REVIEW ARTICLE

FIBROID UTERUS UPDATES IN TREATMENT

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ABSTRACT

Fibroids or leiomyoma of myometrium are the most common benign tumor in females. There are currently many modalities, both medical and surgical, for the management of fibroid in today's practice such that it is often confusing as to which treatment to apply to which patient. Fibroid patients often present with a variety of symptoms and demographic aspect. Therefore a single guideline is not sufficient to encompass the case management for a specific Fibroid patient. Similarly the incidence of uterine sarcoma in patients undergoing fibroid treatment is thought to be minimal, but there is a current debate whether this risk is underestimated. The novel approach towards fibroids has allowed greater extent of uterine preservation but at the cost of decreased direct histological access, hence resulting in delay of diagnosis, especially in the case where uterine sarcoma is a possibility. Therefore gynecologists have to face the clinical dilemma to diagnose accurately and choose the most suitable treatment from the vast array of options available for each patient. The purpose of this article is to reconsider the different methods of treatments available and apply the most tailored treatment in each patient. This is a platform to better counsel for fibroid patients and their management.

KEY WORDS: Fibroid uterus, case management, Ulipristal, Aromatase inhibitors, Invasive procedures.

INTRODUCTION

Uterine fibroid is a benign tumor of smooth muscle of the myometrium. It is one of the most common tumors in females. Research indicates that 70% Caucasian and 80% afro Caribbean women above 50 years age have at least one fibroid.[1,2] Microscopically, fibroids consist of monoclonal cells of uterine smooth muscle embedded in a dense connective tissue matrix, specially collagen, elastin, fibronectin and glycosaminoglycans.[3,4] Although the pathogenesis is still unclear, there is good evidence that their growth is increased by progesterone and estrogen, [5,6] as fibroids seldom appear before menarche [7] and regress after menopause [8]. Uterine fibroids are classified according to their location and number. They can be sub mucosal, subserosal, intramural, pedenculated or single and multiple respectively. Being amongst the most dealt condition by gynecologist; fibroids have considerable health social and financial implications.

Uterine fibroids are managed medically and surgically, including minimally invasive surgery. The recent introduction of Aromatase inhibitors and selective Progesterone receptor modulators has significantly boosted the impact of Medical therapy. Uterine artery embolization (UAE) is the norm for fertility preserving treatment. The novel introduction of radio frequency ablation and ultrasonic wave (MRgFUS) allow further progress of minimal access surgery into the treatment of fibroid. In the last decade, hysterectomy was the sole approach, and has currently been superseded by more advanced minimally invasive methods such as laparoscopic as well as transvaginal myomectomy and hysterectomy, giving a better edge over conventional open surgery.[2]

Furthermore, while the classical open hysterectomy gave the additional benefit of curing undiagnosed conditions, like the rare uterine sarcoma, the physician has to evaluate and balance the risk of minimally invasive approach missing these undiagnosed conditions which result in further mortality and morbidity. Hence, the role of this article is to consider the progress in fibroid treatment and to allow enhanced management.

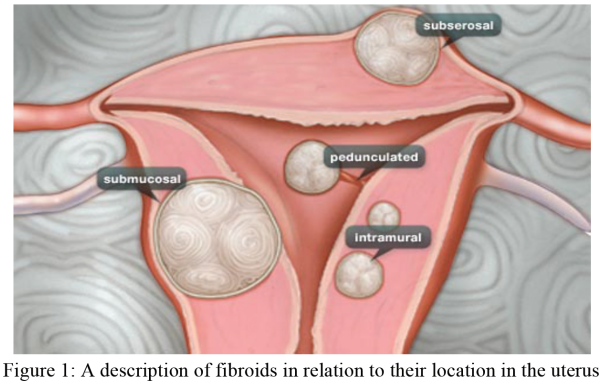

Figure 1: A description of fibroids in relation to their location in the uterus

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DISCUSSION

The Medical Approach

Management of fibroids is cornered on the presentation of the disease and ultimately, the patient wishes. The preliminary step is to exclude other possible causes of the presenting symptoms of PV bleeding, pain, pressure and sub fertility. In current practice, medical therapy is used for short courses only, owing to their considerable side effects and also due to the lack of evidence of their benefit in long term use. The following conditions indicate the use of Medical therapy:

