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Review

Uterine myomas revisited

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ABSTRACT

The present study was planned to review the pathophysiology of uterine myomas and emphasize the principles of logical management on the basis of literature review and synthesis of the author's experience. The growth of uterine myomas, the most common solid pelvic tumors in women, is related to genetic predisposition, hormonal influences and growth factors. The treatment options include pharmacologic, surgical and radiographic interventions. Most asymptomatic myomas can be followed serially for progressive growth or development of symptoms. The various diagnostic and therapeutic advancements available today permit higher management flexibility with safe options, which must be tailored to the individual patients requirement.

Contents

1. Introduction

Uterine myomas, the most common solid pelvic tumors in women, occur in 20–40% of women in the reproductive years and form the most common indication for hysterectomy [1]. They are benign lesions originating mainly from smooth muscles of the uterus. However, the smooth muscle of the uterine blood vessels may also be their source. Depending on their location in the uterus, they may be subserous, intramural or submucous (Fig. 1). They may, at times, acquire a stalk and project through the os as a myomatous polyp (Fig. 2). The relatively uncommon extrauterine sites include the broad ligaments and the round and uterosacral ligaments. Myomas may be solitary or multiple and vary in size from seedlings to those filling whole abdomen. Their growth is clearly associated with exposure to circulating estrogen and hence a growth spurt is exhibited during pregnancy and in the premenopausal years, secondary to more anovulatory cycles. The estrogen receptors in myomas bind 20% more estradiol (E2) per milligram of cytoplasmic protein than the normal adjoining myometrium [2]. The tumors also maintain high sensitivity to estrogen during the estrogen-dominated follicular phase of the menstrual cycle, unlike normal myometrium. However, this analogy fails to apply to adolescent girls, who frequently have puberty menorrhagia due to anovulation but no associated myomas.

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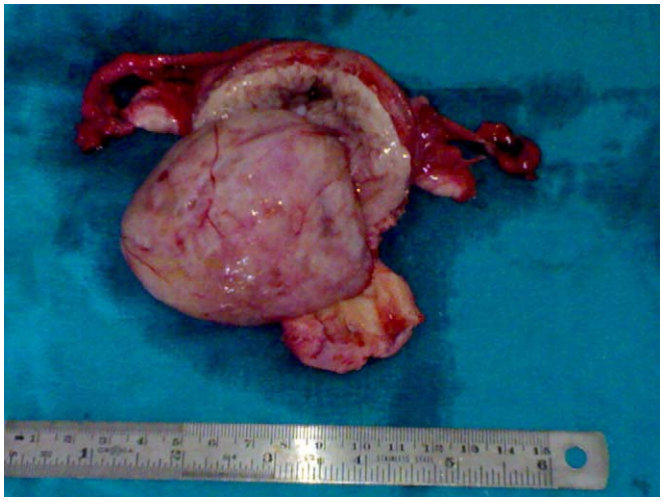

Fig. 1. A large submucus myoma projecting into the cavity of a hysterectomy specimen.

Out of the 202,538 patients between 20 and 50 years of age examined in this tertiary care centre of North India in the last 10 years, 69,328 (34.22%) harboured myoma(s). Of the 64,093 abdominal hysterectomies carried out in the last decade at this Institute, 34,268 (55.18%) were for solitary or multiple myomas.

2. Clinical features

The majority of women with uterine myomas are asymptomatic [3]. Among the symptomatic ones, the presentation usually correlates with size, site and concomitant degenerative changes in these tumors. Excessive menstrual bleeding, on account of local vascular changes in the endometrium, is the most frequent symptom produced. Endometrial venule ectasia, increased endometrial surface area, associated endometritis, dysregulation of local growth factors and aberrant angiogenesis may contribute to menorrhagia [3].

