and these include:²

- Diversity in the size, location, number of fibroids, and symptoms.
- Symptoms of fibroids that may be associated with other conditions or diseases, such as ovulatory dysfunction, endometriosis or endometrial polyps.
- Asymptomatic fibroids that may go undetected till an incidental diagnosis by examination or investigation.

In a cross-sectional survey, symptoms of spotting and/or bleeding between periods were reported in 74.9% and heavy menstrual bleeding reported in 73.4% of women with uterine fibroids. As compared to women with no fibroids, women with uterine fibroids were more likely to have severe heavy menstrual bleeding (7.7% vs 16.7%). Among respondents with fibroid related symptoms, 56.4% reported heavy menstrual bleeding as being extremely bothersome.¹¹

At clinical examination, fibroids may present as abdominal or pelvic masses or an enlarged uteri. The examination may be per abdominal, per speculum, per vaginal or obstetric as appropriate.

Diagnostic modalities

These modalities are necessary for confirming the diagnosis, location,² and mapping of myomas and would influence their management.

EXPERT OPINION

Fibroids may be asymptomatic or may present with menstrual disturbances, pain, pressure symptoms, fertility related issues, and obstetric complications.

Ultrasonography

Pelvic ultrasonography is the first-line imaging modality in the detection and evaluation of uterine fibroids.³ Ideally, both trans-abdominal (TAS) and trans-vaginal (TVS) sonography should be performed.³

While TVS is more accurate for the diagnosis of small fibroids, the uterine fundus may lie outside of the field of view when the uterus is bulky or retroverted and this may be better served by a concomitant TAS.^{2,3}

Colour Doppler ultrasonography may be beneficial in special situations to assess vascularity.¹² Trans-rectal should be considered when TVS is not possible or not an option. Saline infusion sonography (SIS) is particularly useful to diagnosis of submucosal fibroids.²

In a cross-sectional study, women presenting with abnormal uterine bleeding, 53.80% were clinically diagnosed as fibroids. While TAS diagnosed fibroids in 37.80%, TVS made the diagnosis in 41.78%. As compared to TAS, the sensitivity of TVS for detection of uterine fibroids was 59.68% vs 82.26%, specificity was 74.36% vs 85.90%, positive predictive value was 64.91% vs 82.26% and negative predictive value was 69.88% vs 85.90%. On TVS, as compared to TAS, the accuracy of detection for fibroids of size less than 2 cm was 88.71% vs 72.58%, for fibroids of size 2–5 cm it was 88.71% vs 82.26% and for fibroids of size >5 cm was 95.16% vs. 93.55%.¹³

EXPERT OPINION

- A pelvic ultrasonography is recommended as the first-line imaging modality in the detection and evaluation of uterine fibroids.
- TVS is more accurate than TAS for the identification of small fibroids.
- Colour Doppler ultrasonography may be done in special situations.
- Trans Rectal may be performed when TVS is not possible or not an option.
- Saline sonography is useful to diagnose submucosal fibroids.²

Hysteroscopy

Hysteroscopy is useful in identifying intrauterine lesions and in differentiating between intracavitary myomas and endometrial polyps.¹⁴ Simultaneous operative hysteroscopy offers the additional advantage of managing the intracavitary fibroids once the diagnosis is made.

For the diagnosis of intracavitary myomas and endometrial polyps, diagnostic hysteroscopy was significantly more accurate than TVS (myomas: $p < 0.001$, polyps: $p < 0.005$) and SIS (myomas: $p = 0.031$, polyps: $p = 0.001$). As compared to TVS, SIS was found to be superior for the diagnosis of intracavitary myomas ($p = 0.003$) and endometrial polyps ($p = 0.005$).¹⁵

EXPERT OPINION

Hysteroscopy is useful in identifying and differentiating between intracavitary myomas and endometrial polyps while offering the additional advantage of simultaneous hysteroscopic myomectomy and polypectomy.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an effective modality for visualizing and documenting the size and location of uterine myomas. It has the unique advantage of distinguishing between leiomyomas, adenomyosis, adenomyomas, and malignancies including sarcomas.^{16,17}

In a study assessing the accuracy of MRI and TVS in myoma mapping and measurement, the mean number of correctly identified myomas was significantly higher with MRI (mean difference, 0.51 ± 1.03 ; $p < 0.001$). In 26 patients with 1 to 4 myomas and uterine volumes < 375 mL, the difference was narrowed to 0.08 ± 0.76 ($p = 0.60$). In large (> 375 mL) multiple-myomas (> 4) uteri, the capacity of TVS for exact myoma mapping fell short of that of MRI.¹⁸

EXPERT OPINION

MRI is recommended for characterizing pelvic masses for which it is more sensitive than ultrasonography.