1. Temporary relief of symptoms for short time period, especially in peri-menopausal period
2. Patients who are unfit to undergo surgery
3. As a preoperative adjunct to shrink fibroid size, reduce vascularity and operative bleeding. Size reduction also helpful in technically difficult open procedures, allowing alternative use less invasive approach, especially in case of laparoscopic myomectomy and hysterectomy and hysteroscopic submucosal myomectomy. GnRHs are well documented for this indication.
4. as part of new research programs, aiding in the further development in treatment.[9]

Medical therapy includes the following:

Gonadotrophin releasing hormone analogs (GnRHa)

GnRHa are commonly used as temporary treatment in preoperative settings to shrink fibroids or peri-menopausal women. A single dose causes pulsatile release of Follicle-stimulating stimulating hormone (FSH) and leutenising hormone (LH) from the anterior pituitary with a subsequent gonadal response. However, repeated injections or supraphysiological dosing cause a reversible inhibition of the hypothalamic-pituitary-gonadal axis via negative feedback mechanisms, and an overall drop of hormone levels. This induces involution and shrinkage of the estrogen sensitive tumor cells. Hence GnRHa induce indirect tumor size shrinkage via neuroendocrine pathways. [10] The Cochrane Systematic Review evaluated the role of GnRHa prior to myomectomy or hysterectomy [11] and showed that perioperative blood loss and rate of vertical incision were significantly reduced by the use of preoperative GnRHa. Fibroid size, uterine volume and overall pelvic symptoms are significantly reduced, allowing easier and faster procedure as well as promoting vaginal approach over abdominal; which in turn reduces hospital admission time. The drawbacks of GnRHa include expensive cost, availability, menopausal symptoms, especially osteoporosis. Furthermore other smaller fibroids may shrink to undetectable size and left out during resection, hence increasing risk of recurrences.

Selective estrogen receptor modulators (SERMs) A

SERMs are non-steroidal estrogen receptor ligands that exhibit organ-specific agonist or antagonist effects [12]. SERMs, like Tamoxifen and raloxifene, are mostly used in estrogen receptor positive carcinoma of breast. SERMs act by altering estrogen receptor efferents, with differential expression of related genes [13] causing fibroid involution. However, due to its hyperplasic effect on the endometrium, Tamoxifen RCTs have not been investigated as a fibroid therapy. Raloxifene has been demonstrated to reduce fibroid in postmenopausal women [14,15] but a recent Italian study with a daily 60mg raloxifene regimen over 2 years, has shown no changes in fibroid size in premenopausal women.[16]

Selective progesterone receptor modulators (SPRMs)

Progesterone acts through nuclear receptors in specific target tissues [18] and has dual effects on fibroid growth. Growth is increased by up regulation of Epidermal Growth Factor and BCL-2 and down regulation of Tumor Necrosis Factor-Alpha; conversely growth is inhibited by down regulation of Insulin-like-Growth-Factor-1 genes. New studies have suggested that progesterone and its gene expression effect may enhance the proliferative activity of fibroids [19, 20] and therefore allowing the possibility of antiprogestins or its receptor modulators to be used as fibroid management with the first antiprogestin, mefepristone (RU486) unveiled 25 years ago, there has been multiple additions to this group, including both steroidal and non steroidal agents with progesterone antagonism or receptor modulation. These are collectively known as Progesterone Receptor Modulators (PRMs) multiple RCTs have demonstrated the potential use of SPRMs as fibroid treatment, especially in reducing pain, size, bleeding and overall debility. A well demarcated advantage over GnRHa is its potential lack of estrogen deficiency and osteoporosis [21]. SPRMs are currently used as an alternative to GnRHa as preoperative treatment or before UAE.

Mifepristone:

Early use of mefepristone in fibroids reported over 40-50% size reduction with a dose of 12.5-50mg daily, along with amenorrhea in most patients [22]. Mefepristone reduced mean uterine volume by 50% and secondary amenorrhea in 40-70% [23]. In some cases, endometrial hyperplasia was documented, hence limiting the long term use amongst suitable patients. There is a need for extensive RCTs to docu-

ment all the apparent effects and long term benefit and mortality and morbidity reduction in the definitive use for this drug in fibroid treatment protocol. An alternative combination of mifepristone with the LNG-IUS could be beneficial in reducing undesirable endometrial hyperplasia, while still promoting a reduction in menses [24]. 100 women took part in a RCT with mifepristone dose of 5mg and 10mg without placebo group for 3 months; both doses resulted in proportional size reduction, uterine volumes and overall improvement in subject condition.

