

Management of Uterine Fibroids - A Review Article

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ABSTRACT

Uterine fibroids, known otherwise as leiomyomas or simply myomas are benign smooth muscle tumours. They are one of the most common benign tumours in females presenting usually in the age group of 30 – 40 years. Although usually asymptomatic and seen as an incidental finding on USG, they may present with a variety of symptoms like menorrhagia and dysmenorrhea. Large sized fibroid may cause pressure symptoms like urinary frequency, urgency, low back pain, etc. They may also be associated with infertility, complications in pregnancy and adverse obstetric outcomes. Most fibroids decrease in size with menopause but symptomatic fibroids may require early intervention. In early days, the only management available for uterine fibroids was surgical hysterectomy, but with advancements in medical pharmacotherapy and surgery, various treatment options have become available like selective progesterone receptor modulators, GnRH antagonists, invasive and minimally invasive surgeries like uterine artery embolization and magnetic resonance guided focused ultrasound surgery, etc. However, there is no universal management which could be applied to each case but management differs with every single patient. Various factors have to be taken into consideration for management of uterine fibroid such as size of the fibroid, its site, the patient's age, symptoms, desire to conceive, etc. Therefore, it is important for the clinician to offer the patient treatment options which best suit her needs and inform her about the pros and cons of every method so that she can make an informed decision. This not only improves patient satisfaction, but also decreases concern about future regret. As the number of treatment options increase, it becomes difficult for the patient as well as the clinician to decide the modality which would best suit the patient's needs. Hence in this article, we have tried to summarize the various treatment options available to a woman with uterine fibroid with their advantages and disadvantages.

Keywords: Leiomyoma, Uterine fibroid; Management of fibroid; Ulipristal acetate; Elagolix GnRH superagonist; Ultrasound surgery; Uterine artery embolization

INTRODUCTION

Uterine fibroids which are the most common pelvic tumor in females are smooth muscle tumors originating from the myometrium of the uterus. About 20 to 25% of women in reproductive age group and nearly 50% of women over 45 years of age are affected by uterine fibroid. Also, African-born women are known to have a 3-to 9-fold increased risk of having uterine fibroid than Caucasian women [1].

The fibroid originates from a single myocyte and hence is monoclonal in origin. The growth of the fibroid is estrogen and progesterone dependent [2]. To begin with, all fibroids are intramural which is the most common presentation. From here they may grow towards the uterine cavity and become submucosal uterine fibroid or grow towards the peritoneal cavity and become subserosal fibroid. The fibroid may even have an extra uterine presentation most commonly presenting as a cervical fibroid or a broad ligament fibroid.

OBJECTIVE

To study the various treatment options available to a woman with uterine fibroid, summarize them stating their advantages and disadvantages and highlighting the recent advances which have occurred in the management.

Risk factors for uterine fibroids

Various risk factors known to cause uterine fibroids are:

Age: Leiomyoma is more common in age group of 30-40 years. Although slow growing, the growth rate also varies with age. Fast growing tumors are seen in women less than 35 years of age whereas in women belonging to older age group, the tumors are slow growing.

Menarche: The risk of developing fibroid is increased by early menarche i.e. before 10 years of age as the years of exposure to estrogen increases [3].

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Parity: Nulliparous women are at a higher risk of developing uterine fibroid as pregnancy is considered to have a protective effect.

Race: African descent women have greater chances of developing uterine fibroids. A US based study reported that the risk of developing uterine fibroids increased by 80 percent in women of African descent by the age of 50 years.

Other factors: Obesity [4], high blood pressure, Vitamin D deficiency [5] and a family history of uterine fibroids are other risk factors for developing uterine fibroid.

Clinical features

50% cases of uterine fibroids are symptomless, however in symptomatic women, the symptoms differ on the basis of size, situation and number of the tumors. Submucosal fibroids usually present with maximum symptoms. In symptomatic females the most common presentation is menorrhagia. Menorrhagia in Indian setting can be life threatening as owing to the low socio-economic status, the patient is usually anemic which gets further aggravated by menorrhagia.

Pain in fibroids may be indicative of degeneration. Dysmenorrhea and pelvic pain impair the quality of life of the patient.

