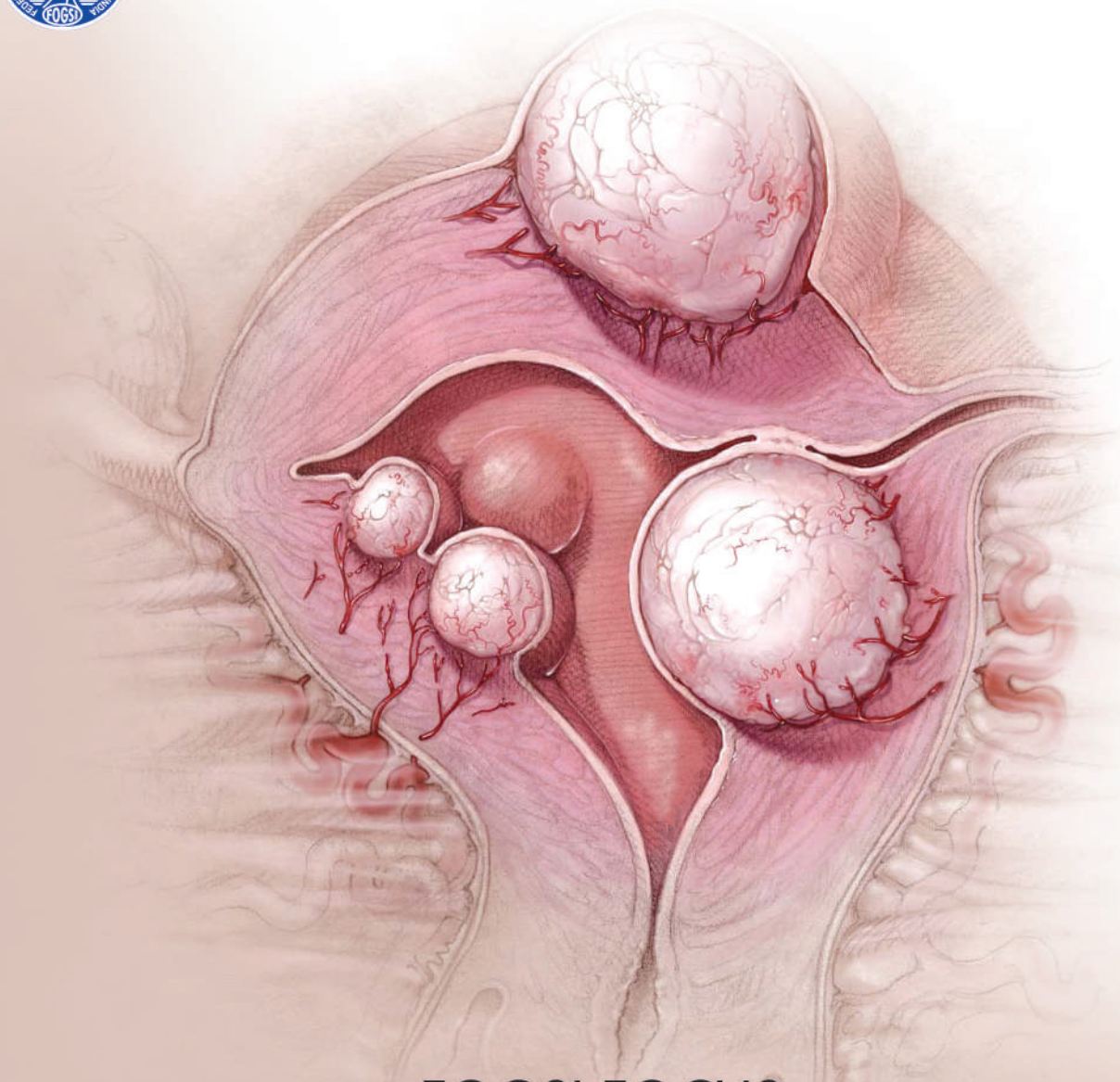

FOGSI FOCUS on

FIBROID

Newer Aspects and Current Understanding

Editor : Dr. FESSY LOUIS T.

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Editor
Dr. Fessy Louis T.
Thalakottoor House, Bismi Gardens, 2nd Avenue,
Marotichuvadu, Edapally Toll, Kochi -682024, Kerala, India
Ph: 0484-2575744, 4015544, Mob : 09846055224
E-mail: fessylouis@gmail.com

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Ph: 32954564 / 23021648 / 23021654 / 23021343
Email: fogsi2007@gmail.com

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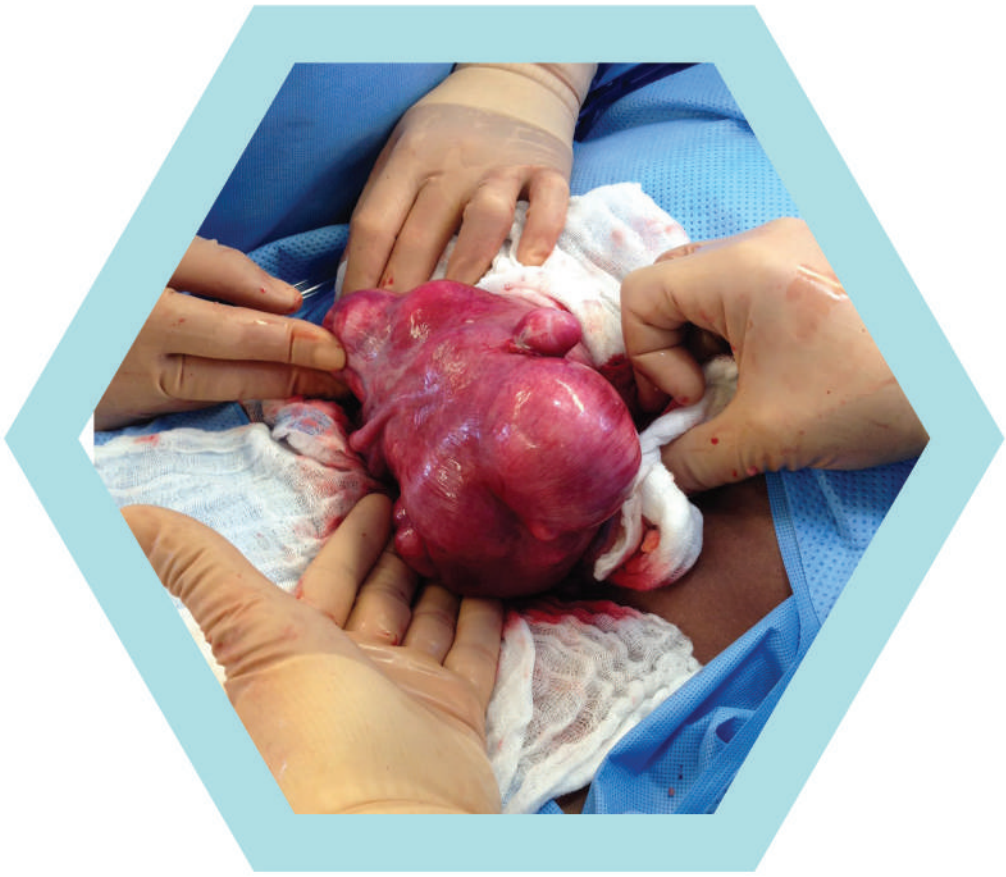

From Editors Desk

Fibroids are the commonest benign tumourin women. It not only decreases the chances of conception, but also increases the chance of abortion.This FOGSI FOCUS on fibroids deals with understanding the risk factors , the use of imaging, the relevance and impact on infertility science , the surgical techniques and the latest controversies.Experts who are best in individual subspecialty have contributed to this FOGSI FOCUS.

I would like to express my heartfelt gratitude to the contributors, who despite of their heavy responsibilities put sincere efforts and spent quality time to make this an outstanding one.

I thank our FOGSI president Dr.Prakash Trivedi and the entire team to have faith and entrusting me the important job of editor of FOGSI FOCUS on Fibroid as All India InternationalAcademic Exchange Committee chairperson FOGSI.

I am also indebted to each FOGSI member for allowing me to serve this prestigious organisation.This FOGSI FOCUS would not have been possible without the support of INTAS pharmaceuticals and we are really grateful to them for their wholehearted support.

I am also thankful to my wife Mrs.Roshin for all the help given to compile this issue. Also Mr.David of Smithi Designs for designing the issue.

I hope this FOGSI FOCUS on Fibroid will bring to you all the updated knowledge and information you seek and go a long way in your practice.

HAPPY READING

Dr. FESSY LOUIS T.
Editor
FOGSI International Academic Exchange CommitteeChairperson

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01

ETIOLOGY AND UNKNOWN FACTS OF **FIBROIDS**

Dr. Prakash Trivedi
Dr. Sylvia Noronha
Dr.Animesh Gandhi
Dr.Soumil Trivedi,
Mumbai.
dr.ptrivedi@gmail.com

Fibroids are very common tumors known to affect women for centuries. It is however surprising that not any significant data is still available to give a clear idea as to what could be the cause of fibroid or what could be the predisposing or risk factors ? There has been prevalence data of fibroids in the white women and African American women, however there is no details of incidence in Asian women.

In spite of high prevalence fibroids still remain enigmatic, the incidence, and progression is incompletely understood. The volume of an enormous health burden related to fibroids in the women may be reduced by significant research work.

In our research we found many factors which were unknown to many, yet definitely contributing to the incidence of fibroids. We would like to enumerate many of these unknown facts of fibroids which is useful for us to find a solution of this huge though benign tumor:

1. We found that if women had a first-degree female relative who had the fibroid detected before the age of 45 then she carries six times higher chances of having fibroids than the control group i.e. 30% vs 5% in controls[1].
2. Age of the women increased incidence of fibroids and at 45 to 50 years of age the incidence of fibroids was 20 times more than women between 25 to 30 years of age (6.2 per thousand vs 0.3 per thousand)[2]
3. It is interesting to note that red meat eating women has three times higher chances of having fibroids compared to women having a vegetarian diet, however of mainly fish eating

women has incidence of fibroid which is close to the vegetarian diet[3]

4. The weight of the patient also has an important bearing on incidence of fibroids, for every 10 Kg rise in weight then it is 18% increase in incidence of fibroids[4].
5. The blood pressure of the women also has an important bearing with incidence of fibroids per every 10 mm rise in diastolic blood pressure there is 10% increase in incidence of fibroids, this is primarily due to damage of the endothelium of the small vessels leading to release of cytokines irritates or stimulates the uterine smooth muscle to grow as the fibroid. Hypertensive women in later years had 24 % reported to be having fibroids and the degree of fibroids were proportionate to the severity of the hypertension[5].
6. A very unusual finding which was noticed that women who had a habit of smoking which may be cigarettes, beedi's etc they had less incidence of fibroids this was probably due to associated lower levels of estrogen[6,7]
7. The use of oral contraceptive and parity also reduced the incidence of fibroids. In the group with the longest use more than 145 months, the risk of fibroids was half that of control. However, if the oral contraceptive was used for the first time between 13 to 16 years of age than this increase the risk of fibroid[8].
8. It was also noticed that women having pelvic inflammatory disease increase the risk of fibroid and if they had three episodes of pelvic inflammatory disease then RR of 3.7, whereas a single episode of Chlamydia against infection conferred the RR of 3.2.[9]
9. The growth rate of fibroids have been always a matter of speculation by gynaecologist however what we noticed was the average growth of the fibroid was 1.25 cm in 2.5 years.[10] Even sometimes a fast-growing fibroid didn't mean that it was sarcomatous.
10. Parity reduced the risk of fibroids 3~5 fold, showed more specifically in the later age as the incidence of fibroids are higher in later age. [11]
11. The recurrence rate of fibroids after removal rate from 25 to 62% by the end of 5 years follow up in nearly 10 to 20% needed a second surgery within 1 to 10 years.[12]
12. The cellular biology of myomas revealed certain interesting findings specially pertaining to infertility. The prolactin level was high in the fibroid tissue especially in the follicular phase. Prolactin acts as a stimulator of the proliferation of Leiomyoma cells by the mitogen activated protein kinase cascade[13]. This was suppressed by anti-prolactin antibodies and also Progestrone showed suppressive effect. [14,15,16,17]
13. Fibroids express aromatase that is strikingly high of levels than the surrounding myometrium nearly 3 times, this then converts the estrogen into an active estradiol which is promoting growth of fibroids. Aromatase mRNA was detectable in 91% of myomas 75% at 2 cm from the myoma and not detectable in disease-free myometrium of the uterus[18,19,20,21,22,23]. And thus fibroids irrespective of size could produce a situation of local hyperprolactineamia and local hyperestrogenimea. Both could be detrimental to conceptions leading to infertility and could also increase the incidence of abortions. Uterine Leiomyoma is even reported in 27% of infertile women[24] and 50% of women with unexplained infertility became pregnant after myomectomy.
14. Pregnancy and the growth of myoma, myomas of less than 5 cm increases in size in the first trimester however myomas which were larger they reduce in the second trimester and all myomas reduced in the third trimester of pregnancy[25,26]. The spontaneous abortion rate was 41% in cases of myomas of significant size this reduced to 19% after myomectomy[27,28,29]. Patients of fibroids with pregnancy had increased incidence of bleeding in thefirst trimester premature rupture of membranes, breech presen tation placental abruption prolonged labour higher caesarean section rate. The estimation of premature labour was 15 to 20%, intrauterine growth restrictions in 10% and malpresentations in 20%. [30,31,32].
15. The risk of malignant transformation in myomas:

Literature suggests Leiomyo sarcoma incidence from 0.23% in premenopausal women to 2% in

postmenopausal women[33]. The incidence of Leiomyosarcoma is .67 per 1,00,000 women per year[34].

Although myomas are prevalent, the research is under funded compared with other non-malignant disease. Treatment innovations have been slow, perhaps because many women have asymptomatic fibroids, myomas benign and mortality is very low [35]. Quite often restricted as hysterectomy was the treatment options given; some women choose to bear with the symptoms and stop seeking treatment. Women who had hysterectomies done for myomas or related symptoms the quality of life questionnaires scores were not satisfactory compared to women who has symptoms due to hypertension, disease, chronic lung disease or arthritis[36]. This may lead physicians to underestimate the true impact of this condition literature review 198 articles pertaining to loot when fibroids, and questions fundamental to understanding outcomes of myoma treatment[37]. Risk and benefit of my treatment with respect to each, childbearing concerns, myomectomy or hysterectomy for symptomatic and asymptomatic myomatous; single or multiple myoma removal; women requiring additional treatment after myomectomy; whereas such treatment needed more than the group of hysterectomy patients done for myoma; and cost concerns of the available treatments. After an exhaustive review of literature, scrutiny of 637 relevant articles and careful study of 200 articles, those investigators found definitive answers to none of these fundamental questions.

Watchful waiting - there is no evidence that failure to treat myoma results in harm, except in women with severe in India from myoma unrelated menorrhagia or hydronephrosis due to back pressure on at least one unit due to fibroid. Predicting future myoma growth or onset of new symptoms is not possible[38]. A non-randomised study of women who had uterus of more than eight weeks size and would choose for hysterectomy or watchful waiting by the end of one year 77% are reported no significant changes in the complain by the end of one year[39]. However 23% opted for hysterectomy during the course of the year. Watchful waiting was more significant as women approached menopause, because there is a limited time to develop new symptoms and after menopause bleeding stops and myomas decreases in size[40].

The medical treatment aromatase inhibitors can be found to lead to inhibiting myoma is by hypoestrogenism but not that ovarian systemic level[41]. Hysteroscopic myomectomy — 196 constitutive women with menorrhagia and presence of one or more submucous fibroid was followed for a mean period of 73 months after hysteroscopic myomectomy [42]. 68% of the women reported satisfaction and ability to lead a normal life 13% required repeated hysteroscopic procedure and nearly the same required hysterectomy 10 patients had recurrent bleeding without further treatment, a total failure rate of 31%. Long term follow-up of 285 consecutive patients with menorrhagia or a Metrorrhagia who had hysteroscopic resection of one or more submucous myoma is found that the additional surgery was required for 9.5% and two years, 10.8% at five years and 26.7% at eight years [43].

Uterine artery embolisation — to date, five deaths have been reported after the UAE: into women from septic shock; in one woman from pulmonary embolus and into uncertain causes [44]. The risk of premature ovarian failure after the UAE was less or equal to 15% along with transient Amenrorrhea. After the UAE Doppler Ridley revealed 35% reduction in ovarian perfusion and 54% had complete loss of perfusion [45]. 34 pregnancies subsequent or UAE, 32% had spontaneous abortion [46]. Of the 164 women keen for future fertility before UAE, during 24 months follow-up 21 achieve pregnancy or had abortion to add elective termination and 89 had live births [47].

Magnetic resonance imaging — and guided focused ultrasound — ultrasound energy can be focused to create sufficient heat at a focal point so that protein is denatured & cell death occurs with 57 degrees at 1 second exposure. Concurrent use of MRI allows precise targeting of tissue & monitoring of therapy by assessing the temperature of treated tissue [48].The advantage of this procedure is very low morbidity & a very rapid recovery to normal within 1 day. 71% had significant reduction in symptoms at 6 months follow up 505 at 1 year but 28% underwent

hysterectomy of the 82 patients treated[49]. One patient had sciatic nerve injury & 5% had superficial skin burns

Morcellation controversy — Tissue retrieval is a unique challenge since long time. Laparoscopic power morcellation if performed in women with unsuspected uterine sarcoma, there is a risk that the procedure will spread the cancerous tissue within the abdomen and pelvis, significantly worsening the patient's likelihood of long-term survival. Evaluation by sonography, Doppler or markers is also not completely reliable to diagnose a case of sarcoma. In a recent meta-analysis the estimated rate of leiomyosarcoma was 0.51 per 1000 procedures or approximately 1 in 2000; restricting the meta-analysis to the 64 prospective studies resulted in a substantially lower estimate of 0.12 leiomyosarcomas per 1000 procedures or approximately 1 leiomyosarcoma per 8300 surgeries [50].

Recent statistics regarding clinical characteristics and management experience of unexpected uterine sarcoma stated that among 4248 patients who underwent myomectomy for presumed leiomyoma, 9 (0.2%) had unexpected uterine sarcoma (1 [<0.1%] had leiomyosarcoma; 8 [0.2%] endometrial stromal sarcoma). The malignancy was identified in 5 (0.2%) of 3068 women who were treated by laparoscopy with power morcellation and 4 (0.3%) of 1180 who underwent laparotomy (P=0.274). Thus the overall incidence of unexpected uterine sarcoma after myomectomy was low and incidental power morcellation of unexpected uterine sarcoma seemed to cause no increase in sarcoma dissemination [51].

The most interesting scientific aspect of this controversy is that even if a leiomyosarcoma is removed by an open en bloc surgery still there is 50% risk of spread or already residual existing disease compared to 60% risk when done by Laparoscopic morcellation, that is, only a 10% risk reduction with open surgery [52,53]. Further with the in-bag morcellation the risk of spread drops down drastically unless originally the sarcoma or cancer was already spread.

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02

CLINICAL PRESENTATION OF **FIBROIDS**

DR ASWATH KUMAR
MBBS., M.D., FICOG
Dip. in Advanced Laproscopy, France
Additional Professor Dept of Gynaecology,
Jubilee Mission Medical College, Thrissur
Chairperson, FOGSI Quiz Committee

DR. SWETHA SETTIPALI
MBBS, DGO, DNB
Senior Resident,Jubilee Mission
Medical College, Thrissur

The most common tumors of the unterstand the female pelvis are leiomyomata. This chapter discusses the pathologic and clinical features of uterine leiomyomata**.** Advances in gynecologic surgery just few decades finally brought this common yet, sometimes fatal disease of women under control[1].

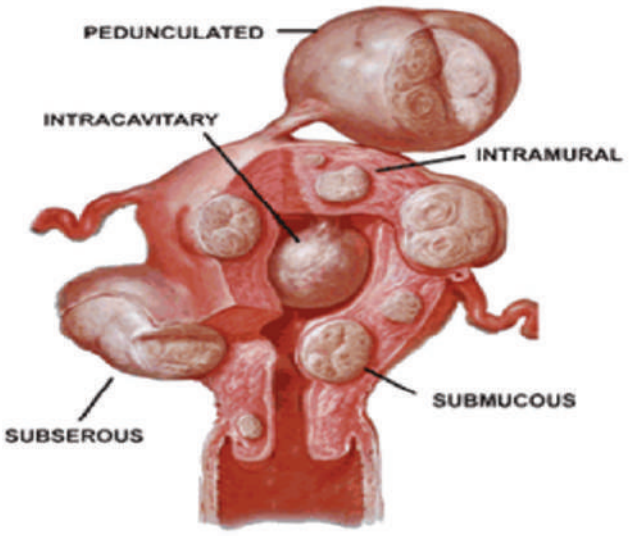
Before the 20th century, no effective treatment was available. Leiomyomata often use to grew to extremely large size and caused great suffering due to bleeding, pain,ureter obstruction leading to renal failure etc., Death from this benign disease was not uncommon. But progress in gynecologic surgery and anesthesia finally allowed the safe removal of these tumors.

Uterine leiomyoma are a major women's health care problem. Hence there is a legitimate reason for interest and concern and has questioned the need for proper approach for the better management of most cases of uterine leiomyomata.

When peeped into the etiology why only few women get victimized by this condition it is known that growth of leiomyomata is dependent mainly on estrogen production.The tumors thrive during the active reproductive years that is years with greatest ovarian activity. Continuous estrogen secretion, especially when un interrupted by pregnancy and lactation, is thought to be the most important underlying risk factor in the development of myomata. Lev-Toaff[2] and colleagues also confirmed that some leiomyomata do enlarge during pregnancy in response to estrogen and progesterone.

After menopause, with regression of ovarian estrogen secretion, growth of leiomyomata usually ceases. Actual regression in the tumor size may occur.

Grossly there are three kinds of fibroids submucous,intramural and subserous leiomyomas . As they enlarge, they can remain intramural,but growth often extends in an internal or external direction.Thus, the tumor can eventually become subserous or submucous in location. Sometimes subserous tumor can also become pedunculated and occasionally parasitic, receiving its blood supply from the omentum , and sometimes submucous tumor can also become pedunculated and may gradually dilate the endocervical canal and protrude through the cervical os.



In general, subserous leiomyomata contain more fibroustissue than submucous leiomyomata. However, submucous leiomyomata contain more smooth muscle tissue than subserous leiomyomata. Sarcomatous change is more common in submucous tumors.

Leiomyomata may undergo changes as a result of infection.Submucous leiomyomata are most commonly infected when they protrude into the uterine cavity, or especially into the vagina. The pedunculated submucous leiomyomathins out the endometrium as it grows inward, and eventually the surface becomes ulcerated and infected.

Occasionally a pedunculated subserous leiomyoma twists, and if an operation is not done immediately, in farction results. Necrosis of a leiomyoma is caused by interference with its blood supply. Necrosis usually occurs in the center of a large tumor simply as a result of poor circulation. Necrotic leiomyomata are dark and hemorrhagic in the interior. Eventually the tissue breaks down completely. So-called red or carneous degenerationis seen occasionally, especially in association with pregnancy. This condition is thought to result from poor circulation

of blood through a rapidly growing tumor.

Thrombosis and extravasation of blood into the myoma tissue are responsible for necrosis and in few situations the omentum becomes adherent to the peritoneal surface of apedunculated subserous myoma and provides what ever blood supply is needed.

Eventually, the pedicle may dis appearor twist, and the myoma will become completely free from the uterus, wander in the upper abdomen, and receive its"parasitic" blood supply from the omentum and other sources.

Asymptomatic fibroids:

Most leiomyomata are asymptomatic. More than 50% of them are asymptomatic[1].There are numerous such symptomless leiomyomata that are removed surgically by either hysterectomy or myomectomy when they would have been better left undisturbed. It is to be noted that the incidence of malignancy in leiomyomatais less than 0.1%, which is far less than the operative mortality rate of hysterectomy in the average hospital. Hence,unless there is some reason to suspect malignant change,the risk of the operation for asymptomatic leiomyomata may exceed the danger of malignancy.

Always a history of rapid growth particularly postmenopausal growth, does indicate removal, even when the tumor produces no symptoms. Signs of rapid enlargement are important in all patients but are even more ominous in older patients. But, it is impossible to predict which patients will become symptomatic in the remaining years.

In younger patients, the most common reason for rapid enlargement of a uterus with leiomyomata is pregnancy. If pregnancy can be ruled out,leiomyosarcoma may be suspected but is rarely found.

Small leiomyomata that are asymptomatic need only to be observed from time to time, with pelvic examinations perhapse very 6 to 12 months and preferably pelvic ultra sonography. If there is uncertainty of the uterine or ovarian origin of a tumor, as may well be the case when the tumor fills the whole pelvis or when a pedunculated tumor is felt in the adnexal region special diagnostic procedures may be indicated

Therefore, if uncertainty about the diagnosis persists, laparoscopy or laparotomy should still be performed. Medical management with GnRH agonists may be useful in women approaching menopause to control symptoms or reduce the size of asymptomatic uterine myoma until menopause.

Nakamura and Yoshimura[3]reported their experience with GnRH agonists in the treatment of uterine leiomyomata in perimenopausal women. One third of them reached menopause after 16 weeks of treatment,thus avoiding the need for surgery.

There is no uniform size of an asymptomatic leiomyomatou suterus that can be used as an indication for hysterectomy or myomectomy.

If the size is the only significant indication for surgery in an asymptomatic patient, trace the exact location of the tumors which is more important than the total uterine mass. When the leiomyomata are located in the cornual area or in the lateral wall of the uterus and obscure the anatomy of the adnexa and broad ligament, the risk of error in the early recognition of an ovarian tumor is greater. Subserousped unculated tumors, as well as intraligamentous tumors, may create problems in diagnosis as they are difficult to distinguish from tumors arising from the adnexal organs.

Friedman and Haas[4] mentioned that many gynecologists advocate removal of leiomyomata when the uterus is about 12 weeks' gestational size or greater, regardlessof symptoms.

The reasons[1] given for surgical intervention include

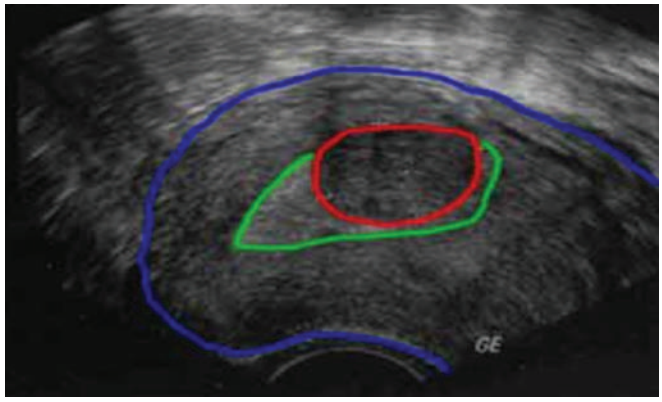
1. The possible malignancy of the pelvic mass
2. The potential for compromise of adjacent organ function if the mass continues to enlarge
3. The greater risk of surgical complications if the mass grows to a larger size
4. The potential for better fertility if myomectomy is performed when the uterus is smaller
5. The possibility of continued growth of uterine leiomyomata if hormone replacement therapy is given after menopause

After the gynecologist is absolutely certain that an ovarian neoplasm is ruled out, an asymptomatic leiomyomata after menopause,can be left undisturbed .

Here comes the role of the ultra sonography. It is the most cost-effective screening mechanism for uterine masses suggestive of myomas. Generally, abdominal scan is unable to detectmyomas less than 2 cm in diameter.

In a series evaluated by Fedele[5] and colleagues using endovaginal ultrasound before hysterectomy, submucous leiomyomas were identified with a sensitivity of 100%. Especially difficulties will arise, if myomas are small or pedunculated, patients are obese, or the uterus is retroverted.

The above picture shows a submucous fibroid.



Transvaginal fluid-enhanced vaginal probe sonography(sonohysterography) is a useful technique to assess myomata that distort the endometrial cavity. The limitation of detection of leiomyomas with this modality is only 0.5 cm sized fibroids.

Symptomatic Leiomyomata:

Less than 50% of patients with uterine leiomyomata have symptoms. There can be single or multiple symptoms and the symptoms mainly depend on the location, size, and number. Th information regarding the symptoms of fibroids.

Abnormal Bleeding:

It is not unusual that even patients with largeuterine leiomyomata may have a history of normal menstruation. Hence, women should be questioned carefully about any recent increases in the amount, duration, and frequency of menstruation. They should be given instructions to maintain a menstrual calendar and monthly record of the number of pads or tampons used each day.

Abnormal bleeding is seen in about one third of patients with uterine leiomyomata. The menstrual flow is usually heavy but it can also be prolonged or both heavy and prolonged.

There is a clinical impression that bleeding is more common and more severe in the presence of submucous tumors. It bleeds freely at menstruation and may also bleed between periods as a result of passive congestion, necrosis, and ulceration of the endometrial endometrial surface over the tumor and ulceration of the contralateral uterine surface. If the submucous myoma is pedunculated, there is usually a constant, thin, blood-tinged discharge in addition to the menorrhagia. An intramural tumor which is just beginning to encroach on to the uterine cavity can also be responsible for menorrhagia.

Actually there are several mechanisms by which fibroids can cause abnormal bleeding. Increased surface area is considered to be most common mechanism. Normally the surface area of the endometrial cavity is 15 cm^2 and the surface area of the endometrial cavity in the presence of leiomyomata may sometimes become more than 200cm^2.

In uterus with fibriods there is a high frequency of endometrial hyperplasia which can be a cause for abnormal bleeding. Yamamoto[6] and coworkers have reported high concentrations of estrone and estrone sulfatase activity in the endometrium overlying a myoma. They suggest that the local hyperestrogenism in the endometrium overlying a leiomyoma may assist in the genesis or enlargement of these tumors.

Presence of leiomyomata interferes with myometrial contractility as well as of the spiral arterioles contractility in the basalis portion of the endometrium.

Ludovici[7] suggested that anovulation and dysfunctional uterine bleeding are commonly associated with uterine leiomyomata.

The prominent and significant change is the presence of endometrial venule ectasia, proximal congestion of veins in the myometrium as well as endometrium. Thrombosis and sloughing of these large dilated venous channels within the endometrium produce heavy bleeding.

There is a debated evidence that supports the concept that prostanoids play a rolein primary menorrhagia and the balance between TXA2 and PGI2 shifted to a relative TXA2 deficiency which is responsible for blood loss in patients with menorrhagia.

An accurate diagnosis is more likely to be made by hysterosalpingography, conventional transvaginal ortrans abdominal US, sonohysterography, MRI, or hysteroscopy. Sonosalpingography provides accurate evaluation of the size of submucous myomata, intracavitary and intramural growth, and location within the uterinecavity, with sensitivity, specificity, and predictive values of 100%.

It is to be noted that in postmenopausal women the myometrial shrinkage may be disproportionately greater than the myoma shrinkage. Therefore, a intramural myoma before menopause may become a submucous after menopause. Sometimes it becomes symptomatic usually with postmenopausal bleeding. In such cases careful pelvic examination, papanicolaou smear, and evaluation of the cervix by colposcopy or biopsy, pelvic US, fractional curettage,and perhaps hysteroscopy in short all basic investigation profile to find out cause of postmenopausal bleeding should be done.

If the bleeding remains unexplained after evaluating for other causes of bleeding the leiomyomatous uterus should be removed because of the risk of sarcomatous change or concomitant presence of endometrial carcinoma.

Pressure symptoms:

Any evidence of pressure on nearby pelvic viscera may be an indicationfor treatment. It is urinary bladder which suffers most oftenfrom such pressure, giving rise to urgency and frequency of urination and sometimes even urinary incontinence.

Occasionally, even acute retention of urine especially a large pedunculated submucous tumor may fill and distend the vagina or rarely overflow incontinence results from a leiomyoma and necessitates surgical intervention. Sometimes a large tumor gets incarcerated in the cul-de-sac, wedging the cervix forward against the urethra and obstructing the urine flow.

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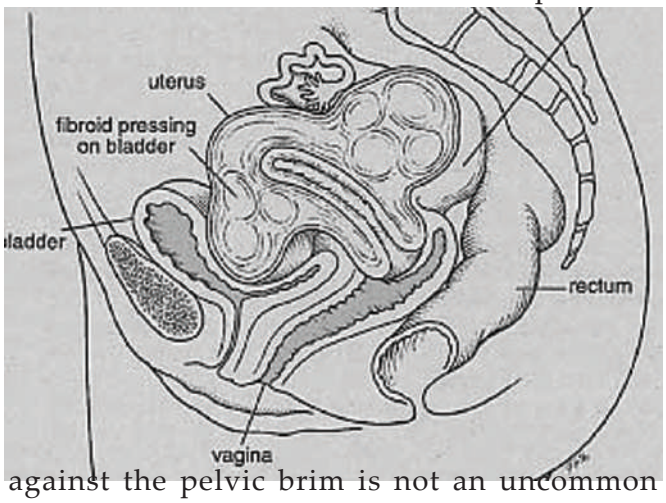
The above picture shows pressure effects on bladder and rectum

Silent ureteral obstruction from pressure



against the pelvic brim is not an uncommon complication of multiple large leiomyomata. If there has been no infection or parenchymal damage to the kidney, this anatomical problem is totally reversible with removal leiomyomata

To restore kidney function removal of the tumor. Chronic bladder neck obstruction from uterine

leiomyomata can be so severe as to cause a remarkable increase in the thickness of the bladder wall and enlargement of the bladder.

The bowel is less apt to show symptoms from pressure than is the bladder. Rarely small intestinescan become entwined with subserous pedunculated tumors,causing intermittent intestinal obstruction

Pain:

Leiomyomata causing pelvic pain or dysmenorrhoea or heaviness or dyspareunia are appropriate reasons for active intervention.

Apedunculatedsubserousleiomyomata twist andgive rise to a clinical picture of acute abdominal pain. During any period of reproductive life, especially during pregnancy an acute carneous or red degeneration of a leiomyoma can occur which is the source for pain.

A symptom complex of menstrual pain coupled with increased menstrual flow acquired in the fourth or fifth decade is suggestive of leiomyomata. But, diffuse adenomyosis can also cause these symptoms, and the differentiation of this condition from a symmetrically enlarged intramural leiomyoma and may require MRI

Always rule out concomitant pelvic disease such as ovarian pathology, pelvic inflammatory inflammatory disease, tubal pregnancy, endometriosis, or urinary tract or intestinal pathology, including appendicitis evening if the women have evidence of fibroids.

Abdominal Distortion:

Any distortion of the normal abdominal wall contour embarrassing the women justify their removal. Such large tumors often give rise to symptoms hence there is ample reason for surgical interference.

Rapid Growth:

In the initial two decades following the introduction of oral contraceptives containing high-dose estrogen, there was a striking increase in the occurrence of large leiomyomata amongyoung women of all racial backgrounds who took these pills.Oral contraceptives with low-dose estrogen are less likely to stimulate growth. Even pregnancy a high estrogenic state is known to show rapid growth.

In fact,Yamamoto[6] and coworkers have reported high concentrations of estrone and estrone sulfatase activity in the endometrium overlying a myoma. They suggest that the local hyperestrogenism in the endometrium overlying a leiomyoma may assist in the genesisor enlargement of these tumors.

Rapid growth of a leiomyomatous uterus is difficult to define in exact terms. Buttram[7] and Reiter have arbitrarily defined it as a gain of 6 weeks or more in gestational size within a year or less. Ultrasonography is a much more objective way of establishing the size of a uterine leiomyoma in the beginning and, when indicated, of evaluating its rate of growth

In the post menopausal patient, rapid growth of a uterine leiomyoma is highly suggestive of a

malignancy[1]. The incidence given by Novak is 0.7%. However, a review of by associates at the Johns Hopkins Hospital the incidence of sarcoma being 0.29%.The malignancy may be asarcomatous change in the leiomyoma itself or carcino main the endometrium causing uterine enlargement. Rarely it can an ovarian neoplasm like mucinous cysts and Brenner tumors, can also produce estrogen stimulates enlargement of the leiomyoma or whose growth may be mistaken for rapid enlargement of uterine leiomyomata.

Infertility:

Numerous factors[1] may be responsible for infertility in a patient with uterine leiomyomata.

1. Anovulatory cycles
2. Interference with sperm transport caused by distortion
3. Increased surface area within the uterine cavity
4. Impingement of leiomyomata on the endocervical canal or interstitial portion of the fallopian tube
5. Interference with prostaglandin-induced uterine contractions
6. Endometrial changes (atrophy, ulceration, focal hyperplasia,and polyps)
7. Vascular alterations (venous congestion,
8. Venul eectasia, impaired blood flow)

But finding a leiomyomata in infertile women is not always an indication for immediate myomectomy. Always rule out any other important associated causes of infertility. Both marital partners should have a complete infertility investigation, and the leiomyomata should be disregarded for a while

The ultimate decision regarding of the tumors depends on their size and location(submucous, large intramural,myomas blocking ostia etc.,). In such cases myomectomy may be rewarded with a subsequent pregnancy. Great tact is required in describing the problem to the patient. . Each case presents its own problems, and the answers depend on the patient's age, her general physical health, her pelvic findings, and most important, her own desires. The best surgical and obstetric judgment is needed to make a proper recommendation.