Ulipristal acetate:

Recently a randomised, parallel group, double blind, placebo controlled phase III trial (PEARL I) evaluated the pharmacologic efficacy and safety of oral ulipristal acetate against placebo for the preoperative symptomatic treatment of fibroids (25l). Eligible patients for surgery were divided randomly in 13 weeks of preoperative ulipristal acetate, 5mg, 10mg and placebo. Primary end points targeted a reduction in fibroid volume and uterine bleeding. Menstrual bleeding was controlled in 91% and 92% of subjects receiving 5 mg or 10 mg of ulipristal respectively and only 19% in the placebo group (P <0.001). Mean changes in overall fibroid size were –21%; –12% and +3% (P = 0.002 ulipristal acetate 5 mg /placebo, and P=0.006 ulipristal acetate 10 mg / placebo). No significant difference between ulipristal and placebo for tenderness and discomfort was reported; but a mild incidence of hot flushes was documented in all groups [25]. Contrasting with GnRha use, no suppression of estrogen was reported in the usage of ulipristal acetate.[25].The same group performed a double-blind, double-dummy phase III trial comparing ulipristal acetate with leuprolide acetate (an injectable GnRHa in PEARL II) and documented moderate to severe hot flushes in 11% and 10% in the 5 mg and 10 mg groups of ulipristal acetate respectively but over 40% with leuprolide acetate.[26] These RCTs demonstrated the effectiveness of ulipristal acetate as an alternative to GnRHa in preoperative settings, with a reduced side pharmacodynamics. Furthermore, SPRM ulipristal acetate is administered effectively via oral route, while it is not the case of GnRHa with solely 3 monthly intramuscular injections. Ulipristal acetate (5mg Esmya [Gedeon Richter, Hungary]) is currently licensed for a limited 3 months use as preoperative treatment of uterine fibroids.

The Faculty of Sexual and Reproductive Healthcare discourage the concomitant usage of progestins, since the competitive nature on the PR is likely to decrease ulipristal efficacy. Non-hormonal contraception is still preferred, even when most women are amenorrheic like in GnRHa usage [27, 28]. Current data on the endometrial effect of SPRMs is still limited, with majority of studies focusing on endometrial changes over short courses, while atypical hyperplasia and malignant change may required years to be detected [29]. Hence the need for a much extended study is justified for long term evaluation.

Aromatase inhibitors:

Aromatase inhibitors (AI) considerably inhibit ovarian and peripheral estrogen production within the first day of treatment [30] and act by blocking the aromatase enzyme which catalyzes the conversion of testosterone to estrogen [31]. New studies have reported that there is a greater expression of aromatase enzyme in fibroid tumor cells of African-American females, as compared to their Caucasian counterparts [32]. In few limited short term trials, aromatase inhibitors like letrozole 2.5mg daily and 1mg and astronomers have been demonstrated effective in fibroid therapy [33]. The major drawback of prolonged aromatase inhibitors usage is bone demineralization, requiring the adjuvant use of oral contraceptive or progesterone [34]. The newly published study of letrozole against triptorelin (GnRHa) over 3 month showed benefit of rapid onset of AIs and lack of classical flare ups of initial GnRHa use; but both significantly reducing fibroid size and overall morbidity [35]. Anastrozole reduced mean fibroid size by 55.7% within 3 months use. [36] The potential role of AIs in the treatment of fibroids is currently being studied in multiple RCTs [37].

Somatostatin analogs:

Growth factors, like insulin growth factor I (IGF-I) and IGF-II, have been demonstrated in the pathogenesis of uterine leiomyoma [38, 39, 40, 41]. As compared to normal adjacent myometrium fibroid cells expresses higher levels of IGF-I/IGF-II receptors [40, 41, 42] furthermore acromegalic patients have been demonstrated to have a higher incidence of fibroids as compared to the normal population [43]. Long-acting somatostatin analog Lanreotide reduces growth hormone secretion and has recently been studied in 7 women with fibroids in Italy[44]. Surprisingly Lanreotide showed a drastic 42% tumor volume reduction in 3 months, hence showing the potential of somatostatin analogs as a novel therapy of fibroids [45] somatostatin analog therapy for other diseases is relatively safe with few incidence of gallstone [46, 47]. Due to the lack of long term studies and the documented adverse effects of growth hormone deficiency in accelerated heard disease, future usage is somatostatin analogs may be

delayed in fibroid treatment.