Fibroid also gives rise to pressure symptoms like bowel abnormality, urinary frequency, pain in lower back, constipation, pressure in the pelvic region, urinary retention, etc.

Uterine fibroids most commonly submucous fibroids can also lead to infertility and recurrent abortions. Various mechanisms have been suggested for infertility caused by uterine fibroids like by altering the anatomy of the uterus, impairment of the blood supply of endometrium and myometrium as well as increased contractility of uterus.

Leiomyomas are also considered to significantly accentuate the risk of cesarean delivery to 33.1% from 24.2 % when compared to a control group in a large retrospective study. The study also proved a greater risk of breech delivery upto 5.3%, preterm delivery upto 15.1%, intrauterine fetal demise and growth retardation upto 3.9% as well as increased risk of premature rupture of membranes upto 3.3% [6]. The chance of undergoing malignant transformation for a uterine fibroid is very low.

Management

The management for a case of uterine fibroid varies with every patient. It depends on size, location, age, patient's desire for pregnancy and symptoms. As the goal of treatment differs with patient's requirements, it is important for the clinician to offer treatment options which best suit the patients' need.

Hence the management can be broadly divided into 3 categories:

1. Expectant management
2. Medical management
3. Surgical management

Expectant management: Clinical surveillance is preferred in asymptomatic females as there is minimal concern of malignant transformation if patient is asymptomatic – follow up ultrasonography every 3 to 6 months irrespective of the size of fibroid is usually done. Watchful waiting is also preferred in premenopausal women with mild tolerable symptoms as uterine

fibroids are known to regress after menopause as they are estrogen dependent.

Medical management: It includes symptomatic management as well as drugs which are known to reduce the volume of the fibroid.

1st line drugs

NSAIDS - Non-Steroidal Anti-Inflammatory Drugs: They provide pain relief as well as reduce hemorrhage when compared to placebo however reduction in hemorrhage is less when compared to tranexamic acid.

Oral contraceptives

Combined estrogen and progesterone pills: The advancement of a fibroid is known to be estrogen and progesterone mediated therefore, initially combined OCPs were thought to be contraindicated for the management. However, recently the use of combined estrogen and progesterone pills has been tried in women with fibroids. They tend to decrease hemorrhage especially progesterone pills by acting on the endometrium and making it thinner but it has no effect on fibroid volume.

Progestins: Trials with depot medroxy progesterone acetate have led to a remarkable reduction in menstrual blood loss, a decrease in fibroid volume and has also induced amenorrhea. Norethisterone is another commonly used progestogen. Therapy with progestins may induce some histopathological changes like increased cellularity and mitotic activity which may have some malignant potential. Hence, history of progestin use shall always be enquired when such changes are noted.

Progestogen-releasing intrauterine system: Levonorgestrel-releasing intra-uterine system (Mirena) has shown better outcomes in decreasing menstrual blood loss however it is suited only for patients who do not have distortion of uterus due to fibroids. Also expulsion of this device from uterus can cause serious complications.

Trenaxamic acid: It is an antifibrinolytic agent given orally known to remarkably reduce menstrual blood loss. It is commonly used for the treatment of menorrhagia. Some studies have reported adverse effects of fibroid degeneration and thrombosis due to use of trenexamic acid however evidence regarding this is lacking.

2nd line drugs

Selective progesterone receptor modulators (SPRM): Use of SPRM has opened new avenues in the management of leiomyomas. As the fibroid is progesterone dependent, a transition or block in progesterone activity at the receptor level leads to growth restriction followed by apoptosis in the fibroid leading to its depreciation. They also induce amenorrhea thereby giving symptomatic relief from bleeding. The best part of this therapy is it is free from hypoestrogenic side effects and bone distortion. Various SPRMs have been tried for treatment like mifepristone, asoprisnil, telapristone acetate, vilaprisan, and ulipristal acetate.

Mifepristone was one of the first progesterone receptor antagonist to be used almost 25 years ago. Although it is more eminently known for its use as an abortifacient, it significantly reduces uterine blood loss, thus relieving menorrhagia and improving the quality of life for the patient. However, it does not have a significant role in reducing fibroid volume.