Management options for uterine fibroids

Expectant Management

Expectant management of fibroids is a valid clinical option for asymptomatic fibroids. The decision to undertake expectant management is made with the woman, after counselling and a discussion of all treatment options. In cases where the uterus corresponds to or is larger than a gravid uterus at 14 weeks gestation, medical and surgical management of fibroids should be discussed and offered as an alternative to expectant management. With expectant management a schedule of periodic annual evaluation is followed to monitor progression in the size or number of fibroids.¹⁹

Definitive Management

The treatment should be individualized and based on the symptoms, size, and location of fibroids. The patients' age, preservation of fertility or the uterus, availability of therapy, and experience of the therapist should be taken into account while deciding the therapy. Symptomatic uterine fibroids may be treated medically, surgically, or with a combination of both.²⁰

Current Medical Therapy

Medical therapies act by controlling symptoms, reducing the fibroid volume, and reducing menstrual blood loss.²¹ Since estrogen upregulation of both estrogen receptors (ERs) and progesterone receptors (PRs) during the follicular phase is followed by progesterone induced mitogenesis during the luteal phase, medical management of uterine fibroids involves use of hormonal therapies for uterine fibroids as also for controlling uterine bleeding.²⁰

Traditionally medical management for fibroid related symptoms was by nonsteroidal anti-inflammatory drugs and tranexamic acid, combined oral contraception, the levonorgestrel releasing intrauterine system, progestins, and gonadotropin-releasing hormone agonists (GnRHa) and danazol. Recently, a new class of medications has become available for the treatment of fibroids, the selective progesterone receptor modulators (SPRMs).²²

Selective progesterone receptor modulators (SPRMs)

Since progesterone is essential for fibroid growth, progesterone antagonists and/or PRMs now have a significant role in the management of fibroids. SPRMs are progesterone receptor ligands that have agonist, antagonist, partial, or mixed effects on progesterone target tissues.^{14,20} SPRMs such as ulipristal acetate (UPA), mifepristone, asoprisnil, and telapristone acetate have been investigated in various trials. All of these agents are reported to decrease leiomyoma size and reduce uterine bleeding in a dose dependent manner.¹⁴

The potential advantages of SPRMs include retaining fertility in women having delayed childbearing, providing symptomatic relief in women nearing menopause, preventing the need for surgery in women with symptomatic fibroids, allowing for fertility treatment and preventing recurrence of fibroids after surgery.²³

Ulipristal acetate

Ulipristal acetate, an orally active synthetic SPRM, has a tissue-specific partial progesterone antagonist effect. UPA has been recommended for the following indications:²⁴

- The preoperative treatment of women with fibroids of 3 cm or more in diameter
- Intermittent treatment in women who are not eligible for surgery, for example where the risks of surgery outweigh the benefits or where the woman declines surgical treatment

The clinical efficacy and safety of UPA, both with regard to preoperative administration as also with intermittent administration as long-term treatment for patients with symptomatic uterine fibroids, have been shown in several clinical studies.^{22, 25, 26,27} UPA may be used in a dose of 5 mg for up to 4 courses in women with heavy menstrual bleeding and fibroids of 3 cm or more in diameter.

Intermittent long-term treatment of fibroids with UPA has the advantage of rapid and reliable bleeding control, a reduction in the size of the fibroids, and an improvement in the symptoms that in many cases, can prevent a hysterectomy or fibroid enucleation.²⁸ Besides UPA has also been reported to improve the quality of life of patients with fibroids.⁸

Clinical evidence and usage

Ulipristal acetate in a dose of 5 mg daily for 13 weeks has been shown to be effective in decreasing both the intensity of bleeding as also the size of uterine fibroids.²⁷ The medical regimen of UPA has 13 weeks of therapy considered as a single course.

The PEARL I study was a double-blind, randomized, placebo controlled, multicentre trial that showed significant reduction of fibroid volume compared to baseline after 13 weeks of 5-10 mg UPA ($p < 0.001$). The Pearl II study showed that the use of 10 mg UPA for 12 weeks was comparable to the monthly use of 3.75 mg of leuprolide acetate for 3 months for the improvement of symptoms such as uterine bleeding and the reduction in fibroid size. PEARL III study investigated the impact of a 10-day course of the progestin norethisterone acetate (NETA) on the timing and magnitude of menstruation during the UPA off-treatment period. Compared to the placebo, NETA was associated with the expedited return of menstrual bleeding and also a significant reduction in menstrual bleeding in the UPA off-treatment period. Use of UPA 10 mg daily for up to 4 courses showed progressive reduction in the fibroid volume and the menstrual bleeding with increase in duration of therapy. Women receiving NETA experienced the return of menstrual periods after a median of 15 days following the end of the fourth UPA treatment course, in contrast to 30 days among women receiving the placebo ($p < 0.001$).²²

The VENUS I compared 5 and 10 mg UPA doses to placebo. UPA was superior to placebo for rate of amenorrhea and time to amenorrhea. Three months of UPA reduced the impact of fibroid related symptoms on daily activities compared to the baseline evaluation.²² The primary advantage of UPA over GnRHa was the rapid control of uterine bleeding within 5 and 7 days with 10 and 5 mg UPA doses respectively, in contrast to 21 days with leuprolide acetate ($p < .01$) and results in significantly less frequent side effects.²⁷

A systematic review of surgical outcomes of patients undergoing myomectomy after preoperative treatment with UPA, reported no increase in the overall technical difficulty of laparoscopic myomectomy. Patients who received UPA had lower diameter and volume of the largest myoma, lower total myoma volume, and higher hemoglobin levels in comparison with those without any preoperative treatment. The operative time was shorter in patients treated with UPA and the intraoperative blood loss and the hemoglobin drop were significantly lower. UPA did not have a major impact on the consistency of uterine myomas and on the difficulty encountered in enucleation.²⁹

The most commonly reported adverse events associated with UPA treatment are headache and breast tenderness, although these are also reported in a similar proportion of placebo treated patients. Among women receiving multiple courses of UPA in the long-term studies, the incidence of adverse events did not increase with successive treatment courses. In contrast to leuprolide acetate monotherapy, treatment with UPA was associated with maintenance of estradiol levels within the mid-follicular range. As a result, UPA treatment was associated with a lower prevalence of menopausal symptoms such as hot flashes and no evidence of increased bone resorption.³⁰