Miscellaneous drugs:
In 2007, a preliminary study favoured cabergoline as a medical treatment of fibroid with a reported volume decrease of 50% in 6 weeks [48]. This same group subsequently compared cabergoline against the GnRHa diphereline and published comparable results in terms of volume reduction of tumor and improvement in the clinical, sonographic and preoperative outcomes.[49]

Gestrinone was recently evaluated in Italy for its anti-estrogen and anti-progesterone properties in fibroid growth.

Catechins of green tea:
Catechins are a class of bioflavonoid with antioxidant and anti-inflammatory effects. The most important green tea catechins include epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin. EGCG appears to arrest every step of tumorgenesis by altering messenger cascades of cell inflammation, transformation, proliferation and ultimately neoplasms including fibroids. The typical green tea prepared with 1g leaf in 100 mL water infused for 3 minute yields 250–360 mg tea solids; of which catechins account for 30%–42% [50].

Uterine Artery Embolization
UAE was first introduced in 1994 and is a better option than hysterectomy [51]. UAE is a minimally invasive radiological technique that has been offered to women with symptomatic fibroids. A Cochrane review in 2014 done on 793 women showed good response with UAE than with surgery (myomectomy and hysterectomy) with quicker recovery and early return to work. However, UAE was associated with some minor complications and an almost five-fold rise in the likelihood of further interventions within 2–5 years. The long-term follow-up showed no difference in the rates of ovarian failure[52].

One study of 66 women, 26 treated with UAE and 40 with myomectomy, showed no difference in live birth rates [52]. The common side effects reported were post procedure pain and vaginal discharge but major complications were rare. Out of more than 100 000 procedures, 12 deaths have been reported all over the world for UAE, demonstrating an estimated UAE mortality rate of 1 in 10 000 women compared with 3 in 10 000 women for hysterectomy [53].

The HOPEFUL study, which included a 5-year follow-up after UAE or hysterectomy, demonstrated that both treatments were safe [54]. A meta-analysis including randomised and nonrandomized clinical trials also suggested that UAE was associated with a lower rate of major complications compared with surgery. However, UAE had an increased risk of reintervention (OR 10.45; 95% CI 2.65–41.[55]

The Surgical Approach
Most fibroids require only careful observation with regular assessment, as they are generally asymptomatic, confined to the pelvis and seldom malignant.[58]. Surgery is considered for:
1. Abnormal uterine bleeding which is refractory to medical therapy;
2. A high index of suspicion of malignant change
3. Postmenopausal fibroid growth
4. Gross uterine cavity distortion
5. Sub fertility with possible fallopian tube compression, recurrent miscarriages
6. Intractable pain, uterine bleeding and secondary anemia, pelvic pressure symptoms, dyspareunia, dysuria and other symptoms causing decline in quality of life and daily activities

Invasive Procedure:
Abdominal myomectomy:
Myomectomy is the preferred procedure for symptomatic and for solitary or pedunculated fibroids in women wishing to retain uterine mass. Ever since submucosal fibroids have been associated with sub fertility and recurrent miscarriages, myomectomy is favoured prior to Gonadotrophin stimuli for IVF and for oocyte retrieval in bulky fibroids [56]. Furthermore this still remains a topic of controversy as some debate the intervention in large otherwise asymptomatic fibroids that do not distort intrauterine cavity, while some prefer the intervention only in cases of bulky myoma causing cavity distortion and recurrent unaccountable IVF failures [57]