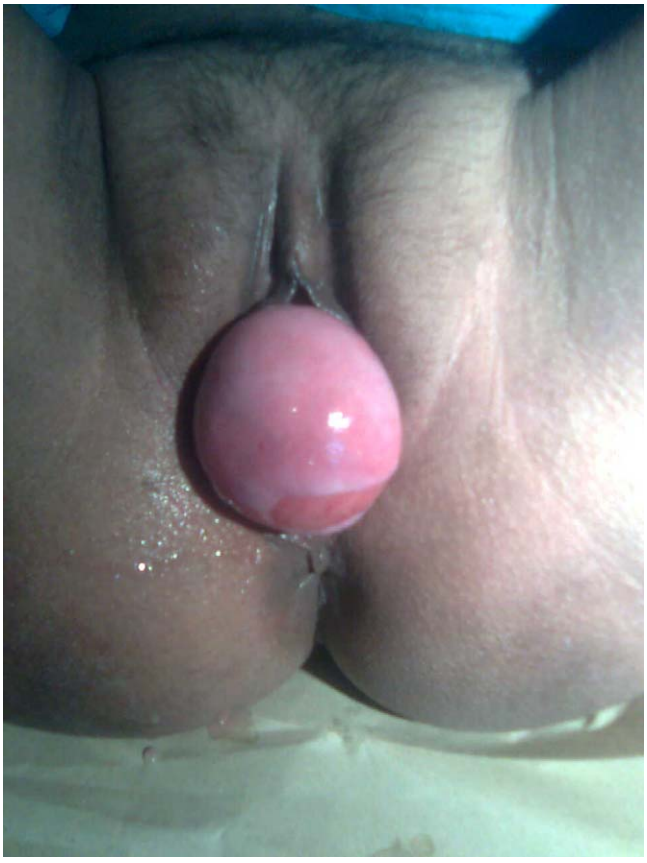

Fig. 2. A prolapsed anterior cervical lip bearing a myoma.

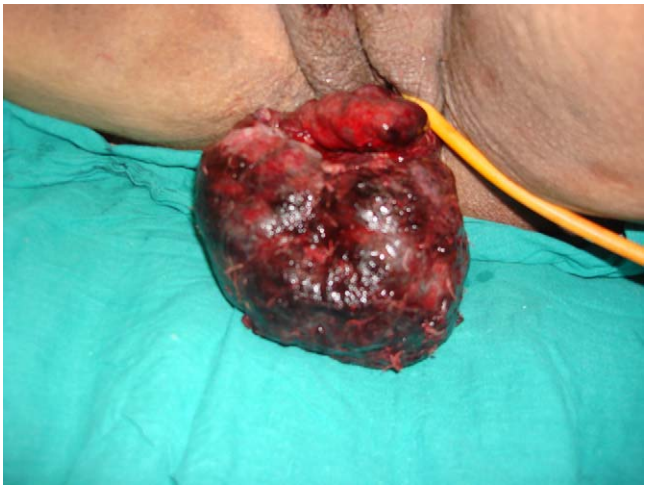

Fig. 3. A large necrotic myomatous polyp lying prolapsed outside the introitus.

Pain is usually associated with torsion of a pedunculated myoma, cervical dilatation by a submucous myoma tending to negotiate through the os, carneous degeneration in pregnancy or the extremely rare sarcomatous transformation. Fig. 3 depicts a myomatous polyp which had prolapsed outside the introitus in a postmenopausal woman after a fall. She had been consulting physicians for pelvic and low back pain and had chosen to ignore the occasional postmenopausal spotting. It is not advisable to attribute pain to uncomplicated myoma.

Pressure effects on the adjoining urinary or gastrointestinal tract may be caused by a cervical or an incarcerated posterior wall myoma in the cul-de-sac. Rarely, a large myoma arising from the uterosacral ligament may impinge on the bowel (Fig. 4).