Safety Concerns

There was concern regarding UPA induced increased risk endometrial changes in women treated for uterine fibroids. Since then these changes are considered as having normal endometrial histology with a few unclassifiable endometrial samples termed to have progesterone receptor modulators associated endometrial changes (PAECs). Studies have since concluded that these PAECs did not have any long-term implications and disappeared after cessation of the therapy.²³

Following reports of serious liver injury, including liver failure leading to transplantation, the European Medicines Agency (EMA) concluded a review of UPA, carried out by EMA's Pharmacovigilance Risk Assessment Committee in May 2018. The EMA recommended that the following measures to minimize the risk of the rare but serious liver injury with UPA:

- Contraindication in women with known liver problems;
- Liver tests before, during, and after stopping treatment;
- Use for more than one treatment course to be restricted to women who are not eligible for surgery.

EXPERT OPINION

- Ulipristal acetate is effective in reducing bleeding, fibroid volume, and improving anemia in the patients with uterine fibroids.
- While a single course of 3 months can be used preoperatively for delaying surgery, up to four consecutive courses may be used as medical therapy.
- Baseline liver function tests are advised before starting UPA and treatment is deferred or suspended when the results are more than twice the upper limit of normal. This is followed by periodic monitoring of LFTs, during and after the course of UPA.

Mifepristone

Mifepristone is a progesterone receptor modulator that has almost pure antagonistic properties and may directly decrease the progesterone receptor in the myometrium and

leiomyoma.²⁰ Mifepristone has been evaluated for reduction of symptoms in fibroids in perimenopausal women with a considerable amelioration in symptoms observed.

Clinical evidence and usage

Starting with a dose of 25 mg daily for 3 months, a maintenance dose of 10 mg daily is recommended thereafter.

A statistically significant reduction in myoma size was observed. After the treatment was stopped in perimenopausal women, the symptoms subsided completely and they had a smooth transition to menopause, whereas the symptoms returned in those aged 40–45 years. Mifepristone is a promising drug for the conservative management of leiomyomata, especially in perimenopausal age.²⁵

Another study showed that, in comparison to tranexemic acid and mefenamic acid, mifepristone given in bi-weekly doses was found to be safe, efficacious, and cost effective for the management of uterine fibroids. Women (n=120) in pre-menopausal age group with complaints of menorrhagia, Pictorial Bleeding Assessment Chart (PBAC) scoring ≥ 100 and at least one fibroid of ≥ 2.5 cm in size were included in the study. Six months of treatment with mifepristone resulted in marked clinical improvement; size reduction of 36.99% in intramural and 39.39% in submucosal fibroids.²⁶

GnRH analogues

GnRH agonists have been used preoperatively in fibroid management. However because of their side-effect profile, with climacteric complaints and reduced bone density, they have only been used over a brief period of 3 to 6 months.^{20, 28}

Clinical evidence and usage

Following treatment with GnRH-agonist goserelin for 3 months prior to surgical myomectomy, a 35% reduction was observed after 4 weeks in 81% of the cases, and after 8 weeks in all cases.³¹

A Cochrane review of 21 RCTs demonstrated that the use of GnRH α for 3–4 months before fibroid surgery reduced both uterine volume and fibroid size. Compared with no treatment prior to hysterectomy, GnRH agonists were beneficial in the correction of pre-operative iron deficiency anemia, as well as in reducing intra-operative blood loss and operative time, increased postoperative hemoglobin and hematocrit values, and decreased postoperative complications and length of hospital stay. They also increased the proportion of hysterectomies performed vaginally rather than abdominally and decreased the proportion of vertical incisions compared with no treatment.³²

A recent cross-sectional prospective case series study has demonstrated that the combination of triptorelin with letrozole reduced the mean fibroid size from 15.05 ± 57.20 cm to 13.56 ± 39.39 cm ($p=0.012$) and fibroid volume from 72.78 ± 110.6 to 50.96 ± 64.2 ($p=0.116$).

This treatment could also prevent surgery in cases that have multiple fibroids, are perimenopausal, anemic, and are otherwise candidates for surgery.³³

EXPERT OPINION

- GnRH analogues can be used prior to hysteroscopic myomectomy and hysterectomy to reduce the uterine volume and vascularity.
- Evidence has shown that in hysteroscopic myomectomy and hysterectomy GnRHa use can correct pre-operative anemia, reduce intra-operative blood loss and operative time with an increase in postoperative hemoglobin and hematocrit values, and decrease postoperative complications and length of hospital stay.
- GnRHa is not recommended before conventional and laparoscopic myomectomy due to a possible loss of planes.
- Because of their side-effect profile, with climacteric complaints and reduced bone density, GnRHa can be used over a brief period of 3 to 6 months.