Endometrial sampling is further enhanced by the use of hysteroscopic visualization, especially in cases of intrauterine polyps, papilloma, foreign body or IUCD. In recent survey, surgery is delayed for 4 to 6 weeks to minimize chances of infection after hysteroscopy. Proper preoperative preparation in patients of paramount importance, with strict optimisation of blood panels, Myomectomy is carried out by either laparoscopic or laparotomy approach. Meta analysis of 6 RCTs with 576 patients indicate laparoscopic myomectomy confers less preoperative blood loss, pain complaint, faster recovery period of less than 2 weeks, and fewer complication rates but at the cost of

longer operative time and higher operative skills [59]. The conclusion of the study implied that laparoscopic myomectomy in specific patients yielded better outcomes with better operative skills of the surgeon, especially in long term complications of uterus repair and risk of uterine rupture or pregnancy events, hemorrhage and adhesion formation. 531 subjects taking part in subsequent 10 RCTs for the evaluation of haemostasis with IV oxytocin, intramural vasopressin analogs, vaginal misoprostol, pericervical tourniquet chemical dissolution with sodium 2 mercaptoethane sulfonate (MESNA), intramyometrial bupivacaine adrenaline, tranexamic acid and enucleation of fibroid by morcellation steps while still attached to uterine body [60]. All these procedures are associated with better haemostasis except oxytocin and morcellation which have no role in operative bleeding. Furthermore the operative morbidity hasn't been proved to be higher compared to hysterectomy [57]. Following extensive myomectomy, a subsequent cesarean is recommended, irrespective of endometrial opening site.

Hysteroscopic myomectomy:

Hysteroscopic myomectomy is performed in cases of abnormal uterine bleeding, history of recurrent miscarriages, sub fertility and is contraindicated In cases of suspected endometrial malignancy, inability of cavity distension or lesion circumnavigation and deep extension of tumor. 20% of treated subjects will require further treatment in next 10 years, mostly due to re growth of inadequate myoma resection or new fibroids [56]. The European Society of Hysteroscopy divides submucosal fibroids in 4 categories to assist the surgeon in planning his approach [63]. Class T: O denotes all pedunculated submucosal myomas and Class T: I with submucosal myomas extending less than 50% into myometrium. Class T: II are myoma extending beyond 50%into the myometrium. Class T: 0 and Class T: I can be approached hysteroscopically by average skilled surgeon and Class T: II is reserved for highly experienced Surgeons or through abdominal approach.

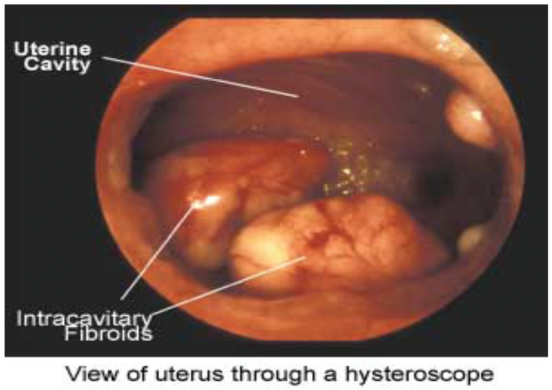


Figure 2: View of Uterus through a hysteroscope

Vaginal myomectomy:

Bulky fibroids arising from uterus can fill the vagina and cause intermenstrual bleeding, foul smelling discharge, dyspareunia and urinary obstruction. These masses are mostly enucleated per vaginum with the stalk ligated. In some rare cases, then may complicate into uterine inversion, especially masses arising from uterine fundus.

Laparoscopic myomectomy:

Laparoscopic myomectomy in sub fertile females with intramural myomas yields similar outcomes to laparotomy, with pregnancy success more likely affected by other infertility factors [63] rupture of gravid uterus after laparoscopic myomectomy is related to inadequate myometrium reconstruction during surgery. All females undergoing laparoscopic myomectomy should be counselled of a risk of future hysterectomy if required. It is not uncommon to find diffuse leiomyomatosis in patients waiting for myomectomy. And for future conception, a period of 4 to 6 weeks should be allowed for proper healing.

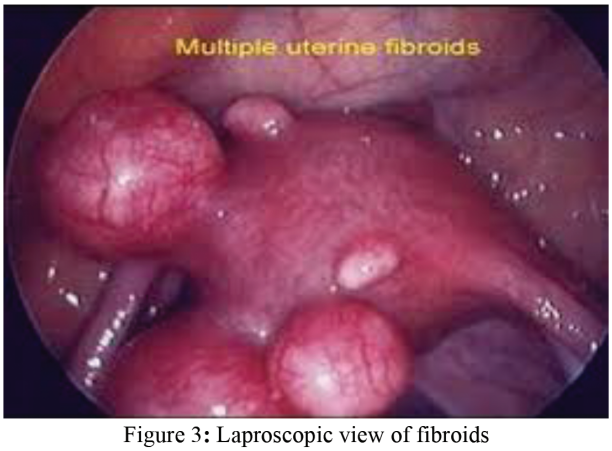


Figure 3: Laproscopic view of fibroids

Hysterectomy:

