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Advances in management of uterine myomas

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1. ABSTRACT

Uterine myomas, the most common benign solid pelvic tumors in women, occur in twenty percent of them in reproductive years and form the most common indication for hysterectomy. Various factors affect the choice of the best treatment modality for a given patient. Asymptomatic myomas may be managed by careful follow up. Medical therapy should be tried as a first line of treatment for symptomatic myomas while surgical treatment should be reserved only for appropriate indications. Myomectomy would be preferred over hysterectomy in those wishing subsequent childbearing. Preoperative GnRH-analogue treatment reduces the myoma size and vascularity but may render the capsule more difficult to resect. Poor surgical risk women with large symptomatic myomas or those wishing to avoid major surgical procedures may be offered uterine artery embolization. Serial follow-up for growth and symptoms may be appropriate for asymptomatic perimenopausal women. The present article reviews the available therapeutic modalities for uterine myomas.

2. INTRODUCTION

The treatment modalities for uterine myomas include expectant management, medical therapy, conventional surgical options and newer and less invasive approaches. Age, parity, childbearing aspirations, extent and severity of symptoms, size, number and location of myomas, associated medical conditions, the risk of malignancy, proximity to menopause, and the desire for uterine preservation are some of the factors affecting the choice of the therapeutic approach. Hence, the treatment should be individualized. It must be recognized that all conservative management options allow the possibility for new leiomyomas to form, and preexisting small or undetected leiomyomas may exhibit significant growth, necessitating another treatment. The risk of recurrence must be balanced against the potential benefits of uterus sparing procedures, such as lower morbidity and retention of fertility.(1) If malignancy is suspected, the treatment must be surgical.

3. EXPECTANT MANAGEMENT

Asymptomatic women with leiomyoma of the uterus of less than 12 weeks size may be suitable candidates for expectant management, especially those approaching menopause. However, an enlarged uterus may rarely cause significant compression of uterus that could compromise renal function. Piscitelli *et al* demonstrated ureteral dilatation in 56% patients with uterine size of 12 weeks or more, but no dilatation in those with uterine size less than 12 weeks.(2) Women eligible for expectant management may report for follow up every 3-6 months when a detailed history and clinical examination is carried out to note the uterine size and rate of growth of the tumor.

4. MEDICAL THERAPY

Various medications both hormonal and non-hormonal, have been tried to control the symptoms produced by fibroids. These include antifibrinolytics, the non-steroidal anti-inflammatory agents, oral hormonal pills, danazol, gonadotropin releasing hormone agonists, levonorgestrel impregnated intrauterine system, aromatase inhibitors, mifepristone, selective progesterone receptor modulators and CDB-2914. Most medical therapies cause a significant but temporary reduction in myoma size and improve symptoms in most cases. These interventions may prepare the patient for surgery and in some cases render surgery unnecessary if, in the interim, the patient enters menopause.(3) For reproductive purposes the effect of medical therapy is less obvious as the myomas tend to regrow on discontinuation of therapy.

4.1. Antifibrinolytics

Tranexamic acid, a synthetic derivative of lysine, exerts it antifibrinolytic effect through reversible blockade of lysine binding sites on plasminogen molecules, thus inhibiting the activation of plasminogen to plasmin, which in turn is responsible for fibrin degradation. It has been used as a first line non-hormonal therapy for heavy bleeding associated with uterine fibroids and dysfunctional uterine bleeding.(3) It was approved for use for heavy menstrual bleeding by United States Food and Drug Administration (US FDA) in 2009. Prolonged treatment may theoretically increase the risk of deep vein thrombosis, most studies reveal the incidence of thrombosis in women treated with this agent to be similar to that in untreated cases. (3)

4.2. Non steroidal anti inflammatory drugs (NSAIDs)

NSAIDs are effective in reducing dysmenorrhoea and heavy menstrual losses by acting as antagonists of prostaglandins, the agents that stimulate uterine contractility resulting in pain. Aspirin, ibuprofen and naproxen are effective for dysmenorrhoea. However, long term use of these agents may produce gastric ulcers and gastrointestinal bleeding. Peura (2002) suggested that over use of NSAIDs contributes to gastrointestinal adverse effects and anemia by inhibiting the cyclooxygenase-1 enzyme. (4)

4.3. Oral contraceptive pills

These drugs are often used to control menorrhagia and dysmenorrohea. However, as myomas are estrogen dependent, they may exhibit an increase in size with combined pills. For some women, the benefits of hormonal contraception outweigh the risk of this adverse affect and uterine fibroids should not be considered a contra-indication for oral contraceptive use.(5) Besides, the estrogen content of most combined oral contraceptive pills available these days is extremely low and this may be insufficient to enhance tumor growth. The progestin-only contraceptive options may be better in this regard as they reduce menstrual bleeding from the estrogen primed endometrium without the concerns of exogenous estrogen administration.