Aromatase inhibitors

Myometrial cultured cells over express aromatase P450 and synthesize sufficient estradiol to accelerate the growth of own cell. Aromatase inhibitors block the aromatase activity and growth of leiomyomata. Letrozole, an aromatase inhibitor, inhibits the conversion of androgen into estrogen.²⁰

Clinical evidence and usage

Letrozole has been reported to significantly reduce the myoma size and volume and also improve the associated symptoms. Letrozole 2.5 mg a day for 12 weeks was administered in premenopausal women aged between 30 and 55 years with menstrual or pressure symptoms and having a single intrauterine myoma of size 4 cm, with or without one or more additional myomata each of size 2 cm or less. The mean myoma size was observed to reduce from 5.4 ± 1.3 cm to 4.3 ± 0.9 cm ($p < 0.05$) and the myoma volume exhibited a reduction of 52.45% ($p = 0.00$) at the end of 3 months. The symptomatology score showed a significant improvement that persisted up to 3 months after cessation of therapy.³⁴

Another study showed that preoperative treatment with letrozole significantly decreased the intraoperative blood loss and the time required for hysterectomies or laparoscopic myomectomy of large uterine myomas in premenopausal women. The total operative time (mean \pm SD, range) was significantly lower in the letrozole group (121.5 \pm 19.9 min; 89-181 min) than in the non-treated group (134.4 \pm 16.8 min; 111-185 min; $p < 0.001$).³⁵

Another study showed that preoperative treatment with triptorelin and letrozole significantly decreased the operative time and the volume of fluid absorbed during hysteroscopic resection of submucous myomas.³⁶ This combination has also been reported to prevent

surgery in cases with multiple fibroids, perimenopause, anemia, and candidate for surgery. A single dose of triptorelin 11.25 mg with 2.5 mg of letrozole daily for 4 weeks with add-back therapy and calcium carbonate was administered. This was followed by a second dose of triptorelin 11.25 mg 3 months after the first injection. This led to a mean fibroid size reduction from 15.05±57.20 cm to 13.56±39.39 cm (p=0.012) and fibroid volume reduced from 72.78±110.6 to 50.96±64.2 (p=0.116).³³

EXPERT OPINION

The current evidence is insufficient to support the use of aromatase inhibitor drugs in the treatment of women with uterine fibroids to support routine use though this seems to be a promising option for medical treatment.

Levonorgestrel-releasing intrauterine system

There are no randomized trials evaluating the use of levonorgestrel-releasing intrauterine system (LNG IUS) for the treatment of menorrhagia related to uterine leiomyomas. Observational studies and systematic reviews have shown a reduction in uterine volume and bleeding and an increase in hematocrit after placement. This treatment also provides contraception for women who do not desire pregnancy. The LNG IUS is not recommended in the presence of intracavitary leiomyomas amenable to hysteroscopic resection.³⁷

EXPERT OPINION

The levonorgestrel-releasing intrauterine system can be used in women with intramural myomas, who do not desire pregnancy in the near term.

Combined oral contraceptives (COCs)

Combined hormonal contraceptives help control menstrual bleeding, but they do not reduce fibroid size.³⁸ Evidence regarding the use of COCs as treatment for women with symptomatic fibroids is very scarce and of low quality.³⁹

Antifibrinolytic agents

Tranexamic acid an antifibrinolytic agent is useful in the treatment of idiopathic heavy menstrual bleeding, but has not been well studied in leiomyoma-related heavy menstrual bleeding.³⁸

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have not been extensively studied in leiomyoma-related heavy menstrual bleeding. They can be useful in this population as they decrease painful menses.³⁸

EXPERT OPINION

Combined oral contraceptives, tranexamic acid, and NSAIDs are used as symptomatic treatment to reduce bleeding and dysmenorrhea.

Surgical management strategies

Hysterectomy

Hysterectomy is considered a permanent solution for the symptomatic leiomyomas in women who have completed childbearing. Hysterectomy is also indicated in a woman with completely asymptomatic fibroids which continue to enlarge after menopause without HRT and may raise concerns of leiomyosarcoma.²⁰

Laparoscopic hysterectomy (LH)

Laparoscopic hysterectomy has become the favoured surgical approach to replace laparotomy. A study has shown that total laparoscopic hysterectomy generates low levels of pain and allows for the same day discharge. Patients may leave the hospital in less than 5 hours after surgery.⁴⁰

Clinical evidence and usage

Evidence has shown that LH to treat uterine fibroids is associated with less surgical trauma, a shorter procedure, and rapid postoperative recovery. A study was conducted to evaluate the curative effects of LH performed to treat uterine fibroids and determine the impact of the procedures on ovarian blood supply. Abdominal panhysterectomy was set as the control group; with the other group of patients treated with LH set as the observation group. The duration of operation, amount of bleeding and time to recovery after the procedure were significantly lower in women ($p < 0.05$) undergoing LH. The levels of PRL (prolactin), E2 (estradiol), FSH (follicle stimulating hormone) and luteinizing hormone, and other ovarian function markers in the LH group were lower one month after the operation, but still significantly higher than those of control group ($p < 0.05$). The impact of the surgery on the ovarian blood supply was less marked in the patients undergoing LH as their levels remained higher than those of patients in the control group ($p < 0.05$). The numbers of patients with completely healed abdominal muscular layers were significantly higher in the LH group than those in the control group, at every different time point examined (1, 4, 8, and 12 months after surgery; $p < 0.01$).⁴¹

A study was conducted to evaluate the outcomes in LH with morcellation compared with abdominal hysterectomy for the presumed fibroid uterus and to examine short and long term complications and death. The decision-tree analysis predicted fewer overall deaths with LH compared with abdominal hysterectomy (98 vs 103 per 100,000). Although there were more deaths from leiomyosarcoma after LH (86 vs 71 per 100,000), there were more hysterectomy-related deaths with abdominal hysterectomy (32 vs 12 per 100,000). The laparoscopic group had lower rates of transfusion (2400 vs 4700 per 100,000), wound infection (1500 vs