Hysterectomy is the prevalent gynecological surgery performed in females out of which 33.5% are done for fibroid treatment [66]. It is also treatment of choice with completed family planning or in case of suspected malignancy. The uterus may be approached through laparotomy laparoscopic or vaginal route. Non-descent vaginal hysterectomy of myomatous uterus has recently received appreciable interest, with the surgery preferred in uterine size only up to 12 weeks, beyond which skilled surgeon may prefer morcellation or wedge resection or bisects on or coring. Contraindications to such procedure are lack of skilled surgeon, presence of adhesions, lower abdominal or pelvic pathology, and previous pelvic surgery. 61.5% of subjects having hysterectomy also undergo bilateral oophorectomy [67]. The decision to preserve the

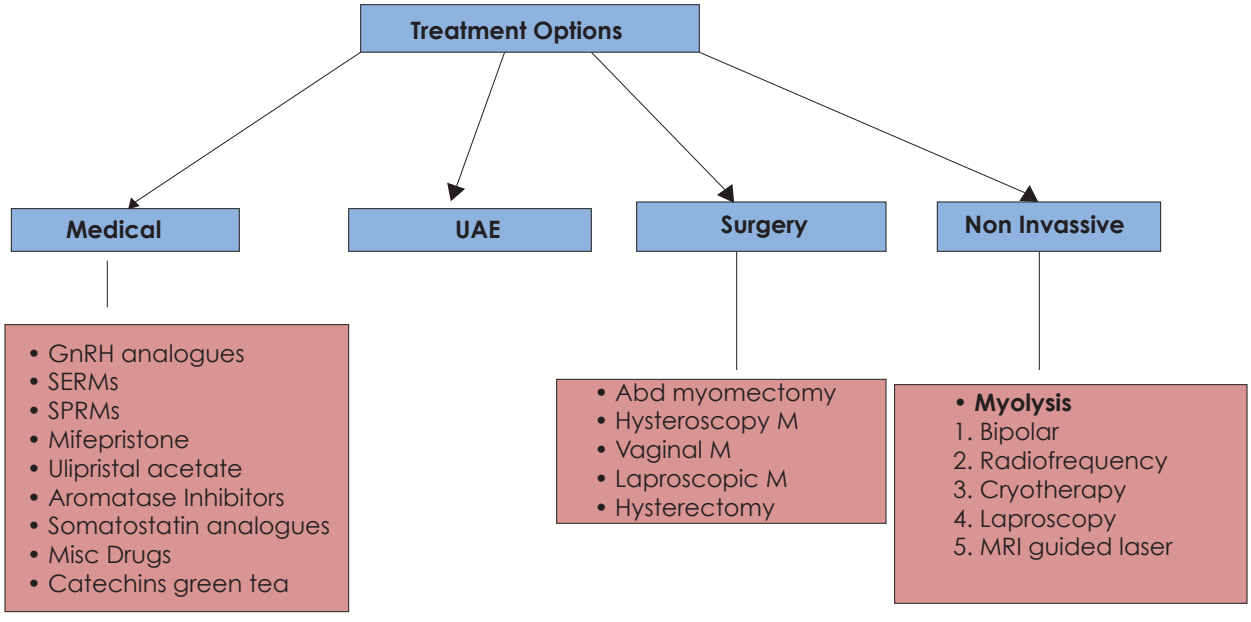
healthy ovaries still remains a topic of controversy with majority in favour of sparing ovaries in subjects below 45 years age.

Non invasive procedures:

Myolysis:

Multiple forms of myolysis such as bipolar, radiofrequency, cryotherapy, laparoscopy, and MRI guided laser are suggested alternatives to invasive myomectomy in women who wish to preserve fertility [68, 69]. Carbon dioxide laser is used to vaporize small fibroids directly during laparotomy while larger sized fibroid are excised. Reduced bleeding and more precise excision seem to be the major advantage. Few submucosal fibroids have been treated with Nd: YAG laser with some degree of success, but incomplete removal still is the major drawback.

Management Options for Fibroid



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