Pregnancy-Related Problems:

Most patients with uterine leiomyomata usually don't have any difficulty in conceiving and carrying their pregnancies to term without complications.The only problem encountered may be a difficulty in estimating gestational age from uterine size.

But some leiomyomata are associated with a significantly increased risk of spontaneous abortion. Buttram[7] and Reiter reported that 41% had spontaneous abortions. This rate was reduced to 19% after myomectomy.

There are several mechanisms[1] that have been proposed to explain the occurrence of spontaneous abortion from leiomyomata.

1. Disturbances in uterine blood flow
2. Alterations in blood supply to the endometrium
3. Uterine irritability
4. Rapid growth or degeneration of leiomyomata during pregnancy
5. Difficulty in enlargement of the uterine cavity to accommodate for the growth of thefetus and placenta
6. Interference with proper implantation and placental growth by poorly developed endometrium or by subjacent leiomyomata
7. Implantation in a thin, poorly vascularized endometrium over a submucous leiomyoma is doomed to failure

Uterine leiomyomatasometimes may also be associated with otherobstetrical concerns, including premature delivery,pelvic pain, stillbirth, and interstitial pregnancy

Compared with controls, women with myomas

during pregnancy had an increased

1. Intrauterine growth restriction (6.8% vs. 1.9%),
2. Placental abruption (2.8% vs.0.7%),
3. Abnormal presentation (16.9% vs. 2.4%),
4. Cesarean section rate (57.7% vs. 10.8%),
5. Premature rupture of membranes(9.6% vs. 5.5%),
6. Blood transfusion rate (4.2% vs. 1.4%).

All of these outcomes were statistically significant[1].

Red or carneous degeneration of leiomyomata during pregnancy is associated with pain, tenderness over the tumor, low-grade fever, and leukocytosis. Management should be expectant with analgesic medications and bed rest . Operation isnot indicated unless some other surgical causes like appendicitis, abruption, torsion ovary are suspected.

A leiomyoma in fact in any location may interfere with labor and delivery by causing an abnormal presentation, or by obstructing the pelvis.

A submucous leiomyoma in the lower uterine segment may entrap the placenta, necessitating manual removal. Indeed,it may cause postpartum hemorrhage.Immediate hysterectomy may be necessary to control the bleeding. Sometimes chronic uterine inversion results if the prolapsing submucous leiomyoma is attached to the top of the endometrial cavity and pulls the uterine fundus downward through the cervix.

An intramural leiomyoma in an involuting puerperal uterus can also become infected when endometritis is present. Even septicemia may result occasionally.

Other Signs and Symptoms:

There are some unusual problems associated with uterine leiomyomata which may require treatment. Ascites, uterine inversion and sudden in traperitoneal hemorrhage are few of them.

Occasionally patients present with polycythemia. Islands of extramed

ullaryerythropoies is have been found in leiomyomata. Arteriovenous shunts within the tumors have been found and may be etiologically important in polycythemia. If the tumor obstructs the

ureters and causes back pressure on the renal parenchyma, erythropoiesis can be stimulated.The polycythemia in these cases is cured by hysterectomy.

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03

IMAGING OF **LEIOMYOMA** AND **ADENOMYOSIS**

Dr, Narendra Malhotra,
M.D., F.I.C.O.G, F.R.C.O.G.,
Global Rainbow Healthcare
NH-2, Agra-282007

Dr. Jaideep Malhotra,
M.D., F.I.C.O.G, F.I.C.S.,
Global Rainbow Healthcare
NH-2, Agra-282007

Dr. Diksha Goswami,
MD,DNB,MRCOG,FNB
Global Rainbow Healthcare
NH-2, Agra-282007

Imaging of fibroids

Fibroids or Uterine Leiomyomas are the commonest uterine tumours. Its incidence is about 20-25% in parous women which usually decreases with increasing parity[1]. It is a benign hormone dependant tumor composed of interleaved bundles of smooth muscle with varying amount of fibrous connective tissue.

Most leiomyomas are asymptomatic but can present in 20-50% women as menorrhagia, dysmenorrhoea infertility.

Anatomically leiomyomas are classified as[2] :

a) Intramural

b) Submucosal

c) Subserosal

The imaging modalities available for the diagnosis include :

a) Ultrasonography — Transabdominal Sonography; Transvaginal Sonography

- Gray Scale Imaging
- Color Flow Mapping
- Duplex Doppler
- 3D/4D Ultrasonography

b) Magnetic Resonance Angiography

The role of imaging is to determine the number, location and structure of the fibroids. The main technique is USG that can be performed with endocavitory transducers in case of small myomas but in larger ones, a suprapubic approach is more informative.

Ultrasonography :

a) Gray Scale Imaging : Ideally both transabdominal and transvaginal scans should be combined. Transvaginal sonography has substantially improved the diagnosis of fibroids compared to Transabdominal Sonography. While transabdominal scans are of limited utility in obese patients , in transvaginal approach when uterus is bulky or retroverted fundus may lie out of the field of view.

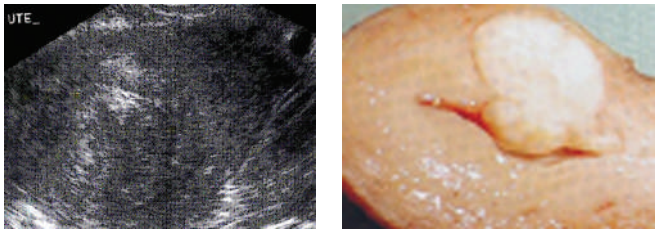

Fig 1.Transabdominal Scan. Leiomyoma (a) well defined, discrete, hypoechoic mass (b) Gross specimen of the same

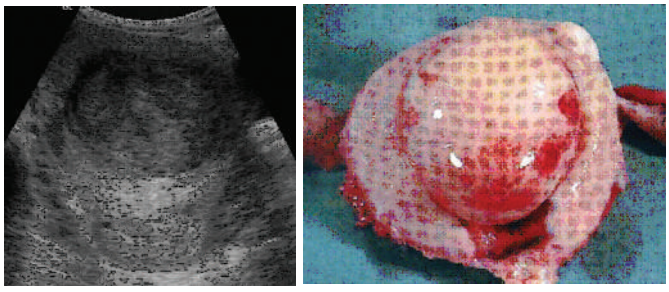

Fig 2. Transabdominal Scan. Leiomyoma (a) Well circumscribed mass with hypoechoic periphery (b) Gross specimen of the same

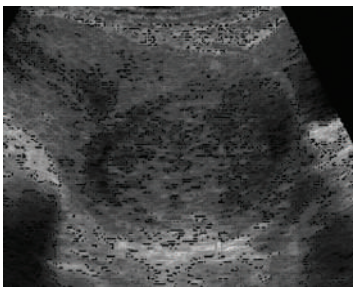

Fig 3. Transabdominal Scan. A Cervical Leiomyoma

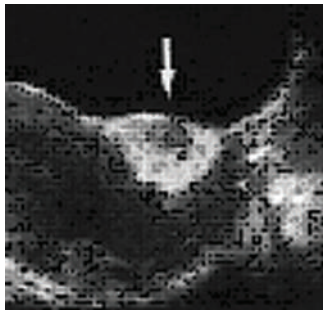

Fig 4. Unusual Sonographic appearance of the Leiomyoma. Hyperechoic mass suggestive of Hyaline, Fatty or Red degeneration.

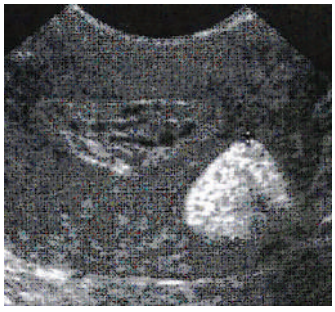

Fig 5. A small hypoechoic leiomyoma in the anterior myometrium with preserved endometrial outline.

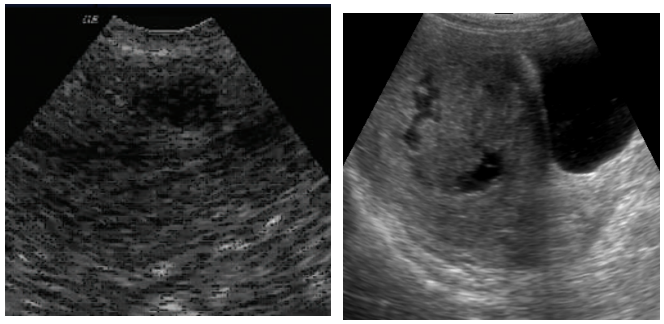

Fig 6. Transabdominal Scan. Leiomyoma with cystic degeneration

Sonographic appearance of leiomyomas depends on relative proportion of muscle bundle and fibrous tissue. Degeneration affects the Imaging appearance.

Leiomyomas are characteristically hypoechoic well defined, discrete, round or ovoid masses (Fig. 1, 2). These have a well defined plane of cleavage with adjacent myometrium[3] (Fig. 3). They cause uterus to appear bulky or distort the uterine contour. Myomas with fatty and hyaline degeneration may appear hyperechoic (Fig. 4). Few myomas may also be isoechoic. Endometrial outline is preserved (Fig. 5) but there may be contour abnormality with mass effect. Calcified myomas may show posterior shadowing. Cystic degeneration (Fig. 6) may be seen with small anechoic areas on sonography.

Sharp, discrete, recurring shadows (Refractory shadowing[4]) is typical of leiomyomas. It is defined

as presence of 3 or more well defined shadows originating from within a mass. Shadows originating from echogenic lead points are presumed to be from calcifications, therefore not considered. Histopathologically these correlate with edges between smooth muscle whorl and boundaries between smooth muscle and fibrous connective tissue. Since large fibroids can cause secondary hydronephrosis , one must scan the KUB region in these cases.

b.) **Sonohysterography :**

This technique involves instilling saline in the uterine cavity in order to well delineate intracavitary lesions . SHG is more accurate than transvaginal sonography in detecting submucous fibroids and differentiating from mucous polyps. Combining SHG with TVS is convenient , less expensive and less time consuming to perform compared with magnetic resonance imaging[5]. SHG is also a precise tool in identifying location of submucous fibroids and aids in planning subsequent hysteroscopic surgery[5].

Table 1. Comparison of SHG features of submucous fibroids and endometrial polyps[5]

	Submucous fibroid	Endometrial polyp
1.	Usually hypoechoic	Homogenous hyperechoic masses
2.	Multiple feeding vessels on doppler (Fig 7)	Single feeding artery
3.	Broad based ,can extend beyond basal layer	Don't extend beyond basal layer, can be sessile
4.	Usually single	Can be multiple
5.	Usually larger masses more than 20 mm	Usually measure less than 20mm

b) Role of Color Flow Mapping and Duplex Doppler

Leiomyomas show a characteristic circumferential flow pattern (Vascular Ring)[6]. Spectral analysis show a low resistance (RI < 0.4), high velocity flow velocity waveform pattern

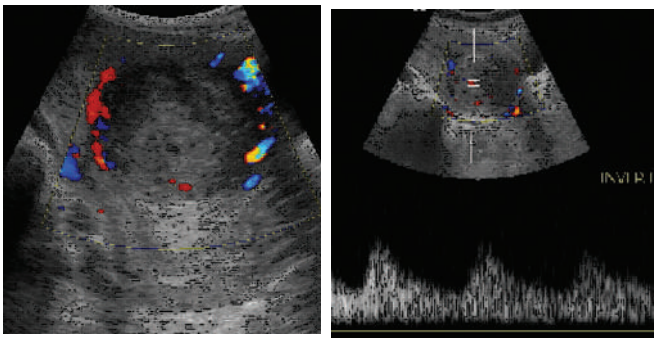

Fig 8. (a) Peripheral vascularity in a well defined, hypoechoic mass in anterior myometrium suggestive of Leiomyoma (b) Spectral Analysis shows high velocity, low resistance flow velocity waveform pattern.

Table 2 : Accuracy of Endovaginal Sonography in the diagnosis of Leiomyomas

	Sensitivity	Specificity
Fedele et al[3](1992)	96.1%	83.3%
Botsis et al[7](1998)	95.1%	82%

c) **Role of 3D/4D Ultrasound**

3D Protocols have emerged as an extremely useful adjunct for evaluation of uterine fibroids. Many studies have shown an enhanced diagnostic accuracy. The essence of images include volume information acquisition which can then be used in various ways (Fig.8).

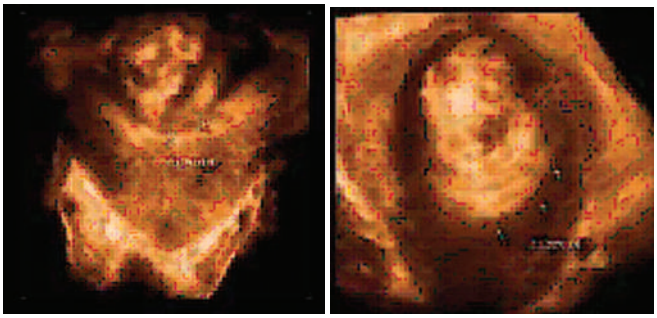

Fig 8. Appearance of Leiomyoma.

It helps in better localization of lesions with required information needed for surgery. Imaging can also help in planning treatment for the patient. Scoring systems have been devised which help decide feasibility of hysteroscopic surgery for submucous fibroids. STEPW or LASMAR presurgical ultrasound score[8] includes five criteria

and found to correlate well with ease complete or incomplete removal of the myoma by hysteroscopic myomectomy.

d.) CT : CT is rarely indicated for imaging fibroids but mostly incidental finding. Typical finding is that of bulky irregular uterus or mass in continuation of uterus. It may be helpful for determining complications if MR imaging is not available. In case of acute torsion there may be enhancement of the rim but no central enhancement. Fibroids appear hypodense after contrast enhancement.

e.) MR Imaging : MR Imaging is currently considered as the most accurate imaging technique for the detection and localization of leiomyomas. Its potential of differentiating between the various uterine layers enables an accurate classification of the lesions[9] into submucosal, intramural or subserosal location. MRI can help identify small lesions 5mm diameter and especially helpful in diagnosing fibroids at unusual locations. The usual uterine leiomyomas have a typical appearance at MR imaging : well circumscribed masses of homogenously decreased signal intensity compared with that of the outer myometrium on T2 weighted images whereas the signal intensity is intermediate on T1 weighted images (Fig.9). Cellular Leiomyomas can have relatively higher signal intensity on T2-weighted images and demonstrate contrast enhancement. Some leiomyomas may have a high signal intensity rim representing dilated lymphatic vessels, dilated veins or edema (Fig.10). Leiomyomas with hyaline or calcified degeneration have an appearance similar to that of usual ones. Those with cystic degeneration show high signal intensity on T2-weighted images and cystic areas do not enhance.

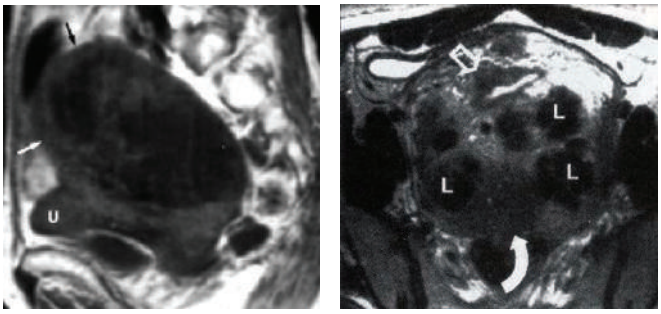

Fig 9. (a) T1 W Image. Well defined, iso-intermediate signal intensity mass suggestive of Leiomyoma (b) T2 W image. Multiple, small low signal intensity masses.

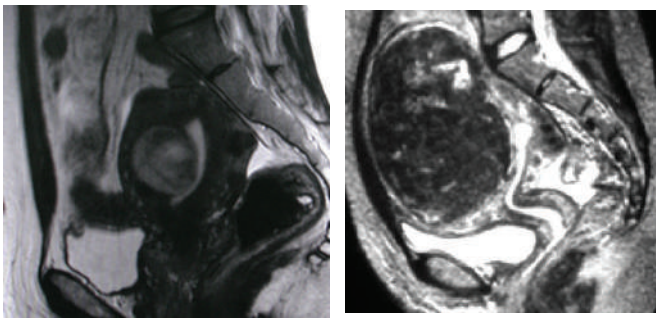

Fig 10. T2 W image. (a) Leiomyoma with Cystic degeneration (b) Leiomyoma with hyperechoic rim.

Leiomyomas with myxoid degeneration show very high signal intensity on T2 weighted image and enhance minimally. Leiomyomas with red degeneration may exhibit an unusual pattern[10] : peripheral or diffuse high signal intensity on T1-weighted images and variable signal intensity with or without hypointense rim on T2-weighted images.

MR imaging has a role in treatment of Leiomyomas by helping in surgical planning and monitoring the response to medical therapy whenever US is unable to assess the global morphology and in patients with Adenomyosis with coexistent leiomyomas (Table 4). Also useful in predicting and assessing the response to uterine artery embolization . Fibroids demonstrating high signal on T1W images prior to embolization have poor response to UAE due to poor blood supply while high signal on T2W images is a good prognostic feature[11]. It is also helpful in evaluation of changes in leiomyoma volume after embolization.

Differential Diagnosis

- Adenomyoma (Table 6)
- Leiomyomas also need to be differentiated from retroverted uterus, uterine malformations and enlarged uterus from other causes.

Imaging in adenomyosis:

Adenomyosis exists in two different forms; diffuse and local. In the former,

foci of adenomyosis are distributed within the myometrium while in the latter

form, nodules of hypertrophic myometrium and ectopic endometrium are

noted. Transvaginal sonography (TVS) has substantially improved the ability to diagnose adenomyosis preoperatively whereas in the past it was mainlya histopathological diagnosis. Different sonographic features of adenomyosis include uterine enlargement not explainable by the presence of myomas , globular uterus , poor definition of the

endometrial–myometrial junction, asymmetrical thickening of the anterior or

posterior wall, (fig 11) ,lack of contour abnormality or mass effect, anechoic lacunae or cysts of poorly circumscribed areas within the myometrium 1-7 mm diamter , subendometrial echogenic linear striations being hyperechoic and located near the endometrial– myometrial interface , heterogeneous myometrium, defined by the presence of an indistinctly defined myometrial area with decreased or increased echogenicity .

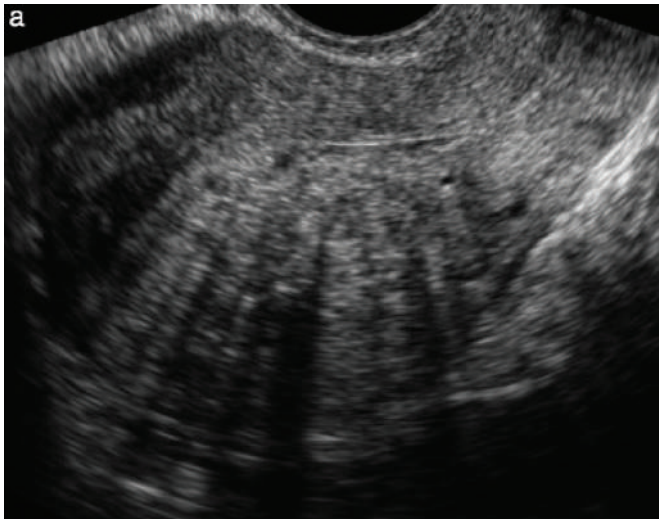

Fig11 :Heterogenous myometrium, globular uterus with ill defined endo-myometrial interface suggestive of adenomyosis

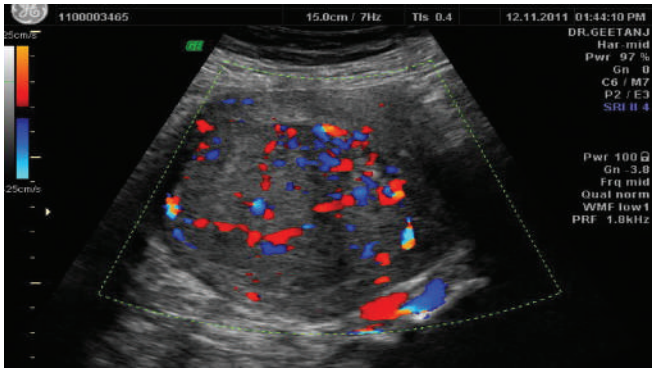

Fig 12 Peripheral vascularity seen in adenomyosis

Study by Bazot et al[12] suggests that transvaginal ultrasound and MRI have similar

accuracy for the diagnosis of adenomyosis while MRI is expensive and is not always available. However, in women with associated disorders, such as uterine fibroids, the diagnostic accuracy of transvaginal ultrasound is lower than is that of MRI.

Table 3 : Accuracy of Endovaginal Sonography in the diagnosis of Adenomyosis

	Sensitivity	Specificity	PPV	NPV
TVS Bazot et al 2001)	65 %	97.5%	92.8%	88.8%
Kepkep[13] et al 2007	80.8%	62.4%	55.3%	84.4%
MRI	77.5%	92.5%		

Table 4 : Comparing USG with MRI in presence and absence of coexistant Adenomyosis

		Sensitivity	Specificity
Adenomyosis	TVUS	33.3%	78%
With Myoma	MRI	66.6%	82.1%
Adenomyosis	TVUS	97.8%	97.1%
Without Myoma	MRI	86.7%	100.0%

Bazot et al. found that among the sonographic criteria, myometrial cyst was the most sensitive and specific finding for adenomyosis, and heterogeneous myometrial areas had poor accuracy. Among all the sonographic features evaluated by Atri et[14] and Kepkep et al , subendometrial echogenic linear striations, subendometrial echogenic nodules and asymmetrical myometrial thickness demonstrated the best specificity and PPVs in the diagnosis of adenomyosis. According to Kepkep et al , subendometrial linear strations had the highest specificity and PPV, and was considered to be the most specific finding

for differential diagnosis, although its detection on ultrasound is uncommon.

MRI in adenomyosis

The inner layer of the myometrium (the sub-endometrial halo) or **Junctional zone** is hypoechogenic in TVS, but in MRI it is seen as seen as a low-signal-intensity band on a T2-weighted image. The changes in the junctional zone as junctional zone hyperplasia (focal or

diffuse) may precede or be the first signs of adenomyosis. foci of increased high signal intensity in the junctional zone. In suspect cases, this sign has a very high diagnostic specificity for adenomyosis

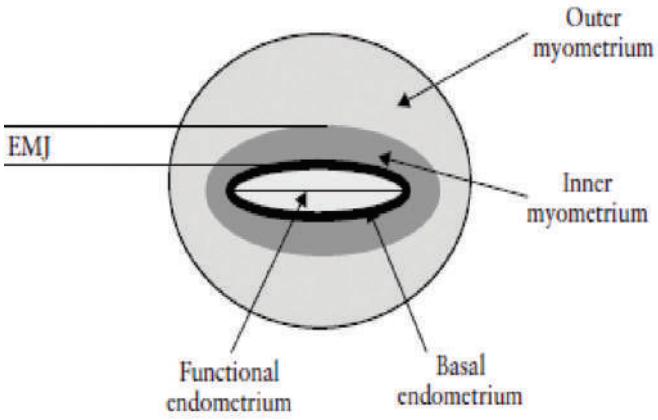

Fig 13. Junctional zone

The accuracy of MRI for diagnosis of adenomyosis is dependent upon the used MRI sequences for image formation and should be a T2-weighted sequence . Features used to define adenomyosis include[15]

- Maximal junctional zone thickness (JZ) of 12mm as the most optimal cut-of

- JZ of 8–12mm with subjective impression of a localized thickening of the junctional zone, poorly defined borders, or high signal intensity spots .

- Difference between the maximum and minimum JZ thickness more than 5 mm

and a difference of more than 5 mm (slightly better diagnostic marker)

When the established criteria of JZ were used for diagnosis of adenomyosis, MRI had a higher diagnostic accuracy than TVS, but the two techniques were almost equal, and both techniques demonstrated a sufficient diagnostic accuracy for diagnosis of adenomyosis.

The combination of TVS and MRI offers the highest sensitivity for diagnosis of adenomyosis, but combining the two techniques may reduce the specificity, except in difficult cases where it is of benefit.

Bazot et al. used the established criteria (JZ 12 mm), combined with other criteria and found a coexistence of adenomyosis in 27% of patients with mainly deep endometriosis.

Thus adenomyosis may often be seen in patients with severe symptomatic endometriosis. These patients could benefit from a preoperatively evaluation by MRI, which may give the most

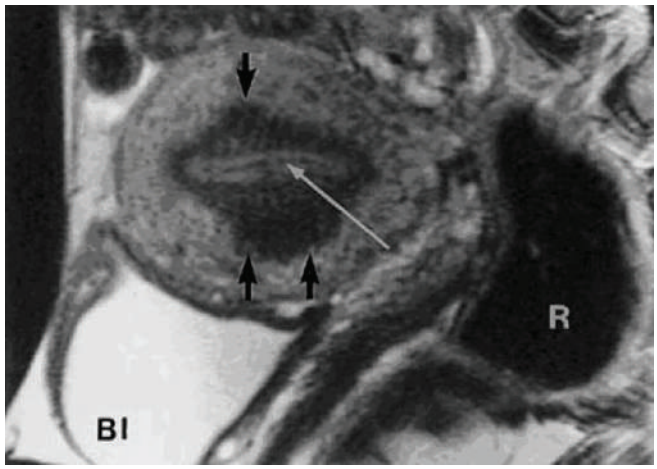

Fig 14: MRI showing adenomyosis aith increased JZ thickness

accurate information on both the extent of endometriosis and presence of adenomyosis

Role of 3D scan in Adenomyosis

Adenomyosis is considered to be a pathology that initially affects the endomyometrial junctional zone (JZ). The JZ is a distinct, hormone-dependent uterine compartment at the endomyometrial interface that was visualized more than 20 years ago by magnetic resonance imaging (MRI) and correlates sonographically to the subendometrial halo or the hypoechoic tissue seen beyond the endometrial basal layer. Despite the apparent lack of histological distinction between the JZ and the outer myometrium on light microscopy, these two zones are in reality structurally and biologically different.

The presence of adenomyosis causes hyperplasia and hypertrophy of myocytes

surrounding heterotopic endometrial tissue that can be seen on T2-weighted MRI as

diffuse or focal thickening of the JZ. The heterotopic endometrial tissue may be seen as small foci of increased signal intensity in the JZ . Even with high frequency

probes (5–10 MHz), sonographic evaluation of the

JZ seems to be imprecise due to the difficulty in obtaining optimal views with which to differentiate between the inner and outer myometrium. Some two dimensional (2D) sonographic studies report only the

subjective impression of a poorly defined JZ as a diagnostic criterion for adenomyosis, but with low sensitivity . On the coronal section of the uterus, obtained with three-dimensional (3D) TVS, it is possible to visualize the JZ more clearly with certain postprocessing. arrangements. Using 3D-TVS, a volume of the uterus was then acquired in order to obtain the coronal view. 3D volume box exceeding the uterus by 1 cm on each side. On the coronal view the JZ appeared as a hypoechoic zone around the endometrium. Using VCI modality with 2–4-mm slices it can be viewed clearly in all planes of the multiplanar view while it is poorly visualized in most patients by 2D-TVS. Disruption and infiltration of the described and the JZ thickness was measured as the distance from the basal endometrium to the internal layer of the outer myometrium. 3D reconstruction of uterine anatomy in the coronal plane provides new and unrivaled views of the JZ obtaining coronal views of the uterine cavity, it is possible to assess the lateral and fundal aspects of the JZ, which are impossible to visualize clearly on standard 2D imaging. 3D-TVS of the JZ the same objective parameters that radiologists generally consider for the diagnosis of adenomyosis by MRI.

JZmax e"8 mm and JZdif e"4 mm were significantly more accurate in diagnosing adenomyosis than were 2D features. Also, the subjective evaluation of infiltration and disruption by endometrial tissue in the JZ appears to be a very accurate tool for the diagnosis of adenomyosis. Modification of JZ thickness and protrusion of the endometrium into the inner myometrium could represent an early stage in the development of adenomyosis[16].

Table 5. Comparison of 2D TVS and 3D in diagnosing adenomyosis

	Sensitivity	Specifity	PPV	NPV
2D	75%	90%	86%	82%
3D	91%	88%	85%	92%

Table –6 : Comparing the sonographic appearances of Leiomyoma with Adenomyoma

	Leiomyoma	Adenomyoma
1	Discrete, well circumscribed	Poorly circumscribed
2	Hypoechoic, well defined periphery	Ill defined periphery
3	Mainly hypoechoic also iso / hyperechoic	Heterogenous echopattern
4	Endometrial outline is preserved	Poor definition of endometrial outline
5	Contour abnormality and mass effect seen	No contour abnormality or mass effect
6	Refractory shadowing	Edgy shadowing may be seen
7	Calcification is common	Uncommon
8	Cystic degeneration may be seen	Subendometrial myometrial cysts (0.5-1.5 cm)
9	Myomas with red degene rationshowprobetenderness	Probe Tenderness ++
10	Peripheral Vascularity	Scattered Vascularity
11	PI of tumor vessels & uterine vessels = /<1.17	> 1.17

In conclusion, diagnosis of Leiomyomas and adenomyosis has a high accuracy rate in expert hands, a good equipment and with use of endocavitory probe (T.V.S.).

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04

MEDICAL MANAGEMENT OF UTERINE LEIOMYOMA: A COMPREHENSIVE REVIEW

Dr. S. Santhakumari
MD DNB FICOG
Malla Reddy Medical College for Women
Consultant Care Hospitals
ICOG Secretary 2015 -2018
Vice President FOGSI 2013

Dr. Kiranmai Devineni
MD FICOG
Assistant professor, OBGYN, Osmania Medical College Hyderabad.
Joint secretary OGSH 2011-2013,
Scientific convener AICOG 2011 hyderabad.

Abstract

Uterine leiomyomas are the commonest benign tumors that affect women of reproductive age worldwide. They are frequently associated with symptoms that impact on quality of life like abnormal uterine bleeding, pain, dysmenorrhea. Treatment traditionally was usually surgical with either hysterectomy or myomectomy being performed. Although myomectomy conserves the uterus, it may be associated with complications that might not enhance the chance of pregnancy. For those concerned about fertility and who want to avoid or delay surgical treatment, alternatives are being explored. New medical treatments are also being evaluated – among which the progesterone receptor modulators are promising.They induce amenorrhea and a degree of fibroid shrinkage whilst having minimal effect on ovarian function. This article gives a comprehensive overview of medical management of leiomyoma.

Introduction

Uterine leiomyomas, or fibroids, are benign, hormone-sensitive, smooth-muscle tumors that occur in 20 to 40% of women of reproductive age.[1,2]Menstrual abnormalities- menorrhagia is the most common abnormality in about one third women with myomas. The other common symptoms are pelvic pain,dysmenorrhea, and pressure effects, depending on the site of myoma which may adversely affect quality of life and fertility. Fibroids are the most common indication for hysterectomy. Open Myomectomy or hysteroscopic removal, uterine artery

embolization, and various other interventions performed under radiologic guidance are the other options apart from hysterectomy which is the commonest surgical procedure .[3-4]

Medical therapy is a choice in women with symptomatic myomas who opt for nonsurgical methods, consider fertility preservation or a less aggressive surgery after shrinkage of the uterine volume[5]

It's a well-documented fact that fibroid growth and maintenance are stimulated by estrogen and affected by cyclic hormonal changes. Both Estradiol and progesterone receptors have been identified in myomatous tissue. The proliferative and mitotic counts were higher in the secretory phase and mitotic activity was significantly higher with progestin therapy. AromataseP450, an estrogen synthase which has been identified within myomas may enable myomas to synthesize their own estrogen and promote myoma cell growth[6].

Progesterone has a dual effect on myomas. It upregulates EGF and Bcl-2 protein and stimulates leiomyoma cell growth and inhibits myoma cell growth by down regulating IGF-1 expression.[7]

Local growth factors may mediate effects of estrogen and progesterone on myoma growth. Understanding the molecular events involved in the transformation of a normal myometrial cell into a neoplastic cell and the subsequent growth of these leiomyoma cells will be important in determining the pathogenesis of these tumors and providing new targets for treatment.

In this chapter the various available therapies for the medical management of myomas are presented and the current status of the medical management reviewed.

Estrogen And Progestin Therapy:

Combined hormonal contraceptives and progestational agents appear to have limited efficacy in the treatment of uterine leiomyomas[8,9]. Most studies have evaluated these medications in conjunction with GNRH analogues. Oral contraceptives were associated with a significantly decreased mean duration of menstrual flow from 5.8 to 4.4 days and increased mean hematocrit from 35.8% to 37.8% and no significant difference in mean uterine size as noted by bimanual examination and ultrasound at 12 months. These drugs may be useful in some women with heavy menstrual bleeding, but they do not appear to be effective in decreasing bulk symptoms. There is one study that suggests that oral contraceptives started before age 16 may be associated with an increased risk of fibroids [10]

Regarding progestin studies have shown mixed results. Several have documented a decrease in the size of a myomatous uterus during progesterone therapy apart from reducing the amount of bleeding, increase in the hematocrit.

Levonorgestrel-releasing intrauterine system: is one of the options as a local treatment for menorrhagia and symptomatic myoma. An enlarged or distorted uterine cavity due to myoma or sub mucosal myoma amenable for hysteroscopy resection is a contraindication for LNG IUS [11]

Observational studies and systematic reviews have shown a reduction in uterine volume and bleeding, and an increase in hematocrit after placement of LNG IUS [12-15].There are no randomized trials evaluating the use of levonorgestrel-releasing intrauterine system (IUS) for the treatment of menorrhagia related to uterine leiomyomas. The device is a proven, effective, reversible treatment for menorrhagia and is now approved by the US Food and Drug Administration (FDA) for this indication. Contraception for women who do not desire pregnancy is another advantage. Sixty-seven premenopausal women with myomas of 12 weeks or less with menorrhagia and who desired LNG IUS for contraception were studied and found that LNG-IUS as an effective treatment for menorrhagia due to uterine myomas for such patients.[12]The levonorgestrel-releasing intrauterine system improves health-related quality of life significantly at relatively low cost. It is the most effective medical treatment for menorrhagia and comparable to surgical interventions. [16]

Progestin implants, injections, and pills - the effectiveness of progestin-only contraceptive steroids for treatment of leiomyomas is controversial. Progestin-only contraceptives cause endometrial atrophy and thus provide relief of menstrual bleeding-related symptoms. Hence they can be considered for treatment of mild symptoms, especially for women who also need contraception. Progesterone is a growth factor for myomas as in breast tissue and may even be more important than estrogen. Though there is consistent evidence from studies that these agents

may be associated with a decreased risk of leiomyoma formation [17,18] further studies are necessary to evaluate the current and long-term effects of these therapies.[19].

GnRH Agonists: It is an analogue of endogenous GnRH and binds to pituitary GnRH receptors (GnRH-R). This leads to synthesis and release of the luteinizing hormone and follicular stimulating hormones. GnRH agonist might be the most effective drug in the medical management of myomas. It has a half-life longer than GnRH leading to continuous exposure of GnRH-R to the activity of GnRH agonists. Downregulation of GnRH-R results in a decreased level of gonadotropins and reduced production of the ovarian hormone [20–22]. Ultimately GnRH agonists produce a transient menopausal condition.

The GnRH agonists cause reduction in the volume of myomas and the uterus [22]. The decrease in myoma volume ranges from27% to 70% [23-25] GnRH agonist contributes to the shrinkage of myoma volume by inducing a transient menopausal status thereby resulting in low estrogen and low progesterone. Subsequently, cellular changes like cellular atrophy, a decrease in cell proliferation, and reduced trophic mediators or uterine blood flow have also been described. Since GnRH agonist results in the menopausal status, menorrhagia can be alleviated [26] and myoma-related anemia can also be successfully treated.

The various forms of GnRH agonists are leuprolide, buserelin, nafarelin, histrelin, goserelin, deslorelin, and triptorelin. They maybe administered by different routes like intramuscularly, subcutaneously or by intranasalabsorption. Maximal reduction of uterine and myoma size is achieved within the first 12 weeks of therapy [26].Menorrhagia and related anemia are controlled in the first month of treatment and the pain and pressure symptoms relieved in the first 2 months. However, the effect of GnRH agonists on the reduction of myoma size is temporary. After discontinuation of GnRH agonist, it takes about four weeks for reversal of anti-estrogen effects [27]. Most myomas regain their initial size within about 6 months after stopping of GnRH agonist treatment. The rate of enlargement is also rapid compared with natural enlargement [28], and leads toa return of initial symptom

Advantages of GNRH –A : A systematic review[22] of 26 randomized controlled trials evaluating the use of GnRH in patients before hysterectomy and myomectomy concluded that the use of GnRH analogues for three to four months prior to fibroid surgery reduces both uterine volume and fibroid size. A midline incision can be converted to transverse incision and an abdominal procedure can be converted to a vaginal procedure. They are also useful in the correction of pre-operative iron deficiency anemia and also decrease intra-operative blood loss

The GnRH agonists have a greater effect in myomas with greater unbound progesterone receptors[29], and myomas which show increased blood flow by Doppler ultrasound [30]. In the management of myomas, GnRH agonists are currently assumed as an adjuvant therapy for preoperative preparation. The therapeutic effect of GnRH agonists is less pronounced in myomas with hypoechoic changes, [31] hyaline changes or in fibroids with collagenous tissue [32], Pedunculated or cervical fibroids [33].