4.4. Progestogens

Progestational agents are thought to produce a hypoestrogenic effect by inhibiting gonadotropin secretion and suppressing ovarian function, apart from exerting a direct antiestrogenic effect at the cellular level. Biochemical studies suggest that progesterone, progestins, and the progesterone receptors modulate myoma mitotic activity. Several clinical trials demonstrate that progestins inhibit and/or reverse the ability of hypoestrogenism induced by a gonadotropin-releasing hormone agonist to shrink uterine myomas, suggesting a critical role for progesterone in growth of myomas.(6) However, recent evidence that the antiprogesterone mifepristone decreases myoma size raises concerns about this mechanism. (7) Common adverse effects of progestational agents include cramps, nausea, vomiting, headache, constipation, decreased libido and emotional instability. Rarely, they may cause urticaria, flu-like symptoms, genital yeast infection, myalgia and susceptibility to diabetes. Moreover, the beneficial effects of these agents are transient.

Asoprisnil, an orally active selective progesterone receptor modulator (SPRM) is being studied for management of symptomatic uterine leiomyomata. Its use is associated with a statistically significant reduction (91%) in frequency and intensity of uterine bleeding in these women. (8) The exact mechanism of action of this agent is not discernible but a down regulation of collagen synthesis through up-regulation of extracellular matrix metalloproteinase inducer is proposed.(9) The SPRMs offer the advantages of progesterone antagonism without their adverse effects.(3)

4.5. Danazol

Danazol, a synthetic isoxazole derivative chemically related to 17-ethinyl testosterone, has been reported to

be an effective therapy to shrink fibroids and control their symptoms.(3) However, there is no evidence from randomized controlled trials demonstrating that the benefits of danazol therapy outweigh the risks in treating uterine fibroids. It creates a high androgen and low estrogen environment resulting in shrinkage of fibroids. Its use may cause acne, hirsuitism, weight gain, irritability, hot flushes and breast atrophy.(10) Hence, patient compliance could

be an issue and a cautious dosing may help overcome the unpleasant adverse effects.

4.6. Levonorgestrel intrauterine device (LNG-IUD)

Use of levonorgestrel intrauterine device is associated with significant reduction in total myoma volume, average uterine size and marked reduction in menstrual blood loss, though bleeding disturbances may occur in about 68% women with its use.(11) Its use also significantly increases hemoglobin and serum FSH levels but has no significant effect on ovarian volume and function.(12) The proliferation rate of uterine myoma cells is suppressed after treatment with LNG at a minimum concentration of 10 mcg/ml.(13) The inhibitive effect correlates positively with LNG concentration and incubation time LNG-IUS has been found to be more effective than combined oral pills in reducing menstrual blood loss in women with fibroid-related menorrhagia.(14) However, women with large myomas may also have more frequent spontaneous expulsion of the LNG-IUD and the device may be more suitable for an undistorted uterine cavity.(3)

4.7. Gonadotropin releasing hormone analogues (GnRHa)

GnRH analogues (GnRHa) have also been used successfully to achieve hypoestrogenism both as a primary means of conservative therapy for myomas or as an adjunct to myomectomy. With continued administration of a GnRH agonist, the production of ovarian hormones decreases to menopausal or castrate levels and the myomas being estrogen dependent decrease in size. However, these effects are transient and the myomas usually return to pretherapy size within a few months of discontinuation.(15) The reduction in myoma volume by preoperative GnRH analogue therapy may facilitate a hysteroscopic resection of a submucous myoma with less blood loss although the tissue planes tend to become more fibrotic and adherent after this therapy.(16) The amenorrhea induced by preoperative GnRH analogue therapy may help in building up hemoglobin levels, thus enabling presurgical blood donation for subsequent auto transfusion. Menopausal symptoms, osteoporosis and pelvic pain are some of the adverse effects of this therapy and a hormonal add-back, if given, may negate the beneficial effects on myoma size.(17) Danazol administration has been tried after 6 months of GnRHa therapy in an effort to prolong the therapeutic effects of GnRHa. The bone mineral content that is substantially reduced during GnRHa treatment is reported to significantly improve with danazol, though a rebound of uterine volume due to its antiprogesterone effect is a possibility.(18) In perimenopausal women, however, a 3-6 month GnRH analogue therapy may eliminate the need for surgery.