6300 per 100,000), venous thromboembolism (690 vs 840 per 100,000) and incisional hernia (710 vs 8800 per 100,000), but a higher rate of vaginal cuff dehiscence (640 vs 290 per 100,000). LH resulted in more quality adjusted life years (499,171 vs 490,711 over 5 years). This study showed that the procedure related complications associated with laparotomy balanced the risk of leiomyosarcoma in morcellation with LH. It provides patients and surgeons with estimates of risk and benefit on which patient centered decisions can be made.⁴²

EXPERT OPINION

- Fibroids are the most common indication for hysterectomy globally.
- Hysterectomy may be offered as a permanent treatment for symptomatic leiomyomas in women who do not want to preserve fertility and their uterus and have been counselled regarding other options and the consequences of hysterectomy
- Hysterectomy is offered in asymptomatic enlarging fibroids after menopause without HRT when there is a suspicion of malignancy
- Vaginal and laparoscopic hysterectomy are preferred over abdominal hysterectomy depending on the surgical skills and expertise, facilities, and the patient's choice

Myomectomy

If the uterus has to be retained, regardless of the fertility desire, an alternative to hysterectomy is myomectomy. If the fibroids are associated with heavy menstrual bleeding, pelvic pain and/or pressure symptoms, and reproductive issues, removal of fibroids is suggested. Myomectomy can be performed by laparotomy, minilaparotomy, laparoscopy, hysteroscopy, or a combination of these according to the number, size, and location of fibroids.²⁰

Hysteroscopic myomectomy

Hysteroscopic myomectomy should be considered as the first line conservative surgical therapy for the management of symptomatic intracavitary fibroids. Experienced surgeons can remove submucous myomas (types 0, I, and II) up to 4 to 5 cm in diameter hysteroscopically.²⁰

Clinical evidence and usage

Submucous fibroids protrude into the uterine cavity and can usually be removed hysteroscopically. This is a less invasive, simpler and safer approach compared with abdominal myomectomy. In fact, submucosal fibroids may be difficult to locate during abdominal operations and they may be left behind such that AUB symptoms persist.⁴³

Where possible hysteroscopic myomectomy is performed in a single surgical procedure, according to the FIGO type and the size of myoma with it being reported in a study that the overall surgical provision in a single-step procedure was 88.28%. Due to the lack of the intramural component of myomas, all type 0 myomas were resected in only one surgical

procedure by classical slicing. Concerning type 1 and type 2 myomas, the need for a multiple procedures occurred mainly in type 2 myomas. Myomas with intramural components were treated with the cold loop technique. Their findings showed a high probability of success in one step surgical procedure (88.59% and 82.55% respectively) even in the cases of type 1 and type 2 fibroids.⁴⁴

Laparoscopic myomectomy

The laparoscopic approach has been known to have several benefits and is considered to be superior to laparotomy for myomectomy in terms of less blood loss, diminished postoperative pain, fewer overall complications, faster recovery, and significant cosmetic advantage. The procedure however takes a longer time to accomplish and requires extra training, surgical expertise, and specialized equipment. The absence of multilayer closure in cases of deep intramural leiomyoma or to the injudicious use of electrosurgical energy during myomectomy has been reported to be a possible cause of uterine rupture during pregnancy.^{14,20}

Clinical evidence and usage

A study was conducted to compare the efficacy of laparoscopic myomectomy and abdominal myomectomy in restoring fertility and to evaluate the obstetric outcomes. Febrile morbidity (> 38 degrees C) was more frequent in the abdominal than in the laparoscopic group (26.2 vs 12.1%; $p < 0.05$) and laparotomy caused a more pronounced hemoglobin drop (2.17 ± 1.57 vs 1.33 ± 1.23 ; $p < 0.001$). The post-operative hospital stay was shorter in the laparoscopic group (142.80 ± 34.60 vs 75.61 ± 37.09 h; $p < 0.001$).⁴⁵

EXPERT OPINION

- Myomectomy is an option for women who wish to preserve their uterus. It may enhance fertility and benefit heavy menstrual bleeding, pelvic pain and/or pressure and reproductive issues.
- Hysteroscopic myomectomy should be considered as the first-line conservative surgical therapy for the management of symptomatic intracavitary fibroids.
- Laparoscopic myomectomy should be preferred over abdominal myomectomy as it is associated with advantages of faster recovery, less blood loss, diminished postoperative pain, fewer overall complications, and cosmetic advantage.
- Pregnancy may be planned 3 months after myomectomy.
- There are growing concerns regarding morcellation because of the chance of dissemination of undiagnosed malignancy. It must be stressed that leiomyosarcomas are rare and there are no accurate methods to diagnose them.
- The current recommendation is to discuss the benefits and risks of morcellation with the woman and perform contained morcellation where ever possible
- Morcellation should be used judiciously used in perimenopausal women and in cases with a high index of suspicion.

Alternatives to surgical intervention

Many women suffering from fibroids wish to avoid surgery because of medical comorbidities or personal preference.⁴⁶ Such patients may be treated with minimally invasive uterine sparing alternatives.