Disadvantages: The significant disadvantages of GnRH agonists due to hypo -estrogenism-related effects namely postmenopausal hormonal deficiency symptoms and bone loss [34,35].Steroid "add-back "or reduced dose can restore the estrogen partially

Add back therapy: Oral veralipride, a benzamide derivative, can alleviatethe vasomotor symptoms [36]. Raloxifene or tibolone may be the ideal add back therapy to prevent bone loss while preserving the efficacy of GnRH agonists [37,38].Tibolone reduces hot flushes significantly.

GnRH antagonists:

The present indications for GnRH antagonists are to prevent premature LH surge in controlled ovarian hyper stimulation, in treatment of advanced prostate cancer. The GnRH antagonists suppress the GnRH release within four to eight hours of administration without flaring up. They compete with endogenous GnRH for the receptors on pituitary sites. The three commercially available GnRH antagonists are cetrorelix ganirelix and abarelix. The suppression of ovarian hormones starts at about 48 hours and the estradiol level falls to a minimum at about 1 week after administration.The response to treatment is

variable and shrinkage of myomas varies from 25% to50% in about 2 to 8 weeks.GnRH antagonists appear to be less reliable than predicted by the established usage of GnRH agonists.

Aromatase inhibitors:

Aromatase is an estrogen synthetase an enzyme expressed by myomas. Aromatase inhibitors appear to be a promising therapy for myomas especially if they can be adapted to act preferentially on myomas and not on ovarian estrogen synthesis. Ovarian estrogen synthesis is inhibited directly there by producing a hypo estrogenic state. The serum estrogen levels decrease within 24 hours in contrast to the flare up followed by hypo estrogenic state observed with GNRH antagonists.Further research is necessary on this group of medication in reproductive age population.

SERMs:

They are non-steroidal agents that bind to estrogen receptor and modulate its effects. they exhibit either agonist or antagonist effects depending on the target tissue. A study on tamoxifen for its effects on myomas has concluded that [39] it had only marginal benefits for treating symptomatic myomas and associated with unacceptable side effects.

Another SERM raloxifene was studied in post-menopausal women with a dose of 60mg/day compared with a placebo for a period of 12 months. A significant decrease in both uterine size and myoma size was noticed with minimal effect on normal myometrium (40.) A combination of raloxifene and GnRH agonists (41) showed a greater response when compared to GnRH alone. There was no noticeable change in bone mineral density and endometrium in about 18 months of study. The important adverse effect was hot flushes.

Progesterone receptor modulators:

Mifepristone is a progesterone receptor modulator which when bound with progesterone receptor acts as an antagonist. Myoma has greater concentrations of progesterone receptors than surrounding uterus. It mimics a state similar to that of early follicular phase, and also alters the vascular supply of myomas. [42]. The dose used was 12.5mg to 50mg /day. The most common side effect was vasomotor symptoms. Six clinical trials of mifepristone were reviewed by Steiner and colleagues' treatment for symptomatic myomas[42]. Though the studies were small, not placebo controlled or blinded and overall heterogeneous, they consistently demonstrated the effectiveness of mifepristone on mean myoma and uterine volume. Symptomatic relief from all myoma symptoms and 91% rate of amenorrhea was observed. But endometrial hyperplasia may limit the long term use of mifepristone in myomas.

Selective progesterone receptor modulators:

They demonstrate progesterone specific agonist or antagonist activity which is dependent on target tissue. Asoprisnil and Ulipristal are the two drugs widely studied. Asoprisnil is an SPRM which affects only endometrium with no effect on ovulation. The doses used in trials are from 5mg to 25 mg /day [43]. The exact mechanism has to be elucidated and further research is required to establish the usefulness of this novel therapy.Ulipristal acetate is also a selective progesterone receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without effecting estradiol levels or anti glucocorticoid activity.[43, 44]Ulipristal 5 mg and 10 mg and placebo was administered randomly in 2:2:1 ratio in women with heavy menstrual bleeding anemia and myomas for thirteen weeks. This was a randomized, double-blind, placebo-controlled, trial in six countries [45], in which the effectiveness in relieving symptoms, reducing myoma volume and adverse effects profile was studied. [46]

Ulipristal acetate (at a dose of 5 mg or 10 mg) for 13 weeks before planned surgery was successful in controlling menorrhagia, reduction in fibroid volume, and reducing pain and discomfort. Headache, discomfort, or tenderness in the breasts were the commonest adverse events in the ulipristal acetate group. Estradiol levels with ulipristal were maintained, in the midfollicular range.In contrast, GnRH agonists substantially reduce estrogen levels, with associated risks of bone loss. The endometrial proliferative changes observed were found to be reversible after 6 months.

Androgens:Two androgenic preparations danazol and gestrinone are widely studied in the

treatment of myomas. Gestrinone is a derivative of ethinyl –nortestesterone and has both antiestrogenic and antiprogesterone. Danazol has androgenic, moderate progestogenic, anti progestogenic and anti-estrogenic properties. The effect on myomas continues even after discontinuation of androgenic agents. The androgenic adverse effects are severe and unacceptable like weight gain,edema, hirsutism altered libido and rarely hepatocellular damage, fluid retention and spontaneous pregnancy loss which precludes their use.

Future directions:

An ideal medical therapy should not affect ovulation, implantation, and embryo development. Current medical therapies for myomas include systemic as well as local manipulation of ovarian steroid hormones both estrogen and progesterone apart from minimal systemic side effects. The future therapies may aim at transforming and targeting growth factors involved in angiogenesis or fibrosis.

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05

ART OF HYSTEROSCOPIC MYOMECTOMY- DO'S AND DON'TS

Dr Fessy Louis T
IVF Director & Laparoscopic Surgeon
AMMA IVF & Fertility Centre, Cochin

Dr Jay Mehta
Scientific Director
Shree IVF Clinic & Surrogacy
Mumbai

Uterine leiomyomas or fibroids are those benign masses that usually arise from the muscular part of the uterus. As they grow, they usually migrate to a place of lower resistance, towards the abdominal cavity, thus becoming subserous masses or following the path of the intrauterine cavity thus becoming submucous fibroids. Uterine fibroids seem to affect approximately 20-25% of the women in the reproductive age group[1].

Indeed, submucous fibroids may induce severe clinical symptoms such as excessive bleeding, usually during menses, colicky dysmenorrhea which is predominantly due to the uterus' effort to expel the fibroid out. Submucous fibroids also predispose these women towards a reduced fertility potential[2]. Furthermore, submucous fibroids are associated with chronic endometritis, they may have a greater risk for malignant change and are source of pre-term delivery, abnormal presentation, post-partum haemorrhage and puerperal infections[3].

Hysteroscopic myomectomy currently represents the standard minimally invasive surgical procedure for treating submucous fibroids. The first reported hysteroscopy myomectomy was performed in 1976, when Neuwirth and Amin resected a fibroid using a urologic resectoscope, monopolar current and 32% dextran 70 as distension medium. In 1987, reported on the development of a gynaecologic resectoscope, changing the urologic instrument

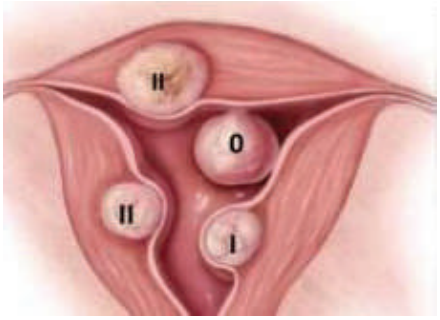
into a continuous-flow device with a 0° optic; cutting current was used but with 1.5% glycine as the distension medium.

Hysteroscopic classification of submucous fibroids:

The classification developed by Wamstaker et al and adopted by the European Society for Gynaecological Endoscopy (ESGE), which considers only the degree of myometrial penetration of the submucous fibroid, is currently used worldwide.

According to this Classification:

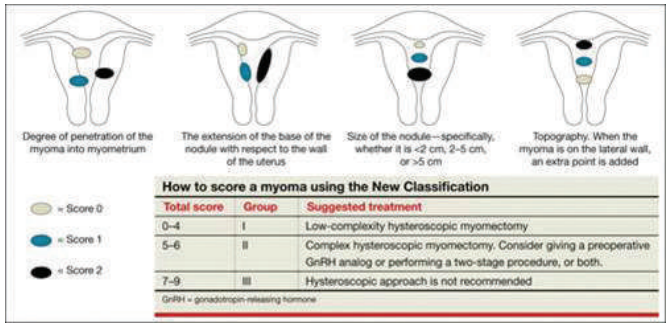
- G0- A fibroid which is completely within the uterine cavity and appears only joined to the cavity wall by a thin pedicle
- G1- A fibroid which has its larger part (>50%) in the uterine cavity
- G2- A fibroid has its larger part (>50%) in the myometrium.



Lasmar et al. in 2005[4]proposed a new preoperative classification of submucous fibroids which considers not only the degree of penetration of the fibroid into the myometrium, but also other parameters including the extension of the base of fibroid with respect to the wall of the uterus, the size of the nodule (cm) and the topography of the uterine cavity.

Lasmar's pre-surgical classification of submucous myomas

Points	Penetration	Size, cm	Base[a]	Third	Lateral wall (+1)
0	0	£2	£1/3	Lower	
1	£50%	>2–5	>1/3 to 2/3	Middle	
2	>50%	>5	>2/3	Upper	
Score	+	+	+	+	



It refers to the extension of the base of the nodule with respect to the uterine wall on which the myoma is located.

- Score 0–4 (Group I): low complexity hysteroscopic myomectomy
- Score 5–6 (Group II): complex hysteroscopic myomectomy, consider preparing with GnRH analogue and/or two stage surgery
- Score 7–9 (Group III): recommend an alternative non-hysteroscopic technique.

Surgical evaluation of submucous fibroids: The most widespread investigative techniques for pre-surgical evaluation are office hysteroscopy, transvaginal ultrasound scanning (TVS) and salinesonohysterography (SSG). SSG has been demonstrated to be superior to TVS in terms of diagnostic accuracy. It allows identifying the exact location of the fibroid as well as the portion protruding into the cavity. SSG could reduce the number of diagnostic hysteroscopies for pre-surgical evaluation. TVS is not as useful as hysteroscopy in assessing the degree of intracavitary development of the fibroid. However, it is irreplaceable in the preoperative assessment as it provides two elements, which would be otherwise unobtainable: the 'myometrial free margin' (thickness of the outer myometrial layer of the fibroid) as well as the presence of any other possibly associated pathology. For a submucous fibroid to be approached hysteroscopically, the 'myometrial free margin' should be at least 1 cm thick or in more expert hands at least a few millimetres thick[5]. In case of a large uterus, with multiple fibroids, or if ultrasound scanning is technically difficult (i.e. obese patients), magnetic resonance imaging (MRI) can provide valuable information, being also helpful in differentiating between fibroids and adenomyosis. Virtual endoscopy is a non-invasive technology used to

display the image of the cavity inside the organ by processing the images acquired by a multislice helical computed tomograph (CT) scanner using 3D computer graphics software as if one is observing the organ by real endoscopy.

Pre-Operative GnRH Therapy:

A recent review by Gutman and Corson[6] reported that 'the most clinically relevant indication for preoperative GnRH agonist use appears to be in patients with submucous fibroids'.

Benefits claimed include the following:

1. Resolution of preoperative anaemia: these drugs create a state of amenorrhea[7], thus enabling patients suffering from menorrhagia to build up their blood counts and reducing the need for transfusion
2. Reduction of endometrial thickness as well as the size and vascularization of fibroids. This results in an improved operator's visibility by limiting blood loss; furthermore, it leads to a reduced fluid absorption (through a reduction of uterine blood flow) and a reduced length and difficulty of surgery.
3. Surgical scheduling- as patients do not necessarily need to be operated in the early proliferative phase, preoperative treatment also has a practical benefit in that it allows surgery to be performed at any time[8].

Universally accepted guidelines on the indications and duration of pretreatment with GnRH agonist (administered either as a long-acting monthly intramuscular injection or with daily dosing) are lacking in the international literature.

Conversely, it is well known that the preoperative treatment with these drugs is associated with some disadvantages[9] including:

(i) high costs
(ii)(side effects (i.e. hot flushes, spotting)
(iii) increased recurrence rate (these drugs may render small fibroids less visible)
(iv) increased risk of uterine perforation (due to a reduced myometrial thickness)
(v)increased risk of the 'sinking' phenomenon (due to a decreased elasticity of myometrial tissue caused by estrogen deficiency).

Furthermore, one retrospective study suggests[10] that preoperative treatment with GnRH agonist does not seem to offer any advantage in terms of short- and long-term outcomes. In particular, those patients treated with GnRH agonist had significantly longer surgical times, compared with untreated patients, which has been ascribed by the authors to an increased cervical resistance to dilatation

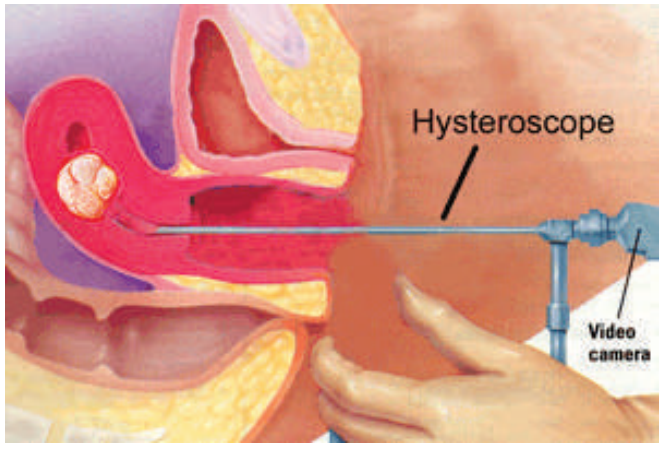
Indications for hysteroscopic myomectomy:

Submucous fibroids have been advocated more than subserous and intramural ones as a cause of AUB, presumably due to distortion of the cavity and to an increase in the bleeding surface of the endometrium.

Most women affected with fibroids are fertile, available evidence suggests that fibroids may interfere with fertility, with submucousal fibroids being reported to exert the most detrimental effects on pregnancy rates. Fibroids might interfere with sperm migration, ovum transport or embryo implantation; these effects might be mediated by alteration of uterine cavity contour causing mechanical pressure or by the occurrence of abnormal uterine contractility.Reproductive problems represent the second leading indication for intervention, though the lack of randomized studies does not allow any definitive conclusion to be drawn regarding the improvement of spontaneous fertility after hysteroscopic myomectomy.

Less frequent reported indications include dysmenorrhea, aspecific pelvic pain and asymptomatic submucous fibroid in a woman candidate to start hormone replacement therapy.

Hysteroscopic Instruments:



The operating hysteroscope (resectoscope) is the instrument that allows the performance of a submucous myomectomy under direct and

constant visual control. It includes a straight-forward telescope (0°) or a slightly fore-oblique 12–30-° telescope with an outer diameter of 3–4 mm; an internal and an external sheaths of 24–27 Fr outer diameter that provide a constant inflow and outflow of distension fluid for generating a continuous and efficient lavage system of the uterine cavity. The operating hysteroscope contains a working element wherein electrosurgical loops or the morcellator can be attached.

The electrosurgical system can be monopolar or bipolar:

- In the monopolar one, from the extremity of the resectoscope (active electrode) the flow of current, in order to close the circuit, must reach the plate (passive electrode). The use of monopolar electrodes requires non-conducting distending solution (sorbitol 5% or glycine 1.5%).
- In the Bipolar both the electrodes are on the same probe and thus the current will only have to pass through the tissue with which the thermal loop comes into contact, thus minimizing the danger deriving from the random passage through the corporeal structures. An intrauterine bipolar diathermy allows the use of an electrolytic uterine distension medium (normal saline).

There are various types of thermal loops with different shapes and sizes.

The diameters of thermal loops for bipolar resectoscopes are usually smaller than loops for a monopolar instrument with the same outer diameter, thus increasing the time required for resection.

The bipolar loop operates in a similar way to a monopolar electrode; however, as tissue contact is not necessary for activation, the electrodes do not 'stick' in the tissue while cutting

Anesthesia:

Resection of small myomas<1.5 cm can be performed using office hysteroscopy without anaesthesia , the majority will necessitate anaesthesia. Regional anesthesia is more preferable to general anaesthesia as it allows us to monitor the level of consciousness of patient which can be affected in cases of fluid overload.

Resection of G0 Fibroids[11]:

Pedunculated myoma: The pedicle can be resected using scissors, or electrosurgical loop and then the detached myoma can be extracted with the forceps through adequately dialated cervix. But sometimes if you resect the pedicle completely the myoma will float in the uterine cavity and it may not get held with the forceps. So partially detaching the pedicle followed by avulsing the myoma with forceps helps in easy removal of the pedunculated submucous myoma. Alternatevely, the detached myoma can be left in place to be delivered spontaneously during the first menstruation following surgery. However, this can result in continuous colicky pain and intrauterine infection.

GO Fibroids with a broader Base:

Intracavitary myoma is repeatedly and progressively sliced from its top towards its base using the cutting loop of resectoscope. In slicing technique the movement of the loop is towards the cervix. Slicing is started from beyond the myoma with the cutting or shaving takes place during backward or return movement of the loop. The resulting fragments can be pushed away from the myoma till they accumulate and interfere with proper visualization, at which the time the fragments can be removed from the uterine cavity by withdrawing the resectoscope with its loop electrode grasping the loop fragments. In cases with large myomas, removal of tissue fragments requires longer time, which is technically demanding. Recently, a resectoscope with automatic chips aspiration has been developed allowing immediate aspiration of the chips without impairing the fluid distension of the uterus. The resection should be stopped when the myoma bed is visualized or when the softness of the muscular tissue is palpated with the inactivated loop, signaling the termination of the resection.

Intrauterine morcellation:

The hysteroscopic morcellator, uses mechanical cutting to reduce the size of the tumour into small pieces and subsequently evacuating these pieces and out of the uterine cavity by aspiration. It has been reported to be safe and effective. Also it is a novel technique to remove intrauterine myoma of grade 0 or 1. The hazards of distension media, risks for perforation and the limitations of the visual field created by resected tissue fragments, all combined to the development of intrauterine morcellation[12].

Resection of G1 and G2 Fibroids: It is advisable to seek help from an expert hysteroscopic surgeon

while treating these fibroids. Though available literature suggests that the resection of large fibroids is possible, the size of these fibroids should be limited to 5-6cm

Two-Step Technique[13]:

Though the initial description of the this technique has been done with the help of using a laser, At present, most surgeons prefer to remove a fibroid through a two-steps procedure, by means of traditional resectoscopic surgery. The technique consists of the following steps:

- First surgical operation: excision only of the intracavitary portion of the fibroid, by means of the usual progressive resectoscopic excision. A hysteroscopic reassessment is carried out 20–30 days after the operation or after the first menstruation to verify that the intracavitary migration of the residual intramural component of the fibroid has taken place: once this has been verified, the second operation can be done.
- Second surgical operation: complete excision, by means of slicing, of the residual component of the fibroid, which has now become intracavitary.

Complications[14]:

Hysteroscopic myomectomy is one of the most advanced operative hysteroscopic procedures as it is associated, particularly for complex cases, with a significantly higher rate of complications than other hysteroscopic procedures. Reported data show a rate of complication ranging from 0.3 to 28%, fluid overload and uterine perforation being the most frequent complications occurring during surgery. Other intraoperative complications include bleeding, cervical trauma and air embolism, while late complications include post-operative intrauterine adhesion and rupture during pregnancy.

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06

INFERTILITY, ART AND **FIBROIDS**

Dr. NanditaPalshetkar

Various synonyms are used to refer to fibroids like myomas, leiomyomas, leiomyofibromas, fibroleiomyomas, fibromyoma. Of all, fibroid is the term most commonly used.

Uterine leiomyomas are the most common benign gynaecological tumours of the uterus and the female pelvis occurring in almost 60-80% of women[1].They are clonal tumours as they arise from a single smooth muscle cell of the uterus and they contain increased extracellular matrix (ECM). 80% fibroids are asymptomatic, incidentally diagnosed on clinical examination or radiological investigation. Around 20% fibroids are symptomatic[1]. They are present in 5-10% of infertile women, but solely responsible for infertility in 2-3% cases [2,3]. Symptomatic leiomyomas are the most common indication of hysterectomy, thus increasing the morbidity, mortality and also causing a huge impact on the economic burden on our healthcare system.

Grossly, leiomyomas are firm, rubbery and on cut surface display whorled pattern of the muscle and fibrous tissue. They are distinct from the surrounding myometrium because of a thin outer connective tissue layer and this arrangement makes it easy for them to be easily "shelled out" during surgery. Thus they are well circumscribed but not encapsulated.

Fibroids are estrogen dependent tumours. Factors which increase and decrease its incidence are as follows (Table 1):

Table 1

Increased leiomyoma risk	Decreased leiomyoma risk
Early menarche	Pregnancy
African-American race	Post menopause
Affected family member (heredity)	Smoking
Obesity	Low dose oral contraceptive pills
Nulliparas	
Delayed pregnancy	
Diabetes Mellitus	
Hypertension	
Polycystic ovary syndrome	
Exposure to diethyl stilbestrol (DES) and phthalates	
Alcohol intake	

Symptomatology:

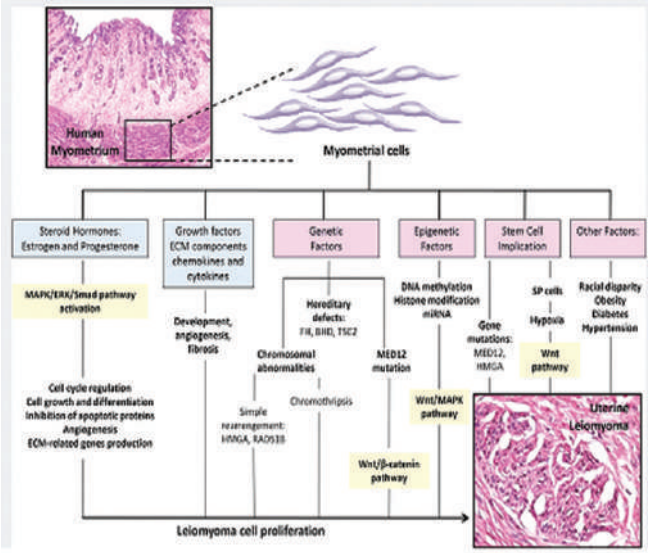
In case of watchful expectancy for asymptomatic fibroids, one must be completely sure of the origin of the tumour – whether uterine or ovarian especially in a case of lateral wall fibroid which may present as an adnexal mass. In case of any doubt, it must be removed as one may miss an early ovarian cancer. Also if there is any evidence of pyelographic damage of the kidney in an asymptomatic fibroid, then also it must be removed. There is no uniform size of an asymptomatic fibroid which is an indication for myomectomy/hysterectomy. In the past, it was recommended to surgically treat asymptomatic myomas whose uterus size exceeded more than 12 weeks, but the recommendations were based on assumptions that have since then been effectively refuted[4,5].

Mechanisms by which leiomyomas adversely affect fertility are as follows[5]:

1. Displacement of the cervix which reduces the exposure to the sperm.
2. Increased surface area or deformity of the endometrial cavity which interferes with the sperm migration and transport.
3. Endometrial vascular changes like venous congestion, venuleectasia, impaired blood flow and endometrial changes like atrophy, ulceration, focal hyperplasia and polyps causing disruption of endometrium and implantation
4. Endometrial inflammation or secretion of vasoactive substances.
5. Altered/impaired vascular perfusion
6. Increased uterine contractility which may affect sperm or embryo transport or implantation
7. The proximal fallopian tubes may be obstructed by the impingement of the fibroid
8. Alteration of the tubo-ovarian anatomy which interferes with the ovum pick up by the tube
9. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity - global decrease in endometrial HOX gene expression. (*Rackow BW, et al, Fertil Steril. 2010 Apr)*
10. Anovulatory cycles are more common with fibroids

Pathogenesis: diagram representing different theories involved in the pathogenesis of uterine leiomyomas[6] [Figure 1]

Figure 1



(FH: Fumaratehydratase, BHD: Birt Hogg Dube syndrome, TSC2: Tuberous sclerosis, Med 12: Mediator complex subunit 12, HMG: High mobility group proteins, SP: side population)

Targeting these leiomyoma stem cells may be the best long term choice for developing therapies to treat this disease.

Classification:

Numerous classifications for submucous fibroids have been developed as follows:

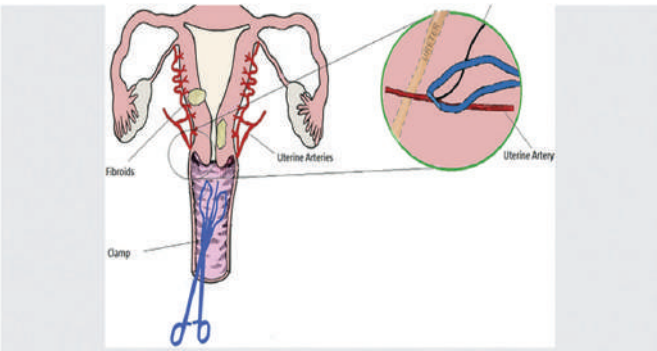
A) The classification developed by Wamsteker et al (1993)[7] and adopted by the European Society for Gynaecological Endoscopy (ESGE) takes into

consideration only the degree of myometrial penetration by the submucous fibroid.
G0: pedunculated intrauterine myoma
G1: has its largest part >50% in the uterine cavity
G2: has its largest part >50% in the myometrium
B) Lasmar et al (2005) [8] proposed a preoperative classification of submucousmyomas which considers not only the degree of penetration of the fibroid into the myometrium, but also other parameters like extension of the base of the fibroid with respect to the wall of the uterus, size of the nodule (cm) and the topography in the uterine cavity (Table 2)

Table 2

Points	Size	Topography	Extension of the base	Penetration	Lateral wall (+1)
0	<2	Lower	</= 1/3	0	
1	2-5	Middle	>1/3 to 2/3	</= 50%	
2	>5	upper	>2/3	>50%	
Score	+	+	+	+	+

Total score calculated
Score 0-4: Group I = low complex hysteroscopic myomectomy
Score 5-6: Group II = complex hysteroscopic myomectomy. Consider preparing with GnRH analogue and/or two stage surgery
Score 7-9: Group III = an alternative non-hysteroscopic technique is recommended
C) More recently, the Federation of Gynecology and Obstetrics (FIGO) classification was published describing 8 types of fibroids including a hybrid class (association of two types of myomas)[9]. This classification offers a more representative map of fibroid distribution. (Figure 2)



Transvaginal uterine artery occlusion. Clamp is placed on the lateral aspects of the cervix, using Doppler ultrasound to identify uterine artery pulsation.
Patel. Novel and promising leiomyoma treatments. Fertil Steril 2014.

Figure 2
Management: Effects of fibroids on IVF outcome[10]:

Some investigators found that uterine myomas have no effect on IVF outcomes until and unless they distort the cavity[11,12].

Other investigators found that the IVF success rates are lower in women with intramural myomas[13], especially if they were larger than 5 cm[14].

Studies have shown that IVF outcome success is markedly improved in women with cavity distorting submucous fibroids following myomectomy[15,16].

What about the effect of fibroids which are not distorting the uterine cavity on the outcome of IVF treatment? This remains poorly understood. In a systematic review and meta analysis by Sunkara et al which included 19 observational studies comprising 6087 IVF cycles, the presence of non-cavity distorting intramural fibroids reduces significantly the live birth rate (LBR) by 21% and the clinical pregnancy rate by 15% per IVF cycle compared with no fibroids. This demonstration of reduction in results does not mean that their removal will restore the LBR to the levels expected in women without fibroids. This does not justify in advocating routine myomectomy for these women as a favourable risk benefit analysis for this is currently lacking[17].

In a retrospective cohort study by Yan L et al which included 249 patients with non cavity distorting fibroids who underwent IVF/ICSI cycles, there was no difference in the IVF/ICSI outcomes, but intramural (IM) fibroids > 2.85 cm in size significantly impaired the delivery rate (DR) of patients undergoing IVF/ICSI. Small fibroids </= 2.85 cm do not affect the main IVF outcome including the clinical pregnancy rate (CPR), miscarriage rate (MR) and DR[18].

Currently it is not possible to achieve consensus regarding the surgical treatment of intramural (IM) fibroids which do not cause mass effect on the uterine cavity[19].

Bulletti et al suggested that before IVF/ ICSI, myomectomy improved the pregnancy outcomes in infertile women with submucous (SM)/ IM fibroids > 5 cm[20].

To summarize the management[10]:

1. Subserous fibroids do not affect fertility or spontaneous abortion and their removal does not confer any benefit.
2. Submucousmyomas lower the fertility rates and their removal increases the chances of conception and live births.
3. Even if intramural fibroids do decrease fertility, it is not proven that their removal will normalize fertility or even be beneficial to the patient.

Medical management: Indicated in women to correct anemia prior to surgery, for those women who do not want to undergo surgery, those not fit for surgery and for those who want a uterus sparing therapy[21].Different classes of drugs are available like progestins, SPRMs, SERMs, aromatase inhibitors, GnRH analogues and other therapy like green tea, Vitamin D which have been covered in the earlier chapter.

Surgical management[22]: In case of symptomatic myomas, myomectomy is clearly indicated.

1. Laparoscopic myomectomy is indicated in:
a. Myomas< 10-12 cm in size
b. No more than 3 to 4 intramural myomas
c. Intramural myomas> 3-5 cm in size with cavity distortion in cases of infertility
2. Hysteroscopic myomectomy is indicated in cases of:
a. Submucousmyomas</= 5 cm in size
b. Partially submucous intramural myomas> 5-6 cm in size (two steps)

Laparoscopy versus laparotomy[23]?

In a randomised controlled trial comparing laparoscopy versus laparotomy in 131 women[24], there was no difference in the fertility outcomes (abortion and ectopic pregnancy rates, preterm delivery, uterine rupture, Caeserean section), while some non-fertility advantages were documented in the laparoscopy group since these women had significantly decreased febrile morbidity, lower haemoglobin drop yet not resulting in different blood transfusion rates and shorter hospitalization.

An RCT by Rossetti et al[25] evaluated the long term outcomes in laparoscopic and abdominal myomectomy which showed that the recurrence rate was not significantly different in the two groups.

Laparoscopic myomectomy is associated with less adhesion formation[26].

Is there any role of pre-op GnRH analogues prior to Laparoscopic myomectomy?

It is not routinely required and is a useful tool for correction of anemia and to obtain shrinkage with consequent optimal mobilization of a single and very large myoma.

Key points for laparoscopic myomectomy[23]

1. In case of previous abdominal/pelvic surgeries where adhesions would be expected, or where uterus is > 14 weeks size, supraumbilical port or at Palmer's point (mid clavicular under the left lower rib) can be used.
2. Controlled hypotensive anaesthesia, modified Trendelenberg position and diluted vasopressin (10 U in 100 ml NS) can be used to reduce haemorrhage
3. Sharp and blunt dissection to be maintained in the plane of cleavage
4. Horizontal incisions on the uterus minimize the blood loss and suturing is also easy.
5. Depending on the depth multi layered suturing may be required
6. All fragments of the fibroids should be removed to avoid iatrogenic parasitic myomas
7. Adhesion prevention barriers like Interceed, etc may be used

One must wait for 3-6 months before planning to conceive.

Hysteroscopic myomectomy:

Is there any role of GnRH agonists prior to Hysteroscopic myomectomy?

A review by Gutmann and Corson[27]has reported that GnRH agonist appears to be beneficial in patients with submucous fibroids. Benefits are improvement of pre-op anaemia, decrease in fibroid size, reduction in endometrial thickness and vascularity thus improving the visibility and and reduced fluid absorption and the possibility of surgical scheduling.

The electrosurgical system can be monopolar or bipolar. The use of monopolar electrodes requires the

use of non-conducting distending solution like glycine. The use of bipolar electrodes allows the use of normal saline.

Hysteroscopic techniques for G0 fibroids[28]
1. Slicing during resectoscopic myomectomy: most commonly used with the help of resectoscope. Procedure to be stopped when the fasciculate fibres of the myometrium are seen 2. Cutting the base of pedunculated fibroids and extraction by forceps or left in situ 3. Office hysteroscopic myomectomy by Bettochi et al for fibroids </= 2 cm[29] 4. Morcellation by intrauterine manipulator 5. Ablation by Nd:yAG laser for fibroids smaller than 2 cm 6. Vaporization of the fibroid by CO2 laser. Disadvantage of 5 and 6 is that there is no tissue available for Histopathological diagnosis

Hysteroscopic techniques for G1 and G2 fibroids[28]
1. Excision of only the intracavitary component (not recommended) 2. Excision by two step procedure for G1/G2 or type 1/2/3 of FIGO 3. One step procedure by slicing with help of resectoscope, cold loop myomectomy, incision on the myoma followed by slicing, hydromassage/manual massage followed by resection 4. Office hysteroscopic myomectomy for fibroids </= 2 cm by Bettochi et al[30]. Here the fibroid is separated with the help of grasping forceps or scissors.

Complications of hysteroscopic myomectomy include Bleeding, cervical trauma, perforation, fluid intravasation and electrolyte imbalance, post op adhesions and uterine rupture during pregnancy

American Association of Gynaecology Laparoscopy (AAGL) recommendations for minimising hystero scopic complications:
1. Post-op bleeding may be reduced by PGF2alpha/ tamponade with inflated balloon catheter 2. Distension media complications can be reduced by monitoring fluid deficit. One must stop surgery if deficit of > 1500 ml and serum sodium levels </= 125 mmol/L 3. Thermal injury can be decreased by activating the electrosurgical unit only when contact with the tissue is there and by not using high voltage current 4. For intrauterine synechiae, one must always do a relook hysteroscopyafter a month or after the next menses

According to some authors, the interval between uterine operation infringing on the myometrium and attempts for pregnancy should not be less than one year from the date of uterine surgery[31].

Newer modality: [32]Robot assisted surgery is a relatively new innovation in laparoscopic surgery that enables the surgeon to conduct the surgery from a computer console which is situated away from the surgical table. The first telerobot, called Zeus, was developed in 1995. The da Vinci robot was developed in 1998 with a 3D stereoscopic vision. The US FDA approved the da Vinci Surgical system for gynaecological surgery in 2005. There are various advantages of the robotic system like the robot's ability to filter and reduce physiological tremor, 3D HD visualization by the camera and assessment of deep areas, micro-motion of the instruments with 360 degree amplitude and 7 degree freedom, comfortable to the surgeon avoiding any occupational injury, facilitated dissection and easy suturing with a short learning injury. The robotic technique facilitates the combination of microsurgery principles into fertility promoting procedures. The main limitation is the cost. RCTs are lacking.

Minimally invasive interventions:

Magnetic resonance guided focused ultrasound (MRgFUS): MRgFUS is a conservative, non invasive, thermoablative technique for symptomatic myomas.It was US FDA approved in 2004. Patients with contraindications to MRI evaluation, such as those with cardiac pacemakers, sensitivity to MRI contrast,or above the weight limitation of the MRI scanner, are notcandidates for this intervention. Obese patients are particularlydifficult to treat, as an increase in subcutaneous tissuemakes it difficult to focus the ultrasound beam on the desiredtarget. The depth is limited to 12 cm from the skin surface[33].Also it is not suitable for women with myomas near sensitive organs like bowel, bladder or behind scar tissue.Rabinovici et al[34]reported 54 pregnancies in 51 women, afterMRgFUS treatment for myomas. Average conception timewas 8 months after treatment. Twenty-one women had successful pregnancies, whereas 14 had spontaneous abortions,and 6 had elective abortions.This technique is promising as a treatment option for womenwho still want to have children, however; additional studies are needed, to evaluate safety profiles.

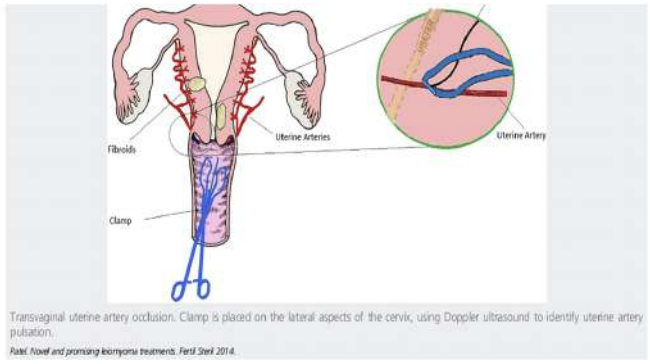
Cryomyolysis[33]: This technique involves a probe with a cooling agent to temperature as low as -180 degrees applied to the myoma, causing coagulation of the supporting blood vessels. Thus the blood supply is diminished resulting in necrosis.Whole procedure takes

1-3 hrs. Not US FDA approved till date.Can be done USG guided or laparoscopically.