Several add-back regimes have been tried in women using GnRHa in an effort to reduce the effects of estrogen deficiency. These include tibolone, raloxifene, progestogens alone, estrogens alone and a combination of estrogens and progestogens. However, a hormonal add-back bears the risk of increase in size and quantity of myomas. Tibolone has a neutral effect in myoma volume, and typical doses of raloxifene have no influence on its growth. Hence, if postmenopausal women with myomas need therapy to control symptoms, tibolone and raloxifene may be more suitable.(19) Besides, tibolone has also been shown to reverse the deleterious effect on cognition that is caused by leuprolide acetate depot. Its addition improves mood and quality of life in women who receive GnRH agonist for symptomatic uterine myomas.(20)

4.8. Aromatase inhibitors

Recently, letrozole, a non-steroidal aromatase inhibitor commonly used in anovulatory infertility in the follicular phase has been suggested to have potential therapeutic role in treatment of leiomyomas.(21) Aromatase, a member of cytochrome p450 super family, is a microsomal enzyme that catalyses conversion of androgens to estrogen. In leiomyoma, both aromatase and 17 beta hydroxysteroid dehydrogenase (17 beta-HSD) type 1 enzymes are over expressed in comparison with normal myometrium.(22) Inhibition of aromatase enzyme by letrozole would block this conversion and hence result in a hypoestrogenic environment. As the growth of leiomyoma is positively correlated to circulating estrogen levels, the hypoestrogenic milieu would be inhibitory to myoma growth.

Literature on the role of aromatase inhibitors in leiomyoma uterus is limited and comprises mainly a few case reports. Varelas *et al* reported a 55.7% reduction in leiomyoma volume and 22.9% reduction in total uterine volume in their study using anastrazole 1 mg daily for three cycles.(22) Mohammed *et al* used letrozole 2.5 mg per day for 12 weeks and found total myoma volume reduction of 45.6% with no significant change in the hormonal milieu.(23) Rapid onset of action and avoidance of initial gonadotropin flare with an aromatase inhibitor may be advantageous for management of women who wish to avoid surgical intervention or in whom surgery is contraindicated. Aromatase inhibitors have been found to be as effective as GnRHa with fewer side effects. Administration of large doses of aromatase inhibitors to prepubertal rats results in increased weight gain, growth plate width, decreased ovarian weight and multiple cysts on ovarian histology.(24) Ovarian toxicity in the form of large abnormal atretic follicles, follicular cysts and depletion of developing corpus luteum has been reported with large doses of anastrazole in female rats.(25) However, lack of knowledge of the effects of body mass index on the efficacy of these agents, absence of long term follow up data and lack of information on subsequent reproductive outcome in humans currently restricts the use of these agents to women without infertility.

4.9. Mifepristone

Since exposure to estrogen and progesterone promotes the growth of uterine leiomyomas, treatment with a well studied antiprogestin mifepristone has been evaluated. The effect of this agent on follicular development, ovulation, endometrial development and function is dependent on the dose and timing of exposure. Low doses of 2-5 mg per day result in anovulation and inhibition of menstruation in over 90% of menstrual

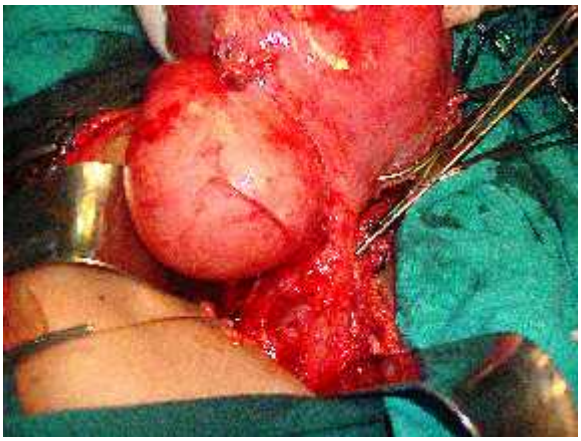

Figure 1. Intraoperative clinical photograph of left false broad ligament myoma at hysterectomy.

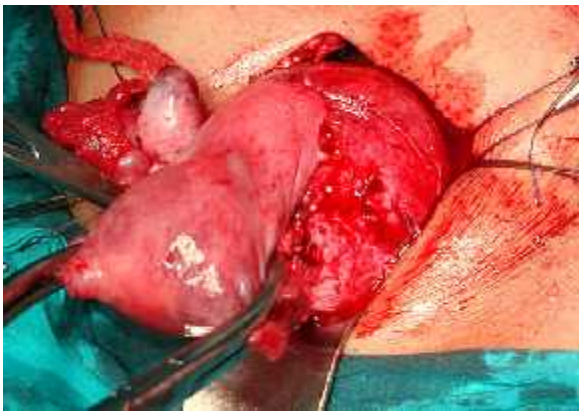

Figure 2. Clinical picture showing uterine body perched atop a cervical myoma at hysterectomy.

cycles.26 Engman *et al* treated 30 women with leiomyoma uterus with 50 mg mifepristone for 3 months prior to surgery and found a 28% reduction in the leiomyoma volume in comparison to 6% for placebo group.(27) Though long-term administration (up to 12 months) of low-dose mifepristone results in myoma shrinkage and amelioration of symptoms; modest rates of low-grade endometrial hyperplasia and hot flashes may also occur with its use.(7)

4.10. CDB-2914

CDB-2194, an antiprogestin, given in daily doses of 10-20 mg for three cycles, has been reported to reduce fibroid size by 36% in comparison to a 6% increase with placebo though the drug is still experimental.(28) Of the 18 women included in the only available study evaluating the role of this drug on myoma volume, six patients each received 10mg or 20mg dose of CDB-2914 daily or an inactive placebo. Only one woman in the study experienced menstrual bleeding during treatment with CDB-2914. Low estrogen levels were evident in the CDB-2914 group and it may be safer than other medical therapies for myoma due to the drug's relatively specific antiprogesterone effect.(28).