The advantages of minimally invasive treatment include preserving the uterus and thereby fertility and a reduction morbidity and recovery time in comparison with hysterectomy.⁴⁷

Uterine artery embolization

Uterine artery embolization (UAE) is effective for treating symptoms of uterine fibroid and in reducing bleeding and fibroid size, but is associated with a higher rate of post procedural complications and a risk of further reintervention.^{14, 47}

Clinical evidence and usage

UAE decreases the length of hospital stay, decreased time to normal activities and decreased likelihood of blood transfusion but may be associated with reduced fertility.

In a retrospective cohort study, researchers evaluated the efficacy and safety of UAE in the treatment of patients with symptomatic uterine fibroids. At three months and one-year follow-up, a significant reduction was observed in mean fibroid volume, uterine size, and dominant fibroid size ($p=0.00$). These changes were associated with symptoms improvement ($p<0.05$). At three months, overall patient satisfaction was 84% which reduced to 75.9% by 12 months (all $p< 0.05$). Complications were reported in 2.5% of the patients [Society of Interventional Radiology (SIR) class D].⁴⁸

In another study, the clinical success of UAE in patients with symptomatic fibroids was 93% (overall) and 96% for menorrhagia. For dysmenorrhoea, at least some improvement was observed in 89% of women, a significant improvement was observed in 75% of the patients and resolution of pain was observed in 56% of the patients.⁴⁹

In a systemic review, after UAE versus myomectomy, pregnancy rate was found to be lower and miscarriage rate higher. The pregnancy rates were 50% in the randomized controlled trial (RCT) and 69% in the cohort studies. The median pregnancy rate was 29% among the case series. After UAE, the miscarriages rate was 64% in the RCT, 34% after cohort studies. In the case series, the median miscarriage rate was 25%.⁵⁰

EXPERT OPINION

- For the treatment of symptomatic uterine fibroids, UAE is recommended as a safe and effective alternative to surgical removal of fibroids in women who wish to preserve their uterus or avoid surgery.
- Women choosing UAE for the treatment of fibroids should be counselled regarding consequences and possible risks.

Magnetic resonance-guided focused ultrasound surgery

Magnetic resonance guided focussed ultrasound surgery (MRgFUS) is a thermal ablation method for treating fibroids. It uses high intensity ultrasound directed to a precise location, resulting in a temperature rise which induces coagulation necrosis within few seconds.^{20, 47, 51}

It can be an alternative treatment of uterine fibroids in select patients with limited efficacy and may be used for patients desiring future fertility. MRgFUS is completely non-invasive and continuous imaging of fibroids and adjacent structures results in optimization of fibroid ablation with minimal damage to the surrounding tissues. Only women with fibroids located immediately beneath the anterior abdominal wall without bowel interposition or scars in the region of interest can be treated with MRgFUS. The procedure has a long average treatment time and only one fibroid may be treated at a time.^{20, 47, 51}

Clinical evidence and usage

In a study evaluating the efficacy of MRgFUS in women with symptomatic uterine fibroids a significant, time-dependent decrease in both symptom severity scores (SSS) and fibroid volume was observed after treatment. At 6 months the average reduction in volume was 41.6% and at 12 months it is was 52.6% ($p < 0.05$). Before treatment, the mean SSS of the patients was 41.7 ± 2.8 while the average SSS was 26.9 ± 3.6 at 3 months, 20.7 ± 3.4 at 6 months, 18.5 ± 3.6 at 1 year, 16.5 ± 7.1 at 2 year and 9.8 ± 3.6 at 3 to 4 years. At all the time points up to 3 to 4 years, the decrease in scores was significant ($p < 0.05$ and $p < 0.001$). The treatment was reported to be safe.⁵²