Radiofrequency ablation[33]: It is minimally invasive.Uses heat produced by oscillations of high frequency alternating with an electric field, creating local tissuedamage and subsequently coagulation necrosis of the area.Ablation temperature is between 85 – 100 degrees.it is done by USG guidance or laparoscopically. US FDA approved since 2008to ablate tumours though more research has been done for lung tumours. Complete ablation of 3 cm myoma takes 5 mins whereas a 5 cm myoma takes 10 mins. Drawback: no real time monitoring to avoid injury to surrounding tissue. More extensive research with larger populations is needed to validate the efficacy and safety of radiofrequency ablation

Temporary transvaginal occlusion of uterine arteries[33]: (Figure 3)It is a non incisional and minimally invasive procedure done on OPD basis, taking 6-8 hrs. No clear status with FDA. Mechanism: temporary occlusion of uterine vessels, resulting in myoma ischemia and thus myoma infarction and later necrosis. Therefore there is decrease in uterine volume as well as improving various symptoms. It is done under GA or epidural anaesthesia. Inclusion criteria include women more than 18 yrs and those who have completed their childbearing.

Figure 3



Transvaginal uterine artery occlusion. Clamp is placed on the lateral aspects of the cervix, using Doppler ultrasound to identify uterine artery pulsation.

Patel. Novel and promising leiomyoma treatments. Fertil Steril 2014.

Uterine Artery Embolization (UAE)[5]:(Figure 4 and 5)

UAE has been used for the treatment of fibroids since the early 1990s. It should be used only for the management of symptomatic fibroids. Patients with pelvic infection, subserouspedunculated fibroids, undiagnosed pelvic mass, severe contrast allergy, prior pelvic surgery/ radiotherapy or coagulopathies are not likely candidates. Several small series have reported that UAE reduces the overall size of the uterus and that of dominant myomas by 40-50% in approximately 90% cases[35,36].Adverse events include contrast allergy (1%), puncture site haematoma, radiation exposure, transcervical fibroid expulsion, amenorrhoea and premature menopause, infection and post-embolization syndrome manifesting as low grade fever, malaise, pelvic pain, nausea and vomiting which requires symptomatic treatment.Successful pregnancies after UAE have been described, but data relating to fertility and pregnancy outcomes after UAE are limited. In a study by Homer et al, the risk of miscarriage increases sfter UAE. In contrast, apart from an increased risk of C-section and PPH, adverse obstetric sequalae like IUGR and prematurity are not likely after UAE[37]. UAE as a treatment of fibroids in women wishing to preserve their fertility should be undertaken with full disclosure to the patient about the limitations of such a procedure and the lack of existing data regarding future fertility and pregnancy outcomes[38].

Figure 4

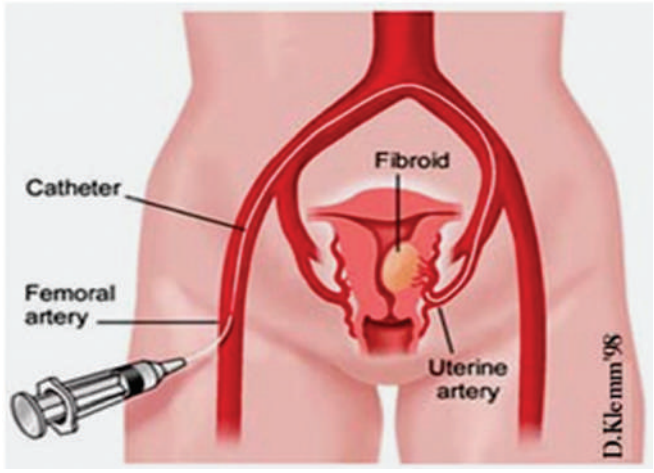
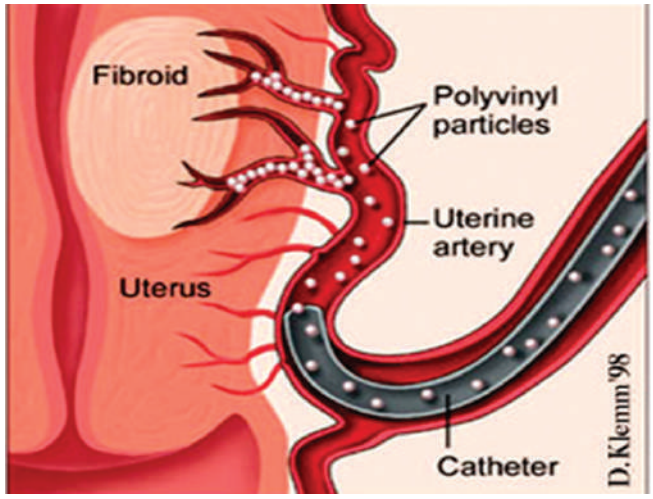


Figure 5



According to ASRM 2008, UAE, myolysis and MRgFUS should not be recommended to women with myomas seeking to maintain or improve their fertility

because their safety and effectiveness in such women has not been established.

Conclusion: Overall evidence suggests that fibroids are solely responsible for infertility in a small proportion of women. Removal of fibroids which impinge upon the cavity and large intramural ones must be removed. One must use a precise surgical technique while performing a myomectomy so that the future fertility is not hampered.

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07

UTERINE ARTERY EMBOLISATION : MYTHS AND REALITIES IN THE MANAGEMENT OF **FIBROIDS**

Dr P.K. Shah
Professor (OBGY Department)
Seth G. S. Medical College and
K E.M. Hospital

Dr Lovely Jethwani
(MD OBG)
Senior Resident
Seth G. S. Medical College and
K E.M. Hospital, Mumbai

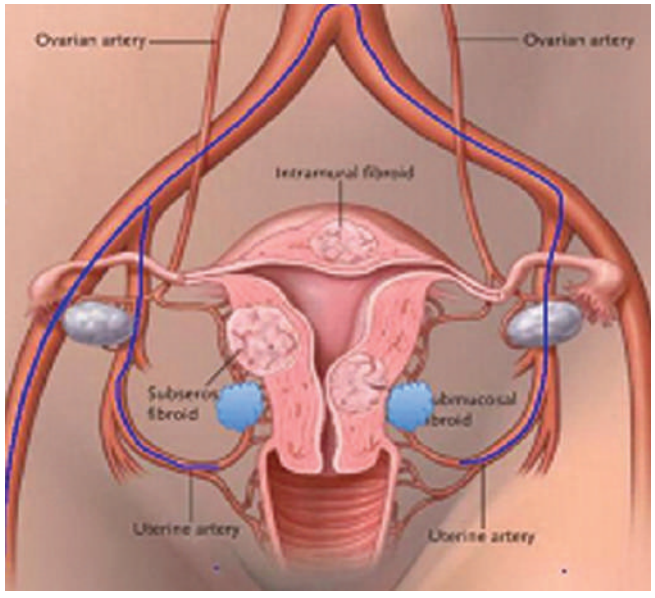
INTRODUCTION:

Uterine fibroids are the most common benign tumors of the female genital tract. Their prevalence increases with age, ranging from 20 to 40 % before the age of 35 and up to 70 % in the African American population after 50 years of age[1]. Fibroids when symptomatic can present with abnormal uterine bleeding, pelvic pain, pressure symptoms and fertility problems. With the rise of the age of first conception, symptomatic fibroids are found frequently in women with a desire of future pregnancy. Until recently, with all medical treatments being contraceptive, surgical myomectomy was the only therapeutic option available for women with symptomatic fibroids wishing to conceive.[2] However, when fibroids are numerous and extensive, a uterus-sparing surgical treatment may be associated with peri- or post-operative hemoperitoneum, recurrence requiring surgical revision and blood transfusion[3], and the risk of emergency hysterectomy[4] or intra-abdominal adhesion formation[5] which also adversely affects fertility. Moreover, for women who had completed childbirth but wished to retain uterus for socio- psychological causes; had paucity of options for effective surgical management. Preventive occlusion of uterine arteries was described during surgical myomectomy as one of the procedures addressing these issues.[6] Since the late 1990s, uterine artery embolization (UAE) has been developed as a new non invasive uterus-sparing therapeutic alternative [7]. However, this modality has been steeped in controversy since its inception, with

misconceptions galore amongst the patient population; as well as various concerns, and the treating gynecologists. This article attempts to clear the air on some of these issues and recite relevant literature and latest guidelines.

UTERINE FIBROID EMBOLISATION:

UAE is an image-guided, minimally invasive procedure done by a trained specialist, most commonly an interventional radiologist in a cath lab or occasionally in the operating room. A sheath is placed into either the right or left common femoral artery. Under fluoroscopic guidance, a flush catheter is advanced into the abdominal aorta. A pelvic angiogram is performed to identify the right and left uterine arteries; ovarian, lumbar, or other collateral parasitic supplies to the fibroid. Once identified, the uterine arteries should be selectively catheterized with a 4 Fr or 5 Fr catheter.The embolic agent such as polyvinyl alcohol (PVA)/Gelfoam/microspheres,(with a diameter in the range of300–750 micrometres, with larger sizes preferred) is injected directly into both the uterine arteries to induce thrombosis.[8]



WHEN TO DO AND NOT TO DO?

In the past, uterine artery embolization for fibroid management was used only to reduce operative blood loss during myomectomy.[7]The first experience with conservative Uterine Fibroid Embolisation (UFE) was published by Goodwin et al in 1997.[9]

UAE is recently indicated as a conservative management for symptomatic fibroids in women who desire treatment; in women in whom surgery is contraindicated or are at high risk for complication during prolonged surgery, or there is history of previous unsuccessful surgery for fibroids. Occasionally women may be referred for UAE for fibroids causing infertility (but without other symptoms). The use of UAE in this situation should be considered with caution after assessment and treatment under the care of a gynaecologist with an interest in assisted reproduction and fertility. Women who wish to opt for a 'uterus conserving' and 'minimally invasive' procedure inspite of not desiring future childbirth, are candidates too.[10]It should not be done in case of active infection in the genital tract, serious doubt as to the diagnosis due to clinical factors or inadequate imaging, asymptomatic fibroids, pregnancy and where a patient would refuse a hysterectomy under any circumstances– even after appropriate counselling that it may be necessary after UAE in only a small proportion of cases.[10]

UAE: MOST PREVALENT MYTHS AND THEIR EVIDENCE BASED REALITIES :

There are certain myths related to UAE, some were based on the results of previous studies and some of them were prevalent without any evidence. All of them being addressed in the following points along with the recently updated evidence based results of the respective studies:

MYTH 1: Many gynecologist are still not advising the embolotherapy because of their doubt about its EFFICACY as compared to the more invasive surgical techniques - hysterectomy and myomectomy.

REALITY: It has been proved that around 80–90% of patients will be asymptomatic or have significantly improved symptoms at one year with an associated 40–70% reduction in fibroid volume.[11]NICE (National Institute of Health Care & Excellence) issued updated guidance in November 2010 stating that the procedure is efficacious for symptom relief in the short and medium term for a substantial proportion of patients [12]. The UK HOPEFUL study (n=1,108)[13] is also a large retrospective study comparing UAE with a matched hysterectomy cohort. The mid-

and long-term advantages are similar, although there is a higher reintervention rate after UAE.

MYTH 2. It is not considered a SAFE technique because of a panel of complications associated with the procedure.

REALITY: Yes, there are complications associated with UAE, most common and benign being the POSTEMBOLISATION SYNDROME (pelvic pain, nausea, low-grade fever and malaise) which lasts for 3-8 days. Symptomatic treatment with opioid analgesics, NSAIDS & antiemetics suffice in most patients. Prolonged (over ten days) and deteriorating symptoms should raise the suspicion of infection for which readmission may be required for parenteral analgesia and fluid resuscitation. Other risks include allergic reactions to iodinated contrast (rare & idiosyncratic to the patient), infection (1% to 2%), ovarian dysfunction (<10%), pain (5% to 10% at >2 weeks), transient (15%) or permanent (3%) amenorrhea, hysterectomy (1% to 2%), Non-target embolisation (particles reaching other vascular beds) inadvertent ovarian embolization or embolisation of a malignancy, and extremely rare hemorrhagic complications related to femoral arterial catheterization (groin haematoma, arterial thrombosis, dissection and pseudoaneurysm). Risk can be minimized through careful patient selection and consultation with gynecologists and interventional radiologists.[14] Overall, UAE is believed to be a safe and effective procedure and is endorsed by ACOG in its practice bulletin published in 2008 (level A recommendation).

MYTH 3: Complications of UFE are more and frequent compared to surgical interventions

REALITY: Unlike surgical treatments for fibroids, most complications of UAE occur more than 30 days after the procedure. They can occasionally occur over a year (up to four years) after the procedure. In FIBROID registry, the incidence of adverse effects in first 30 days was low, and major complications in the hospital and 30 days postdischarge were uncommon (0.66 and 4.8 percent, respectively).[15]There is no need of blood transfusion and general anesthesia in UFE unlike their need in surgery.

Uterine Artery Embolisation v/s Hysterectomy/ Myomectomy:-[6,9,16]

	UAE	Hysterectomy	Myomectomy
Symptom relief	Short & Medium term	Long term	Long term
Hospital stay	Short	Longer	As per surgical approach
Recovery	Fast	Lower	Slower
Complications	After discharge	Mostly before discharge	Before discharge
Reintervention rates	High	None	Low
Cost	Cheaper	Costly	Costly
Uterine sparing	Yes	No	Yes
Fertility	No	No	Yes

MYTH 4: UAE causes Sexual dysfunction.

REALITY: The influence of UAE on sexual function is also a matter of hot debate. Theoretically, sexual function could be impaired because of vaginal discharge or interruption of blood supply to the clitoris, cervix and uterus by the embolic procedure. Sexual function after UAE has been reported as being improved in 26% of women, worse in 10% and unchanged in the remainder.[17] There is no difference in measures of sexual function or body image at two years between patients undergoing UAE or hysterectomy.[18]

MYTH 5: UFE causes menopause / premature ovarian failure

REALITY: Transient amenorrhea may occur in the presence of normal hormone levels secondary to endometrial atrophy with a spontaneous return to normal menstruation within 3-6 months. Non-targeted may result in thrombosis of the ovarian artery, ovarian ischemia/infarction. This might hasten the onset of menopause in older women with less ovarian reserve; in younger women, the changes might affect fertility. But, recently a subgroup analysis from the EMMY trial indicated UAE and hysterectomy affect ovarian reserve equally, as assessed by FSH and LH assay.[19]

MYTH 6: UAE is a replacement for myomectomy for conservation of fertility and future childbirth.

REALITY: While pregnancy and childbirth do occur after UAE[20], impaired fertility and reproductive outcome is reported. Obstetric risks after UAE for fibroids include prematurity, intrauterine growth restriction, abnormal placentation, and increased likelihood of cesarean delivery.[14] Amenorrhea due to adverse effects of

Authors	Treated women	Mean age at embolisation	Obtained pregnancies	Time to conceive (months)	Pregnancy outcome
Ravina et al (2000)	184	36	12	13	5 miscarriage, 3 vaginal birth , 4 cesarean section
Pelage & walker (2002)	400	-	13	-	2 miscarriage, 1 MTP, 8 vaginal birth, 1 cesarean section
Carpenter & Walker(2005)	671	37	26	30	7 miscariage, 2MTP, 2 vaginal birth, 14 cearean section, 1 ectopic pregnancy
Mara et al (2008)	58	32.4	17	18	9 Miscarriage, 1MTP, 1 ectopic,2 vaginal birth, 1cesarean, 1ongoing pregnancy
Redecha et al (2013)	98		8	13	1 misacrriage, 6 vaginal birth, 1 cesarean

UAE on the ovarian reserve[20,21]or on the endometrial volume [22] has been recorded.

A recent prospective cohort study included 66 women who desired a future pregnancy and were treated with UAE for symptomatic fibroids. The women were prospectively followed, and 31 of them (aged 37.3+3.5 years) were actively trying to conceive. In spite of 33.4+14.5 months of attempts, only 1 in 31 women became pregnant and she finally miscarried (monthly fecundability rate 0.1% 95% CI 0–0.3%). Besides the associated confounding infertility factors in the population, UAE might have had a negative impact on fertility in that population, which may not be related to ovarian function.[19] Mara et al reported that although UFE is less invasive than myomectomy and as effective for controlling symptoms, reproductive outcomes appear to be superior in myomectomy patients[23] For these reasons, myomectomy remains procedure of choice for women who would want to bear children in future and UAE remains relatively contraindicated for them.

A large number of similar studies done in the past showing adverse effects on fertility and pregnancy outcomes after UFE given in table no. (1)[24]

MYTH 7: *Fibroid embolisation* damages the 'normal' *uterine* tissue along with fibroid

REALITY: Embolising agent like PVA particles initiates a foreign-body reaction into the lumen of the uterine arteries, thence platelet aggregation and thrombus formation causing arterial occlusion and, ultimately, leads to ischemic necrosis and hyalinization. The myometrium adjacent to an embolized fibroid is noted to be edematous and inflamed but remains viable. Specific histologic effects after UFE with PVA particles were observed by Siskin et al and Aziz et al [25, 26]

MYTH 8: All fibroids are amenable to Uterine Arterial Embolisation.

REALITY: this myth has been debunked when certain kinds of pedunculated / large intracavitary submucosal fibroids, sloughed into the endometrial cavity causing cervical obstruction and sepsis. Also with pedunculated subserosal fibroids, post-embolisation detachment was seen which needed laparoscopic retrieval. Furthermore, in case of large fibroids associated principally with bulk symptoms, volume reduction might not be sufficient to satisfy patient expectations.[8] However, multiple fibroids are not deterrent.

MYTH 9: GnRH agonist prior to UFE improves the outcome of procedure as it does prior to myomectomy.

REALITY: GnRH agonist therapy can lead to constriction of the uterine arteries, more prone to spasm and technically more challenging to catheterize during the UFE procedure, hence should be stopped atleast 60 days preprocedure to prevent treatment failure.[8]

MYTH 10: Another big doubt about UFE is its cure rate as a sole conservative treatment of fibroid

REALITY: UFE does not always cure fibroids, requires reintervention often. In one study, nearly 1 out of 5 women who had UFE had a repeat UFE or a hysterectomy within the next couple of years.[27]

MYTH 11: Non-invasive MRgHIFU (Magnetic Resonance guided High Intensity Focused Ultrasound) is better than minimally invasive UAE for conservative management of fibroid.

REALITY: Both MRgHIFU and UAE result in significant symptom relief and quality of life improvement, but scores was significantly better after UAE resulting in a significant lower re-intervention rate compared to MRg HIFU.[28,29]

CONCLUSION: Till date the studies have declared the safety and efficacy of UAE in the short- and medium-term as an effective treatment for symptomatic uterine fibroids. Several studies have

proven its adverse effect on fertility but there is a need to assess its effect in women with multiple symptomatic fibroids without any additional confounding factor affecting fertility. Further research is required into certain technical aspects of the procedure and fertility. Large-scale studies comparing UAE with myomectomy and MR guided FUS for symptom relief, fertility and pregnancy outcomes and ovarian reserve are required. Further research is needed for optimisation of embolisation technique, including identification of the ideal embolic agent and embolic endpoint.

Currently a multicentre RCT is recruiting in the UK (FEMME) to address this and participation is encouraged[8]

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08

ROLE OF MRI IN FIBROID MANAGEMENT

Dr RishmaPai
MD DNB DGO FCPS FICOG
Consultant Gynaecologist and IVF Specialist at Lilavati and Jaslok Hospitals Mumbai,

Dr HrishikeshPai
MD, FCPS FICOG MSc USA
Consultant Gynaecologist and IVF Specialist, Bloom IVF Centre, Lilavati Hospital Mumbai,

Introduction :

The most common benign tumours in women in the reproductive age are uterine fibroids. [1,2] They are reported to be monoclonal tumors of the uterine smooth muscle cells consisting of large amounts of extracellular matrix that contain collagen, fibronectin, and proteoglycan[3,4].The prevalence rates reported in literature range from 20 – 50%, based on postmortem studies[5] .

As there are trend in delaying pregnancy and starting parenthood in later ages of life, significantnumber of infertile women is found to have fibroids.

Fibroids are seen in 5 to 10 % patients visiting infertility opd, while it is found to be sole cause of infertility only in 2.4 % of patients[6]

There is evidence that not all fibroids needs treatment and only symptomatic fibroids need to be treated. In patients with infertility, fibroids need to be treated when no other cause is found and the existing fibroids might decrease the pregnancy rates or when the fibroids are large or multiple. Most fibroids to be dealt with are submucosal, significant intramyometrial and large subserosal fibroids.

Role of MRI as diagnostic modality:

Most common ways to diagnose fibroids are history suggesting menstrual complaints and pressure symptoms and a 2D transvaginal ultrasound .The other modalities are sonohysterography, hysteroscopy and MRI .

Transvaginal ultrasound is a noninvasive and cost effective method and acceptable by patients. It is thus popular as a first line test to diagnose if the patients has uterine fibroids.

Fibroid has typical hypoechoic appearance on ultrasound but when it is associated with secondary changes like haemorrhage, necrosis, calcification or cystic changes, the diagnosis becomes difficult with routine 2D ultrasound.

There are reports of variable sensitivity and specificity. With advent of 3 D ultrasound , it is now possible to rule out indentation of endometrial cavity by fibroid. TVS has certain limitations as, it is not accurate for small fibroids and subserosal fibroids and also less sensitive to give precise location in respect to endometrial cavity

A systematic review and metaanalysis on diagnostic modality for uterine fibroids, of 19 studies , of which 9 studies were on TVS in fibroids, concluded that transvaginal ultrasound has inconsistent sensitivity (0.21–1.00) and specificity (0.53–1.00)[7]

MRI is a costly but powerful investigatory tool that is particularly useful in establishing the exact position, characteristics and number of fibroids, and their associated relationship with the adjacent viscera.

MRI is especially useful in patients with large fibroids or pedunculated fibroids. It also overcomes the problem of ovaries being lifted out of the pelvis in the presence of a large fibroid.

There is emerging evidence to suggest role of MRI in diagnosis of fibroids. MRI is not the first line for investigation , as it is expensive and patients are not willing to undergo it unless informed about the additional benefits over transvaginal ultrasound MRI holds its place as diagnostic modality mainly in mapping of the fibroids telling us more precisely about position and size in case of multiple fibroids, or those with bulky uterus who might need advanced surgical procedures.[8] Uterine sarcomas are a rare heterogeneous group of tumors of mesenchymal origin, accounting for approximately 8% of uterine malignancies. They comprise leiomyosarcoma, endometrial stromal sarcoma, undifferentiated endometrial sarcoma, and adenosarcoma. Magnetic resonance imaging (MRI) has a developing role in the assessment of these malignancies. Features such as tumor localization, irregular or nodular margins, necrosis, rapid growth, intense contrast enhancement, and restriction at diffusion-weighted imaging can suggest the diagnosis and help differentiate from more common leiomyomas and endometrial carcinoma. MRI is therefore extremely useful in preoperative detection and staging and, consequently, in determination of appropriate management.[9]

A comparative study on 18 women who underwent preoperative USG or MRI before undergoing hysterectomy for symptomatic fibroids observed that PPV and sensitivity of MRI imaging to be 91% and 80% respectively while that of USG was 97% and 40 % respectively. In this study, the sensitivity of MR imaging was two-fold greater than USG, for the detection of uterine fibroids (MR imaging: 80%; US: 40%) using pathological specimens as a gold standard.

The authors concluded that MRI has superior sensitivity and has minimal measurement discrepancies and should be preferentially utilized for assessing fibroids in clinical research studies due to its superior ability to detect smaller lesions[10]
.

Role of MRI in management of Fibroid.

The gynaecologist asseses as many factors like age, symptoms like menstrual and pressure symptom, desire for future fertility, patients affordability and facilities available in the hospital to decide the method to treat and which modality to adopt when treating the fibroids.

The gynecologists can opt for many treatment options like watchful waiting in asymptomatic fibroids, medical treatment for heavy bleeding with medication or the Mirena IUD; hysteroscopic, laparoscopic or abdominal myomectomy; uterine artery embolization; focused ultrasound.

There has been enough evidence on role of hysterectomy in past, with emerging role of myomectomy and uterine artery embolisation has also gained popularity.

MR-guided focused ultrasound:

The Exablate 2000 (In Sightec Inc., Haifa, Israel) was the first clinical MRg-FUS system approved by the FDA for treating uterine fibroids.

It is a non-invasive outpatient, procedure using high intensity focused ultrasound waves to ablate (destroy) the fibroid tissue. MRI is a FDA approved procedure where an interventional radiologist uses magnetic resonance imaging (MRI) to see inside the body and utilises it to deliver the treatment directly to the fibroid.

The ultrasound energy used in MRgFUs passes through skin, muscle, fat and other soft tissues. High-intensity ultrasound energy when directed to the fibroid heats up the tissue and destroys it and thus achieves tissue destruction by method of thermal ablation raising its temperature to 60°-85°C.

Direct ultrasonic energy to a focal point within a fibroid, resulting in tissue necrosis with minimal damage to surrounding tissue. This is afforded through quantitative temperature mapping, also allowing for detection of small temperature elevations in surrounding tissues prior to irreversible damage

Advantages ofMRI guided focussedultrasound :

1] It provides a three-dimensional view of the targeted tissue, allowing for precise focusing and delivery of the ultrasound energy.

2] Enables the physician to monitor tissue temperature in real-time to ensure adequate but safe heating of the target.

3] Immediate imaging of the treated area following MRgFU helps the physician to determine if the treatment was successful.

4] It is noninvasive and can be performed as outpatient procedure and does not need general anaesthesia or overnight hospital stay.

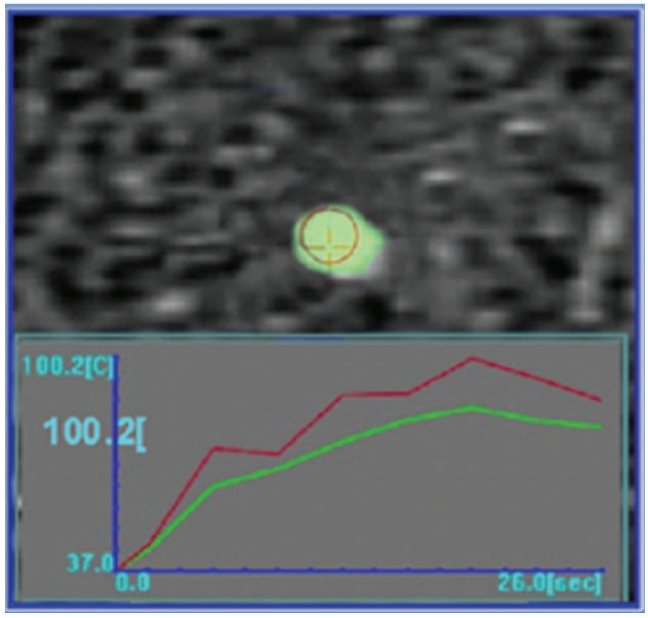
5] It is associated with minimal risks and complications and allows patients to resume normal activities and work in one to two days.

6] It enhances safety and efficacy by MRI-based thermal mapping and offers real-time temperature monitoring and excellent anatomical resolution.

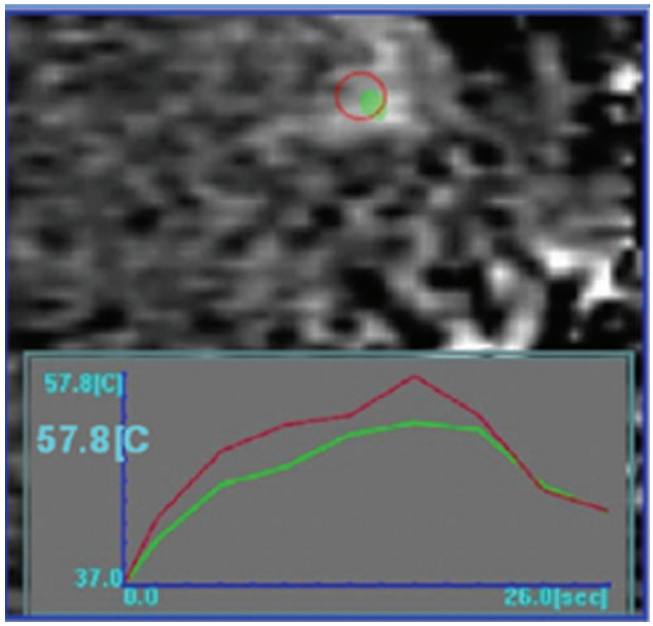
In addition to direct medical benefits, the economic impact of MRgFUS was important to note. The mean time of return to work after MRgFUS was approximately 1 day, compared with 13 days after Uterine Artery Embolisation (UAE) and approximately 6 weeks after abdominal myomectomy or hysterectomy[11]

REAL TIME THERMOMETRY

Temperature buildup during 10 second sonication (3 second intervals)



Too hot



Too cold

Parameters changed based on thermal feedback

Disadvantages:

1] There is need of expensive MR machine .

2] Procedure ablates one fibroid at one time and may need several hours and sittings.

Selection for patients:[12]

1] Most important prerequisite is presence of uterine fibroid and its associated relevant symptoms.

Exclusion criteria:

1] Hemoglobin<10 mg/dl or haemolytic anaemia.

2] Unstable cardiac status like angina, history of myocardial infarction in last 6 months, severe hypertension, patients on pacemaker, patients on antiarrythmia drugs.

3] Patients with cerebrovascular disease in last 6 months.

4] Recent pelvic infection, undiagnosed pelvic mass other than uterine fibroid.

5] Extreme weight with body mass index >110 kg.

6] Those with extensive longitudinal abdominal scar directly anterior to treatment area, as scar absorbs the ultrasound energy, can cause pain or skin burn.

7] Those with nonMRI compatible implanted metallic device

8] **Certain Fibroids are not technically suitable** to this treatment and are to be excluded:

a] More than 6 fibroids >4 cm in size.

b] Fibroid >12 cm of depth away from skin line and those fibroids with more than 50 % of their volume away from maximum focus.

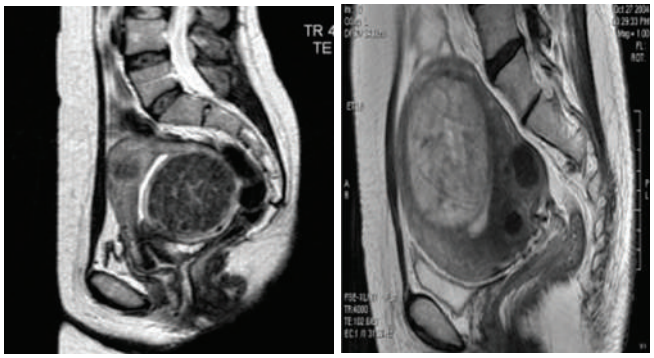
c] Degenerating and Calcified fibroids where calcified pseduocapsule disrupt ultrasound energy which cannot pass into the fibroid.

d] Pedunculated subserosal fibroids with small stalk, as post procedure fibroid may detach and fall into the abdominal cavity needing additional surgical procedure.

e] Must exclude inaccessible fibroids close to sacrum, hidden behind bowel.

f]Those fibroids adjacent to lumbosacral plexus or to any bony surface , as bone absorbs ultrasound waves and get heated , nerves lying adjacent to this heated bone surface get heated and cause nerve damage.

Hypo-intense ("Dark") fibroids are more susceptible than hyper-intense ("white")



Procedure : [flow chart][12]

Steps for preparation of the patient:
Shaving of the abdomen, assessment of any mole or scar.

↓

Insertion of IV line for administration of sedation and urethral catheter is done

↓

Patient placed in prone position over water bath in which transducer is immersed position allows the pelvic structures to fall into the position they would be in during a potential treatment.

↓

The patient's abdomen is acoustically coupled with thetransducer via the water bath using a special gel pad.

↓

100 mg Diclofenac sodium is given as a suppository prior to starting .
Blood pressure, heart rate, oxygenation, and comfort level are monitored throughout the treatment.

↓

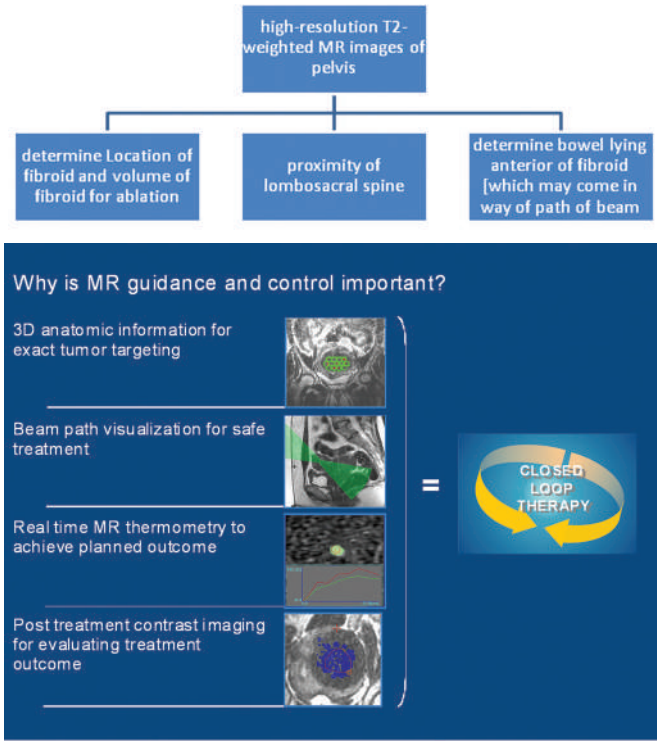
The position of the patient over the transducer is determined from a 3plane localizer and T2-weighted imaging. IV sedation is given.
Regular topping of analgesia and bladder draining is done, as it provides acoustic window

↓

Immediately prior to treatment, T2-weighted MR is used to identify target fibroids and assess

proximity to critical structures including the bowel, spine, and neurovascular bundles.

Imaging consists of several sequences. The fibroid is then outlined and a sonication plan is developed. After low-energy test dose, therapeutic sonications are performed



The **region of treatment** (ROT) is then defined on the targeted fibroid and is drawn such that a margin of at least1 cm is kept from the serosal surfaces to minimise the risk of ablating the serosa which causes severe pain.

Though there is no limit to the percentage of fibroid volume that can be treated but generally a 60-70% of ablation is required for good outcomes.

Density plan used normally is medium but high is used for white fibroid.

The length of the sonications can then be selected and may vary from10 mm to 45 mm.

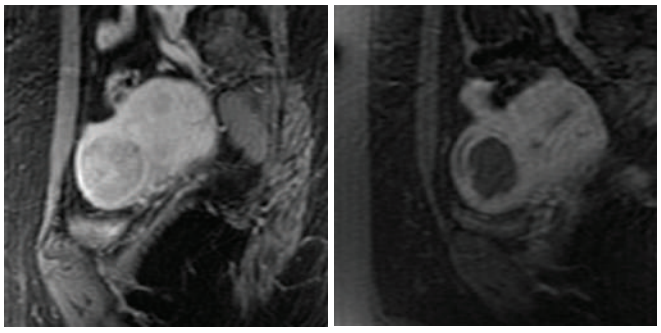
The sonication beam path is carefully checked to ensure that it does not pass through any structures that should be avoided – such as the small bowel that can fall in front of the uterus.

Duration of the treatment :Generally, treating and ablating an 8 cm fibroid takes approximately 3 hours of sonications. Each sonication duration varies from 20 to30 seconds. This is followed by cooling periods of 24 to90 seconds. The cooling periods of 40 to 70 seconds between each sonification programme allows time for the skin to cool down to avoid patient having skin burns.

MR is used to monitor tissue temperature to ensure adequate power delivery and avoid surrounding tissue damage.

At Completion of treatment:a repeat contrast MR is used to determine the area of non perfusionvolume (NPV), which is represented as a volume and percentage ablation of the targeted fibroid.

Single , T2 Hypo intense Fibroids can be easily treated with MR Guided Focused Ultrasound Surgery



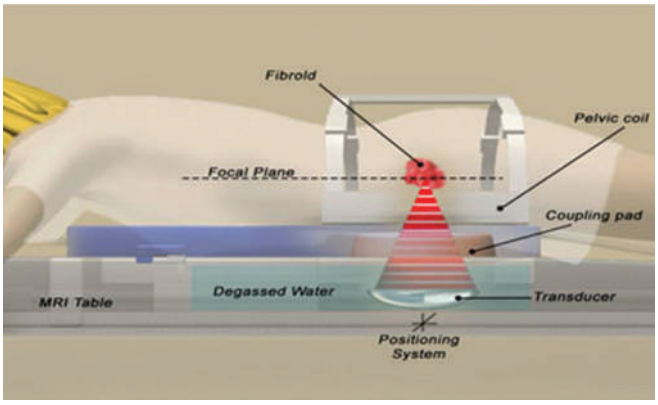
PRE TREATMENT POST TREATMENT

T1 W contrast imagesT1 W contrast images

Post Treatment: patient can be given analgesics and observed for one hour

Instructions: They can resume work and normal activities and do not need any medications.