5. SURGICAL MANAGEMENT

Careful observation is suitable for most myomas as most of them produce no symptoms, are confined to the pelvis, and are rarely malignant.(29) Surgical options may be considered in cases of abnormal uterine bleeding that is unresponsive to conservative management, a high degree of suspicion of pelvic malignancy, growth of myoma after menopause, distortion of endometrial cavity or tubal obstruction in infertile women and in those with recurrent pregnancy losses, pain or pressure symptoms interfering with quality of life and anemia secondary to chronic uterine blood loss. The options may be categorized into hysterectomy and the alternatives to hysterectomy which include myomectomy (which in turn may be laparoscopic, hysteroscopic, robot-assisted, vaginal and open), magnetic resonance guided ultrasound surgery (MRgFUS), uterine artery embolization, myolysis, endometrial ablation and uterine artery ligation.

5.1. Hysterectomy

It is the most common major gynecological surgical procedure performed in women and 33.5% of these are done for myomas.(1) Depending on the size, number and location of the tumors, the skill of the surgeon and the availability of instruments, apart from the open technique, laparoscopy and vagina are the other ports of access to the myoma-bearing uterus. Hysterectomy has been the surgical procedure of choice for myomas when childbearing considerations have been fulfilled or when there is reasonable likelihood of malignancy. It is associated with a high degree of patient satisfaction, eliminates the need for progestational agents and enables the woman to take unopposed estrogen therapy without many concerns. Nevertheless, it is not free from complications. Adhesions and anatomic distortions of the uterus pose an increased risk of damage to the urinary and intestinal tract. Hysterectomy for broad ligament myoma has been reported to carry a ureteric injury risk of 0.4/1000.(30) False broad ligament myomas tend to push the ureter laterally and posteriorly, in contrast to true broad ligament fibroids where the ureter is medial to the myoma. Figure 1 is an intraoperative picture of a broad ligament myoma at hysterectomy. Knowledge of the precise location and origin of the myoma as well as skill and experience of the surgeon is of immense importance in order to avoid inadvertent injuries to the urinary tract. Similarly, large cervical myomas pose difficulty as well as increase the risk of urinary tract injury while application of clamps on the Macenrodt's and uterosacral ligaments. Figure 2 shows a normal sized uterine body sitting atop a large cervical myoma during hysterectomy. Conservation of cervix at hysterectomy has been proposed to reduce the risk of subsequent vaginal vault prolapse and to maintain good sexual function.(31) A supracervical hysterectomy is also associated with a decreased risk of urinary tract injury and requires less operating time. However, the need for cervical screening for cancer cervix in women undergoing supracervical hysterectomy is maintained. Around 61.4% women over 45 years of age undergoing hysterectomy for myoma also undergo concomitant bilateral ophorectomy.(32) The opinion regarding preservation of

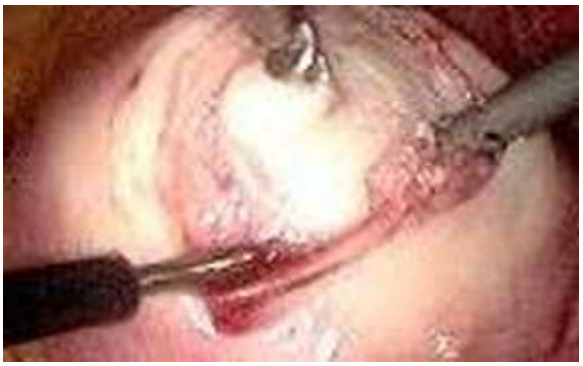

Figure 3. Intraoperative photograph of a large myoma arising from the uterine isthmus and having a large abdominal and a relatively smaller intracavitary extension. A normal sized body of uterus is apparent at the back.

apparently healthy ovaries continues to be divided. At least for women less than 45 years of age, the ovaries should be spared.

5.2. Abdominal myomectomy

Myomectomy has been the procedure of choice for symptomatic myomas in women desiring retention of uterus and often for a solitary pedunculated myoma. However, the number of tumors is no limitation for this procedure. It is a fertility sparing method useful for women who wish to preserve childbearing capabilities. Since submucous myomas have been implicated in the etiology of infertility and recurrent pregnancy loss, myomectomy is recommended by some before gonadotrophin stimulation for in-vitro fertilization and also in women with large myomas that may interfere with oocyte retrieval.(1) Nevertheless, this continues to be a controversial area and the removal of otherwise asymptomatic large myoma which does not distort the endometrial cavity may not be a reasonable proposition in these cases. The procedure may be considered in patients with large myomas, especially those with distorted endometrial cavity and in those with unexplained IVF failures.(18).

