

# Class Room

## Newer Options in Management of Fibroid Uterus

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### Introduction

Leiomyoma, commonly referred to as fibroid is a benign monoclonal tumor arising from uterine myometrial cells. The true prevalence cannot be estimated as there are a lot of asymptomatic patients in whom fibroids may be an incidental sonographic finding. Lifetime risk of a female >45 years acquiring fibroid uterus is 60% with an average of 40 to 80% incidence at 50years.<sup>1</sup> Fibroids can be intramural, submucous or subserous depending on the location within the uterus. Rarely, we also encounter cervical, broad ligament and parasitic fibroids. There is a definite genetic predisposition for the origin of fibroids with further growth stimulated by estrogen, progesterone and growth factors like IGF 1 and IGF 2. Common symptoms include heavy menstrual bleeding, dysmenorrhea, pelvic pain, urinary disturbances and pressure symptoms. They can also be associated with reproductive problems like subfertility and miscarriage.<sup>2</sup> Fibroids can undergo degeneration, torsion, hemorrhage, infection and very rarely malignant transformation.

The most frequently used investigation for diagnosis is transabdominal and transvaginal ultrasound.<sup>3</sup> It can be supplemented by saline infusion for precise diagnosis of sub mucous fibroids. MRI is the most accurate modality for evaluating uterine myomas with sensitivity of 88% - 93% and specificity of 66% - 91%.<sup>4</sup> Symptomatic fibroids and asymptomatic ones that enlarge the uterus to >14 weeks size require treatment. Previously, the standard treatment for fibroids has always been surgical, like myomectomy or hysterectomy. Fibroids are still the most common indication for hysterectomy.<sup>5,6</sup> Hysterectomy is associated with perioperative and postoperative morbidity and mortality.<sup>6</sup> Hysterectomy can be done by abdominal, vaginal and laparoscopic approaches. Myomectomy is the conservative surgical procedure done with the aim of preserving the uterus. It can be done by hysteroscopic, vaginal, abdominal and laparoscopic routes. Surgical treatment is a major public health cost.<sup>7</sup> Symptomatic patients with small fibroids can be expectantly managed with analgesics and antifibrinolytics<sup>8</sup>. There are a wide range of options between expectant management and surgery. The gynecologist has a significant role in proper counselling and aiding the patient for choosing the appropriate management.

### Medical Management

Drugs for managing fibroids can be used safely only for short term with temporary benefits in certain situations like medically unfit perimenopausal patients, preoperatively to reduce the size of fibroids and as a part of research. Antifibrinolytics like tranexamic acid, combined oral contraceptives (COC) and progesterones have been used to reduce blood loss associated with uterine fibroids. The effect of COCs and progesterone in reducing the size of fibroids is not documented.<sup>9</sup>

#### Mirena Intrauterine system (IUS)

The levonorgesterol containing IUS has shown to reduce menstrual blood loss by 74% over 3months without systemic side effects of progesterones<sup>10</sup>. Insertion of the device may require anesthesia at times, which is overcome by recently available equivalents like Emily. There is difficulty expected during insertion especially in large myomas distorting the cavity. Expulsion of the device is also noted in these patients. No significant reduction in myoma or uterine volume was observed in these patients even after 1 year of use.<sup>11</sup>

#### GnRH analogues

GnRH analogues like leuprolide acetate cause inhibition of pituitary gonadal axis and reduce the size of fibroids temporarily<sup>12</sup>, and can be used preoperatively. Hysterectomy becomes easier with reduced blood loss, but in those planned for myomectomy cleavage plane is lost and dissection becomes difficult. Smaller myomas temporarily get unnoticed but recur later. Taking into consideration the cost, side effects like menopausal symptoms and bone demineralization with long term use, they should be used in carefully chosen patients.

#### Selective estrogen receptor modulators (SERM)

SERMs such as raloxifene and ormeloxifene have been tried with the hypothesis that they modulate estrogen receptors in fibroids, causing shrinkage. Raloxifene has been shown to reduce fibroid size in postmenopausal and not pre menopausal women.<sup>13</sup> Ormeloxifene in standard therapeutic dosage of 60 mg for a period of 6 months is effective in preventing

further growth of fibroids and reduces menstrual blood loss . It can be used as an interim treatment to delay surgery.<sup>14</sup>

### Selective progesterone receptor modulators (SPRM)

There is recent biochemical evidence that progesterone stimulates fibroid growth. SPRMs of recent research in treatment of fibroids include mifepristone, asoprisnil, telapristone and ulipristal acetate.<sup>15</sup> These drugs are associated with reduction in pain, bleeding and size of fibroids without side effects of estrogen deficiency as noted with GnRH analogues.

### Mifepristone

This is an antiprogestone used in doses of 5-50mg /day. A dose of 25 mg/day for 3 months effectively controls bleeding, reduces uterine and myoma volume, avoids blood transfusion and hysterectomy in many symptomatic patients.<sup>16</sup> Patient compliance is good because of the low cost and low incidence of side effects. Endometrial hyperplasia is an adverse effect with long term use.

### Ulipristal acetate

This SPRM has been approved for short term therapy of symptomatic fibroids.<sup>17</sup> Daily dosage of 5-10 mg for three months showed effective control of bleeding and reduction in size of fibroids. Long term use causes cystic glandular dilatation of endometrium classified by pathologists as PAEC (PRM induced endometrial changes). These changes should not be considered as hyperplasia. More studies are needed to evaluate the effects on endometrium.

### Aromatase inhibitors

It has been proven that fibroids have increased expression of aromatase enzyme. Drugs like letrozole and anastrozole block conversion of androgens to estrogens and cause shrinkage of fibroids.<sup>18</sup> They are as effective as GnRH analogues but with less side effects. There is insufficient evidence about subsequent reproductive outcome.