Follow up: patients should go for follow up after two weeks and for patients whose treatment was incomplete due to huge fibroid, can be repeated even next day or after one week when patient is ready.
Repeat contrast-enhanced MRI is performed after 6 months to assess the fibroid size



Potential side-effects or complications after HIFU/MRgFUS treatment as described below are actually quite rare[13]

- Pain post procedure and skin burns
- Nausea, abdominal cramping.
- Slight inflammation of subcutaneous fat tissue and of the abdominal muscles
- Paraesthesia of the legs due to irritation of, or damage to the nerves
- Deep vein thrombosis of the legs (very rare)
- Intestinal lesions or intestinal perforation (extremely rare)

Techniques to overcome problems and increase efficacy:
1] As MRI is time consuming, to reduce this time and to prevent overheating of tumour, several techniques like(a) enlargement of ultrasound focus size,[14] and (b) employment **of** gas-filled micro-bubbles during insonation to enlarge the ultrasound absorption of the targeted tissue, c] the defined generation of cavitation bubbles in the focal region by use of short high intensity pulses before or at the beginning of each single abla-tion pulse.[15,16]
2]As fibroids >10 cm are unsuitable for this procedure , to treat them, GnRh analogues can be used to decrease size of fibroid.3 – 6 doses of monthly depot GnRha can be given over a period of 3 – 6 months to shrink the fibroid preprocedure. The treatment session can be divided by splitting fibroid in two regions and treating them at different times.
3] As it is difficult to perform procedure in fibroids close to bone, sonications are performed at least 4 cm from bony structures to minimize the amount of heating of the bone. To avoid this problem several techniques like tilting the beampath to avoid bone,or increasing the frequency of the ultrasound beam, or rectal filling to push the fibroid away from the bone [17] or partial treatment tochange the subsequent orientation/ location of fibroid can be done .

Results :
For pregnancy, the average time from after MRgFUS was 8.2 months and most pregnancies were carried to term with an average fetal weight of 3273 g. The review concluded MRgFUS represents a minimally invasive treatment for uterine fibroids that is ableto improve the quality of life and fibroid size with durability. It is possible that MRgFUS could be the treatment of choice for patients desiring future fertility; however, further investigation is needed[18.]

Similar result was seen by systematic review of 38 studies and about 2500 patients, that assessed fibroid shrinkage, non perfused fibroid volume and patients symptoms with UFS-QOL questionnaire (baseline 3, 4, 6, and 12 months and they concluded that MRg FUS could be considered as a minimal invasive alternative to traditional surgical or radiological procedures for the treatment of symptomatic uterine myomas improving both QOL and subsequent fertility.[19]

A study including 2 systematic reviews, 2 RCTs, 45 cohort study reports, and 19 case reports involving HIFU treatment of symptomatic uterine fibroids concluded that for women failing medical therapy and seeking alternatives to hysterectomy for symptomatic uterine fibroids, MRgHIFU provides a safe and effective, noninvasive, uterine-preserving treatment from which they rapidly recover.[20]

The reduction of fibroid volume is related to the non perfused volume of the tumor immediately after the treatment. Regression of the fibroid size is expected to begin 1 month after the treatment and it becomes obvious usually after 3

months of the treatment. Fibroids in which blood supply decreased immediately after HIFU session decreased in size on follow-up

Significant reductions were noticed in fibroid volumes at six months follow up compared to pretreatment fibroid volume.[21]

A retrospective observational cohort study used healthcare claims for several million individuals with healthcare coverage from employers in the MarketScan Database for the period 2003–2010 to compare one-year all-cause and uterine fibroid (UF)-related direct costs in patients treated with one of the following three uterine-sparing procedures: magnetic resonance-guided focused ultrasound (MRgFUS), uterine artery embolization (UAE) and myomectomy.

Multivariate adjustment of cost outcomes was conducted using generalized linear models in the study sample which comprised 14,426 patient population. Adjusted all-cause and UF-related costs at one year were not significantly different between patients undergoing MRgFUS, myomectomy and UAE[22]

Conclusion:

Symptomatic fibroids need attention and treatment. In the past, myomectomy was the standard treatment. Now medical treatment withGnRH-analogues or ulipristal acetate administration, hormone-releasing intrauterine devices, progesterone-based oral contraceptives, etc and the conservative approach with uterus sparing procedures like UAE, MR guided focussed ultrasound have become popular over surgical approach.

MRgFUS is considered to be relatively safe and effective non invasive treatment modality for treating uterine fibroids in selected patients. It has gained popularity due to its efficacy in symptomatic fibroids. It has benefits of being a uterus sparing procedure, with minimal risks and less time consuming allowing those undergoing it, to resume their activities soon after the procedure.One hinderance to its popularity is the cost, but with more awareness, patients can be informed about benefits . Also studies have proved about similar cost when compared to other procedures. Pregnancy are reported after MR guided focussed ultrasound. With recent mitigation techniques , the inclusion criteria are expanded and more patients can be eligible to this treatment .

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09

MYOLYSIS FOR FIBROID MANAGEMENT. WHERE DO WE STAND ?

Prof. Dr. Sarita Agrawal
MD, FCGP, FICOG, FIAMS
Prof. & Head Deptt. of Obstetrics & Gynecology
All India Institute of Medical Sciences Raipur

Introduction- Approximately 50% of women of reproductive age have fibroids and at least 50% of these women have significant symptoms. However, until 15 years ago, the only surgical options available were hysterectomy and myomectomy and as yet there are no proven effective long-term medical therapies. There has been longstanding research interest in developing minimally invasive alternatives for treating uterine fibroids, including procedures that retain the uterus and allow for future childbearing. The new treatment modalities include: laparoscopic and vaginal myomectomy; uterine artery embolization (UAE); magnetic-resonance-guided focused ultrasound surgery (MRgFUS); hysteroscopic resection, laparoscopic uterine artery occlusion; temporary transvaginal uterine artery occlusion and myolysis by various energy sources. It is, however clear that, each of these procedures has distinct advantages, but also apparent disadvantages & there is no panacea that suits every woman, nor are all treatment types universally available to all women, even in the developed world.

All other procedures are discussed in details elsewhere, in this chapter we will be discussing in details about myolysis.

Myolysis

Myolysis is among the new procedures under development, for the treatment of symptoms related to uterine leiomyoma. The

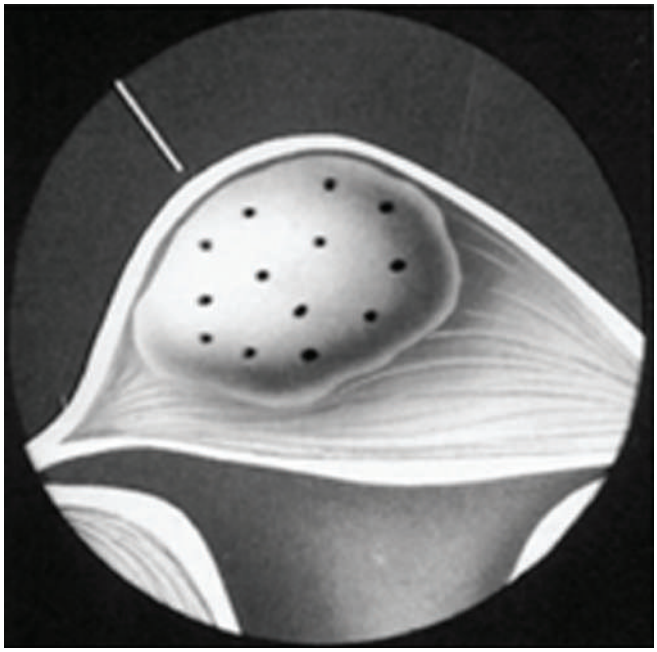
procedure targets the destruction of fibroids using focused energy delivery systems including Nd:YAG lasers, bipolar electrodes, cryomyolysis and radiofrequency ablation performed laparoscopically, transcervically or percuteneous and most recently, focused ultrasound monitored by real time magnetic resonance imaging. Myolysis causes marked devasularisation, protein denaturation & coagulation necrosis leading to shrinkage in size of myoma which improves symptoms. Myolysis was first performed by Mergui in France in 1987. He used an Nd:YAG laser to make multiple punctures in myomas with resultant tissue death and myoma shrinkage. Leukens and Gallinat[1] in 1993 used 1cm to 3cm bipolar needles to destroy myoma tissue. Early methods involved the insertion of probes multiple times into the fibroid and were performed without imaging guidance. There were concerns about serosal injury and abdominopelvic adhesions with these techniques, possibly due to the multiple passes through the serosa. Newer systems using imaging guidance to determine the size and location of fibroids, to guide the probe, and to ensure the probe is in the correct location do not require multiple repetitive insertions & also avoids damage to normal myometrium as optimal energy is applied to the fibroid. Further Herbert A & Goldfarb MD[2] proposed the following criteria for maximizing the success of the myolysis procedure.

1. Limit the procedure to post reproductive premenopausal women.
2. Limit the myoma size to 10 cm, which would have a final result of 3 cm to 4 cm.
3. Administer GnRH agonist for 10 weeks to 12 weeks to obtain maximal tissue shrinkage.
4. Discontinue the process of the GnRH agonist because it does not result in a 30% to 40% reduction in myoma size.
5. Treat menorrhagia concomitantly with a hysteroscopic resection of submucosal myomas, endometrial ablation, or both.

MYOLYSIS TECHNIQUES-

- Laser – Nd YAG - laparoscopic/ percuteneus
- Radio frequency bipolar needle
- Diatharmy
- Crymyolysis- laparoscopic/ percutaneus
- Microwave
- Myoma interstitial thermo therapy (MITT)- Diode LASER & specific optical light
- Focussed ultrasound- USG Guided / MRI Guided

LASER MYOLYSIS- Concept of LASER myolysis first initiated by Donez et al (1989) for hysteroscopic myolysis and later for laparoscopy by Nisolle in 1993. Nd:YAG laser was used to lyse the myoma under laparoscopy vision. Bare LASER fibres introduced perpendicular into the fibroid through secondary port using a power of 80 watt repeated in entire surface of myoma keeping a distance between two holes 5-7 mm. Irrigation with normal saline during procedure to reduce thermal conduction. Interceed used in some case to prevent adhesion formation. In first series of 48 patients of Nisolle et al[3], none required laparotomy for bleeding, no bladder bowel injury, estimated blood loss- 50ml, procedure time- 20-45 minutes depending upon size, no postoperative infections, myoma size shrinkage at 6 wks 4%, at 6 months 41% (18-62%). Major problems reported were intraoperative smoke obscuring the visibility, post operative dense adhesions due to multiple passes & rupture in subsequent pregnancy and also the high cost.



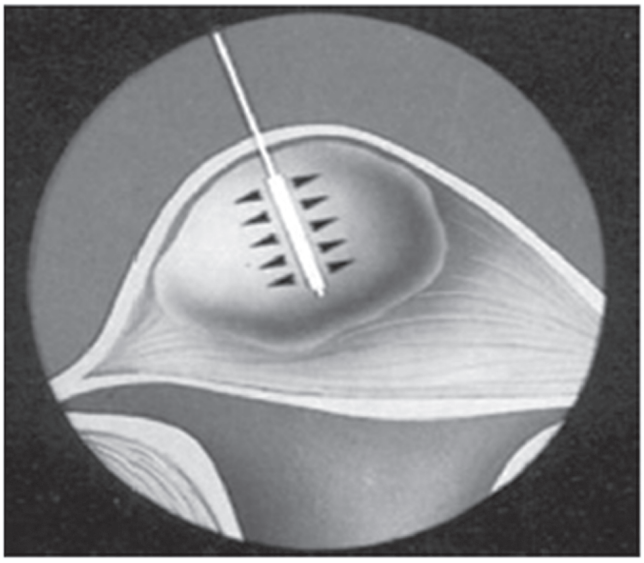
MYOLYSIS WITH BIPOLAR NEEDLE- bipolar needles were developed as an inexpensive alternative to the ND Yag LASER first by Adolphe Gallinat in 1993 (size of needle short 1.5cm appropriate for small myoma), later in 1995 by Goldfarb et al described a 30 cm instrument with 5cm probe that can be passed through laparoscope port and performed circumferential punctures with each pass at 50 watts of coagulating current left for 10 - 15 seconds which would result in a fraction of the total circumferential tissue death, obliterating the feeding vessels & without extensive peritoneal superficial tissue trauma. In a series of 150 patients they observed no serious complications and reported shrinkage of myoma to the extent of 50% & found to be cost effective.

ULTRASOUND GUIDED RADIO FREQUENCY ABLATION- Bruce Lee, MD[4] performed the radiofrequency interstitial tissue ablation (RITA) procedure, percutaneous insertion. The radio frequency ablation needle (15 gauge) is inserted percutaneously under laparoscopic intraabdominal ultrasound guidance. The real time laparoscopic ultrasound helps in accurate targeting so ablation volume can be tailored during surgery this obviates need for multiple ablation & avoids unrecognized ablation of myometrium. In his series of 125 patients the volume reduction was 40% at 36 months & symptomatic improvement of dysmenorrhoea in 98% of the patients by 6 months after treatment. Data on the largest series was initially published in 2013 by Chudnoff et al[5]. This industry-funded prospective and multicenter (9 sites in the U.S., 2 sites in Latin America) study included 135 premenopausal women with symptomatic uterine fibroids, a uterine size of 14 weeks of gestation or less, and 6 or fewer treatable fibroids, with no single fibroid larger than 7 cm. RITA was conducted using the Acessa system. A total of 127 of 135 women (94%) completed the study. From baseline to 12 months, 53 of 127 women (42%; 95% confidence interval, 32% to 49%) experienced at least a 50% reduction in the volume of menstrual bleeding at 12 months. Only 1 woman underwent a surgical reintervention through 12 months. Berman et al[6] in a series of 104 cases stated that quality of life variables improved from baseline to 36 months and that most of the improvement in quality of life occurred in the 3 months following the procedure however 14 required re interventions.

VIZ ABLATE SYSTEM-combines intrauterine RF Ablation system with intrauterine sonography in a single device that can be inserted trans-cervically this system is not yet cleared by USFDA.

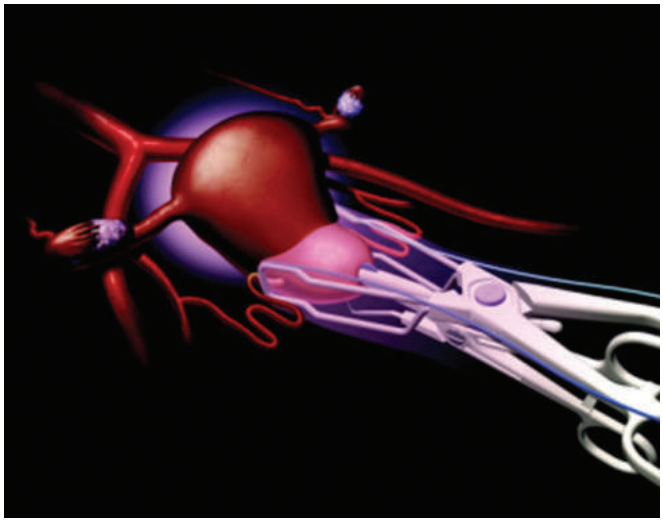
MYOMA INTERSTITIAL THERMO THERAPY (MITT)- Described by Donnez et al. In this procedure after making a hole on myoma serosa through a trocar the special LASER fiber with optical light diffuser is introduced in myoma. The optical light diffuser transmit LASER light in all direction to a precise depth, absorbed by hemoglobin , light then transformed to heat & causes controlled coagulation.

Fig-2 MITT



CRYOMYOLYSIS- Cryomyolysis uses gas cooled cryoprobes in which pressurized gas is expanded through a small orifice to produce cooling. The temperature drops to -90°C in 8 to 10 minutes, creating an expanding ice ball around the probe with a transverse diameter of 3-4 cm and a length of 5- 7 cm. The ice ball can be monitored by ultrasound. This procedure is quite effective in moderate sized myomas. Ciavattini et al[7] reported on 9 cases of pregnancy after laparoscopic cryomyolysis. In 2005, Zupi et al reported the 1-year follow-up of these patients & reported that

mean shrinkage in fibroid size continued until 9 months after surgery, to a mean volume reduction of 60%. Patients reported absence of symptoms.



Schematic diagram of Flostat system

MRI GUIDED PERCUTENEOUS LASER ABLATION - MR guided laser ablation allows real time color- map feedback on the temperature levels achieved & thus allows controlled myolysis. Mean fibroid volume found to be reduced by 31% at 3 months and 41% by 1 year. (Hindley JT et al, 2002[9]) Although this procedure can be performed with local anesthesia, a high incidence of major perioperative complications has been reported.

TRANSCERVICAL MICROWAVE MYOLYSIS ASSISTED (MEA) BY TRANSVAGINAL ULTRASOUND GUIDANCE-

Transcervical microwave myolysis using a guiding needle set in a puncture adaptor attached to a transcervical ultrasonic probe and a microwave applicator 1.6 mm in diameter for myolysis. Kanaoka et al[10] in a preliminary study of 10 patients with severe abnormal bleeding; with either mostly submucosal or intramural myomas of 4 to 7.5 cm reported size reduction by 36% to 69% at 6 months. Subsequently Tsuda A et al[11] in a series of 35 women with single submucosal myoma of sizes ranging between 4-7 cm reported shrinkage by 56.2% at 3 months and 72.5% at at 6 months after the operation. Blood haemoglobin levels had increased significantly at 3 months.

Rene Marty et al advocated the hysteroscopic approach with needle electrosurgery. They advocated simultaneous performance of laparoscopy to ensure that bowel is not attached to the uterus and the instillation of 3 liters of lactated Ringer's solution intra abdominally obviates intestinal hyperthermia. Laparoscopy can be avoided in the virginal abdomen without a history of endometriosis or infection, or if the tumor is well within the myometrium and more than 5 mm from the serosa. This approach opens a new venue for treating intrauterine myomas that were previously treated with hysteroscopic resection & a significant portion of the myomas was often invading deep into the myometrium.

TRANSVAGINAL ULTRASOUND-GUIDED RADIOFREQUENCY MYOLYSIS FOR UTERINE MYOMAS

Under transvaginal ultrasound guidance, a 35-cm long 18-gauge needle electrode with an exposed tip at the distal end is inserted through a needle guide attached to a transvaginal ultrasound probe. Finding the shortest and safest route under transvaginal ultrasound, the needle electrode is guided to the target myoma through the posterior fornix and/or myometrium and/or other myomas as appropriate. The middle of an exposed tip of the needle electrode is positioned at the center of the target myoma. For patients who anticipated pregnancy in the near future, the needle is inserted so as to avoid the endometrium to prevent endometrial damage. The needle electrode is then connected to a generator that operates at 400 kHz with a maximum power of 120 W and at temperatures ranging from 40°C to 99° C. The selected temperature to reach within the tissue is 85°C and the RF generator automatically adjusts the power to maintain the selected temperature. During ablation, cold saline is circulated through an internal water circulation system that applied to the RF generator. The core of the target myoma is ablated until the echo-enhanced area by ablation reached 80–90% of the myoma cross section in a real-time ultrasound.

In a series of 69 premenopausal women with symptomatic uterine myomas treated as an outpatient procedure performed by Chung-Hoon Kim et al[12] there was significant reduction in mean baseline volume of the dominant myomas (P = 0.002). An improvement of menorrhagia & overall symptoms occurred 1, 3, 6 and 12 months after operation (all $P < 0.001$ versus baseline). No major complications were observed. After 12 months, three patients had successfully conceived and delivered

INCISION LESS TRANSVAGINAL DOPPLER DIRECTED MECHANICAL UTERINE ARTERY OCCLUSION-

Olave Istre, MD[13] of Oslo Norway used a Doppler-guided paracervical clamp to occlude the uterine arteries. Each of the 2 clamp blades is connected to a Doppler device & placed transvaginally under doppler guidance, when placed correctly, the flow disappears & Uterine artery occlusion was confirmed by cessation of the audible Doppler signal.The patient is kept with an epidural block for 4 hours to 6 hours and is then clamps released. Postoperative MRI studies have shown fibroid death similar to that occurring with embolization. Although patients had postembolization pain, there are no surgical complications. A major issue is the potential crushing effect on the ureter. Lichtinger[14] observed the effect on the ureter with no untoward results. The Flostat™ system (Vascular Control Systems, San Juan Capistrano, CA, USA), is currently cleared by the United States Food and Drug Administration.

MRI GUIDED FOCUSED ULTRASOUND (MRgFUS)- Stewart et al[15] have shown the technique of delivering intensely focused ultrasound to destroy uterine fibroids with MRI guidance to be effective in reducing fibroid volume. The procedure is also known as "Non-invasive HIFU surgery / Hyperthermia therapy. Ultrasound beams are focused on diseased tissue, multiple sonicaton of 20 seconds each with 90 seconds pause is applied. Due to the significant energy deposition at the focus, temperature within the tissue can rise to levels from 65° to 85°C, destroying the diseased tissue by coagulation necrosis. Concurrent real time MRI allows three dimensional anatomical information for exact tumor targeting, temperature at every treatment point is monitored & the beam is focused so surrounding tissue are not damaged.

Disadvantages-

- Volume more than 900 cubic cm- multiple treatment sessions required
- Number more than 6 symptomatic fibroids- not good candidates
- Closure to sacral bone surface can cause nerve damage hence not suitable or need mitigation technique
- Hypervascular fibroids are difficult to treat
- Large subcuteneous fat /scar may distort the focused USG beams
- Fibroid deeper than 12 cm from the skin or shielded by bowel or bone
- Adenomyosis –results may not improve

Results- Seventy-one percent of women undergoing MRgFUS reached the targeted symptom reduction at 6 months and 51% reached this at 12 months. The magnitude of improvement in symptom severity score (SSS) was greater than predicted, with subjects having a mean decrease of 39% and 36% at 6 and 12 months, respectively. Greater reduction of fibroids > 10 cm in diameter, who were pretreated with GnRH-agonist for 3 months.

ONGOING CLINICAL TRIALS ON ABLATION THERAPY

• Post Market TRUST (Treatment Results of Uterine Sparing Technologies) Study (NCT01563783)[16]: This industry-sponsored RCT is comparing global fibroid ablation, abdominal or laparoscopic myomectomy, and uterine artery embolization. The study is enrolling women who are at least 18 years old and menstruating, have symptomatic uterine fibroids, have a uterine size of no more than 16 weeks' gestation, have fibroids less than 10 cm in any diameter and who desire uterine conservation. The primary outcomes are the relative costs of the procedures and adverse

event rates in the 3 months following the procedures. Estimated enrollment is 260 women and the expected completion date is December 2019.

• **Uterine Leiomyoma Treatment With Radiofrequency Ablation (ULTRA)** (NCT01840124)[17]:

This single-arm uncontrolled case series study plans to include 100 women with symptomatic uterine fibroids who will be recruited from 5 sites in the University of California Fibroid Network. Patients will be treated with the Acessa™ system and will be followed for 3 years. The primary outcome is change in fibroid-related symptoms and a secondary outcome is the pregnancy rate after fibroid treatment. The estimated study completion date is June 2017.

PRACTICE GUIDELINES AND POSITION STATEMENTS

In 2012, the American College of Obstetricians and Gyne cologists reaffirmed a 2008 Practice Bulletin titled "Alter natives to Hysterectomy in the Management of Leiomyo mas."[18] Recommendations based on good and consistent scientific evidence are that abdominal myomectomy is a safe and effective treatment of women with symptomatic leiomyomas and that uterine artery embolization is a safe and effective option for appropriately selected women who wish to retain their uteri. The bulletin contains no recommendations regarding myolysis utilizing laparoscopic or percutaneous techniques.

CONCLUSION - Review of literature reveals that in current practice myomectomy is most commonly offered procedure. Laparoscopic/ hysteroscopic myomectomy is better in experienced hand. UAE & MRg FUS are safer in selected cases with informed discussion. Myolysis shows significant improvement in symptoms however results of large RCT are still lacking & effect on future pregnancies are controversial. Robust research trials therefore are needed in order to establish place of various new uterus conserving options. The new modalities of management of uterine myomas usher in a new generation in the field of women's health. No longer is the patronizing comment "you have had your children and would be better off without your uterus". Alternative treatments for fibroids are available, and hysterectomy is only ONE option, not THE option. The bottom line is "WE have options when it comes to treating fibroids. Make sure your provide patient with the option that is right for her". **YOU HAVE CHOICES – CONSERVE UTERUS.**

TABLE-1

TABLE-1

SURGERY	USE & EFFICACY	SIDE-EFFECTS	REMARKS
Abdominal myomectomy	Procedure of choice for symptomatic myomas in women desiring fertility, large myoma distorting endo. cavity or unexplained IVF failures with cure or ↓ in HMB by 80%	Haemorrhage, adhesion, uterine rupture during pregnancy	Lap myomectomy better in skilled hands Recurrence 5-10%, HMB persists in 10-15% 40-60% pregnancy rate
Hysterosopic myomectomy	For symptomatic submucous myomas (ESH category T:0 & T:1); 90% ↓ in HMB, 20% need additional T/T within 10 yrs	Perforation, haemorrahe, volume overload	Preoperative GnRHa↓ surgical blood loss
Vaginal myomectomy	For large myomas arising from uterine body and filling up vagina	Haemorrahge, injury to bladder	
Lap/robotically assisted lap myomectomy	Suitable for subserous or pedunculated myomas, comparable to laparotomy for intramural myoma in infertile	Uterine rupture during pregnancy	Defer pregnancy for 4-6 months
Hysterectomy	Procedure of choice for myomas if childbearing completed or if reasonable likelihood of malignancy, highest pt satisfaction, no recurrence	Haemorrhage, injury to bladder & ureter, adhesion	NDVH suited for <12wks
Myolysis	Conservative alternative to myomectomy in perimenopausal, 30-50% ↓ in myoma size	Haemorrhage, infection, uterine rupture in pregnancy	Not studied extensively
Uterine artery ligation/ Occlusion (UAO)	Easier to perform than UAE, ↓ blood loss if done with myomectomy, does not affect future fertility, 46% ↓ in myoma vol ume & 78-95% symptomatic improvement	Injury to ureter & bladder, DOR if combined with utero-ovraian anastomosis vessel occlusion	
MRgFUS	98% ↓ in myoma volume & symptoms, symptomatic relief lasts for 2yrs, 16-20% need additional therapy	Non-invasive and safe, No adverse pregnancy outcomes	intermediate intensity fibroids, pre-T/t with GnRHa potentiates effects if ut >10cm, comparable to UAE but limited RCTs
UAE	85% ↓ in MBL & 30%–46% ↓ in dominant fibroid volume, 86% satisfaction vs 70% for hysterectomy, 25% need additional t/t	Persistent ischemic pain, post embolization fever, sepsis, pyometra, severe PES, hysterectomy, ovarian failure, death, pregnancy morbidity	Suitable for symptomatic myoma where surgery contraindicated & pregnancy not desired. Withhold GnRH agonist therapy 12 wks prior to UAE

TABLE-2

SN	PROCEDURE	AUTHUR	YEAR	NO. OF CASES	RESULTS
1	Laparoscopic myolysis with the Nd: YAG laser	Nisolle M et al[3]	1993	48	Myoma shrinkage at 6 months 41% (18-62%). Major problems- intraoperative smokes obscuring the visibility, post operative dense adhesions
2	Myolysis with bipolar needle	Goldfarb et al	1995	150	Myoma shrinkage by 50%, cost effective, no serious complications
3	USG guidance Radiofrequency ablation	Lee BB. [4]	2005	125	Myoma shrinkage by 40% at 36 months & symptomatic improvement of dysmenorrhoea in 98%
		Chudnoff SG[5]	2013	135	50% reduction in bleeding at 12 months.
4	Radiofrequency Volumetric Thermal Ablation	Berman JM[6]	2014	135	14 required reiterventions
5	Laparoscopic cryomyolysis	Ciavattini A[7] Zupi E [8]	2006 2005		9 cases of pregnancy after cryomyolysis Mean volume reduction 60%. & absence of symptoms

better in experienced hand. UAE & MRg FUS are safer in selected cases with informed discussion. Myolysis shows significant improvement in symptoms however results of large RCT are still lacking & effect on future pregnancies are controversial. Robust research trials therefore are needed in order to establish place of various new uterus conserving options. The new modalities of management of uterine myomas usher in a new generation in the field of women's health. No longer is the patronizing comment "you have had your children and would be better off without your uterus". Alternative treatments for fibroids are available, and hysterectomy is only ONE option, not THE option. The bottom line is "WE have options when it comes to treating fibroids. Make sure you provide patient with the option that is right for her".

YOU HAVE CHOICES –CONSERVE UTERUS.

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10

OUR EXPERIENCE OF UNSUSPECTED LEIOMYOSARCOMA IN LAPAROSCOPIC MYOMECTOMY

Dr Alka Kriplani
(MD, FRCOG, FIMSA, FCLS)
Professor & Head
All India Institute of Medical Sciences,
New Delhi

Dr Reeta Mahey
(MD, DNB, MICOG)
Assistant Professor
All India Institute of Medical Sciences,
New Delhi

Uterine leiomyoma (fibroid) is the most common benign pelvic neoplasm among women of reproductive age (1). Surgeries, including myomectomy and hysterectomy, are commonly performed to treat symptomatic leiomyomas. With advances in techniques and devices, laparoscopic surgery has gained worldwide popularity as a minimally invasive surgery.

Power morcellation has revolutionised the procedures of laparoscopic hysterectomy and myomectomy as large uterine masses can be removed through minimally invasive route. But high velocity of morcellator can lead to dispersion of myoma pieces in the abdomen or in the abdominal wall(2),(3). Very rarely these pieces might contain atypical cells (cellular or atypical myoma, leiomyosarcoma) which can later on require repeat medical or surgical intervention(4). Recent popular media attention around surgical management of presumed uterine leiomyoma has created an opportunity to properly define a patient-centered research agenda and clinical management strategy. In its statement, the FDA estimated that 1 in 350 women undergoing hysterectomy or myomectomy for the treatment of fibroids is found to have an unsuspected uterine sarcoma. But in other studies, findings of LMS in presumed nonmorcellated hysterectomy specimens has been reported at 0.23- 0.49%(5), (6).

Till date, around 400 laparoscopic myomectomies have been done in our unit, but no case of unsuspected leiomyosarcoma has been reported in the morcellated specimen. We have encountered

only one case of unsuspected leiomyosarcoma in last 9 years following total laparoscopic hysterectomy which was done outside in a private hospital.

A 48 year P1 L1 patient presented in 2012 with complaint of large lump in left side of abdominal wall. She had undergone laparoscopic hysterectomy 3 years back (2009) for fibroid uterus where the specimen was removed with mechanical morcellator. Histopathogy of hysterectomy specimen was benign leiomyoma. After surgery patient was asymptomatic for 2 years when she noticed a swelling at the site of previous morcellation port. The swelling continued to grow slowly up to 10x8cm size occupying the left hypogastrium and left lumbar area (figure 1A). It was non-tender with irregular margins and cough impulse was negative over the mass. USG revealed a hypoechoic lesion in the abdominal wall involving the rectus sheath with provisional diagnosis of abdominal wall leiomyoma. Fine needle aspiration of the mass also confirmed the benign nature of mass (leiomyoma). MRI abdomen revealed another mass about 4x4cm in the pelvis with similar intensity features (figure 1B and 1C). With provisional diagnosis of leiomyomatosis, laparoscopy was planned which revealed a 3x4cm round well defined pelvic mass near the right infundibulopelvic ligament (figure 1E). Rest of the pelvis was normal with normal adenexa. The bulge of abdominal wall leiomyoma was visible on laparoscopy(figure 1D). The pelvic mass was detached with Harmonic Ace and was put in Endobag. Abdomen was opened at this site of large mass and both the masses were removed through same incision. Patient had uneventful recovery and was discharged in stable condition after 3 days. But to surprise, histopathology of both masses revealed features of leiomyosarcoma with high mitotic activity. PET scan done immediately after surgery and then after 3 months did not report any abnormality. Patient is under follow up since last 3 years and is asymptomatic.

Unfortunately, not all uterine cancers can be diagnosed preoperatively further research is required as investigations are inconclusive. Sensitivity and specificity of few modalities have been evaluated (Table 1)in recent studies. Most sarcomas present with symptoms similar to benign fibroids such as abnormal uterine bleeding (7) but signs like large myoma and rapid increase in size points towards malignancy.

Investigations which may detect presence of sarcoma in case of leiomyoma is as follows:

Ultrasound rarely distinguishes a benign leiomyoma from a malignant mass. If a sarcoma is expected after ultrasound evaluation, magnetic resonance imaging (MRI) may be helpful in further evaluation (8). In our institute, MRI and LDH is done in suspicious cases of large rapidly growing fibroid.

Magnetic resonance imaging (MRI) is the modality recommended for imaging characterization of uterine masses. Its wide range of soft tissue contrast allows for detailed delineation of tumor size, margins, and growth pattern. Unfortunately, the features that suggest LMS on MRI (large size, tissue signal heterogeneity, central necrosis, and ill-defined margins) are features that can also be consistent with benign degenerating uterine myomas. Significant change in size between interval scans, in addition to these features, should raise concern. Administration of intravenous contrast evaluates perfusion, and the larger field of view allows for detection of extrauterine growth such as lymphadenopathy, vascular invasion, peritoneal dissemination, and bone metastases. (9)

Serum LDH levels are also raised in uterine sarcomas. It can be used along with imaging modalities if sarcoma is suspected in a presumed myoma. Goto and colleagues have suggested that elevated total serum LDH with or without pelvic magnetic resonance imaging (MRI) postcontrast T2 image analysis had perfect negative predictive values for LMS(9). These findings deserve further study, particularly as LDH measurements are relatively inexpensive, as they both suggest 90% of suspicious fibroid uteri patients could be triaged preoperatively into low-risk categories.

S.No.	Imaging	Sensitivity	Specificity
1	MRI(9)	100%	96.9%
2	LDH(Total) (9)	100%	87.7%
3	LDH3(9)	90%	92.3%
4	LDH & MRI (9)	100%	99.2%

Positron emission tomography (PET) is may not be useful in differentiating benign from malignant

uterine tumors. Benign fibroids can demonstrate avid tracer uptake in both pre- and postmenopausal women(10). In the setting of known uterine malignancy, however, whole-body fusion PET/ computed tomography (PET-CT) is the most accurate modality to evaluate nodal and extrapelvic metastases(11).

Table 1: Various modalities for detection of leiomyosarcoma

Hematogenous dissemination is the most common route of metastasis, and 50% of women with clinical stage I LMS have evidence of lung metastases at presentation(12). The 5-year survival for a stage I LMS or US is 63% compared with 14% for stage IV malignancies .Importantly, when inadvertent morcellation of either LMS occurs at the time of surgery, there is an increased rate of abdominopelvic recurrence and decreased disease-free survival(13),14).

Patient with retained pieces of myoma can be asymptomatic or can present with pain abdomen, dysparuenia or abdominal lump as in the present case (15),(16). Incidence of atypical variants (including malignancy) is about 1.2% (0.7-2.2%) of all the morcellated specimens(17) The risk of occult malignancy at the time of morcellation in presumed hysterectomy specimen-1/400-1/1000 (AAGL Practise Report, 2014). These iatrogenic implants having malignant tissue behave like metastasis in leiomyosarcoma (4).

In our case, there might be retained pieces of myoma at the time of first surgery, one in the pelvis and other entrapped in the abdominal wall at the site of morcellation port. There are two possibilities; either remained pieces of benign leiomyoma transformed into leiomyosarcoma over 3 years. Other possible explanation is that, these pieces had already component of leiomyosarcoma which were left at the time of first surgery. Second explanation is unlikey because the masses have grown very slowly.

To avoid these complications following steps should be taken:

1. Vigilant examination of abdomen during morcellation.
2. Morcellation should be done by expert or under guidance.
3. Histopathological examination of every myoma specimen should be done carefully from each centimetre of specimen. Also area of necrosis, degeneration, and hemorrhage should be taken for HPE examination.
4. Proper counselling regarding chance of atypical variants/ sarcoma in the morcellated specimen leading to all the complications discussed above. Need of follow up and need of repeat surgical intervention should be explained to these special cases.

The need of informed written consent

Informed consent is not simply signing a document providing permission to operate, but it is also a process of information sharing and dialogue between surgeon and patient regarding risks, benefits, and alternatives regarding a specific procedure. With regard to all forms of tissue morcellation, the following risks should be included in the discussion:

1. Dissemination of malignant tissue in the peritoneal cavity, which may worsen prognosis.
2. Dissemination of benign tissue, which may result in untoward health consequences, including the need for re-operation or additional treatments.
3. Rendering complete pathologic evaluation of a tissue specimen more difficult.
4. Injury to adjacent organs unique to the technique of morcellation.

These risks should be weighed in the context of the benefits of a minimally invasive approach as well as the risks and benefits of expectant management or laparotomy as alternatives. The complications of laparotomy should be noted, including wound infection, blood transfusion, longer recovery periods and the potential for life threatening complications such as venous thromboembolic disease (Level A).(AAGL Practise Report, 2014)

Proposed alternatives

Modified morcellation techniques i.e. minilaparotomy, vaginal morcellation and Contained in Bag Morcellation (CIBM) are upcoming as alternative methods of specimen retrieval to avoid intraperitoneal dissemination of the myoma tissue (17).