A thorough preoperative evaluation is advisable prior to myomectomy. Women with menstrual irregularities and those with risk of endometrial pathology require endometrial histological evaluation before myomectomy, particularly if aged more than 35 years.(1) Hysteroscopy, if available, may be useful at the time of endometrial sampling in diagnosing intrauterine pathology like polyps, foreign bodies or forgotten intrauterine devices. In our opinion, definitive surgery should be deferred for 4-6 weeks after hysteroscopy so as to minimize the chances of disseminated infection.

Optimization of hematological status of the patient prior to surgery is of paramount importance. The anemic woman should be pretreated with gonadotrophin releasing hormone (GnRH) analogues or progestational agents to produce amenorrhea. Stored autologous or donated blood should be arranged for surgery.

The procedure can be carried out by laparoscopy or laparotomy. A meta-analysis of 6 RCTs and 576 patients suggests that laparoscopic myomectomy is associated with less hemoglobin drop, reduced operative blood loss, more patients fully recuperated at day 15, diminished operative pain, and fewer overall complications but longer operation time.(33) The study concluded that if performed by suitably specialized surgeons in selected patients, laparoscopic myomectomy is a better choice than open surgery. However, the quality of uterine repair would influence the risk of uterine rupture during subsequent pregnancy event. Hemorrhage and adhesion formation continue to be other areas of concern after myomectomy. Around 10-50% myomas may recur after myomectomy.(34) In a study evaluating the recurrence of myomas with transvaginal sonography after myomectomy, Fedele *et al* reported a decreased 5-year cumulative probability of recurrence (42%) of myomas in women who gave birth after myomectomy in comparison to those who did not (51%).(35) The therapeutic choice between a myomectomy, hysterectomy or other surgical options should be based on age and the desire for fertility preservation.

The blood loss at surgery correlates with uterine size, weight of myomas removed and the operating time. Various pharmacologic vasoconstricting agents and mechanical vascular occlusion techniques have been tried to minimize surgical blood loss. A meta-analysis of 10 RCTs and 531 participants analyzed the various haemostatic measures used- intramyometrial vasopressin and analogues, intravenous oxytocin , vaginal misoprostol, per-cervical tourniquet, chemical dissection with sodium-2-mercaptoethane sulfonate (mesna), intramyometrial bupivacaine plus epinephrine, tranexamic acid and enucleation of myoma by morcellation while it is attached to the uterus.(36) All these measures except oxytocin and enucleation by morcellation were found to result in reduced bleeding at myomectomy, while oxytocin and morcellation were not found to affect the operative blood loss.

The isthmic myomas may be a class apart among the myomas as far as growth dynamics are concerned. They are reported to be subjected to uterine peristaltic waves in opposite directions during different phases of menstrual cycle, thus resulting in a tangential growth.(37) This may pose difficulty in apprehending the extent and correct anatomic relations at the time of surgery. Figure 3 is a clinical intraoperative photograph taken during myomectomy showing the origin and the abdominal and cervical parts of a large myoma arising from the isthmus of a normal sized uterus. The patient was a 21 year old nulliparous woman presenting with a lump in the abdomen and infertility.

Adequate exposure, haemostasis, careful handling of reproductive tissues and adhesion prevention are some of the general principles of abdominal myomectomy. The operative morbidity associated with this procedure has not been shown to be any higher than that of hysterectomy.(38) When extensive dissection of the myometrium has been necessary during myomectomy,

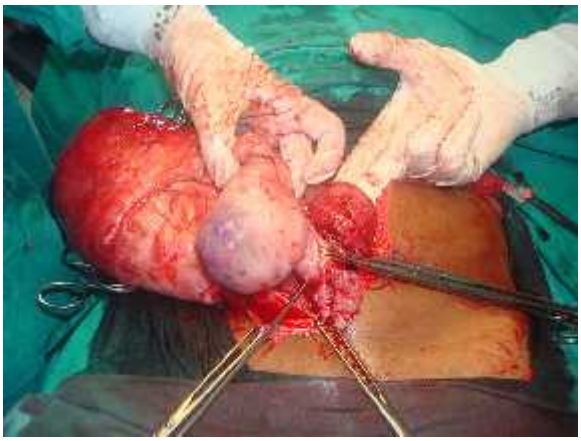

Figure 4. Partial (right sided) inversion of uterine fundus caused by a large stalked myoma arising from the fundus and filling the vagina.

irrespective of the actual opening of the endometrial cavity, a subsequent cesarean delivery is advisable. A high cesarean section rate (46.2%) is more likely after previous removal of intramural myoma(s).(39)