Myomas rarely produce infertility. The incidence of myomas in infertile women without any obvious cause of infertility is estimated to be 1–2.4%. The relationship between leiomyomas and infertility remains a subject of debate [4]. A submucous myoma may distort the endometrial cavity and interfere with

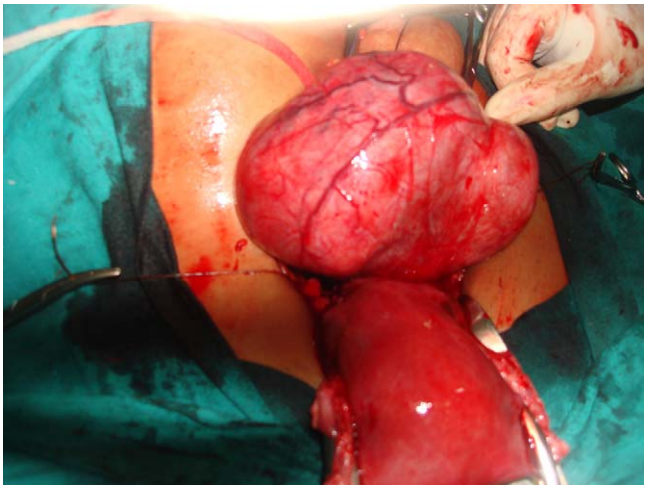

Fig. 4. An intraoperative photograph showing a large, lobulated myoma originating from the left uterosacral ligament in a 50-year-old woman.

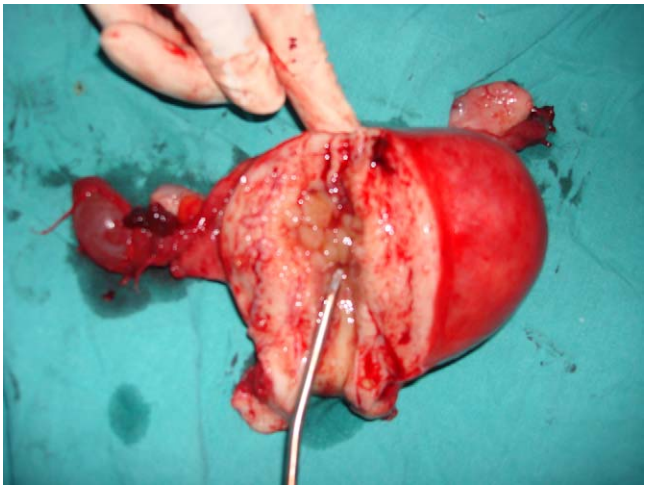

Fig. 5. A total hysterectomy specimen showing a large myoma on left side of uterus and concomitant endometrial hyperplasia and polyposis.

sperm transport or blastocyst implantation or severely displace the cervix out of the vaginal alignment. Distortion of the endometrial cavity by myomas is associated with decreased pregnancy rates and higher risk of spontaneous miscarriage after in vitro fertilization [5]. Similarly, intramural myomas may cause obstruction/dysfunction of the fallopian tubes. Studies have reported an improved reproductive outcome after myomectomy in otherwise asymptomatic women [6].

Sarcomatous transformation in myomas is an extremely rare event, occurring in 0.13–0.23% cases [7]. Considering that most myomas are never removed, and not all those that are removed undergo histologic evaluation, even this figure appears to be an overestimation. However, an association of myomas with endometrial hyperplasia and endometrial carcinoma has been reported, the mechanism being hyperestrogenemia in all three. Around 28% of endometrial carcinoma cases may have an associated myoma [8]. Fig. 5 shows a hysterectomy specimen with a myoma and concomitant endometrial hyperplasia.

3. Growth patterns

Rapid growth of a myoma is defined as an increase in uterine size by 6 weeks' gestational size in 1 year. Rapid growth of these tumors in non-pregnant young women and in postmenopausal women should arouse suspicion of malignancy, although the risk of malignancy even in these women is very low [7]. As the uterine size varies with the phase of menstrual cycle and the tissue response to hormonal stimulation, 6-monthly pelvic examination at a uniform time in the cycle is desirable.

Ultrasonography cannot only aid in evaluation of growth but also detect pressure hydronephrosis. Intravenous pyelography is only occasionally required as an aid to outline renal pelvicalyceal and ureteral characteristics. Magnetic resonance imaging (MRI) can discriminate a myoma from an ovarian mass better than computed tomography. Hysterosalpingography may delineate the contour of the endometrial cavity and fallopian tubes in infertile women with myomas. Occasionally, peritoneal distribution of the contrast media may outline the silhouette of a large pedunculated subserosal myoma.