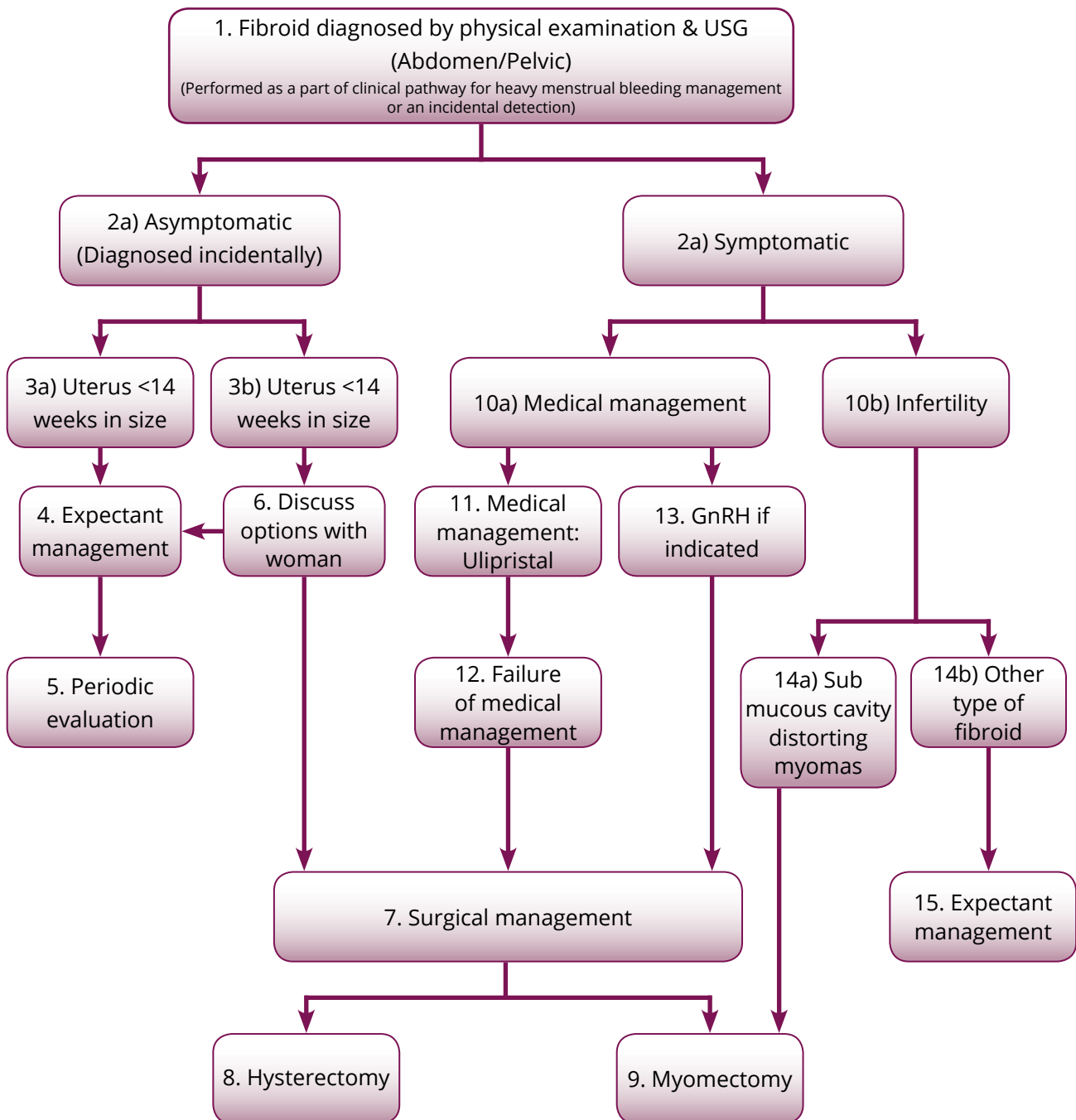
The reported rate of minor complications after MRgFUS was 3.9% and serious complications which included a skin burn, a fibroid expulsion, and persistent neuropathy in 1.1%. The overall re-intervention rate was 58.64% in a 5-year follow-up study. But in those treatments with non-perfused volume $> 50\%$, the re-intervention rate was 50%.⁵³

A study of reproductive outcome after MRgFUS treatment reported a mean time for conception as 8 months with live births in 41%, spontaneous abortion in 28%, and elective pregnancy termination in 11%.⁵⁴

EXPERT OPINION

For the treatment of symptomatic uterine fibroids, MRgFUS is recommended as an alternative to surgical removal in women who wish further fertility with limited efficiency.

Algorithm for the management of uterine fibroids⁵⁵



Overview of treatment of uterine fibroids⁵⁶

Asymptomatic women

- Expectant management of asymptomatic women, except in the case of a woman with moderate or severe hydronephrosis or a woman with a hysteroscopically resectable submucous leiomyoma who is planning pregnancy (Grade 2C).

Postmenopausal women

- In the absence of postmenopausal hormonal therapy, leiomyomas generally become smaller and asymptomatic in postmenopausal women; therefore, intervention is not usually indicated.
- Periodic evaluation should be undertaken to exclude sarcoma in a postmenopausal woman with a new or enlarging pelvic mass. The incidence of sarcoma is 1 to 2 percent in women with a new or enlarging pelvic mass, abnormal uterine bleeding, and pelvic pain (Grade 2C).

Submucosal leiomyomas

- Hysteroscopic myomectomy is recommended for women with appropriate submucosal leiomyomas that are symptomatic with bleeding or pregnancy loss (Grade 1C).
- The procedure allows future childbearing, usually without compromising the integrity of the myometrium, but is also an appropriate option in women who have completed childbearing since it is minimally invasive.
- Abdominal myomectomy may be performed in women with significant symptoms and a submucous leiomyoma(s) not amenable to hysteroscopic resection.

Premenopausal women

Women who desire fertility

- Hysteroscopic myomectomy is the preferred approach to submucosal leiomyomas. Given the lack of information about the safety of pregnancy after other invasive procedures, abdominal or laparoscopic myomectomy is recommended for the treatment of symptomatic intramural and subserosal leiomyomas in women who wish to preserve their childbearing potential and who have no major contraindications to a surgical approach (Grade 1B).
- However, for women for whom risk of intraoperative conversion to hysterectomy is high or women considering a future pregnancy other options such as uterine artery embolization and magnetic resonance guided focused ultrasound may be considered appropriate treatment options. However they have to accept some impairment of fertility balanced by a non surgical treatment and an expedited recovery phase.

Women who do not desire fertility

- Hysterectomy is the definitive procedure for relief of symptoms and prevention of recurrent leiomyoma related problems. However even if women do not desire fertility there could be symptom relief with alternatives to hysterectomy.
- GnRH agonists prior to a potentially complicated hysterectomy or hysteroscopic myomectomy may be used if a reduction in uterine or myoma volume is expected to facilitate the procedure or if there is significant anemia which has not responded to iron therapy (Grade 2B).
- Progesterone receptor modulators-Ulipristal acetate are now considered to be a first-line therapy where they are available with appropriate patient selection and monitoring (Grade 1A).
- For women with abnormal uterine bleeding related to leiomyomas who wish to undergo the least invasive procedure, a trial of placement of a levonorgestrel-releasing intrauterine system may be preferred over other drug therapies (Grade 2C).
- Several less invasive options, both surgical and using interventional radiology, are available for symptomatic women who have completed childbearing but wish to retain their uterus. There is no high-quality evidence to recommend one procedure over another.
- Since fertility and pregnancy outcome may be adversely affected after many of these procedures, with the exception of myomectomy these procedures are not recommended for women with any possibility of planning a future pregnancy (Grade 2C).