In recent times, Ulipristal acetate has given the most promising results. It leads to a control in the fibroid volume and a decrease in

myoma associated bleeding in majority of cases. The treatment is considered safe at the level of endometrial changes as endometrial changes get reversed by 6 months after the end of therapy. The common adverse effects encountered were breast tenderness and headache [7-9].

Selective estrogen receptor modulators (serm)

Various studies on the pathophysiology of fibroid have shown that estrogen acts on uterine fibroid and stimulates its growth via ER- α .

Use of tamoxifen and raloxifene were studied on fibroids. Though Tamoxifen decreased menstrual blood loss, it had no significant impact on fibroid volume and also lead to various side effects like hot flushes and dizziness. Hence, its use is not recommended. The effects on raloxifene were unclear.

GnRH receptor blockers

These are of two types:

GnRH superagonists: These drugs act by causing activation of GnRH receptor for a prolonged time causing desensitization of the receptor and decreased GnRH levels [10]. The drugs were first used in 1983 for conservative treatment of fibroids and provided prompt relief from menorrhagia and considerable size reduction of the fibroid. However, in the later studies it was found out that though the size decreased for the time the drug was given, fibroid's recurrence and relapse of symptoms occurred soon after discontinuation of treatment. Also, the therapy could not be used for a prolonged time (more than 6 months) due to the adverse effects of hypoestrogenism such as osteoporosis.

To try using the therapy for a prolonged time, an ADD BACK THERAPY has also been tried involving the use of low dose estrogen and progesterone along with superagonist which has not only prolonged the duration of treatment but also improved compliance as shown by a review in 2012 [11].

Its usefulness was studied extensively in pretreatment before surgery. Use of GnRH superagonists before surgery significantly reduced the size of myoma to be resected, reduced intraoperative blood loss, relieved symptoms while the patient awaited surgery and also improved hematological parameters as proven by a randomized control trial involving 71 hysterectomies [12].

GnRH antagonists: These drugs act by competing with the gonadotropin releasing hormone for the receptors on cell membranes, inhibiting gonadotropin secretion which ultimately decreases estrogen production. The drugs under this category are ELAGOLIX, OBE-2109, SKL-2670, SKL-2496 and RELUGOLIX.

Elagolix is the most researched among these drugs. Various trials have proved its efficacy in reducing heavy blood loss due to fibroids by rapidly suppressing LH levels and to a lesser extent the FSH levels [13]. Common side effects reported with its use are headache, abdominal pain and hot flashes. Adding a low dose add back regime to elagolix considerably decreased the hot flashes [14].

In 2018, Elagolix was approved by the US-FDA for use in the treatment of pain due to endometriosis.

Recently in May 2020, a combination preparation of ELAGOLIX, ESTRADIOL and NORETHINDRONE ACETATE under the trade name of ORIAHNNTM has been approved by the US - Food and Drug Administration for treatment of heavy menstrual blood loss due to uterine fibroids [15]. It can be given for a duration of 24 months. It is the first ever drug to be approved for such a condition.

Surgical management

As per the general classification, Fibroids or leiomyoma are divided into 4 broad types which are submucosal, intramural or subserosal. At first conservative treatment is given, if the patient does not respond to it then surgical management is preferred. There can be two possible situations and according to those situations surgery is decided. The very first thing is whether the family of the patient is complete or not. If the family is incomplete, then the preferred surgery is myomectomy. In the case scenario where the family of the patient is complete, there can be 2 possible ways to treat such a case. First one is minimally invasive treatment which consists of 2 methods which are uterine artery embolization and magnetic resonance guided focused ultrasound surgery. If both of these minimally invasive methods fail, then the treatment of choice is total abdominal hysterectomy which comprises complete removal of uterus along with its associated structures.

Myomectomy

Myomectomy can be performed in 3 ways according to the type of fibroid being treated. In case of type 0 or type 1 fibroid as per FIGO classification the myomectomy performed is hysteroscopically. In case of type 2 or intramural fibroid (as per FIGO classification), myomectomy is performed laparoscopically. Abdominal myomectomy is done for better prognosis and to minimize the chances of recurrence. Each technique has its own set of advantages and disadvantages.