4. Treatment options

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 therapeutic approach. Hence, the treatment should be individualized.

5. Hormone treatment

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. Their effects are transient and the myomas return to pretherapy size within a few months of discontinuation [9]. 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 [10]. The amenorrhoea induced by preoperative GnRH analogue therapy may help in building up hemoglobin levels, thus enabling presurgical blood donation for subsequent autotransfusion. 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 [11]. 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 [12]. In perimenopausal women, however, a short-term GnRH analogue therapy may eliminate the need for surgery.

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. However, recent evidence that the antiprogesterone mifepristone decreases myoma size raises concerns about this mechanism [13]. Besides, the beneficial effects of these agents are transient.

Use of levonorgestrel-IUD (LNG-IUD) 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 [14].

6. Indications for surgery

Careful observation is suitable for most myomas as most of them produce no symptoms, are confined to the pelvis, and are rarely malignant [15]. 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 the menopause, distortion of the 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 anaemia secondary to chronic uterine blood loss.

6.1. Hysterectomy

Hysterectomy is the most common major gynaecological 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 the 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

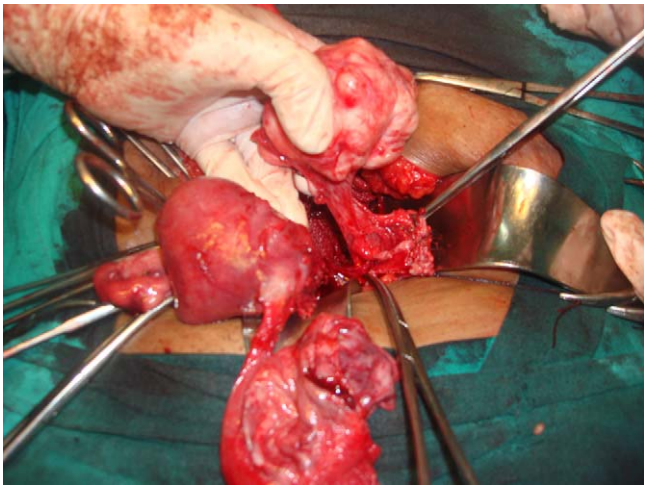

Fig. 6. An operative photograph of enucleation of a true left broad ligament myoma.

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 [16]. Fig. 6 depicts the enucleation of a true broad ligament myoma while Fig. 7 is an intraoperative picture of a false broad ligament myoma and an enlarged body of uterus containing a solitary smooth myoma. 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. Knowledge of the precise location and origin of the myoma as well as skill and experience of the surgeon are of immense importance in order to avoid inadvertent injuries to the urinary tract. Similarly, large cervical myomas pose difficulty as well as increasing the risk of urinary tract injury during the application of clamps on the Mackenrodt's and uterosacral ligaments.

Conservation of the cervix at hysterectomy has been proposed to reduce the risk of subsequent vaginal vault prolapse and to maintain good sexual function [17]. 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 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 [18]. Opinion regarding preservation of apparently healthy ovaries continues to be divided. At least for women less than 45 years of age, the ovaries should be spared.

6.2. Abdominal myomectomy

Myomectomy has been the procedure of choice for symptomatic myomas in women desiring retention of the uterus and often for a solitary pedunculated myoma. However, the number of tumors is no limitation for this procedure. Since submucous myomas have been implicated in the aetiology 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 an 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 a distorted endometrial cavity and in those with unexplained IVF failure [12].

A thorough preoperative evaluation is advisable prior to myomectomy. Women with menstrual irregularities and those with risk of endometrial pathology require endometrial histologic evaluation before myomectomy, particularly if aged more than 35 years. 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 the hematological status of the patient is of paramount importance. The anemic woman should be pretreated with GnRH analogues or progestational agents to produce amenorrhoea. Stored autologous or donated blood should be arranged for surgery.