It is important to note that, currently, any form of morcellation can be associated with iatrogenic dissemination of cancer; therefore, minimally invasive gynecologic surgeons should consider several alternatives to morcellation for specimen removal (19). Laparoscopic approaches to supracervical hysterectomy, myomectomy, or

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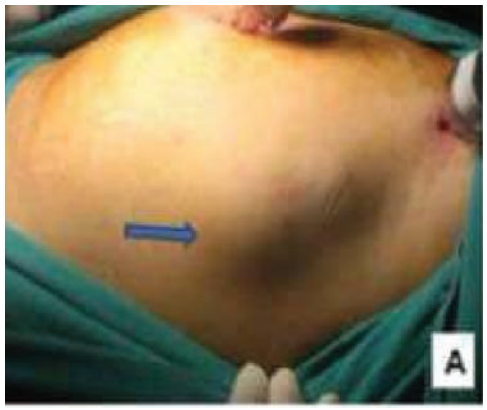
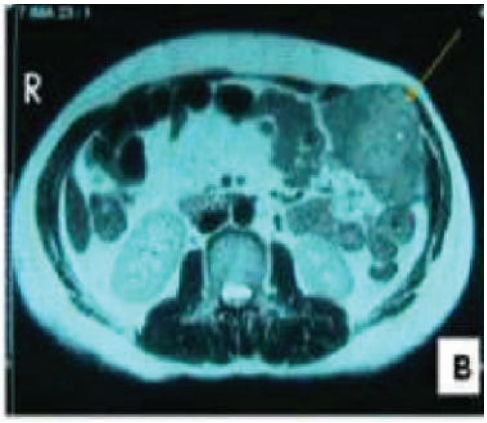
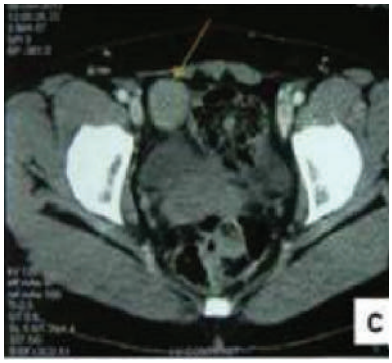


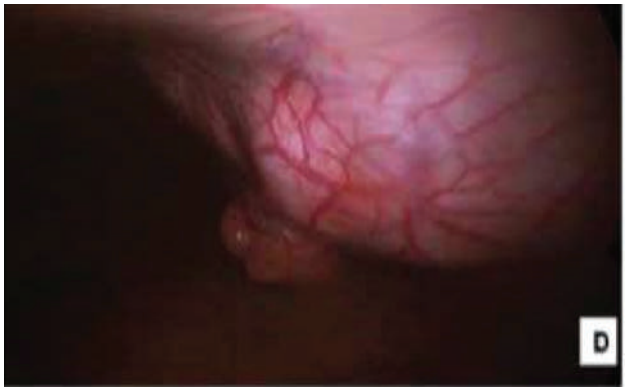
(A)- Abdominal mass occupying left hypogastrium and lumber area at previous morcellation site.



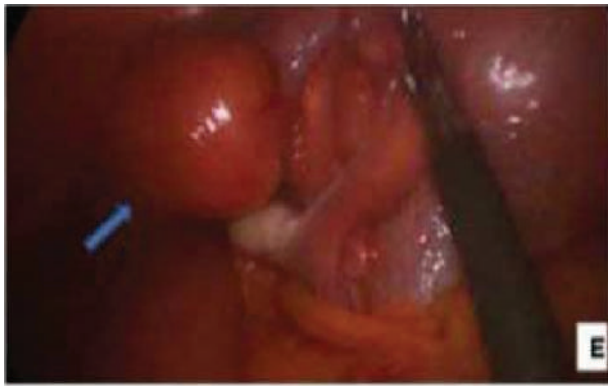
(B) MRI showing Hypointense lesion(10x8cm) occupying left abdominal wall involving rectus sheath.



(C)- MRI showing hypoeintense mass(4x4cm) in right adnexa separate from ovary



.(D)- Laparoscopic view showing inner side of the abdominal mass.



(E)- Pelvic mass (4x4cm) near right Infundibulopelvic ligament.

total hysterectomy in which the specimen is too large to fit through the vagina can be performed with subsequent removal of the specimen through a mini-laparotomy. Manual morcellation within an endoscopic bag is also a viable option described in the literature and often practiced in gynecologic oncology(20). In this technique, tissue is placed within an endoscopic bag, the edges of the bag are then brought outside of the body with or without extending the port incision, and power morcellation is performed. Vaginal approaches to manual morcellation within a bag have also been described (21). Feasibility studies of power morcellation within an isolation bag are currently ongoing but have been limited by manufacturers pulling power morcellators from the market (22).

To conclude, the literature is still sparse regarding the risk of leiomyosarcoma in a presumed fibroid. Further large number trials are required to evaluate the sensitivity & specificity of different imaging and biochemical modalities

to make optimal cut-offs to differentiate between benign and malignant lesions.

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11

OUR EXPERIENCE OF UNSUSPECTED UTERINE SARCOMA IN LAPROSCOPIC **MYOMECTOMY**

Dr. P G Paul
Consultant Gynaecologist and Endoscopic surgeon,
Paul's Hospital,
Centre for advanced endoscopy & infertility, Cochin

Dr. Aditya S Khurd,
Dr. Reena Garg,
Dr. Manju Thomas

Introduction

We have been offering minimal invasive surgery for symptomatic fibroids since 1993. We had published our experience of myomectomy, newer techniques, pregnancies following myomectomy and complications of myomectomy. [1,2,3,4] Laparoscopic myomectomy became more popular after introduction of power morcellation. [5] Recently this technique has come under scrutiny because of the risk of unintended morcellation of uterine sarcoma in cases operated for presumed leiomyomas. Traditionally incidence of leiomyosarcoma is quoted as one in thousand,but recent publications have quoted the incidence as 1 in 350 to 1 in 600. [6] We also have encountered few cases of sarcomas in our series of myomectomy and hysterectomy. In this article we are sharing our experience of unsuspected uterine sarcomas in laparoscopic and hysteroscopic myomectomy.

897 women underwent laparoscopic or hysteroscopic myomectomy for presumed uterine leiomyomas from 2003 to 2014, at Paul's Hospital, an advanced Laparoscopy and Infertility Centre in Kochi. We had 3 patients who were diagnosed to have uterine sarcoma on histopathological examination. 2 of them were diagnosed as leiomyosacoma (LMS) and 1 case was diagnosed as endometrial stromal cell sacoma (ESS). We also had 5 cases of sarcoma out of 1781

patients who underwent total laparoscopic hysterectomy for presumed myomas.

Case 1:

2004 –12 years old girl, who had attained menarche 1 year back, presented with 2 episodes of menorrhagia. She was admitted in a private hospital 2 weeks earlier, for the same complaint and had been transfused with 3 units of packed cell volume for anaemia (Haemoglobin 5 gm %). Dilatation and curettage was also done outside. Histopathological examination showed necrotic tissue. On examination mass was palpable per abdomen upto 14 weeks. On ultrasonography uterus was enlarged with a heterogeneous mass in endometrial cavity measuring 2.5 cm x 2 cm. On hysteroscopy, a submucous myoma was noted. Myoma was resected with loop electrode completely and the myoma bed was coagulated with ball electrode. The myoma tissue was removed from the uterine cavity using flushing curettage. Specimen weight was 60gms. Low grade endometrial stromal cell sarcoma was diagnosed on histopathological examination. Patient did not undergo any further surgical treatment and died after 4 years of surgery.

Case 2:

2007 - 34 years P0A1, presented with secondary infertility, menorrhagia and backache since 1 month. On clinical examination, mass was palpable per abdomen upto 14 weeks size. On ultrasonography, uterus was enlarged uterus to 14 cm with a single large 7cm fundal fibroid, both ovaries were normal. On laparoscopy uterus was enlarged to 14 weeks with a fundal fibroid with degenerative changes (Fig.1, 2). Laparoscopic myomectomy was done. The myoma was removed from the peritoneal cavity using power morcellation. Specimen weight was 200gms. Histopathological examination showed leiomyosarcoma. Patient underwent Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy at another centre followed by chemotherapy. Patient deceased 2 years after surgery.

Case 3:

2013 - 37 years nulligravida presented with primary infertility for 7 years. Patient had undergone a laparoscopic myomectomy 8 months before and a second laparoscopic myomectomy attempt was abandoned due to dense adhesions 1 week before. On clinical examination mass was palpable per abdomen, upto 14 weeks. Ultrasonography revealed an enlarged uterus with an anterior wall subserous myoma measuring 10 x 9 cm and a posterior wall subserous myoma measuring 2.7 x 2.1 cm, both ovaries were normal. On laparoscopy omental and bowel adhesions were released.

Uterus was found to be enlarged with an anterior wall subserous myoma of 10cm buried under the omental and bowel adhesions. (Fig.3, 4) Laparoscopic myomectomy was performed. The myoma was removed from the peritoneal cavity using power morcellation. Specimen weight was 180gms. Histopathological examination was consistent with leiomyosarcoma. Patient received chemotherapy following myomectomy followed by Total Abdominal Hysterectomy with Bilateral Salpingo-oophorectomy at another centre7 months later. Patient is alive at present.

Discussion

Uterine sarcomas comprise less than 1 % of gynaecologic malignancies and 2-5% of all uterine malignancies [7].Malignant pure mesenchymal uterine tumour / uterine sarcomas encompass endometrial stromal sarcoma (ESS), Leiomyosarcoma (LMS) and undifferentiated sarcoma. [8]Leiomyosarcoma occurs with a peak incidence at age 50 years. [9] It accounts for 30% of all uterine sarcoma. [7] The common presenting symptoms/signs include abnormal vaginal bleeding, pelvic pain and/or pelvic mass which is very similar to our LMS patient's complaints &clinical profile. LMS tends to spread hematogenously rather than by local growth. Regional lymph node positivity and distant metastasis are uncommon at the time of diagnosis. Unfortunately the symptoms mimic those seen with benign leiomyomas .Therefore diagnosis of LMS is often first established by a pathologist after surgical removal for presumed leiomyoma. [10]

ESS, a very rare malignant tumour arising from endometrial stroma, accounts for 0.2% of all uterine malignancies. In the WHO 2003 classification, ESS are divided into (a) endometrial stromal nodule (b) Low grade endometrial stromal sarcoma and(c) undifferentiated endometrial or uterine sarcoma. Most patients are in the age group 42 to 53 years.More than half the patients are pre-menopausal. Young patients and girls may be affected. [11]. AUB is the most common presenting symptom. Uterine sarcomas have a poor prognosis with an overall survival rate of less than 50% even when presenting at an early stage. [12] Our ESS patient, aged 12 years, expired 4 years after surgery.

There are several studies focussing on the incidence of uterine sarcomas in patients operated on for presumed leiomyomas. Parker et al. has concluded the total incidence of uterine sarcomas among patients operated on for uterine leiomyomas to be extremely low - 0.23 % (1in 435 women)[13]. According to Leing et al, the incidence of uterine LMS in population of women referred for anticipated benign fibroids was 0.54% (1 in 183women). [14] The incidence of LMS in our hospital was 0.22%(1 in 449 women) and ESS was 0.11% (1 in 897 women) and the combined incidence of uterine sarcoma (LMS+ESS) was 0.33%(1 in 299 women). (Fig.5)

Conclusion

The incidence of uterine sarcomas in patients being operated for presumed leiomyomas in our centre is 0.33 % (1 in 299 women). There is a risk, however small it may be, of unintended morcellation of uterine sarcomas in these patients. Patients who are being considered for power morcellation should be adequately counselled about the risks, benefits and alternatives before undergoing the procedure.

FIGURE LEGENDS-

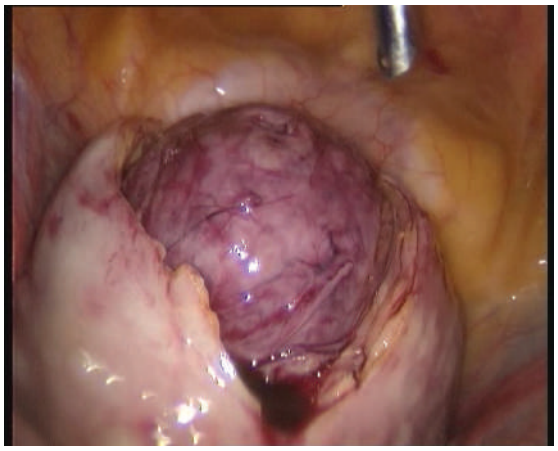


Fig.1 - Tumour visible after myometrial incision

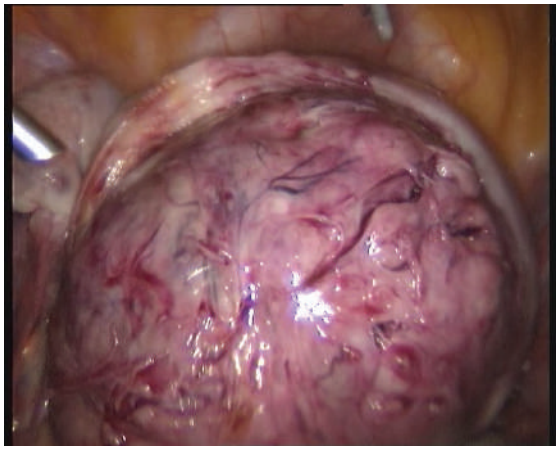


Fig.2 - Well demarcated soft tumour

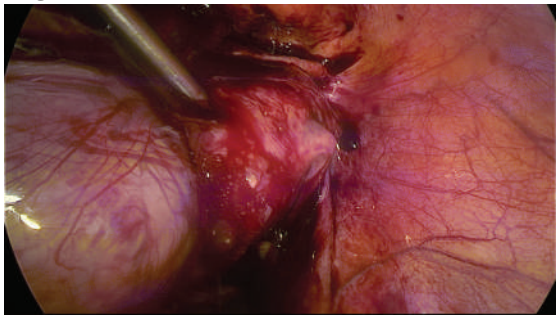


Fig.3 - Anterioruterine wall subserous tumour

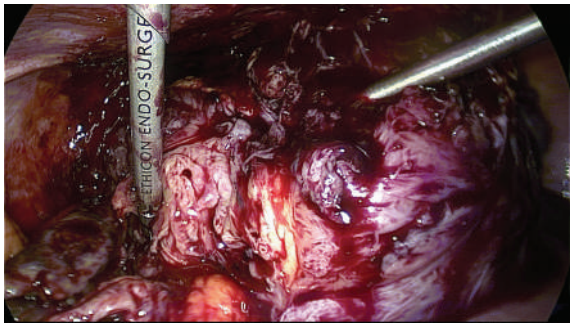
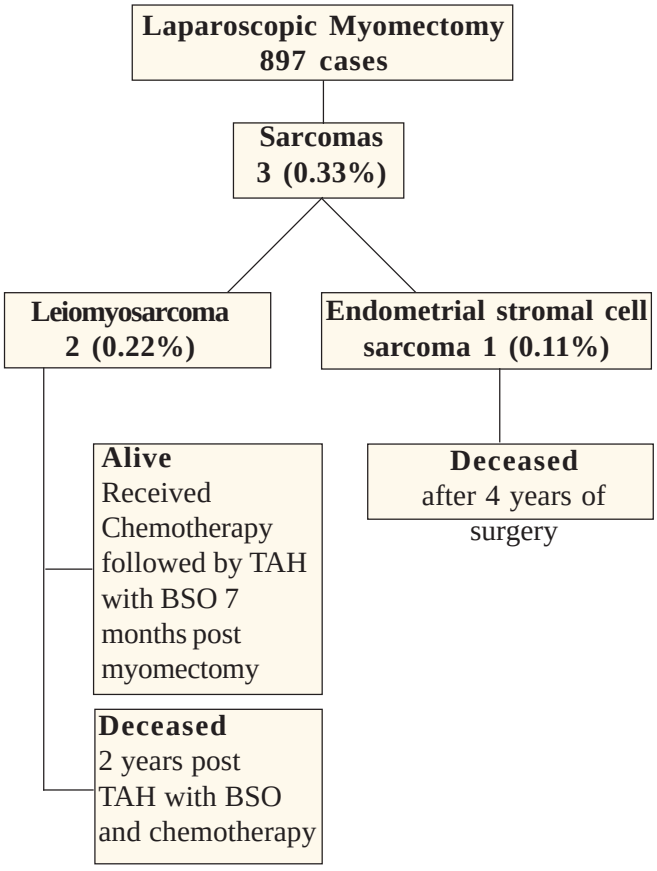


Fig.4 - Soft highly vascular tumour after adhesiolysis

Fig.5–Study flowchart

Fig. 5 – Study flowchart



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12

CONTROVERSIES NEW SOLUTIONS FOR LAPROSCOPIC MORCELLIATION IN FIBROID

Dr. Prakash Trivedi,
MD; DGO; DNB; FCPS
Diploma in Pelviscopic Surgery (Germany)
Advanced Hysteroscopic Surgery (France)

Dr. Soumil Trivedi,
DNB
Fellow in minimal Access Surgery- Gynaecology)

Co-Authors
Dr. Animesh Gandhi
Dr. Sandeep Patil

Most gynecologists are well aware of the recent developments surrounding laparoscopic morcellation. Things have unfolded rapidly since the December 18th, 2013 coverage by The Wall Street Journal.

The article was sparked by the case of a physician who underwent a routine laparoscopic hysterectomy for presumed symptomatic uterine fibroids. A preoperative workup did not indicate a suspicion for malignancy, and laparoscopic morcellation was performed for tissue extraction. Unfortunately, pathologic examination revealed an occult leiomyosarcoma.

Significant media coverage followed The Wall Street Journal article and there was a strong call for a change in morcellation practices. Later it was decided to significantly limit the use of laparoscopic morcellation for patients undergoing surgery for uterine fibroids, encouraging morcellation inside of a containment bag ,based on pioneering work by Dr. Anthony Shibley, who first introduced this concept 2 years ago.

On April 17th the FDA issued an advisory discouraging the use of power morcellation during hysterectomy or myomectomy for uterine fibroids. The FDA did not issue a moratorium on the use of power morcellation, but encouraged physicians to seek alternatives.

It did not take long for industry to respond. On April 28th a major company announced that it would discontinue supplying its morcellator until further notice. At that time, its morcellator had approximately 80% market share, so the impact of this decision will have widespread implications.

Background

Electromechanical morcellation was first introduced to the market almost 20 years ago and has since enabled surgeons to offer patients a minimally invasive approach to hysterectomies and myomectomies.

The benefits of minimally invasive surgery are well known and include faster recovery, less pain, less blood loss, and lower risk of overall morbidity and mortality. However, laparoscopic morcellation has important drawbacks that include the risk of severe trauma, tissue disruption that makes pathologic diagnosis more difficult, and dispersion of the morcellated tissue throughout the abdominal cavity. Less-serious consequences of tissue dispersion include cases of endometriosis and adenomyosis as well as leiomyomatosis, which are estimated to occur in 0.9% of patients having laparoscopic morcellation.

A more serious consequence is dissemination of occult malignancy. The estimated incidence of occult leiomyosarcoma in patients having surgery for presumed leiomyomata is between 1:200 and 1:1100, with the FDA quoting a risk of 1 in 350 based on its comprehensive review of the literature. Many have challenged these numbers, especially because most of the publications come from large referral centers, which could inflate the prevalence estimates.

Tissue retrieval is a unique challenge since long time. Originally it was for dermoid cyst, doubtful ovarian masses removed in lap sac or endobag reducing the risk of spillage, though if the spillage was from a non - malignant mass, the consequences were not dangerous. However, laparoscopic power morcellation if performed in women with unsuspected uterine sarcoma, there is a risk that the procedure will spread the cancerous tissue within the abdomen and pelvis, significantly worsening the patient's likelihood of long-term survival. Evaluation by sonography, Doppler or markers is also not completely reliable to diagnose a case of sarcoma. In a recent meta-analysis the estimated rate of leiomyosarcoma was 0.51 per 1000 procedures or approximately 1 in 2000; restricting the meta-analysis to the 64 prospective studies resulted in a substantially lower estimate of 0.12 leiomyosarcomas per 1000 procedures or approximately 1 leiomyosarcoma per 8300 surgeries. By withdrawing morcellation & not giving the benefits of Laparaoscopic Surgery specially in young infertile women with fibroids or Laparoscopic Hysterectomy in patients with low risk for ULMS is debatable.

Thus, any kind of tissue disruption at the time of surgery may significantly worsen the prognosis for patients with an occult sarcoma or other pathology.

What should the gynecologist do?

Given the risk of occult malignancy, does it make sense to abandon all minimally invasive approaches for patients who are having surgery for symptomatic uterine fibroids?

Because a myomectomy ultimately involves some tissue disruption, should myomectomy be abandoned as a surgical procedure? What about noninvasive treatment options that leave the presumed fibroid inside the body, such as uterine artery embolization, MRI-guided focused ultrasound, and radiofrequency ablation?

It would be a step in the wrong direction to counsel all patients with symptomatic uterine fibroids to undergo total abdominal hysterectomy. That would result in increased patient morbidity and remove the option of future fertility for women who would rather retain their uterus.

In our opinion, patients with symptomatic fibroids who desire future fertility should still be offered this treatment option. However, they need to be adequately counseled that removing fibroids from the uterus involves some tissue disruption and that this must be balanced against their desire for future fertility.

One can predict that the extent of the tissue disruption and dispersion may be limited if open morcellation is avoided in these cases. In addition, it is likely that providers may counsel patients more toward a total laparoscopic hysterectomy versus a supracervical hysterectomy because the former may not involve morcellation, provided

that the specimen is small enough to fit through the vagina intact.

On May 9th, ACOG released a special report titled "Power Morcellation and Occult Malignancy in Gynecologic Surgery." It advises practitioners to quote patients a rate of 1/500 for undiagnosed sarcoma and also recommend extensive patient counseling as well as offering alternatives to laparoscopic power morcellation.

AAGL issued a Statement as a reply to FDA stating that it is possible that different risk profiles exist among the various methods of morcellation, but specific data are lacking with respect to these differences (Level C). Hysteroscopic removal of symptomatic submucosal uterine myoma in premenopausal women need not be exchanged for definitive treatment (i.e. hysterectomy) simply to avoid morcellation (Level A).Women with asymptomatic uterine myoma can be managed expectantly (Level A).Laparoscopy has well-documented advantages over laparotomy regarding surgical complications and patient outcomes (Level A).Sarcomas have been diagnosed after alternative uterine-preserving treatments such as Uterine Artery Ligation. The same challenges in preoperative diagnosis of uterine sarcoma apply to these surgical alternatives (Level C).The use of morcellation within specimen retrieval pouches for containment of benign or malignant uterine tissue requires significant skill and experience, and the use of specimen retrieval pouches should be investigated further for safety and outcomes in a controlled setting (Level C).

It would be ideal to be able to predict preoperatively whether a presumed fibroid is actually a malignancy. Unfortunately we do not have reliable ways to determine this. Demographic factors such as age or rapid tumor growth are not helpful, especially because occult malignancy may be present in women in their 20s and 30s.

Preoperative imaging shows promise, but its clinical utility is yet to be determined. Two preliminary studies using MRI with lactacte dehydrogenase isoenzyme 3 measurements or with diffusion-weighted imaging demonstrate promising results, but more research is needed before recommending routine MRIs before all surgeries for presumed leiomyomas.

The cost of such a measure would be significant and the chance of false-positive results is high, given the rarity of these conditions.

What Technique should the gynecologist adopt?

Laparoscopic Myomectomy is an art of three in one technique:

1. Removal of fibroid from the uterus
2. Reconstructing the uterus with very efficient methods of Laparoscopic suturing
3. Removing the separated fibroid from the abdominal cavity either vaginally or by morcellation.

Total Health Care Technique of performing In-bag morcellation of fibroids and uterus:

The steps of Laparoscopic Myomectomy and Laparoscopic Hysterectomy remain the same as done in a standardized fashion leaving the fibroid or uterus separated in the peritoneal cavity. The left lower port is widened to pass a 10 mm port and further with a finger mechanically stretched to make easy passage of the soft plastic sleeve carrying the bag.

As shown in Figure 1 there is a medium size strong plastic bag in the shape like stomach but with a wider opening. The wide opening of the bag is folded and introduced in a one side openable plastic cannula, which is designed to carry the bag inside the abdomen replacing the left lower 10 mm port (Figure 2). Once the bag is seen inside the sleeve in the abdomen through the laparoscope, the assistant holds only the bag with a 5 mm atraumatic grasper allowing the removal of introducing plastic sleeve. The remaining part of the mouth of the bag is pulled systematically with atraumatic graspers held in sequence by the surgeon and assistant (Figure 3). Once full bag is inside the abdomen, the 10 mm port is reintroduced with a reducer to carry a 5 mm instrument. The wide ring of the opening of the bag is identified and held by the assistant and surgeon, with a single tooth grasper surgeon holds the specimen and transfers it inside the bag (Figure 4). The opening of the bag is systematically closed bringing one end close to the left lower 10 mm port carrying a 5 mm grasper. The two parts of the opening of the bag are held together and pulled out withdrawing the 10 mm cannula. And then holding the two margins

of the mouth, the bag is mechanically pulled by two hands of the surgeon bringing the entire mouth of the bag outside the left lower port. The camera keeps a constant watch to see that the specimen is always inside the bag. Now from the right lower port with a 5 mm grasper, the duodenum shaped part of the bag, which we call as the ear with a hole, is held at the tip and rail-roaded inside the 10 mm cannula of the optics. Care is taken to keep the right semiflexed leg low to allow free movement of the 5 mm grasper holding the ear to be easily rail-roaded inside the 10 mm cannula which is withdrawn. Externally this part of the bag is seen at the umbilical region. This part of the bag which is like the ear has a 5 mm hole which is widened to introduce the 10 mm trocar which will carry the optics. Once in place, the optics is introduced and CO2 insufflation is started. The optics and the screen clearly show opening of the bag with the specimen within and the mouth of the bag coming from the left lower port is blocked by the assistant. Once everything is in place a 12 mm morcellator hand piece with a blunt tip trocar is introduced under vision inside the bag from the left lower port. A clear vision makes you visualize that the bag has replaced practically as the peritoneal lining with all abdominal structures outside the bag but the specimen is within the bag in front of the morcellator.

The unique feature of the morcellator handle is that the sharp inner blade is not fully exposed but only a rim is seen with a hood of the morcellator hand piece. A 10 mm single tooth grasper is introduced inside the morcellator which will hold the specimen and morcellation is done under vision (Figure 5). The projecting hood of the morcellator hand piece protects the sharp circular inner cutting blade & the specimen gets morcellated exactly in the fashion of orange peeling of 10 mm long pieces. With a series of long strips the whole specimen is morcellated. The bag now contains the small bits of morcellated remnant pieces and the blood of specimen side (Figure 6). The morcellator hand piece is removed blocking the mouth of the bag to prevent unnecessary scatter of tissue or fluid on the face of surgeon or assistant. The 10 mm optics and the trocar carrying the optics are removed.

A knot is tied on the long ear shaped plastic, below the hole next from the left lower port under external vision the bag is pulled out and one can see the knotted part of the ear getting withdrawn inside the umbilicus into the abdominal cavity and then comes out from the left lower port (Figure 7).

The optics is reintroduced from the 10 mm umbilical port and under vision with a port closure device the left lower port is closed. A good look of the entire peritoneal cavity confirms hemostasis and also clearly shows that not a drop of specimen side fluid or a small piece of the specimen is seen within the peritoneal cavity.

Technical Issues:

- Care has to be taken that the abdominal opening for the morcellator to enter should be adequate for free movements.

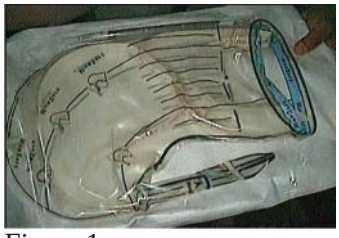
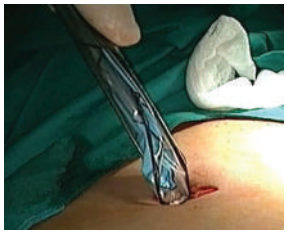


Figure 1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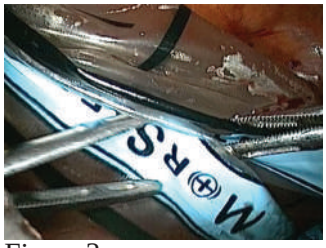
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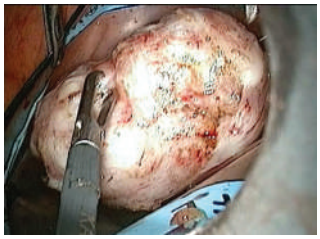
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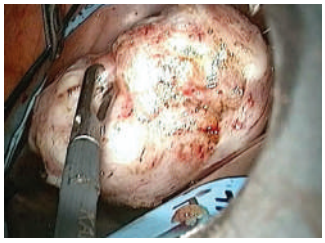
Figure 5

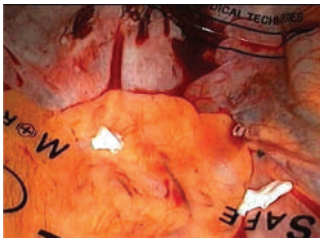
Figure 6

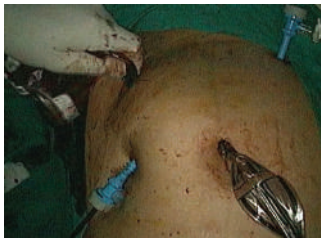
Figure 7

• The mouth of the bag once out from lower left port, the ear has to come out from the Umbilical port without any twists. Thus, the learning curve would include making sure to align the two marked parallel lines of the bag to the optics, to avoid the twist.

When faced with technical difficulty in one such case, sharp part of Rotocut was used to puncture the bag, and to our surprise complete morcellation without any spillage, in the bag itself, was possible.

Emphasis would again be on the technique which is simple, dependable and achieves all the functions of no spillage of any tissue material from the specimen into the peritoneal cavity.

Recent statistics regarding clinical characteristics and management experience of unexpected uterine sarcoma stated that among 4248 patients who underwent myomectomy for presumed leiomyoma, 9 (0.2%) had unexpected uterine sarcoma (1 [<0.1%] had leiomyosarcoma; 8 [0.2%] endometrial stromal sarcoma). The malignancy was identified in 5 (0.2%) of 3068 women who were treated by laparoscopy with power morcellation and 4 (0.3%) of 1180 who underwent laparotomy (P=0.274). Thus the overall incidence of unexpected uterine sarcoma after myomectomy was low and incidental power morcellation of unexpected uterine sarcoma seemed to cause no increase in sarcoma dissemination.

Take-home message

The controversy of morcellating a fibroid or uterus which may have unsuspected malignancy or Leiomyosarcoma is voiced and over hyped beyond genuine scientific proportion. We have a few groups of patients and activists who put laparoscopic morcellation to a total disrepute, in contrary to recent meta-analysis suggesting the actual risk of an unexpected leiomyosarcoma not more than 1 in 2000 cases or probably even less. Benefits of laparoscopic morcellation should be given as an option alongwith vaginal removal of the specimen, especially in young and deserving patients, wherein benefits of laparoscopic minimal access surgery with a quick recovery should be extended after proper counseling. The new In-bag morcellation technique as described would easily take care of fibroids or uterus upto 26 weeks in size or weighing upto 2 kgs.

The most interesting scientific aspect of this controversy is that even if a leiomyosarcoma is removed by an open en bloc surgery still there is 50% risk of spread or already residual existing disease compared to 60% risk when done by Laparoscopic morcellation, that is, only a 10% risk reduction with open surgery. Further with the in-bag morcellation the risk of spread drops down drastically unless originally the sarcoma or cancer was already spread.

The In-bag morcellation technique appears to handle the issue of ULMS & allows Laparoscopic Myomectomy & Hysterectomy with fair safety. The scientific focus should be directed towards diagnosing leiomyosarcoma or a malignancy prior to surgery far more accurately with methods which are yet not totally identified.

It is likely that much innovation will take place in this area in the coming months. Endobags that are specifically designed for contained morcellation will greatly facilitate this process and make it easier for surgeons to incorporate this into their practice.

Completely automatic tissue extraction devices are also being developed and may become commercially available in the next 1–2 years. These devices enable automatic morcellation in a contained environment without the need for a rotating blade or bag insufflation.

Ultimately, as innovation enters this arena, future patients will benefit as surgeons become better equipped to offer minimally invasive options for their conditions.

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13

CAESAREAN MYOMECTOMY

V P Paily
MD, FRCOG
Consultant, Rajagiri Hospital,
Alwaye, Kerala
vppaily@gmail.com

Introduction

Fibroid uterus is observed in about 2%of pregnancies. Fibroids are detected at various stages of pregnancy because of the widespread use of ultrasound scans . When detected in early pregnancy it presents a big dilemma to the pregnant woman as well as her obstetrician. The issues to be considered are whether to continue the pregnancy or terminate it or do a myomectomy straight away. But, faced with fibroid complicating pregnancy during a caesarean section (CS), the crucial decision to be made is whether to remove the fibroid during the same surgery (myomectomy or hysterectomy) or whether to leave it alone. Conventional advice is not to attempt myomectomy. The reason quoted was the unmanageable bleeding that may ensue and even end in hysterectomy. However, leaving the fibroid alone during CS also is reported to have problems. There is the risk of excess bleeding (PPH) due to poor contractility of the uterus, inversion of uterus, extrusion of fibroid into cavity and vagina, degeneration and subsequent infection. These risks justify considering myomectomy during caesarean delivery. Of late, the fear of unmanageable bleeding during caesarean myomectomy has been mitigated after several reports have appeared indicating the safety and feasibility of myomectomy during caesarean delivery.

We have followed a policy of doing myomectomy during CS since the 1990s. Our experience has encouraged us to recommend it as a

standard policy of management when fibroids are observed during caesarean section.

The problems to be addressed when met with fibroids during caesarean delivery are the following.

1. Which fibroids are to be removed?
2. What steps are available to control bleeding during myomectomy?
3. What is the appropriate technique of myomectomy to be followed?

These aspects will be discussed here.

Which fibroids are to be removed?

Generally it can be stated that if the fibroid merited removal, had it been in a nonpregnant uterus, its removal should be attempted during caesarean section as well. If the fibroids are small, especially subserous or intramural, it wouldl be advisable to leave them alone. A submucous fibroid is particularly prone to cause problems in the postpartum period and should be removed irrespective of its size. It may get extruded, undergo degeneration, get infected, lead to sub involution or rarely result in inversion of uterus. Small submucous fibroids may be missed unless one has the habit of palpating the uterine cavity before closing the uterine wound.

Certain other locations deserve special mention. A cornual fibroid is likely to cause more bleeding. Another challenging location is the lower segment where the fibroid may come in the way of the uterine incision to deliver the fetus. An added dilemma will be, whether to remove the fibroid before delivering the fetus or after, and whether to cut through the fibroid for extracting the fetus. As a general principle we follow the policy of removing the fetus before attempting removal of the fibroid. If myomectomy is attempted before removal of the fetus, it can lead to excessive bleeding and sometimes delay and difficulty in delivering the fetus with consequent birth asphyxia. Hemostatic procedures like use of tourniquet or vasopressin are not advisable until the fetus is delivered.

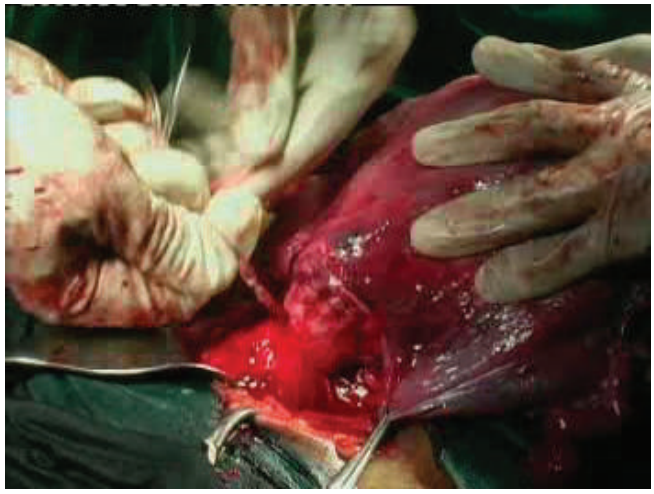
Steps to reduce blood loss during caesarean myomectomy

Uncontrollable bleeding was the reason quoted against myomectomy during CS. As a corollary, if we have means to avoid this problem of excessive bleeding, caesarean myomectomy will become possible and practical. Victor Bonney, well known for the technique of myomectomy in the non pregnant state advocated against doing it during caesarean section for fear of uncontrollable bleeding. But Bonney's followers like Howkins and Stallworthy had a different view[1]. Stallworthy argued that the myometrial contraction that can be induced with oxytocics will help to reduce the bleeding.