5.3. Hysteroscopic myomectomy

This procedure is indicated for abnormal bleeding, history of pregnancy loss, infertility and pain while suspicion of endometrial malignancy, inability to distend the cavity or circumnavigate the lesion and tumor extension deep into the myometrium are the chief contraindications. Around 20% women will need additional therapy within 10 years of this procedure, mainly due to incomplete removal or new myoma growth.(1)

Warnsteker (1993) published a study of 51 hysteroscopic myomectomies and concluded that fibroids which were over 50% intramural should only undergo hysteroscopic surgery in very well selected cases, in order to reduce the need for further surgery.(40) The European Society of Hysteroscopy classifies submucous myomas according to the extent of myometrial invasion into 3 categories to help the hysteroscopist plan the surgical approach.41 Category T:O includes all pedunculated submucus myomas. Submucus myomas extending less than 50% into the myometrium are classified as T:I, while those with greater than 50% penetration are classified as T:II. Category T:O and T:I can be removed hysteroscopically by a surgeon with modest previous experience while Category T:II myomas should be resected abdominally, and hysteroscopic resection should be reserved for highly skilled hysteroscopic surgeons. Lasmar *et al* proposed a new presurgical classification of submucus fibroids for evaluating the degree of difficulty of hysteroscopic myomectomy, based on not only the degree of penetration of the fibroid into the myometrium but also the distance of the base of fibroid from uterine wall, the size of the nodule in centimeters and the topography at uterine cavity.(40) They concluded that classification based on these parameters is better for assessing the difficulties of a hysteroscopic myomectomy than the Classification of the European Society of Endoscopic Surgery. 'Resectoscopic slicing' still represents the 'gold standard' technique for treating fibroids G0, even if several other effective techniques including ablation by neodymium-yttrium-aluminum-garnet laser, morcellation and office myomectomy have been proposed. There is still no single technique proven to be unequivocally superior for treating fibroids G1 and G2. Most techniques aim at the transformation of an intramural fibroid into a totally intracavitary lesion, thus avoiding a deep cut into the myometrium. At present, the 'cold loop' technique seems to represent the best option as it allows a safe and complete removal of such fibroids in just one surgical procedure, while respecting the surrounding healthy myometrium.(40)

Reduction in myoma volume by preoperative GnRHa therapy may facilitate a hysteroscopic resection of a submucus myoma with less blood loss although the tissue planes tend to become more fibrotic, adherent and less clear after this treatment.(16)

5.4. Vaginal myomectomy

Large myomas arising from the uterine body may fill the vagina (myoma in statu nascendi) and result in intermenstrual bleeding, unhealthy discharge or urinary retention. Most of these can be enucleated per vaginum and the stalk ligated. Rarely, they may form the etiological basis of a uterine inversion, particularly the large ones arising from the fundus (Figure 4).

Milovanovic and colleagues described the technique of posterior vaginal myomectomy in a series of patients while Carminati *et al* described the anterior approach with no laparotomic conversions. (42,43) The identification and the section of the anterior uterine bladder pillars after anterior colpotomy is an important surgical step in the anterior approach. Secondly, use of specific retractors of variable lengths and widths to fit into the vagina aid the procedure. Morcellation is useful for large myomas and the average operative time, blood loss and postoperative stay of anterior approach is comparable to the posterior approach.(43) The vaginal route of myomectomy is a useful alternative to the abdominal and laparoscopic approaches in well selected patients and experienced hands.

5.5. Laparoscopic /robotically assisted laparoscopic myomectomy

Superficial subserous or pedunculated myomas are best suited for laparoscopic or robotically assisted laparoscopic removal. Their removal is effected by either morcellation, utilization of a colpotomy incision or myolysis. Laparoscopic myomectomy in infertile women with intramural myomas offers comparable results to laparotomy and the pregnancy rates tend to be affected by other associated infertility factors.(44) Uterine rupture during pregnancy after laparoscopic myomectomy has been attributed to inadequate reconstruction of myometrium during surgery. The finding of a diffuse leiomyomatosis in a woman posted for myomectomy is not uncommon. For those who desire conception, a delay of 4 to 6 months

before attempting pregnancy is recommended after myomectomy to allow for myometrial healing.

The robot-assisted laparoscopic myomectomy has been found to be associated with significantly decreased estimated blood loss, complication rates and length of hospital stay but higher operative time and professional and hospital charges in comparison to an open (laparotomy) approach.(45)