### Somatostatin analogues

There is a proven role for IGF1 and IGF 2 in the initiation and growth of fibroids. Lanreotide, a long acting somatostatin analogue which reduces growth hormone secretion is shown to reduce myoma size.<sup>19</sup> Not many side effects have been reported except gall stone formation. These group of drugs have a potential for novel therapy, for fibroid uterus.

### Others

Use of Cabergoline ,a dopamine agonist reduced fibroid size by about 50% within 6 weeks<sup>20</sup>. Gestrinone with antiestrogen and antiprogestone properties has been reported to reduce myoma size by 60%<sup>21</sup>. This drug has androgenic side effects which will restrict its usage. Vitamin D and green tea extracts are observed to have potential role in treatment of fibroids. More clinical trials are required before we initiate their routine use in clinical practice<sup>22</sup>.

## Minimally Invasive Procedures

Uterine artery embolization, Magnetic Resonance guided focused ultrasound therapy (MRgFUS) and myolysis are minimally invasive alternative procedures to surgery in the treatment of fibroids.

### Uterine Artery Embolization

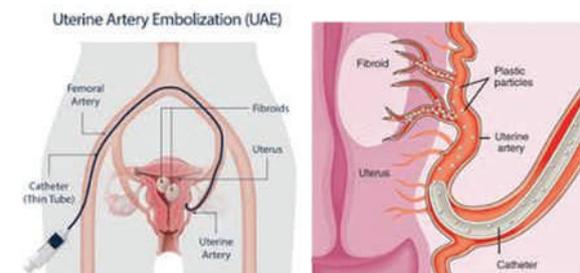


Fig 1 : Uterine artery embolization technique

Source of image : British Fibroid Trust.org.uk

Uterine artery embolization (UAE) for fibroids also known as uterine fibroid embolization is an image guided minimally invasive procedure to treat symptomatic fibroids. Under fluoroscopy guidance embolic agents are injected into arteries that supply fibroids which cause them to shrink (Fig 1). The size has been reported to reduce by around 50%.<sup>23</sup> The procedure requires availability of a specially trained interventional radiologist. The ideal candidates are premenopausal women with symptomatic fibroids <24 weeks size, without coexistent endometriosis or adenomyosis. It is not indicated in postmenopausal women, pregnancy, infertility, renal diseases and those with allergy to the contrast. The advantages are it is a minimally invasive safe procedure with rapid recovery and permanent shrinkage of fibroids.

The procedure is done under local anesthesia supplemented with sedation. A catheter is introduced through femoral artery to reach the uterine artery and specifically to branches that supply the fibroid under fluoroscopy guidance. Polyvinyl alcohol particles or Trisacryl gelatin microspheres are injected into the catheter until they block blood flow to the fibroid. The duration of the procedure is around 1 hour and patients need to rest for 6 hours. Post procedure pelvic pain and fever require analgesic use for 2 weeks. Some patients have vaginal discharge and bleeding.<sup>24</sup> Immediate complications include hematoma formation, thrombosis, pseudoaneurysm, infection, post embolization syndrome - a flu like illness. Late complications include amenorrhea, premature menopause and adhesion formation . Fibroid expulsion occurs in 10% patients especially with submucous fibroids.

### Magnetic resonance guided focused ultrasound procedure (MRgFUS)

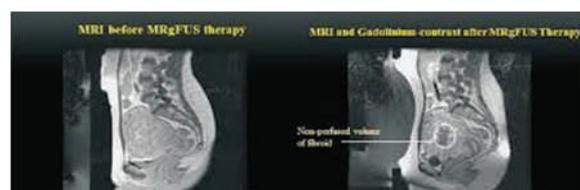


Fig 2 : MRI image of MRgFUS therapy

Source of image : UCSF Radiology – University of California,

MRgFUS or High frequency focused ultrasound (HIFU) is a non invasive treatment option for fibroids. This uses high intensity focused ultrasound to destroy the fibroids under real time monitoring (Fig 2). Symptomatic fibroids preferably 1- 4 in number which are enhancing in MRI show good results<sup>25</sup>. The procedure is contraindicated in patients with adhesions due to previous surgeries, pedunculated fibroids, co-existent adenomyosis and those in whom MRI is contraindicated. Effects on fertility is still unknown. The procedure is done under mild sedation . After proper positioning in MRI chamber ,the frequency and acoustic power are modified to produce appropriate therapeutic temperature of 70 to 80°C which will induce tissue necrosis<sup>26</sup>. Post procedure complications include skin burns, thermal bowel injury, Deep Vein Thrombosis and sciatic nerve damage. Shrinkage of fibroid may occur in over 3-4 months while pelvic pain, pressure symptoms and abdominal pain tend to resolve earlier.

### Myolysis

Various forms of myolysis using cryotherapy, bipolar, radiofrequency, laparoscopy, MRI guided laser have been done with variable results.<sup>27</sup>

VizAblate is a new transcervical device that combines real time intrauterine sonography with radiofrequency ablation for treatment of fibroids. This device avoids thermal injury to bowel and bladder. This can be considered for future use.<sup>28</sup>

Laparoscopic USG guided radiofrequency volumetric thermal ablation of uterine myoma is done using a device Accessa<sup>29</sup>. Further research is required to enable its wider usage.

Carbon dioxide and Nd: YAG laser are used for devascularizing myomas especially submucous types<sup>30</sup>.

### Uterine Artery Ligation

It is similar in principle and results to UAE but easier to perform. Simultaneous occlusion of uterine ovarian anastomosis achieved better resolution of symptoms with less effect on future fertility<sup>31</sup>.

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