T echniques to reduce bleeding

We have found isthmial tourniquet to be very effective in reducing bleeding during myomectomy in the non pregnant situation. When the fibroids were in the cornual regions, tourniquets were put in the infundibulo pelvic ligaments as well. This experience has been extrapolated to caesarean myomectomy since the nineteen nineties.

The method is simple. A sterile plastic suction catheter (size 8 Fr) is passed around the isthmus of the uterus by piercing the broad ligament at an avascular area medial to the round ligament on both sides. The two ends are then crossed over in front of the cervix and twisted repeatedly until the catheter compresses the sides of the cervix. It is important to tighten it well so that the uterine arteries on both sides will get occluded. An artery clamp is applied on the twisted catheter close to the cervix so that the catheter does not get loose. Alternatively, the ends can be tied into a tight knot. The tourniquet is left in situ until the myomectomy wound is sutured completely, including the serosal layer(Fig.1).



In case the fibroids are close to the cornual region, the ovarian artery can be a significant contributor of blood supply to the myoma bed. The tourniquet can be applied to one or both infundibulo pelvic ligaments just lateral to the ovaries. One risk is that the thin walled veins in the infundibulo pelvic ligament may get torn while the tourniquet is tightened . To avoid this complication, we include the ipsilateral round ligament also in this tourniquet so that it helps to avoid direct pressure on the veins. A size 6 Fr suction catheter can be used to put a sliding knot as the tourniquet to compress the vessels. To prevent the knot from getting loose a clamp is applied to the catheter just distal to the knot. The same opening in the broad ligament through which the isthmial tourniquet was applied is used to pass the catheter around the round ligament and infundibulo pelvic ligament.

The technique of injecting vasopressin into the myoma, that is used in laparoscopic myomectomy, may be employed here as well. We have been reluctant to use this method fearing the theoretical risk of the enhanced vascularity of pregnancy allowing too much of the drug to enter the circulation and cause complications such as bradycardia or hypertension.

Some have recommended using high dose oxytocin drip throughout the myomectomy to keep the uterus contracted and reduce the bleeding. We have not found it very helpful in reducing the blood loss.

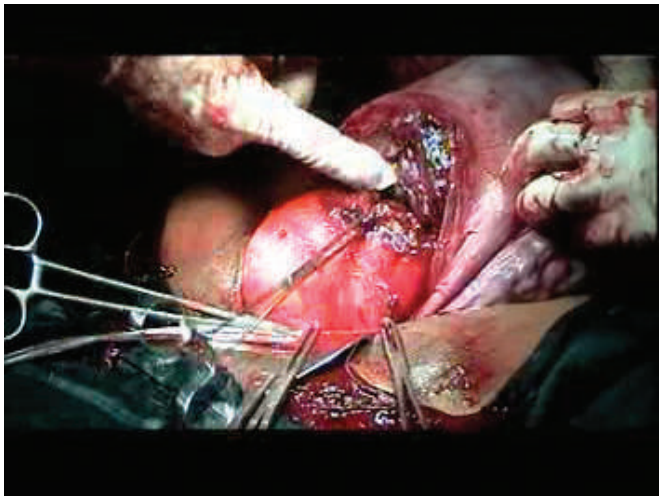
Surgical technique of myomectomy

The principles of incision into the pseudocapsule and enucleation of the fibroid, as in open myomectomy of gynaecological cases, are followed here also. It is important to make sure that the incision goes deep to the pseudocapsule and that the size of the incision is big enough to extract the fibroid without difficulty. A layered closure is followed with multiple interrupted stitches for the deeper layers to occlude the cavity. The superficial myometrium and serosa are approximated with meticulous hemostasis. The tourniquet is to be released only after the entire suturing is over. Any bleeders from the edges should then be taken care of with separate stitches or cauterisation.

Technical modifications followed in gynaecological myomectomy, like tunnelling, can be used here also. However, it is prudent to reduce the number of incisions on the posterior surface of the uterus whenever possible.

Transcavitary approach to remove fibroids on posterior walls can easily be accomplished as the cavity is open because of the caesarean incision.

Fibroids in certain situations need special mention. Lower segment fibroids will often pose a challenge. The dilemmas are whether to remove the fibroid prior to removal of the fetus , whether to incise through the fibroid if it is in the lower segment incision site, whether to deliver the fetus through the upper segment etc. We have found that often it will be possible to find a space for incision and delivery of fetus before attempting Myomectomy (Fig.2). Once the fetus is safely removed, the fibroid can be tackled in an unhurried fashion, after applying a tourniquet as described earlier.



Cornual fibroids also are challenging particularly because they draw blood from dual sources – the uterine and ovarian arteries. However, tourniquets for the isthms of the uterus and the infundibulo pelvic ligaments will help to reduce the bleeding and complete myomectomy safely. An added risk is that of compromising tubal patency while suturing back the myoma bed.

Cervical fibroid is a big challenge during caesarean myomectomy just as in the nonpregnant setting. Fortunately, on most occasions it will be possible to deliver the fetus before enucleating the fibroid. The challenges are mainly because of the difficulty in access, especially to apply the tourniquet, the proximity of the bladder, the increased blood supply coming from vaginal arteries and the

potential to damage the ureter. Our strategy is to remove the fetus through an incision above the fibroid and then to try to ligate both uterine arteries. Although at times, this may be difficult because of the circumferential expansion of the isthmus, itwill be possible most of the time. An alternative approach is to tie the uterine arteries at their origin or to do bilateral internal iliac artery ligation. Yet another approach is to inject vasopressin into the fibroid and do the myomectomy as in the nonpregnant setting. However the concern about excess vasopressin being absorbed has prevented us from trying it.
Submucous fibroids are the ones with maximum potential for problems postpartum. The risk of postpartum hemorrhage is maximum in this group. In addition, the fibroid may increase the risk of retained placenta and puerperal sepsis. The degenerated fibroid is particularly prone to infection and may get expelled piecemeal. A fundal submucous fibroid can present with the unique complication of inversion of the uterus. Removal of the submucous fibroid from the pedicle or myoma bed can usually be controlled with mattress stitches.

Personal Series

January 2000 to July 2004

Total obstetric cases	: 1671
Cases of fibroids complicating	: 24(1.44%)
Vaginal delivery (fibroids left alone)	: 8
(Two had myomectomy later)	
CS myomectomy	: 8
Cesarean hysterectomy	: 7
Cesarean & later myomectomy	: 1

Hysterectomy was chosen only in those who had completed their family, had multiple fibroids and were of the older age group.

Unusual Case

One of our cases deserves special mention because of its rarity and unusual complications. This patient had multiple fibroids on the posterior wall keeping the uterus acutely retroflexed. With the uterus enlarging as the pregnancy grew, this led to sacculation. During caesarean section the bladder was found unusually pulled up and attempts to enter the uterine cavity were futile until the lower segment vertical incision was extended to the upper segment. Initial vertical incision had involved the posterior wall of the isthmus. After delivering the fetus the mistake was recognised and the incision on the anterior and posterior walls of the uterus had to be separately stitched with a dilator kept in the cervical canal to prevent accidental coaptation of the two walls. A tourniquet around the isthmus helped to complete removal of the fibroids (myomectomy) with minimal blood loss.

Literature review

Attitude towards myomectomy varies widely in different parts of the world. But, of late there is radical change in the attitude towards **caesarean** myomectomy, accepting it as a feasible option. Ouyang and Norwitz, authors of the article "pregnancy in women with uterine leiomyoma (fibroids)" in the " UpToDate" series, state that they limit elective myomectomy at caesarean delivery to patients with symptomatic pedunculated fibroids[2]. They avoid intramyometrial myomectomy because of the risk of severe **hemorrhage.** They quote, among others, Exacoustos and Rosati who reported a series of nine patients who underwent myomectomy during caesarean delivery, of which three (33%) were complicated by severe hemorrhage requiring puerperal hysterectomy[3].This report was in 1993. Since then the outlook towards caesarean myomectomy has changed. We feel that the excess bleeding in their series was because of the reluctance to use hemostatic procedures like tourniquet to control the bleeding. It is a simple procedure as is shown in the figure and described in the text.
Contrary to the above statement against caesarean myomectomy, there are quite a few articles supporting myomectomy during caesarean delivery. Awoleke has written on the published papers from Africa[4]. This is significant because in Africa there is a high incidence of fibroids complicating pregnancy. There, women are reluctant to undergo hysterectomy for fibroids complicating pregnancy. Hence a myomectomy during caesarean delivery helps them to retain the uterus and avoid another major surgery for interval myomectomy.

Machado[5] et al presented a series of eight patients undergoing caesarean myomectomy for lower segment fibroids. They used high dose oxytocin for reducing blood loss. However, blood loss in the series was in the range of 900 to 3200 ml. We feel that other hemostatic procedures like tourniquet would have helped to reduce the blood loss considerably.

Roman[6] et al compared the blood loss in 111 women undergoing caesarean myomectomy with 257 who had only caesarean section. There was no significant difference in blood loss between the two groups. There are many other authors reporting similar experience. Li Hui[7] reported a large series in Chinese women and arrived at similar conclusions.

Conclusions

Even though there is no consensus in the literature on caesarean myomectomy, its technique and feasibility, our experience strongly supports the practice of caesarean myomectomy. The key to success and minimising blood loss is the use of hemostatic procedures like isthmial tourniquet and vasopressin injection. If these steps are followed, a policy of liberal caesarean myomectomy is possible.

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14

SMOOTH MUSCLE TUMOUR OF UNKNOWN MALIGNANT POTENTIAL (STUMP)

Dr. Neeta Warty
Specialist – Obstetrics, Gynaecology & Laparoscopic Surgeon

Neoplasms of the uterus arise from endometrium, stroma or the myometrium andtumours arising from the myometrial smooth muscle (myomas) are the commonest gynecologic tumoursaccounting for 70 %to 80% of the gynecological tumours by the age of 50 years[1].

Uterine myomas may be asymptomatic or may be associated with varied symptoms and these clinical symptoms may require an operative intervention in terms of myomectomy or hysterectomy. Further to that with the increased awareness and demand for conservative surgery of the uterus, the knowledge of the various types of leiomyomas is of profound importance. Most of these tumours are benign (leiomyomas) but may rarely be malignant (leiomyosarcoma), requiring aggressive management.

As our understanding of the pathologies increased a new breed ofmyomas came into existence, which could not be classified, as benign or malignant but having a significant rate of recurrence and requiring aggressive management. They were defined as STUMP (Smooth Muscle Tumourof Uncertain Malignant Potential).

Leiomyoma-Variants

Mitotically Active Leiomyoma (MAL)
Cellular Leiomyoma (Fig 1)
Leiomyomatosis (Fig 2)
EpitheloidLeiomyoma
Leiomyomatosis (Fig 3)

Benign Metastasizing Leiomyoma
Diffuse Peritoneal

Intravenous

Leiomyoma WithBizzare Nulei Leiomyoma With Vascular Invasion

Types Of Uterine Cancers

ENDOMETRIAL ORIGIN	MYOMETRIAL ORIGIN
Adenocarcinoma	Endometrial Stromal Sarcoma
Adenosquamous carcinoma	Mullerian Sarcoma or Carcinosarcoma
Serous Carcinoma	Leiomyosarcoma
Clear Cell Carcinoma	

STUMP

Definition

The term STUMP was originally described in the literature by Kempson in 1973[2] and the current World Health Organization classification indicates that "A Uterine SMT (Smooth Muscle Tumour) Not Diagnosed Unequivocally As Benign Or Malignant Should Be Defined As STUMP."[3]

Incidence:

The reported incidence of atypical leiomyomas is about 0.5% of all uterine mesenchymal tumours.[1]STUMP recurrence rate ranges between 8.7% and 11%, but poor data is available in the Literature.[4]It is plausible that SMTs defined as STUMPs may be variants of leiomyomas with unusual pathologic features. On the other hand, some tumors regarded as STUMPs may in reality be under diagnosedleiomyosarcomas. In fact various evidence has shown that recurred STUMPs may represent a form of "borderline" tumor or a low-grade leiomyosarcoma.

Age distribution

Median age at presentation is similar in patients diagnosed with leiomyomas that is 30 years approximately. An interesting observation is that patients affected by STUMP complicated by subsequent disease recurrence were younger than those with an uneventful follow-up.[5]

Clinical Presentation:

The clinical presentation of STUMPs resembles that of uterine leiomyomas. Typical clinical features include abnormal vaginal bleeding, symptoms of anemia, rapidly growing pelvic mass, pressure symptoms, pelvicpain, infertility etc.

Diagnostic Criteria

Uterine SMT's (Smooth Muscle Tumours) have historically been classified as benign leiomyomas and malignant leiomyosarcomas on the basis of:

1)CytologicalAtypia,
2) Mitotic Index (MI) and
3)Presence or Absence of Tumor Cell Necrosis (CoagulativeTumour Cell Necrosis, CTCN)

The Stanford criteria for the histologic diagnosis of malignant SMT (leiomyosarcoma) reported by Bell et al[6]. include at least two of the following criteria:

1) Diffuse Moderate-to Severe Atypia,
2) Mitotic Count of at least 10 Mitotic Figures (MF)/10 high power fields (HPFs) and
3) Tumor Cell Necrosis

Cellularity, which is a subjective diagnosis, tumor borders and their relations with the surrounding myometrium represent additional but less weighted morphologic criteria in the diagnosis of STUMP.

The lack of uniform diagnostic criteria and the diagnostic uncertainties of STUMP have resulted, in a possible overdiagnosis of this neoplasia. In actuality, as reported by Ipet al[7], the diagnosis of STUMP is appropriate when a tumor shows any unusual combination of the 3 above mentioned features but does not satisfy the Stanford criteria for leiomyosarcoma.

Subtypes

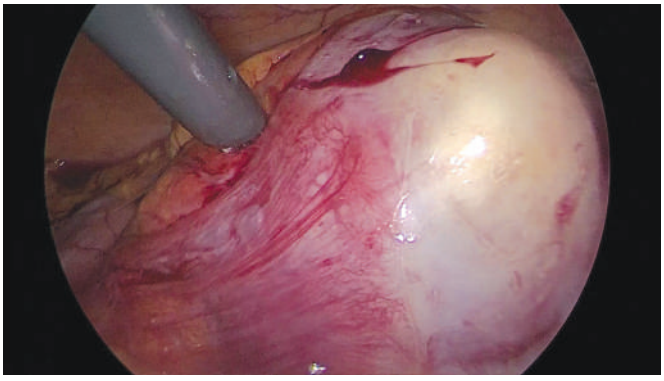
Criteria used by Bell etalinclude moderate to severe cytologicatypia and <10 MFs/10 HPFs in absence of tumor necrosis. In contrast, O'Connor and Norrisrender a diagnosis of STUMP when there are 5-9 MFs/10 HPFs and mild (grade 1/3) nuclear atypia[8].

The diagnostic terms derived from the Stanford study by Bell et al include the following subtypes:[2,3,7]

1) Atypical Leiomyoma with Limited Experience (AL-LE),
Focal Moderate To Severe Atypia,
<20 MF/ 10 HPF,
No Tumor Cell Necrosis
2) Atypical Leiomyoma, Low Risk of Recurrence (AL-LRR)
Diffuse Moderate To Severe Atypia,
<10 MF/ 10 HPF,
No Tumor Cell Necrosis.
3) Smooth Muscle Tumor of Low Malignant Potential (SMT-LMP),
Absent To Mild Atypia.

<10 MF/ 10 HPF,
Tumor Cell Necrosis,
4) Mitotically Active Leiomyoma, Limited Experience (MAL-LE)
Tumor With A High Mitotic Index (>5 And <19 Mitoses Per High-Power Field) is now considered a benign variant of leiomyoma and differs from STUMP because of the lack of recurrences and metastases outside the pelvis[8]

The factor most strongly associated with malignant behaviour seems to be CTCN, which is characterized by an abrupt transition between viable cells and necrotic areas. The prognostic importance of CTCN is such that it should be differentiated from other types of innocuous morphologic changes (namely hyalinising necrosis), necrosis associated with superficial ulceration of submucousleiomyomas and hemorrhage within leiomyomas.[9]
Intraoperative evaluation — During myomectomy, some tumor characteristics may raise suspicion of an abnormal pathology.
Gross characteristics of the mass — Loss of the typical whorl pattern, Homogeneous texture



Yellow colour (Fig), softconsistency, areas of hemorrhage or degenerative changes, Absence of a bulging surface when the capsule is incised, Ill-defined margins, the mass may be difficult to excise, although this may also be true of an adenomyoma or certain leiomyomas due to degenerative change or prior treatment with a gonadotropin-releasing hormone (GnRHagonist or antagonist) or myomectomy done in a patient with a previous recent pregnancy. STUMP has been reported in subserosal, intramural as well as submucous specimens.

Whenever a doubtful pathology is encountered it is better to perform extraction of the specimen in a contained environment (morcellation in bag) or delivery of specimen by minilaparotomy. In cases wherein an alternate access is possible,vaginal extraction in hysterectomy or colpotomy may be a better option. And in cases overtly appearing malignant a conventional laparotomy maybe advisable.

Hence it is mandatory that an appropriate informed consent of the patient after adequate pre operative counseling explaining all the risks and possibilities is taken and patient is given a choice as to decide regarding the mode of surgery to prevent future complications. However it may be worthwhile to mention that considering the rarity of occurrence of these pathologies it may be inappropriate to not offer the patient the benefit of minimal access surgery and the reduced morbidity.

Management:

With the advent of minimal access surgery and the demand for conservative treatment (Myomectomy) and intraperitonealmorcellation, localpostoperative recurrence and metastatasization have to be taken care of.Due to the rarity of these cases it is very difficult to form a standard treatment protocol.

Hence it may be better if the mandatory preoperative evaluation tests including an LDH level (Isoenzyme 3) and a dynamic MRI if possible be performed in all cases of fibroids especially scheduled for conservative surgery so as to differentiate from a leiomyosarcoma[9].

In the event of STUMP diagnosis in myomectomy specimens, considering the proved possibility of recurrence, hysterectomy represents the gold standard for those women who have completed their childbearing. However in cases wherein myomectomy is performed as a fertility enhancing surgery patients need extensive counseling regarding the unknown clinical behaviour and outcome ,accounting for the patient age,number,size and location of the residual myoma and a risk benefit approach should be presented balancing the fertility and pregnancy outcome vs risk of recurrence and metastasis. Successful pregnancies following fertility sparing

surgery have been reported however these patients should be adequately informed of the risk of recurrence and a strict follow-up program through clinical and imaging techniques is mandatory.[4,10,11,]

STUMPs may recur either as STUMPs or as leiomyosarcomas. The treatment of choice in the event of a recurrence is surgical excision followed by adjuvant therapy, such as pelvic irradiation, chemotherapy (doxorubicin and cisplatin), medroxyprogesterone and gonadotropin-releasing hormone analogue.[2,4,12-15] While the efficacy of adjuvant therapy is generally accepted, an uneventful clinical course was noted even in the absence of such treatment .If the efficacy of progesterone is confirmed, progesterone-releasing intrauterine device (LNS-IUS) may be a valid option in the event of fertility sparing surgery [16].

In cases wherein there have been use of any morcellation techniques, which has not been a contained morcellation and a post operative pathology report of STUMP or any other types of atypical myomas is obtained, surgical re-exploration procedure after morcellation of STUMPs is advisable given the high likelihood of detecting peritoneal implants. A secondary surgical assessment is warranted because findings could potentially change a patient's treatment and provide prognostic information to improve counseling. Based on the results of her re-exploration procedure, the patient with malignant implantscanbe started on megestrol for suppression of her disease. Unfortunately, computed tomographic scans are unlikely to be helpful for determining if surgical re-exploration is needed because they cannot reliably detect lesions smaller than 4 mm in size and the implants seen at surgical re-exploration rarely exceed this threshold.however a large study conducted states that the occurrence of peritoneal recurrence after laparoscopic myomectomy of atypical leiomyoma is very rare.[17]

Follow up

Clinical management and follow-up of this disease remain a matter of debate

As reported by Ip et al. STUMPs are characterized by the possibility of delayed recurrences. However they present a highest median survival following recurrence as opposed to aggressive malignant uterine neoplasia. Recurred STUMPs are biologically low-grade LMS; However, using current analysis methods this diagnosis is not attainable until a recurrence develops.

There is a potential role of immunohistochemistry of p16 and p53 in identifying the more aggressive form of

STUMPs.

Furthermore there is lack of consensus regarding implementation of follow-up protocols .Ip et al suggest an intense follow-up program with an evaluation performed every 6 months in the first 5 years followed by annual surveillance for the next 5 years. Follow-up visits should consist of a history, general and pelvic examination and imaging studies including chest radiography, pelvic ultrasonography and Computed tomography or magnetic resonance imaging.

Conclusions

The classification of smooth muscle cell neoplasms of the uterus with unknown malignant potential remains controversial. Some Authors suggest that perhaps even certain types of "benign leiomyomas", due to the aggressive clinical behaviour, which characterizes them, should be included in the present classification

Patients with STUMPs must be counseled regarding the potential risk of recurrence as leiomyosarcoma. A multidisciplinary management carried out by a team composed of gynaecologist, dedicated pathologist (with expertise in gynaecologicalpathology) and oncologist is mandatory for early detection of this disease and to establish the treatment of choice and follow up program. Even though STUMPs demonstrate a low-grade malignancy, a prolonged survival rate and delayed recurrence, patients with STUMPs require closer surveillance than a yearly examination because of the non-neglible risk of metastases even many years after initial diagnosis. On this basis, we believe that patients affected by STUMP should receive a long-term surveillance through clinical evaluation and imaging techniques.

Finally, in accordance with Atkins et al. and Ip etal, the possibility to test by immuno histochemical assay the over expression of p16 and p53 on histological samples, may be useful, in the next future, to identify the cohort of patients at increased risk of recurrence which may benefit from "personalized" surgical-oncological

strategies. Although the Society of Gynecologic Oncology and the National Comprehensive Cancer Network (NCCN) have not issued specific guidelines for these tumor subtypes it is reasonable to use the NCCN guideline for uterine sarcoma that was updated in August2014

NCCN recommendations include computed tomographic imaging of the chest/abdomen/pelvis every 3 to 6 months for the first 2 to 3 years and every 6 months for an additional 2 years. We can limit imaging to every 6 months given the indolent nature of these tumors and the potential risks of cumulative radiation exposure.

Also obtaining estrogen receptor and progesterone receptor expression status on all STUMPs and ESSs will be helpful. The prevalence of estrogen receptor/progesterone receptor positivity is high. This can guide counseling for oophorectomy in premenopausal women and provides valuable information regarding the potential usefulness of hormonal therapy. The profile of high PR expression (2+ or 3+) and low p53 expression (0 or 1+) is 100% specific for the non-sarcomatous diagnosis[19].Very few studies have analyzed STUMPs with recurrences. Different histological classifications (not always using the Stanford criteria), diagnostic methods, length of follow-up and lack of detailed histological information make it difficult to compare the findings and draw conclusions. Guntupalli et al reported three patients (7.3%) had a recurrence during the follow-up period, one patient presented with a pelvic mass and a pulmonary nodule, and two patients presented with retroperitoneal and pelvic masses. Berretta etal.presented a report of 3 cases with STUMPs. One patient developed diffuse lung metastases 9 years after the original diagnosis. Amant et al reported a retroperitoneal/ pelvic relapse after 4 years in a patient diagnosed with a STUMP and treated with hysterectomy and adnexectomy. Previous studies suggest that STUMPs are usually clinically benign, but they should be considered as tumors of low malignant potential because they can occasionally recur or metastasize to distant sites, years after hysterectomy. There seems to be no consensus as to which histological features of STUMPs predict a higher probability of recurrence, the location of recurrence (sites reported include pelvis, abdomen, liver, lungs, lymph nodes, humerus, retroperitoneum, and uterus-if hysterectomy not performed), time to recurrence (between 15 months to 9 years), and histological type of recurrences (STUMP or leiomyosarcoma)[6,20,21] . There are no demographic characteristics or any serum oncological markers to suggest predictive of recurrences[8,22,23].

A few studies have identified Immuno Histochemistry (IHC) markers as a predictor of recurrences. Poorer prognosis is associated with the presence of p16 and p53 IHC positivity. The IHC, including Ki-67, ER, and PR, is useful to distinguish between cases of malignant uterine SMTs and those of uncertain or borderline histology. Overexpression of Ki-67 labeling index is frequently associated with leiomyosarcoma.

To sum it all ,it is a better and a safer strategy to assume that any myoma can be a STUMP or any of the variants or a Leiomyosarcoma and retrieval of the same should be universally in a contained environment. All specimens have to screened preferably by a pathologist specifically experienced in evaluating gynecologic specimens and familiar with the histological appearances of the various variants.

Non operative management for SMT of the uterus must be prescribed after thorough preoperative evaluation so as not to under diagnose a probable STUMP or other Atypical Variants. Larger number of studies are required to develop universal guidelines for the management and surveillance of STUMP and recurrence in STUMP.

Better Tissue retrieval techniques neeed to be developed to minimize the risk of possible dissemination. And lastly but most importantly a thorough counselling of all patients with uterine myomas impressing the need for specialized investigations,various tissue retrieval techniques especially in Minimal Access Surgery,risks of recurrence and surveillance required in cases of detection of an abnormal pathology post surgery and the absence of definitive guidelines as to the further monitoring in patients diagnosed of the same and hence a definitive surgery like hysterectomy may be a safer option.

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DISSEMINATED PERITONEAL LEIMYOMATOSIS

Dr.Nutan Jain
(M.S. - Obs. & Gynae.)Director
Vardhman Infertility & Endoscopy Centre,
A-36, South Civil Lines, MahavirChowk,
Muzaffarnagar-251001,

Dr.Monika Ranwa
M.S. Obs& Gynae (Clinical Research Fellow)
Vardhman Infertility & Endoscopy Centre,
A-36, South Civil Lines, MahavirChowk,
Muzaffarnagar-251001,

Dr.AjayAgrawal
M.D. Obs& Gynae (Clinical Research Fellow)
Vardhman Infertility & Endoscopy Centre,
A-36, South Civil Lines, MahavirChowk,
Muzaffarnagar-251001,

Introduction

Leiomyomas represent the most common gynecologic and uterine neoplasms. Approximately 20%–30% of women older than 35 years have uterine leiomyomas that present clinically. However, leiomyomas occasionally occur with unusual growth patterns or in unusual locations that make their identification more challenging both clinically and radiologically. Examples of leiomyomas with an uncommon growth pattern include Disseminated peritoneal Leiomyomatosis (DPL), intravenous Leiomyomatosis(IVL), benign metastasizing leiomyomas, retroperitoneal leiomyomas, and parasitic leiomyomas[1]. These groups of smooth muscle tumors resemble uterine leiomyomas at both gross and microscopic levels but present in atypical locations.

Disseminated peritoneal leiomyomatosis (DPL) also known as diffuse peritoneal Leiomyomatosis or Leiomyomato sisperitonealis disseminata (LPD), was first described in 1952 by Wilson and Pale[2] and named byTaubertet al[3]. in 1965. It is a rare but well-documented disorder characterized by presence of multiple smoothmuscle, myofibroblastic and fibroblastic nodules on peritonealsurface of pelvic and abdominal cavity in woman of reproductive age[4]. This benign disorder is often confused with peritoneal carcinomatosis, because their macroscopic appearances are very similar. Disseminated peritoneal leiomyomatosis is usually discovered accidentally during other procedures, such as laparoscopy, cesarean section, laparotomy, tubal ligation, *etc*. Etiology is uncertain but

Disseminated peritoneal leiomyomatosis seems to be amultifactorial disease with a genetic or hormonal component (high levels of estrogen and progesterone) which leads to metaplasia of peritoneal mesenchymal cells.

Clinical presentation

Fewer than 150 cases of Disseminated peritoneal leiomyomatosis have been reported in the literature to date[5].Most times, the patients are asymptomatic,and the disease is incidentally found, so there is a possibility that the disease incidence is higher than the number of casesdescribed in the literature[6]. Only few cases present with abdominal/ pelvic pain, rectal or vaginal bleeding and, more rarely, with gastrointestinal disorders.The disease is usually seen in women of reproductive age, associated with increased estrogen and progesterone levels such as pregnancy (Fig 1) or prolonged oral contraceptive use and/or combined hormonal replacement therapy, and oestrogen-secreting ovarian fibrothecoma. The notable point with this condition, which occurs in association with pregnancy in 70% of cases, is that its macroscopic appearance can be mistaken for peritoneal carcinomatosis[7].Postpartum spontaneous regression is the rule[8].Disseminated peritoneal leiomyomatosis has also been reported in postmenopausal females[9].Familial occurrence of Disseminated peritoneal leiomyomatosis, albeit rare, has been reported[10].Most Disseminated peritoneal leiomyomatosis cases are clinically benign and some may regress partially or completely[11]. Alternatively they can also progress, recur or undergo malignant transformation[12].

Disseminated peritoneal leiomyomatosis can occasionally be confused with intra-abdominal carcinomatosis[13]. Presentation of Disseminated peritoneal leiomyomatosis mimicking ovarian torsion has been reported[14]. The diagnosis of Disseminated peritoneal leiomyomatosis is based on surgical findings and histopathologic examination to exclude possible malignant transformation or other malignancies, such as gastrointestinal stromal tumors (GISTs) [15].

Pathogenesis

Multiple peritoneal leiomyomas were first described in a case report in 1952, as a feature associated with a granulosa cell ovarian tumor. However, only in 1965, the condition was named "leiomyomatosisperitonealisdisseminata" and characterized as an entity related to uterine leiomyomas. Since then, isolated cases have been described, without consensus about the histogenesis of this rare condition.The pathogenesis of Disseminated peritoneal leiomyomatosislargely remains unclear because it is a rare condition. Nonetheless, there are several theories in the literature including hormonal, subperitoneal mesenchymal stem cells, metaplasia, genetic, or iatrogenic after morcellation of myoma during laparoscopic surgery. The largest series[15] of Disseminated peritoneal leiomyomatosis was published in 1982.The authors described twenty patients with an age ranged from twenty two to fourty two years; half of them were pregnant or immediately postpartum. The basic pathogenesis of Disseminated peritoneal leiomyomatosis is a multicentric metaplastic change of the submesothelial connective tissue of theabdomen due to an abnormal response to ovarian hormonalstimulation, be it normal or elevated[16]. That hypothesisalso might account for the association of diffuse peritonealleiomyomatosis with endometriosis(Fig 2), as the subcoelomi cmesenchyme is thought to be capable of differentiating intovarious tissues, including endometrial glandular epithelium[17]. However, it is difficult to admit that a rare disease, such as Disseminated peritoneal leiomyomatosis, can have the same origin and hormonal influence as that of endometriosis, an extremely common condition. According to some authors, exposure to estrogen isthe primary mechanism involved in the development of leiomy omatosisperiton ealisdisseminate. Since female gonadal steroids play an important role in the pathogenesis of Disseminated peritoneal leiomyomatosis, it is generally associated with high levels of exogenous and endogenous female gonadal steroids[18] .Two cases have been reported associating the disease with the utilization of tamoxifen for the management of breast cancer. Another theory[19] is that the primary tumor might be an inadequately diagnosed low-grade leiomyosarcoma with low malignant potential as FIGO has described it in classification of leiomyosarcoma. However, none of the characteristic findings of leiomyosarcoma

such as coagulative tumor necrosis, severe nuclear or cytological atypia, elevated mitotic activity, or complex cytogenetic rearrangements have been observed in DPL. Despite its unusual location and growth pattern, the macroscopic and histological findings of Disseminated peritoneal leiomyomatosis are quite similar to uterine leiomyoma.

Moving from traditional "open" surgical techniques to laparoscopy requires the surgeon to morcellate the Leiomyomas in order to remove a large volume of tissue through laparoscopic ports which are at most only 12–15 mm in diameter. Mechanical devices utilized for morcellation yield a large number of small tissue fragments which spill within the peritoneal cavity and are rarely completely recovered. The seeding and proliferation of the tumor or uterine cells over abdominal organs, peritoneum, abdominal wall, and even the subcutaneous incision sites can lead to this rare condition. Leaving fragments of myoma in the abdominal cavity might contribute to the development of Disseminated peritoneal leiomyomatosis, so one should avoid leaving fragments of the uterus or myoma tissue in the abdominal cavity after morcellation. More than 10 case studies reported the development of subcutaneous, parasitic or disseminated leiomyomas after laparoscopic approach to uterine leiomyoma, most probably due to implantation and growth of the tumor particles throughout the abdomen or subcutaneous tissue [20].

Cytogenetics study suggests that functional alteration of a potential gene may play a role in Disseminated peritoneal leiomyomatosis development from uterine leiomyoma. In a study authors analyzed both the original uterine leiomyoma and the subsequent Disseminatedperitoneal leiomyomatosis by molecular cytogenetics to assess the role of chromosomal abnormalities in Disseminated peritoneal leiomyomatosis pathobiology. Interestingly, all of the chromosomal aberrations detected in their case of Disseminated peritoneal leiomyomatosis, including r(1)(p34.3q41), del(3)(q23q26.33), and t(12;14)(q14.3;q24.1), are characteristic chromosomal abnormalities detected in uterine leiomyoma[21].

Diagnosis

We have recently reported a case of Disseminated Peritoneal Leiomyomatosis (under publication). A 34 year old woman presented to us with the history of primary infertility and menorrhagia. Pelvic examination revealed an irregularly enlarged uterus with multiple myomas which was confirmed on transvaginalsonography. On laparoscopy ,we found hundreds of small myomatous nodules of 3-6mm diffusely studded all over the peritoneum(Fig 3), lateral pelvic side wall(Fig 4), uterovesical pouch and pouch of douglas, round ligament and even the fallopian tubes. (Fig 5) Segments of bowel were also riddled with numerous myomas. (Fig 6) Uterus was enlarged and studded all over with multiple myomas (Fig 7)of different sizes. Hysteroscopy also revealed multiple myomas in the uterine cavity. All bigger uterine myomas were enucleated and myoma bed sutured. Some of the nodules had been excised for pathological study. Microscopic examination displayed features consistent with smooth muscle cell proliferation, thus confirming the diagnosis of Disseminated Peritoneal Leiomyomatosis (Fig 8). Medroxyprogesteronewas given for 6 months without signs of disease progression.

Most of the time, the patients are asymptomaticand the disease is incidentally found. In symptomatic cases imaging techniques such as ultrasound and MRI examination are required for detection of Disseminated peritoneal leiomyomatosis. Sometimes the imaging diagnosis may be difficult, consideringthat radiological findings may suggest the presence of a malignant condition. The tiny peritoneal nodulesof disseminated peritoneal leiomyomatosis may also bebelow the resolution of all radiologic techniques. When disseminated peritoneal leiomyomatosis nodules are of sufficientsize, approximately 6mm or larger, 18F-FDG PET/CTmay be used to distinguish isometabolic activity of disseminated peritoneal leiomyomatosis from hyper metabolic uptake of leiomyosarcoma. Diagnosis is confirmed by biopsy of the nodules after surgrery which reveals the presence of smooth-muscle cells with no atypia or necrosis, fibroblasts and myofibroblasts.Immunohistochemical staining shows positivity for actin, myosin, and desmin.It is usually an accidental finding during surgery.

Finding on laparotomy overlaps with the appearances of peritoneal carcinomatosis, malignant mesothelioma, peritoneal gastrointestinal stromal tumour, and primary peritonealserous carcinoma. It has been suggested that leiomyomatosis peritoneal disseminata should be considered as diagnosis during surgery when patient has coexistingleiomyoma or diffuse leiomyomatosis of uterus with noomental caking or ascites.Differential diagnosis of Disseminated peritoneal leiomyomatosis includes parasitic leiomyoma, intravenous leiomyomatosis and other primitive or secondary peritoneal carcinomatoses.

Management

With the increasing rate of hysterectomy through laparoscopic approach to uterine fibroids, the unique complications of laparoscopy with morcellation, especially seeding and proliferation of tumor cells over abdominal organs and peritoneum, are becoming more significant and may necessitate review of current surgical protocols to prevent future seeding of the pelvic region with tumor particles.

There is no consensus about the ideal management of Disseminated peritoneal leiomyomatosis. Treatment varies depending on factors such as the size of the nodules.A conservative approach is recommended for this benigncondition. However, chances of its malignant transformationare more compared to solitary leiomyoma, as suggested byrecent reports. Although the cell of origin of this tumor is still controversial, the tumor is benign, and the acceptable treatment to date is total hysterectomy with bilateral salpingoophrectomy. If this tumor occurs in the omentum, an omentectomy should also be performed. Hence, depending on the extent of the disease, first-line treatment for Disseminated peritoneal leiomyomatosis is surgical excision or cytoreductive surgery. Discontinuation of hormone intake (e.g. oral contraceptives/ excess estrogen), treatment with progestins, or both has resulted in regression of unresected tumor masses. Systemic chemotherapy with doxorubicin and carbazine (off-label use) has been suggested as a treatment option for the rare cases of unresectable or metastatic tumors[22]. When surgical castration is not possible for age or desire for children, a close follow up is recommended. The condition tends to resolve spontaneously following delivery in cases where it developed during pregnancy. Prognosis is usually good. Death has however been observed in some cases presenting unresectable or metastatic tumors.