5.6. Magnetic resonance-guided focused ultrasound surgery (MRgFUS)

In October 2004, the United States Food and Drug Administration (FDA) approved MRI-guided focused ultrasound treatment of uterine fibroids in humans, which is being sold as ExAblate in the US. The FDA defined the eligibility criteria for enrolment for MRgFUS treatment of uterine myomas. The patients should be more than 18 years of age but premenopausal and should have completed childbearing (although there are no documented adverse effects on fertility or pregnancy).The uterine size should be less than 20 weeks pregnancy and the targeted fibroid should not be larger than 12 cm as up to this much tissue only can be currently treated in two 3-hour treatment sessions. The FDA currently limits the targeted volume to be not more than 50% of the volume of each fibroid ablated and no sonification should be closer than 15 mm to a serosal surface of the uterus for safety reasons. The fibroid should not only be accessible but its centre should also be within 12 cm from skin surface. Although MRgFUS was initially approved for use in premenopausal women only, with expanded experience, the FDA changed the labeling of the device in 2009 to include women with symptomatic myomas and desirous of future childbearing. Fibroids that do not enhance with a screening MRI with gadolinium do not benefit from this therapy. The rise in temperature of the tissue receiving the high intensity focused ultrasound (HIFU) and the resultant protein denaturation and irreversible cell damage form the basis of this treatment modality.(46) The method uses multiple exposures of high intensity focused ultrasound energy on the target fibroid to raise the tissue temperature to levels high enough to destroy it. The Magnetic Resonance Imaging not only allows a three dimensional precise view of the target tissue, but also provides a quantitative, real time thermal images of the treated area. Symptomatic women who are otherwise free of any contraindication to MRI and desiring a non-invasive therapeutic outpatient option for myoma are suitable candidates for this modality. Women with extensive adenomyosis, endometriosis, calcified fibroids, dermoids, surgical clips, metallic intrauterine contraceptive devices and cardiac pacemakers should avoid MRgFUS. Pregnancy and abdominal wall scars in the path of the ultrasonic beam should also be excluded (as scarred tissue has high ultrasonic absorption and may result in thermal skin damage.(47) The procedure is performed in fasting state, in prone position under intravenous conscious sedation after inserting a self retaining catheter in the urinary bladder. The therapeutic ultrasonic beam has a frequency between 1 and 1.5 MHz and delivers phased pulses of thermal energy. A reduction of up to 98% in myoma volume and symptoms has been reported with this non-invasive treatment for symptomatic myomas.(48) However, the efficacy of MRgFUS correlates with signal intensity of T2-weighted magnetic resonance images. Those with low signal intensity (Type 1) on pretreatment images are more likely to shrink than those with intermediate (Type 2) and high signal (Type 3) intensity.(49) The larger the non-perfused volume (NPV) immediately after treatment, the greater are the volume reduction and symptom relief. Thus, Type 1 and 2 fibroids are suitable for this treatment while Type 3 myomas are not.(50)

Women having a myoma volume of more than 500 cc may be pretreated with a GnRHa for 3 months in an attempt to reduce the size to improve the efficacy of thermal ablation.(51) Small myoma size, intramural location, fewer number and T2 hypodensity are important predictors of treatment success.(52) Symptomatic improvement lasts for over 2 years and 16-20% women may need additional theapy.(53) Although there is paucity of large randomized controlled trials between MRgFUS and UAE, initial reports suggest MRgFUS is comparable in efficacy, safety and cost effectiveness to UAE.(54)

5.7. Uterine artery embolization (UAE)

This procedure, first described for management of myomas in 1995, attempts to limit growth by limiting the blood supply to the myoma. Polyvinyl alcohol particles of 500 µm size are passed through a fluoroscopically guided transarterial catheter inserted in the common femoral artery to selectively occlude the arteries supplying the myoma. This short interventional radiologic, FDA approved procedure which is no longer 'experimental' or 'investigational' requires a short hospital stay and is recommended for large symptomatic myomas in women who do not wish or are poor candidates for major surgery. Goodwin *et al* reported the long-term outcomes from the FIBROID Registry based on a 3-year study of 2112 patients who underwent uterine artery embolization for symptomatic leiomyomas.(55) The procedure was found to be associated with improvement in quality of life and a subsequent need for hysterectomy, myomectomy or repeat uterine artery embolization in 9.79%, 2.82% and 1.83% patients, respectively. Persistent ischemic pain, postembolization fever, severe postembolization syndrome, pyometra, sepsis, hysterectomy and even deaths have been reported after the procedure.(56) Inadvertent embolization of vesical artery, which sometimes arises from a common trunk with the uterine artery, may increase the risk of bladder necrosis. Inadvertent end-organ damage requiring hysterectomy, ovarian failure and fatal pulmonary embolism have also been reported after this procedure.(57) Technical failure, defined as an inability to successfully catheterize and embolize both sided uterine arteries, occurs in 1-2% patients and may be due to anatomic variation, operator inexperience or persistence of effects of GnRH agonists. It is advisable to withhold GnRHa therapy if UAE is planned as the GnRHa related constriction of the uterine vessels may cause technical difficulty during the procedure. UAE should preferably be done after 12 weeks of stoppage of GnRHa therapy.