Grades of Recommendation	<ol style="list-style-type: none"> 1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients 2. Weak recommendation: Benefits and risks closely balanced and/or uncertain
Grades of Evidence	<ol style="list-style-type: none"> A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

SUMMARY OF EXPERT OPINION

- Risk factors of fibroids include early menarche (younger than 10 years), increasing age (before onset of menopause), family history of uterine fibroids, nulliparity, and high BMI.

- The FIGO and ESGE systems should be used for classification of fibroids and pre-surgical classification should be considered for selected clinical situations.

- Since the pathophysiology of fibroid development is influenced by hormones, progesterone and progesterone receptors along with genetic factors and disturbance of aromatase function are now acknowledged as the most significant factor. Progesterone and its receptors hence represent potential targets for inhibiting growth of myomas.

- Fibroids may be asymptomatic or may present with menstrual disturbances, pain, pressure symptoms, fertility related issues, and obstetric complications.

- A pelvic ultrasonography is recommended as the first-line imaging modality in the detection and evaluation of uterine fibroids.
- TVS is more accurate than TAS for the identification of small fibroids.
- Colour Doppler ultrasonography may be done in special situations.
- Trans Rectal may be performed when TVS is not possible or not an option.
- Saline sonography is useful to diagnose submucosal fibroids.

- Hysteroscopy is useful in identifying and differentiating between intracavitary myomas and endometrial polyps while offering the additional advantage of simultaneous hysteroscopic myomectomy and polypectomy.

- MRI is recommended for characterizing pelvic masses for which it is more sensitive than ultrasonography.

- Ulipristal acetate is effective in reducing bleeding and fibroid volume, and improving anemia in the patients with uterine fibroids.
- While a single course of 3 months can be used preoperatively for delaying surgery, up to four consecutive courses may be used as medical therapy.

SUMMARY OF EXPERT OPINION

- Baseline liver function tests are advised before starting UPA and treatment is deferred or suspended when the results are more than twice the upper limit of normal. This is followed by periodic monitoring of LFTs, during and after the course of UPA.
 - GnRH analogues can be used prior to hysteroscopic myomectomy and hysterectomy to reduce the uterine volume and vascularity.
 - Evidence has shown that in hysteroscopic myomectomy and hysterectomy GnRHa use can correct pre-operative anemia, reduce intra-operative blood loss and operative time with an increase in postoperative hemoglobin and hematocrit values and decrease postoperative complications and length of hospital stay.
 - GnRHa is not recommended before conventional and laparoscopic myomectomy due to a possible loss of planes.
 - Because of their side-effect profile, with climacteric complaints and reduced bone density, GnRHa can be used over a brief period of 3 to 6 months.
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- The current evidence is insufficient to support the use of aromatase inhibitor drugs in the treatment of women with uterine fibroids to support routine use though this seems to be a promising option for the medical treatment.
-
- The levonorgestrel-releasing intrauterine system (LNG IUS) can be used in women with intramural myomas, who do not desire pregnancy in the near term.
-
- Combined oral contraceptives, tranexamic acid, and NSAIDs are used as symptomatic treatment to reduce bleeding and dysmenorrhea.
-
- Fibroids are the most common indication for hysterectomy globally.
 - Hysterectomy may be offered as a permanent treatment for symptomatic leiomyomas in women who do not want to preserve fertility and their uterus and have been counselled regarding other options and the consequences of hysterectomy
 - Hysterectomy is offered in asymptomatic enlarging fibroids after menopause without HRT when there is a suspicion of malignancy
 - Vaginal and laparoscopic hysterectomy are preferred over abdominal hysterectomy depending on the surgical skills and expertise, facilities, and the patient's choice

SUMMARY OF EXPERT OPINION

- Myomectomy is an option for women who wish to preserve their uterus. It may enhance fertility and benefit heavy menstrual bleeding, pelvic pain and/or pressure, and reproductive issues.
 - Hysteroscopic myomectomy should be considered as the first-line conservative surgical therapy for the management of symptomatic intracavitary fibroids.
 - Laparoscopic myomectomy should be preferred over abdominal myomectomy as it is associated with advantages of faster recovery, less blood loss, diminished postoperative pain, fewer overall complications, and cosmetic advantage.
 - Pregnancy may be planned 3 months after myomectomy.
 - There are growing concerns regarding morcellation because of the chance of dissemination of undiagnosed malignancy. It must be stressed that leiomyosarcomas are rare and there are no accurate methods to diagnose them.
 - The current recommendation is to discuss the benefits and risks of morcellation with the woman and perform contained morcellation where ever possible
 - Morcellation should be used judiciously in perimenopausal women and in cases with a high index of suspicion.
 - For the treatment of symptomatic uterine fibroids, UAE is recommended as safe and effective alternative to surgical removal in women who wish to preserve their uterus or avoid surgery.
 - Women choosing UAE for the treatment of fibroids should be counselled regarding consequences and possible risks
-
- For the treatment of symptomatic uterine fibroids, MRgFUS is recommended as an alternative to surgical removal in women who wish further fertility with limited efficiency

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