The procedure can be carried out by laparoscopy (Fig. 8) or laparotomy. A meta-analysis of six randomized controlled trials (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

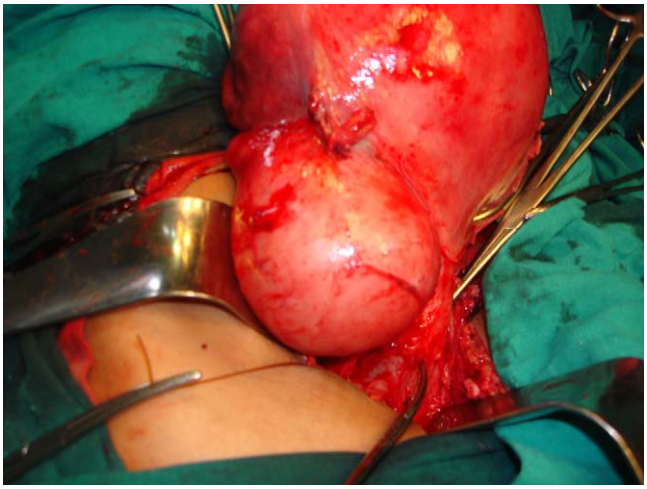

Fig. 7. An intraoperative picture of a false broad ligament myoma and an enlarged body of uterus containing a solitary, smooth myoma.

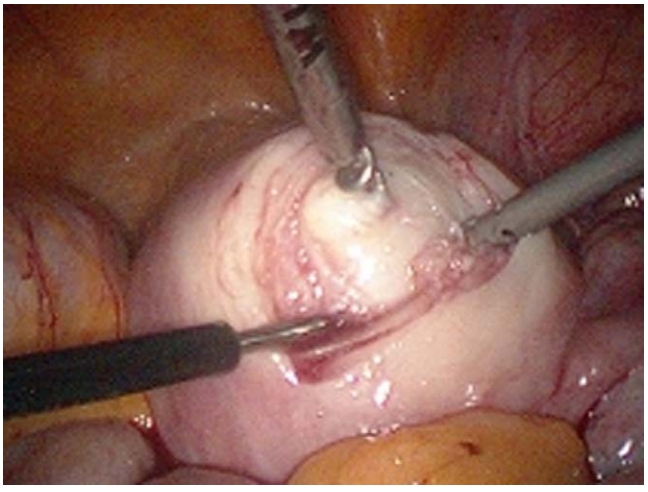

Fig. 8. A laparoscopic myomectomy in progress.

operation time [19]. 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. Hemorrhage and adhesion formation continue to be other areas of concern after myomectomy. The therapeutic choice between myomectomy, hysterectomy or other surgical options should be based on age and the desire for fertility preservation.

The blood loss at surgery correlates with the 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 hemostatic measures used – intramyometrial vasopressin and analogues, intravenous oxytocin, vaginal misoprostol, pericervical 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 [20]. 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.

Isthmic myomas may be a class apart among 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 tangential growth [21]. This may pose difficulty in apprehending the extent and correct anatomic relations at the time of surgery. Fig. 9 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, hemostasis, 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 [22]. When extensive dissection of the myometrium has been necessary during myomectomy, irrespective of the actual opening of the endometrial cavity, a subsequent cesarean delivery is advisable.

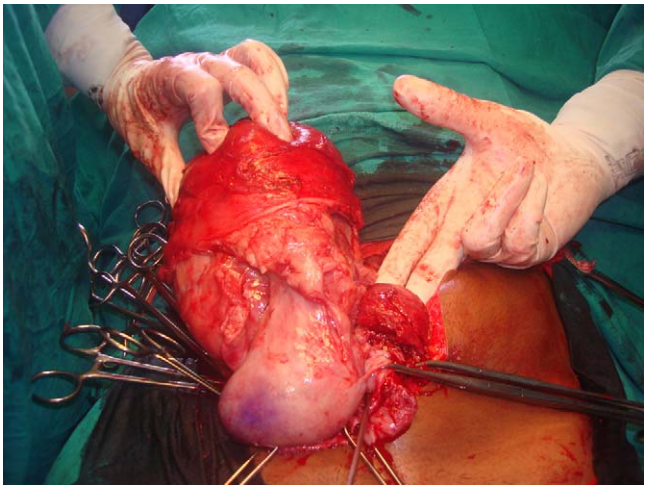

Fig. 9. An operative photograph taken during myomectomy of a huge anterior isthmic myoma with both intracervical and abdominal extensions. The normal sized body of uterus is visible behind the large myoma.