A retrospective cohort study showed that UAE has much fewer serious adverse effects than hysterectomy

(Odds Ratio 0.25) and similar rates of satisfaction.(58) In this study, 86% women treated with UAE would recommend the procedure to a friend in comparison to 70% of those who underwent hysterectomy. The Embolization versus Hysterectomy (EMMY) trial, a prospective randomized comparison in 177 women, found that UFE is a good alternative to hysterectomy; both procedures led to improved health-related quality of life at 24-month follow-up.(59)

Fertility preservation may be an important issue for some women undergoing UAE. Although successful pregnancies have been reported after embolization, an increase in the risk of spontaneous miscarriage has been reported after UAE in comparison to laparoscopic uterine artery ligation.(60,61) In a comparative study of UAE with nyomectomy in 118 patients, Mara *et al* reported that although UAE is less invasive than myomectomy and as effective for controlling symptoms, reproductive outcomes appear to be superior in myomectomy patients.(62)

5.8. Endometrial ablation

The technique refers to the destruction of endometrium by a short burst of electrical or laser energy. A premenopausal woman who has completed childbearing and has a benign cause of menorrhagia (including submucus fibroids or polyps up to 2 cm in size) are considered suitable candidates for this therapy. Women with previous classical cesarean or transmural myomectomy scars, suspected/ known uterine malignancy, active pelvic inflammation or those wishing for fertility retention are contraindications for this modality of treatment. The procedure, carried out under local anesthesia and sedation, is a day care therapy. High failure and recurrence rates are expected in the presence of larger or intramural fibroids.

5.9. Myolysis

Various forms of myolysis – bipolar, cryo, radiofrequency, laparoscopic and MRI guided laser, have been tried as conservative alternatives to myomectomy in women wishing uterine preservation.(63,64) Carbon dioxide laser has been used to directly vaporize small myomas at laparotomy, while medium and large myomas are excised. Typically, patients are pretreated with a 2- to 6- month course of GnRH agonist to cause shrinkage of myoma. The procedure involves multiple insertions of probes laparoscopically or percutaneously (guided by MRI) into the myoma.

The published literature on the various myolysis techniques is limited, inconsistent and of poor quality. As a result, the technique is considered 'investigational'. Goldfarb published the largest case series of 75 patients with symptomatic fibroids 5-10 cm in diameter who underwent Nd:YAG laser myolysis.(34) He reported no complications and a regression in myoma size which remained stable after 6-14 months of follow-up. On comparison with bipolar needle myolysis, Goldfarb found the shrinkage induced by it to be comparable to that by Nd:YAG laser.(35) Chapman reported that the use of interstitial laser photocoagulation in 300 women with symptomatic myomas is associated with an improvement in menorrhagia, abdominal pain and bladder discomfort.(39)

Cryomyolysis is a technique in which freezing temperatures of -180 degrees centigrade are created with a cryoprobe inserted into the center of the myoma. Several freeze/thaw cycles are used to induce shrinkage in myoma size. Zupi *et al* reported a 25% initial reduction in size of myomas which were not pretreated with a GnRHa.(65) The shrinkage of myoma continued until 9 months after surgery, to a mean volume reduction of 60%.

The MRI guided percutaneous Nd:YAG laser or cryomyolysis requires a high field open machine and is reportedly associated with a 31% reduction in myoma size.(66) Myolysis devascularises the myoma, however, incomplete removal may be an issue of concern at times.

5.10. Uterine artery ligation

This procedure attempts to limit the blood supply to the uterus by a vaginal or laparoscopic ligation of the uterine artery. The procedure shares its underlying principle with UAE but is relatively easier to perform. Akinola *et al* found the uterine artery ligation to be as effective as UAE while Hald *et al* found it to be less effective in direct comparison to UAE.(67,68) A combination of uterine artery occlusion (UAO) and simultaneous blockage of anastomosis between uterine and ovarian vessels may be better than UAO alone in terms of long term symptom control and reintervention rates.(69) However, women undergoing simultaneous utero-ovarian anastomosis vessel occlusion are at greater risk of a significant increase in serum FSH levels at the first month after surgery thus reflecting a diminished ovarian function.(70)

6. CONCLUSION

Asymptomatic myomas can be managed by reassurance and careful follow up. Medical therapy should be tried as a first line of treatment for symptomatic myomas while surgical treatment should be reserved only for appropriate indications. Hysterectomy has its place in myoma management in its definitiveness. However, myomectomy, rather than hysterectomy, should be performed when subsequent childbearing is a consideration. Preoperative GnRH-analogue treatment before myomectomy decreases the size and vascularity of the myoma but may render the capsule more fibrous and difficult to resect. Uterine artery embolization is an effective standard alternative for women with large symptomatic myomas who are poor surgical risks or wish to avoid major surgery. Its effects on future fertility need further evaluation in larger studies. Serial follow-up without surgery for growth and / or development of symptoms is advisable for asymptomatic women, particularly those approaching menopause. Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) represents an alternative modality of conservative treatment of uterine myomas and is comparable to efficacy, safety and cost to UAE.

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