Hysteroscopic myomectomy: The procedure is very commonly employed for recession of submucosal fibroids. Small fibroids (<2cm) can even be removed on an OPD basis. For large size fibroids, (Type 1 to 3 myomas as per FIGO classification) a two-step procedure could be used. In the first step, the protruded portion of the myoma is resected or ablated which leads to the residual myometrial component migrating towards uterine cavity increasing the myometrial thickness allowing complete and safe excision of the large fibroid [16]. Hysteroscopic myomectomy reduces bleeding and improves chances of fertility [17] but also has disadvantages of recurrence, incomplete excision and adenomyosis.

Laparoscopic myomectomy: This is considered as a difficult procedure to learn but has various advantages over the traditional methods like faster recovery and decreased post-operative morbidities. It also provides a significant cosmetic advantage. In this process, a vertical or transverse incision may be used depending on site of myoma with the help of a 10mm or 5m scope depending on the gynecologist's preference. The intraoperative bleeding could be significantly reduced by uterine artery ligation [18].

The disadvantages of this procedure include risk of dispersing the tissue fragments during morcellation which could lead to adenomyotic masses in the pelvic cavity [19]. Laparoscopic myomectomy is also contraindicated in multiple myomas (>4cm) in different sites of uterine cavity or an intramural fibroid >10 cm in size.

Hysterectomy

Hysterectomy is the surgery of choice for women who do not wish to get pregnant again. It provides the gift of a good quality of symptom free life to women with fibroids. The various ways in which hysterectomy could be performed are abdominal hysterectomy, laparoscopic hysterectomy, vaginal hysterectomy and laparoscopically assisted vaginal hysterectomy. Vaginal hysterectomy provides several advantages over other methods

like a decreased surgery time, lesser hemorrhage and a shorter hospitalization [20]. However its limitation is it cannot be used to remove large sized myomas.

Laparoscopic hysterectomy has an added risk of spread of benign or malignant tissue into the surroundings. Abdominal hysterectomy is the least preferred one as it is linked with an accentuated risk of infection, more blood loss and an increased recovery time.

Uterine artery embolization

It is an interventional radiology procedure in which the uterine arteries are obstructed by passing an occluding agent into one or both the uterine artery thus decreasing the blood supply to the fibroid and uterus. It is a minimally invasive procedure preferred in women who have symptomatic uterine fibroids having no wish to preserve fertility but want to preserve the uterus. Although it is a safe procedure, it may be associated with risks of abdominal pain due to necrosis of uterine fibroid, vaginal expulsion of the myoma, diminished ovarian reserve and an increased risk of infection. Also, there is a 15-32% increased risk of requiring a reoperation within 2 years of uterine artery embolization as compared to a 7% risk with myomectomy [21]. The contraindications to this procedure include active infection in the pelvic region, allergy to contrast media, pregnancy and chronic kidney disease.

Magnetic resonance guided focused ultrasound surgery

It involves the usage of MRI to detect and define the myoma and then using ultrasound energy to ablate the fibroid and cause coagulation and tissue necrosis in the fibroid. Since the advent of this technique, various new methods have been introduced to perform it like site-specific treatment, volume reduction therapy, and vessel-targeted therapy. Factors to be considered before performing this procedure are size and number of fibroids, their proximity to critical structures, weight of the patient, etc. Typically, patients having uterus of size more than 24 weeks, weighing more than 115 kg, having abdominal scar or any other contraindication to MRI are excluded [22]. Although the literature is scant on this topic [23-27] but pregnancy after undergoing this procedure is associated with a lot of complications, hence it is not preferred in women belonging to the reproductive age group. Also, the risk of requiring reoperation is high. Overall the procedure is well accepted with very few intraoperative and post-operative complications.

CONCLUSION

The management of uterine fibroids has seen various advancements in the recent times which has opened new horizons for women of various age groups whether they wish to conceive or not. The recent discoveries about the pathophysiology of uterine fibroids will improve our understanding for management of fibroid even further. Also, the approval to ORIAHNN by US FDA has led to a groundbreaking impact in the arena of treatment of fibroids. Improvement in surgical and therapeutic modalities has not only decreased mortality but decreased the morbidity rates all over the world.

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