6.3. 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]. The European Society of Hysteroscopy classifies submucous myomas according to the extent of myometrial invasion into four categories to help the hysteroscopist plan the surgical approach [23]. 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. Fig. 10 depicts the procedure of hysteroscopic myomectomy.

Reduction in myoma volume by preoperative GnRHa therapy may facilitate 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 [10].

6.4. 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 [24]. Uterine rupture during pregnancy after laparoscopic myomectomy has been attributed to inadequate reconstruction of myometrium during surgery. All women wishing to undergo myomectomy should be willing for a hysterectomy, if need be. The finding of diffuse leiomyomatosis in a woman posted for myomectomy is not uncommon. For those who desire conception, a delay of 4–6 months before attempting pregnancy is recommended after myomectomy to allow for myometrial healing.

6.5. Uterine artery embolization

This procedure, first described for management of myomas in 1995, attempts to limit growth by limiting the blood supply.

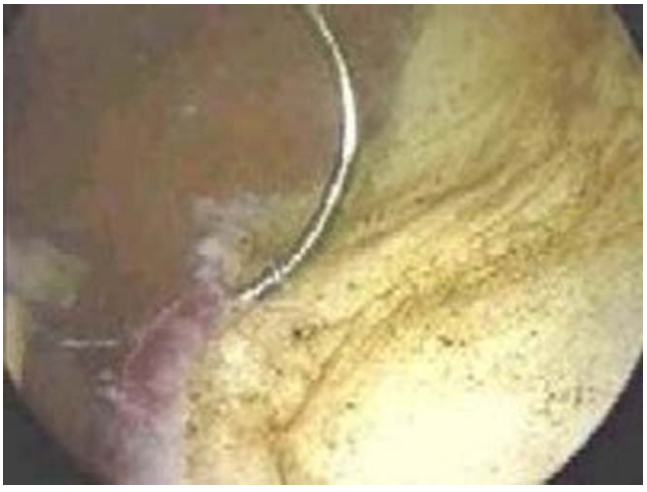

Fig. 10. An operative picture of hysteroscopic myomectomy.

Polyvinyl alcohol particles 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 procedure 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 [25]. 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 [26]. Ovarian failure may ensue in 1–2% patients, though successful pregnancies too have been reported after embolization [27].

6.6. 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 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 [28]. A reduction of up to 98% in myoma volume and symptoms has been reported with this non-invasive treatment for symptomatic myomas [29]. However, the efficacy of MRgFUS correlates with signal intensity of T2-weighted magnetic resonance images. Those with low signal intensity on pretreatment images are more likely to shrink than those with high signal intensity [30]. 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 [31].

6.7. Myolysis

Various forms of myolysis – bipolar, cryo, radiofrequency, laparoscopic and MRI-guided laser – have been tried as conservative alternatives to myomectomy in women desiring uterine preservation [32,33]. Carbon dioxide laser has been used to directly vaporize small myomas at laparotomy, while medium and large myomas are excised. Improved hemostasis and greater precision at removal appear to be the chief advantageous but the technique has not been tested in larger series of patients. Some submucous myomas have been successfully treated by Nd:YAG laser which devascularises the myoma, however, incomplete removal may be an issue of concern at times.

7. Comments

A clear understanding of the pathogenesis, clinical presentation and available management tools is vital for successful treatment of any woman with myomas. Various factors affect the choice of the best treatment modality for a given patient. 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 the menopause.

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