Conclusion

Disseminated peritoneal leiomyomatosis is a very rare disease which can be seen only by some gynecologists during their professional career. Although spontaneously and completely regresses in the majority of cases after delivery or ending of use of contraceptives,regular monitoring of patients by bimanual and ultrasound examinations is needed. It has to be taken into account in dealing with a patient with abdominal masses, and especially after a previous myomectomy or hysterectomy**.** The other important practical issue with Disseminated peritoneal leiomyomatosisis the potential misdiagnosis of disseminated malignancy.

Given its low incidence and possible unfamiliarity to themedical community, Disseminated peritoneal leiomyomatosis is not often considered in thedifferential diagnosis of multiple peritoneal nodules. On several occasions, unnecessary radical resections have been performed for this condition, with life threatening results. Leiomyomas should be considered in the differentialdiagnoses of intraperitoneal or retro peritoneal masses distinct from the uterus.

One should avoid leaving fragments of the uterus or myoma tissue in the abdominal cavity after morcellation. Disseminated peritoneal leiomyomatosis occurring after morcellation can be prevented by the newer concept of LAM (laparoscopy assisted myomectomy), myoma retrival through posterior colpotomy and electromechinicalmorcellation (EMM) in an endobag. Although this complication is extremely rare, consideration should be given to informing patients about this risk prior to laparoscopic hysterectomy with morcellation.

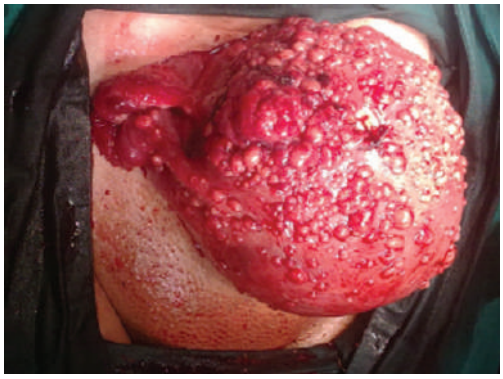

Fig 1:- Intraoperative view of the gravid uterus with disseminated peritoneal leiomyomatic nodules. Source:RajkoFureš et al (2015) with permission

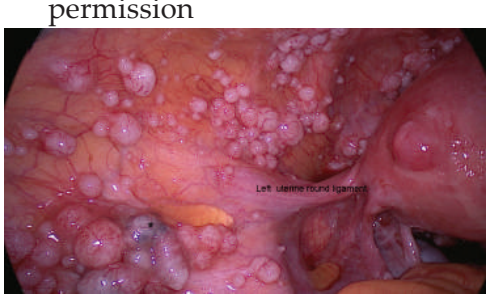

Fig 2:- Laparoscopic image showing multiple nodules of various size on the peritoneal surfaces, suggestive of Disseminated Peritoneal Leiomyomatosis associated with endometriosis. Source: Carvalho FM et al (2012) with permission

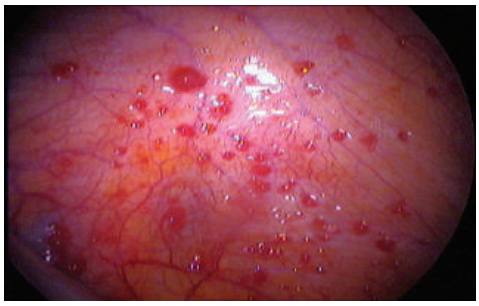

Fig 3:- Small multiple myomas studded over parietal peritoneum

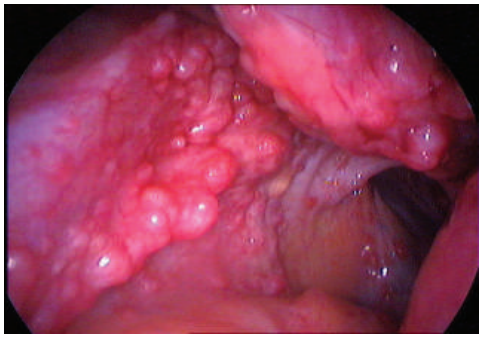

Fig:-4:-Multiple small myomas studded over lateral pelvic sidewall

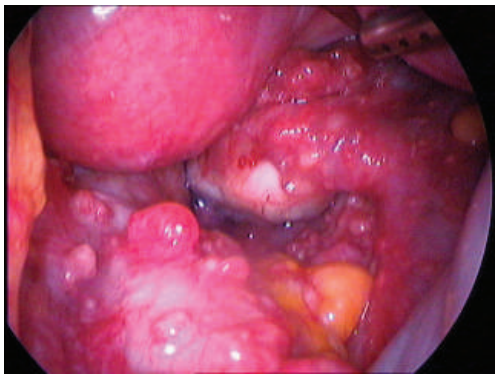

Fig 5:-Multiple small myomas seen over the tubes, ovaries and lateral pelvic sidewall

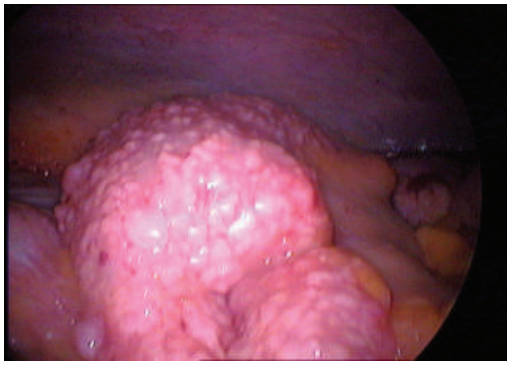

Fig 6:- Multiple small myomas studded over the bowel

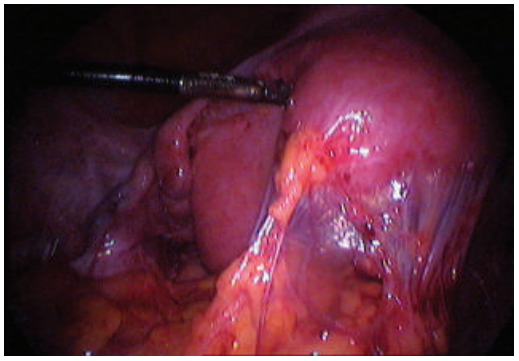

Fig 7:- Multiple large myoma with dense adhesions of omentum and bowel

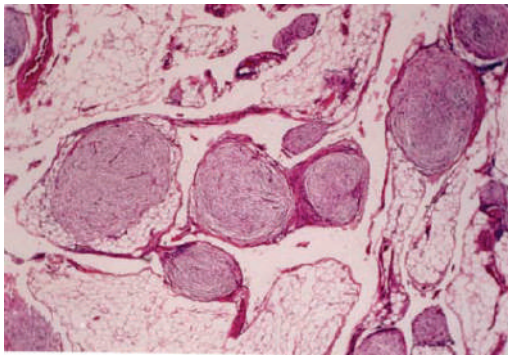

Fig8:- Histopathology slide image showing features consistent with leiomyoma. Source: MoodNI et al (2003) with permission.

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16

UNUSUAL PRESENTATION OF FIBROIDS

Dr B Ramesh,
MD (BOM), DGO, FCPS, DFP,
Diploma in Gynae Endoscopy (USA),
Fellowship in Assisted Reproduction (UK,

DrRachanaGhanti,
MS (OBGY),
Pursuing Fellowship in GynaeLaparoscopy,
DepartmentofGynae Laparoscopy,
Ramesh Hospital, Bangalore

Introduction

Leiomyomas are the most common tumours of the uterus. They are responsible for about 1/3rd of hospital admissions to Gynaecology Department. Growth of leiomyoma is dependent on oestrogen production. The tumour thrives during the period of greatest ovarian activity. Continuous oestrogen secretion especially when uninterrupted by pregnancy and lactation is thought to be the most important risk factor in development of myomata. After menopause, with regression of ovarian oestrogen secretion, growth of leiomyoma usually ceases.

Submucosal fibroids are located in the muscle beneath the endometrium of the uterus and distort the uterine cavity; even small lesion in this location may lead to bleeding and infertility. A pedunculated lesion within the cavity is termed an intracavitary fibroid and can be passed through the cervix. Subserosal fibroids are located underneath the mucosal (peritoneal) surface of the uterus and can become very large. They can also grow out in a papillary manner to becomepedunculated fibroids. Ultrasonography, CT and MRI can be used to diagnose uterine fibroids. Magnetic Resonance guided Focused Ultrasound, is a non-invasive intervention (requiring no incision) that uses high intensity focused ultrasound waves to destroy tissue in combination with magnetic resonance imaging (MRI), which guides and monitors the treatment.

Clinical features

Typical symptoms	Atypical symptoms
Menorrhagia	Tenesmus
Pain	Chest pain
Dysmenorrhea	Abdominal symptoms
Infertility	Dyspnea
Pressure symptoms	Pruritus
	Hiccup or internal bleeding
	Vaginal protruding mass/ uterine inversion
	Hematuria
	Deep dyspareunia

Table 1 – Shows typical and atypical symptoms of fibroids

Typical symptoms of uterine myomas

The symptoms of this disease are mainly related to the physical changes in the pelvic organs arising from the onset of this tumor and may present in women of any age but usually in women between menarche and menopause. When a female of reproductive age presents with symptoms like menorrhagia, dysmenorrhea, giddiness, pallor, dyspnea,urinary frequency, and constipation, it may be common to quickly assume a diagnosis of uterine fibroids. On the other hand, some unusual or atypical symptoms like acute abdominal pain, and pain between periods or internal bleeding do occur in patients with a well-established diagnosis of uterine fibroids that may be ignored, leading to a misdiagnosis and further delay in medical management. Here, we would like to discuss these symptoms in detail.

1. Compression symptoms

The symptoms related to myomasare primarily those of physical changes to the pelvic organs due to the presence of an enlarging mass[1,2,3].These symptoms, similar to those of an enlarged pregnant uterus, may lead to a suspicion of conception in some premenstrual victims. Pelvic heaviness or a dull aching sensation, such as that experienced by women in early pregnancy, might be the only symptom of this slow-growing tumor. Increased urinary frequency and urgency can also develop, especially when these tumors arise from the anterior wall of the uterus. In addition, these symptoms might worsen with the onset of menses, thereby aggravating menses-related symptoms[3].

2. Menses-related symptoms

Abnormal menstruation, including excess or prolonged bleeding, is believed to be the most common symptom and is experienced by about 30% of women with myomas.However, the most common menses-related symptom is menorrhagia[20, 21,22.] Since the exact cause effect relationship between myoma and excess menstrual bleeding is poorly understood, women with this disease are more likely to report gushing-type bleeding, even if the uterine myoma was small.Other symptoms of anemia, including pallor, fainting, dyspnea, and fatigue might result from massive blood loss whenever menses begins, and could worsen during menses. In addition to the general discomfort caused by symptoms of acute and colic pain during menses, these symptoms substantially interfere with the health and life quality of women, often leading to surgical intervention.

3. Pain-related symptoms

About one-third of women with myomas experience pelvic pain. Dysmenorrhea seems less common in this group.

Atypical symptoms of uterine myomas

Other atypical or unusual presentations of this disease might be encountered in well-established or new cases, and represent either the existence of a special form of leiomyomatosisor a changed status of this disease; immediate treatment may be necessary.

1. Uncommon compression-related symptoms

Other atypical compression symptoms are also found in women with uterine myomas. For example, the masses arising from the posterior wall might cause rectal symptoms like tenesmus, back pain or constipation, though they appear to be less common. These symptoms might worsen when menses comes and can aggravate the symptoms related to menses.Flank pain, especially on the right side, is an atypical symptom of the uterine myoma, and is due to compression of The ureter, although its incidence is far below our expectation.

Transient relief after lying on the opposite side might be reliable evidence of the existence of this compression[9].

2 Cardiac symptoms

Cardiac symptom and atypical symptoms secondary to vascular involvement or dissemination Cardiac symptoms like chest pain might occur in a rare condition known as intravenous leiomyomatosis[10].Benign smooth muscle fibers invade the venous channels of the pelvis and, even though they grow slowly, they might grow into the vena cava and right heart and cause these unusual symptoms. Surgical intervention with primary excision and follow-up antiestrogen therapy for prevention is recommended to treat these cases. This mechanism might explain the occurrence of distant myomas with more unusual symptoms like urination difficulty and urethral obstruction from a leiomyoma of the bladder, and visual impairment from an orbital leiomyoma.[11-14]

3 Abdominal symptoms

Abdominal symptoms mimicking pelvic carcinomatosis multiple pelvic growths with various compression symptoms with or without ascites will raise the suspicion of pelvic carcinomatosis. However, another rare benign condition, leiomyomatosis peritonealisdiss eminata (LPD), which is caused by the direct seeding of myomatous cells on the surface of the peritoneum, could be the possible diagnosis. It is believed that LPD is associated with recent pregnancy or previous operation for myoma using a morcellator.[15,16]

4. Respiratory symptoms

Dyspnea with pleural effusion, pelvic mass and ascites mimicking Meigs syndrome is another rare carcinoma-like presentation of this disease. Leiomyoma arising from the uterus[17],ovary[18],or fallopian tube[19]might be the only diagnosis.

5. Pruritus

Pruritus with multiple raised skin lesions on the limbs is unusual and is the only symptom of piloleiomyoma[20].However, the coexistence of uterine myoma and cutaneous

Leiomyoma nodules might be the initial symptom of piloleiomyoma. Renal evaluation should be done first in cases of piloleiomyoma, before conservative follow-up is recommended, because piloleiomyoma is often accompanied with renal carcinoma.

6. Hiccup or internal bleeding

Unusual symptoms like hiccup or internal bleeding might result from a subserosalmyoma with rapid growth. While the former might be irritation of the vagus or phrenic nerve and deserve a more thorough evaluation before operation[21,22],the latter might be due to rupture of superficial vessels and deserve prompt diagnosis and emergency management[23,24].

7. Vaginal protruding mass or uterine inversion

Sometimes submucousmyoma induces uterine inversion, which results in hemorrhage.If this rapid growth occurs in a menopausal woman, then malignant change must be highly suspected,and imaging might help to distinguish benign and malignant uterine masses[25,26].

8. Urinary symptoms

Uterine fibroid can atypically present with hematuria and ureteric colic, and cause extrinsic ureteral obstruction. Although the uterine fibroid is the most common benign tumor of the female upper genital tract and the one most likely to cause ureteral obstruction in females , it rarely obstructs the ureter. Common causes of ureteral obstruction include endometriosis, abdomino-pelvic malignancies, retroperitoneal fibrosis, aortic aneurysm, and recurrent appendicitis.

RARE VARIETIES

Broad ligament fibroid

Broad ligament is a very uncommon site for presentation of leiomyoma. On account of their size and nature (pedunculated or sessile), clinically leiomyomas may present variably.

It may present with complaints of lower abdominal pain of long duration, associated with menstruation. On developing a long tenacious stalk, the subserosal leiomyoma may become a wandering or migrating leiomyoma. Occasionally such masses become adherent to the surrounding structures such as broad ligament or omentum or retroperitoneal connective tissue, where they receive auxillary blood supply and lose their original attachment to the uterus. They are then called as parasitic leiomyoma. On histological evaluation, they exhibit features similar to those

of their uterine counterparts. Patients usually present with lower abdominal pain, mass per abdomen or pelvic mass. Para-ovarian leiomyoma can present as inguinal masses or acute abdomen. Rarely, pedunculated leiomyoma undergo torsion and present with acute abdomen. Giant fibroids are known to arise from the uterus, but occasionally from the broad ligament. Sometimes broad ligament leiomyoma may be associated with massive ascites and bilateral pleural effusion.

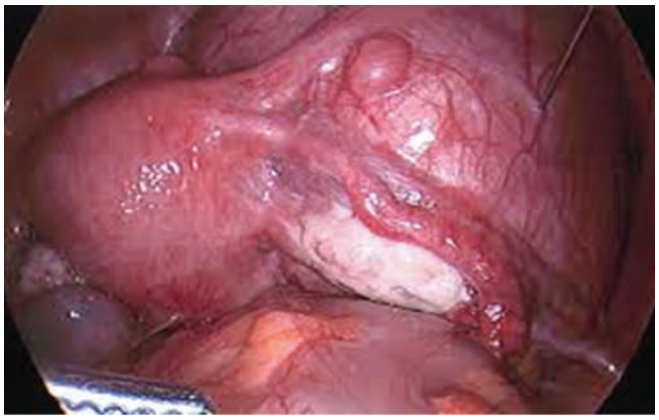

Fig 1 – Broad ligament fibroid

Retroperitoneal fibroids

Introduction

Some unusually located extra-uterine leiomyomata have been reported; retroperitoneal leiomyoma being among them. The origin of such tumors is still obscure; a parasitic origin as well as Müllerian cell rests or smooth muscle cells in the retroperitoneal vessels wall have been suggested. An 'iatrogenic' origin for such growths is also a possible theory. The origin of uncommonly located leiomyomata is an unexplored issue that merits more investigation.

Incidence

The incidence of retroperitoneal leiomyomata is quite low, and it is even lower for those extending to or originating in the abdomen. Of the reported retroperitoneal leiomyomata, 73% are located in the pelvis[27]. Most of the published case reports diagnosed the cases clinically as retroperitoneal growths with high suspicion of malignancy without suspecting their leiomyomatous nature [28-33].

Origin

The origin of such tumors is a puzzling issue with much scientific debate. Poliquin and coworkers observed a 40% association of retroperitoneal leiomyomas with uterine counterparts or a history of hysterectomy due to uterine leiomyomata[27]. Zaitoon suggested the parasitic theory for such tumor growth [28] while Stutterecker *et al.*claimed that Müllerian cell rests or smooth muscle cells in the retroperitoneal vessels wall are the putative origin [30]. Kho and Nezhat proposed an 'iatrogenic' origin for such growths while analyzing a case series of extra-uterine leiomyomata, mostly of retroperitoneal or intraperitoneal location with no visible connection to the uterus. They found out that 83% of their case series had previous abdominal operations, and 67% had myomectomies, most of them via laparoscopy with morcellation [34].Thorough radiographic imaging of sonographically diagnosed leiomyomata is important, especially for those which are large in size or present in an uncommon location. Several theories have been postulated regarding the origin of retroperitoneal leiomyomata; however, the exact etiology is still an unexplored issue that merits more investigation.

Vaginal wall fibroidsIncidence

Leiomyomas in female genital tract are common in the uterus and to some extent in the cervix followed by the round ligament, utero-sacral ligament, ovary, and inguinal canal.[35]Occurrence in vagina is very rare. Vaginal leiomyomas are commonly seen in the age group ranging from 35 to 50 years and are reported to be more common among Caucasian women.[36] They usually occur as single, well-circumscribed mass arising from the midline anterior wall[35,37] and less commonly, from the posterior and lateral walls.[38] They may be asymptomatic but depending on the site of occurrence, they can give rise to varying symptoms including lower abdominal pain, low back pain, vaginal bleeding, dyspareunia, frequency of micturition, dysuria, or other features of urinary obstruction These tumors can be intramural or pedunculated and solid as well as cystic. Usually these tumors are single, benign, and slow growing but sarcomatous transformation has been reported.[39]

Diagnosis

Preoperatively, diagnosis by ultrasonography may be difficult, but magnetic resonance imaging

usually clinches the diagnosis. In magnetic resonance imaging, they appear as well-demarcated solid masses of low signal intensity in T1- and T2-weighted images, with homogenous contrast enhancement, while leiomyosarcomas and other vaginal malignancies show characteristic high T2 signal intensity with irregular and heterogeneous areas of necrosis or hemorrhage.[40,41] However, histopathological confirmation is the gold standard of diagnosis and also beneficial to rule out any possible focus of malignancy.

Treatment

Surgical removal of the tumor through vaginal approach, preferably with urethral catheterization to protect the urethra during surgery, is usually the treatment of choice. In case of large tumors, however, an abdomino-perineal approach is preferred.

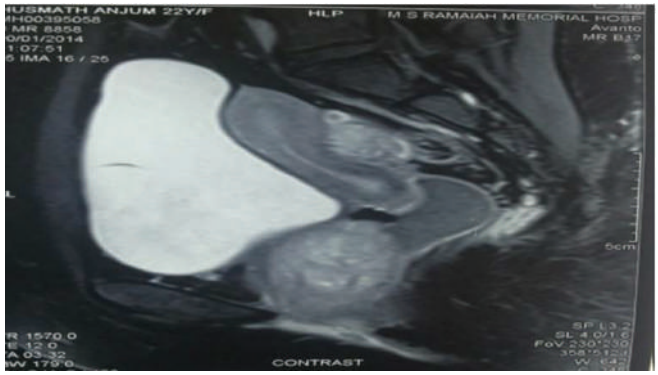

Fig 2 – vaginal wall fibroid

Bizarre leiomyoma[62]

An unusual atypical smooth muscle tumor was first described in the stomach by Martin and associates in 1960. Variously called bizarre leiomyoma, leiomyoblastoma, clear-cell leiomyoma, and plexiformtumorlet, these atypical smooth tumors probably all belong together. The term epithelioid leiomyoma was adopted by the World Health Organization. Kurman and Norris have proposed that this term be used for all atypical leiomyomata.

Histologically, the characteristic feature is the mixture of rounded polygonal cells and multinucleated giant cells present in epithelioid clear-cell and plexiform patterns.
Clinically, in the uterus most of these tumors are benign. They may rarely exhibit malignant potential. Malignancy is difficult to predict from histological criteria because some metastases occurred from tumors that demonstrated very few mitoses. Kurman and Norris have suggested, however, that epithelioid neoplasm's having more than five mitotic figures per 10 high-power fields should be called epithelioidleiomyosarcomas and that the term epithelioid leiomyoma should be applied when there is a lower level of mitotic activity.

Although combination therapy (surgery plus radiation therapy or chemotherapy) may not be indicated for a patient with an epithelioid leiomyoma, follow-up should be considered essential, as emphasized by Klunder and colleagues

.Intravenous leiomyomatosis[62]

An unusual benign form of leiomyomata uteri, it was first recognized at the turn of the 20th century and has been reported sporadically since then. Before 1982, about 50 cases had been reported, according to Bahary and coworkers. Probably at least that many have been reported since. Marshall and Morris presented the first detailed report of this entity in the American literature in 1959.

The characteristic feature being the extension of the polypoid intravascular projections into the veins of the parametrium and broad ligaments. Although there may be some difficulty in distinguishing such lesions from low-grade sarcoma, they are distinctly different histologically from stromatosis uteri because the intravenous plugs are mainly smooth muscle in origin. In 1966, Edwards and Peacock collected 32 cases of intravenous leiomyomatosis, in which approximately 50% of the cases, the intravenous tumor was confined to the parametrium; in 75%, it extended no further than the veins of the broad ligamentwhich suggested that the severed intravenous extensions are probably incapable of independent parasitic existence and remain dormant after removal of the uterus. Total surgical excision of the tumor should be attempted for successful therapy. Another study done by Norris and parmley showed two of three patients with incomplete resection had a recurrence; the recurrent tumor was excised surgically, and the patients were alive and free of disease 5 and 11 years after operation. The authors

concluded that this tumor behaves clinically like a benign neoplasm, although its worm like extensions may involve uterine, vaginal, ovarian, and iliac veins. The uterine veins in the broad ligaments are the most common sites of extension. The mitotic index is quite low, with the most active lesions showing only one mitosis per 15 high-power fields.

Extension of benign leiomyomatosis up the vena cava and into the right atrium has been reported in several cases, with a fatal outcome in some. Before 1994, approximately 27 cases of intravenous leiomyomatosis extending to the heart were reported. Several recent cases requiring open-heart surgery to remove the intracardiac tumor thrombosis have been successful and without recurrence. All reported cases occurred in women. Tierney and colleagues reported that substantial quantities of cytoplasmic estradiol and progesterone receptors were found in the right atrial tumor removed from a patient with intravenous leiomyomatosis. Their patient was treated with the antiestrogen tamoxifen because of residual tumor in the vena cava that could be estrogen dependent.

Both intravenous leiomyomatosis and benign metastasizing leiomyoma have been reported to metastasize to the lung. As suggested by Banner and coworkers, by Horstmann and associates, and by Evans and colleagues, oophorectomy may be indicated in patients with these conditions, again because of the possibility that these tumors may be estrogen dependent or that estrogens may have the ability to stimulate their development, whether in a uterine or extrauterine location and whether they appear to be endothelial or mesenchymal in origin.

The possibility of metastases from a histologically benign uterine leiomyoma has been discussed by Idelson and Davids and by Clark and Weed. When such a case occurs, it is usually settled by finding a sarcomatous component in the leiomyoma or by finding evidence of intravenous leiomyomatosis. However, multiple cases have now been reported in which a benign uterine leiomyoma metastasized. Idelson and Davids' case showed metastases to the aortic lymph nodes. The patient reported by Cramer and associates had metastatic tumor to the omentum, ovary, periaortic lymph node, and lung. In each location, the histology and estrogen receptor content of the tumor resembled those of a benign leiomyoma. The recommended treatment consists of surgical removal with castration and little or no estrogen replacement.

Leiomyomatosisperitonealisdisseminata[62]

Leiomyomatosis peritonealisdisseminata is sometimes confused with intravenous leiomyomatosis. However, only subperitoneal surfaces of the uterus and other pelvic and abdominal viscera are involved with leiomyomatosisperitonealisdisseminata, and invasion of the lumen of blood vessels does not occur. Only about 15 cases have been reported, according to Pearce. All occurred in patients in the reproductive years who often had large uterine leiomyomata and were usually pregnant or taking oral contraceptives. The condition is likely to be confused with a disseminated intraabdominal malignancy, but it is entirely benign histologically and clinically. Parmley and colleagues have demonstrated the histologic similarities between this peritoneal lesion and the decidual change of the mesothelium in the pelvis, and they propose that the condition represents a benign reparative process in which fibroblasts replace soft peritoneal decidua. They suggest that this fibrocytic reaction occurs during pregnancy and especially in the postpartum period, resulting in nodules with a pseudoleiomyomatous pattern. Similar findings have been noted in patients with endometriosis treated with prolonged Enovid therapy. These findings indicate that prolonged and continuous stimulation of sub peritoneal decidua by either endogenous or exogenous estrogen or progesterone is important in the pathogenesis of this condition. Parmley and coworkers suggest that the condition is more appropriately called disseminated fibrosingdeciduosis. Goldberg and associates, on the other hand, on the basis of electron microscopy studies, believe that the tumors arise from smooth muscles of small blood vessels. This has been confirmed by Ceccacci and colleagues. It has been possible to show a continuum from fibroblastic cells through myofibroblasts to leiomyocytes. Although the cell of origin of this tumor is still controversial, the

tumor is benign, and the acceptable treatment to date is total abdominal hysterectomy and bilateral salpingo-oophorectomy. If this tumor occurs in the omentum, an omentectomy should also be performed to define more clearly the histologic nature of the lesion.

In attempting to distinguish between benign and malignant disease in a patient with uterine leiomyomata who also has unusual clinical findings, it is appropriate to keep the entities mentioned earlier (intravenous leiomyomatosis, atypical bizarre leiomyoma, benign metastasizing leiomyoma, and disseminated intraperitonealleiomyomatosis) in mind. Although they all have features similar to those of malignant disease, they are almost always benign and amenable to treatment. One should also remember that benign uterine leiomyomata have been associated with pseudo-Meigs syndrome in a few cases. Meigs reported five cases in 1954. In these cases, the ascites did not reappear after removal of the uterine leiomyomata.There is a high frequency of endometrial hyperplasia when the uterus contains leiomyomata. Degligdish and Loewenthal reported that cystic glandular hyperplasia is often found in the endometrium at the margin of the leiomyoma. Yamamoto and coworkers have reported high concentrations of estrone and estronesulfatase activity in the endometrium overlying a myoma. They suggest that the local hyperestrogenism in the endometrium overlying a leiomyoma may assist in the genesis or enlargement of these tumors.

Iatrogenic parasitic fibroids

In the minimallyinvasive procedures, the removal of different sizes of myomathrough small wounds requires fragmenting the myomas in theabdominal cavity. However, this morcellation processmay disseminate viable myoma particles in the abdominal cavity.In rare instances, minute myoma particles may survive andbecome implanted into tissue. In the past 7 years, the incidence of iatrogenic parasitic myomas has increased because of the increaseduse of minimally invasive surgery. Iatrogenic parasitic myomanevertheless remains a rare late complication with an incidence of <1%.Parasitic myoma is a rare type of pedunculatedsubserosalmyoma that is partially or completely separated from the uterus andreceives alternative blood supply from another source such as the omentum and mesenteric vessels [47]. The prevalence of minimally invasive surgery has led to a new type of parasitic myoma: the iatrogenic parasitic myoma[47, 48]. In some papers, this kind ofmyoma is called disseminated peritoneal leiomyomatosis (DPL)[49,50,51]. This suggests a subset of DPL that is secondary to trans coelomic dissemination of a primary uterine leiomyoma ratherthan a de novo peritoneal metaplasia[52].the symptomsof iatrogenic parasitic myoma do not appear to be specific. The most common symptoms are pain, mass sensation, and deep dyspareunia.From the literature review, most (78%) patients received laparoscopic myomectomy with morcellation for their first surgery, andthere were often multiple lesions with varying sizes (range,0.8 to 30 cm). Parasitic myoma occurred at various sites, including the port site, intestines, peritoneum, and omentum in the abdominal cavity. These sites are also the dependent part of the abdominal cavity and receive abundant blood supply, which suggests seeding of myometrial tissues during morcellation[47]. Carefully checking these sites and changing the patient's position after surgery is suggested. The interval between the initial surgery and the second surgery ranged from 2 to 108 months (on average, 47.2 months). Previous reports have strongly suggested an association between minimally invasive surgery and iatrogenic parasitic myoma; however, the exact surgical procedure leading to parasitic myoma has not been discussed. Because an electrictissue morcellator is often used for fragmenting myomas, the productionof tiny remnant fragments of myoma tissue may be closely related to the later occurrence of iatrogenic parasitic myoma. A fewcases of disseminated leiomyomas have also been reported after abdominal hysterectomy[54,55,56] abdominal hysterectomy[53, 55,56], which suggests that factorsother than morcellation may be responsible for the recurrence. Minute fragments ofmyoma tissue will beproduced if the morcellator is not sufficiently sharp. These minute fragments can easily be missed and left in the abdomen, and may become implanted into peritoneal or omental tissue. Therefore, it is imperative to ensure that the morcellator is sufficiently sharp. For fragile

myomas, the fragments can be collected into an endobagand removed completely. If morcellation is performed after the enucleation of multiplemyomas, specimens may be missed and remain in the abdomenbecause of the Trendelenburg position, especially when the myomasare small. Hutchins and Reinoehl[57] described retained myomas after laparoscopic subtotal hysterectomy with morcellation because their specimens were lost during morcellation. Therefore, in situ morcellation may decrease the incidence ofretained myoma tissue in the abdomen during surgery[58,59,60,61]. Prior to completing the surgery, myoma remnants in the abdominalcavity should be carefully removed. At the end of surgery,vigorous irrigation with normal saline with a concomitant change in position is useful. Long term follow up is likewise recommended to detect the occurrence of parasitic myoma even in menopausal patients because of the potential of malignancy. For patients with suspected malignant myomas, a total abdominalhy sterectomy is recommended. If malignancy is an incidental finding in laparoscopic my omectomy, complete cancer staging surgery is mandatory. The incidenceof iatrogenic parasitic myomas in the literature has increased because of the increased use of minimally invasive surgery. All patients should be followed up for at least 1 year. Insitu morcellation may also help reduce the incidence of parasitic myomas

Table 1
Review of the literature of parasitic myoma after surgery.

Study	No. of cases	Diagnosis	First operation	Morcellation	Interval (mo)	Signs and symptoms	Second operation	M (no.)	M size (cm)	Location	Histology
Ostrzenski, 1997 [10]	1	Uterine leiomyoma particle growing	LM	Yes	2	Mass	Lapa	1	1	Port site	Leiomyoma
Hutchins and Reinoehl, 1998 [18]	1	Retained myoma	LASH	Yes	1	Abdominal pain	Lapa	5	4	Liver, gallbladder	Leiomyoma
Rajab et al, 2000 [14]	1	DPL	TAH + BSO	Yes	24	Abdominal distension	Lapa	m	12	CDS, suprapubic, small bowel, liver	Multiple leiomyomatosis disseminata
Sharma et al, 2004 [15]	1	DPL with malignant change	TAH	Unknown	84	Abdominal swelling	Lapa	m	7	Omentum, mesentery	Leiomyosarcoma arising in leiomyomatosis peritonealis disseminata
LaCoursiere et al, 2005	1	Retained myoma	TLH	Yes	10	Dyspareunia, dysuria, and pelvic pain	LM	4	4	Abdomen and pelvis	Leiomyoma-cervical tissue
Donnez et al, 2006 [23]	1	Iatrogenic peritoneal adenomyoma	LASH + BSO	Yes	60	Pelvic pain, dyspareunia	LM	1	4	CDS	Adenomyosis
Paul and Koshy, 2006 [8]	1	Multiple peritoneal parasitic myomas	LM	Yes	30	None	LM	3	2	Port site, fundus, right paracolic gutter	Leiomyoma
Sinha et al, 2007 [9]	2	Postlaparoscopic hysterectomy myomas	LM/TLH	Yes	12, 36	Pain, mass	LM	2, 3	10, 15	Sigmoid colon serosa, lateral pelvic wall, CDS, diaphragm dome	Leiomyoma
Takeda et al, 2007	1	Parasitic peritoneal leiomyosis	LM (*in situ*)	Yes	72	Mass	LM	5	6	Omentum, round ligament, pelvic sidewall, CDS	Leiomyoma
Moon et al, 2008	1	Parasitic leiomyoma	LM	Yes	36	Mass	Lapa	1	3	Port site	Leiomyoma
Kumar et al, 2008	1	DPL	LM	Yes	11	Abdominal distension	Lapa	6	30	Omentum, colon	Leiomyoma
Epstein et al, 2009	1	Parasitic myoma	LM	Yes	18	Pelvic pain	LM	2	8	Omentum, sigmoid colon	Leiomyoma
Thian et al, 2009 [13]	1	DPL	LM	Yes	29	Mass	Lapa	>50	15	Omentum, colon, abdominal wound	Leiomyoma
Wada-Hiraike et al, 2009	1	Aberrant myoma	LAM	Scalpel	54	Mass	Lapa	1	15	Previous operation site	Leiomyoma
Kho et al, 2009	9	Parasitic myoma	6 LM, 1 TAH, 2 M	8: 6 LSC and 2 Lapa	75	Pain, menorrhagia, dyspareunia, pelvic pressure		(3; all are LM)		Pelvis (14/15), GI tract (6/15), upper abdomen (1/15)	Leiomyoma
Al-Talib and Tulandi, 2010 [11]	1	DPL	LASH	Yes	84	Mass	Lapa	16	9	Abdomen and pelvis	
Larraín et al, 2010	4	Iatrogenic parasitic myoma	2 LM, 2 TLH	Yes	99	Pain, vaginal mass	3 LM, TVM	4	4–7	Pelvis, vagina, CDS	Leiomyoma
Payyapilly et al, 2010 [24] Nezhat and Kho, 2010 [25]	1	Parasitic myoma Iatrogenic parasitic myoma	LAM	Scalpel	36	Infertility	LM				
Pezzuto et al, 2010	2	Bowel leiomyoma	2 LM	Yes	132	None	LAVH, M	3	3,5	Intestine	Leiomyoma
Cucinella et al, 2011 [22]	4	Parasitic myoma	LM, TAH	Yes	24,72,72,108	Mass, pain, dyspareunia	LM	1,2,3,5	1.8,3.5,6,6		Leiomyoma
Current report	1	Parasitic myoma	LM	Yes	87	Mass	LM	2	6	Small intestine, left tube	Cellular leiomyoma

BSO = bilateral salpingo-oophorectomy; CDS = cul-de-sac; DPL = disseminated peritoneal leiomyomatosis; GI = gastrointestinal; LAM = laparoscopic-assisted myomectomy; Lapa = laparotomy; LASH = laparoscopic subtotal hysterectomy; LAVH = laparoscopic-assisted vaginal hysterectomy; LM = laparoscopic myomectomy; LSC = laparoscope; m = multiple; M = myomectomy; TAH = transabdominal hysterectomy; TLH = total laparoscopic hysterectomy; TVM = transvaginal myomectomy.

Other Clinical Manifestations·

Less than 0. 5 percent of women with leiomyomas develop *myomatouserythrocytosis syndrome*. This may result from excessive erythropoietin production by the kidneys or by the leiomyomas themselves (Kohama, 2000; Yokoyama, 2003). In either case, red cell mass returns to normal following hysterectomy.· Leiomyomas occasionally may cause *pseudo-Meigs syndrome*. Traditionally, Meigs syndrome consists of ascites and pleural effusions that accompany benign ovarian fibromas. However, any pelvic tumor including large, cystic leiomyomas or other benign ovarian cysts can cause this. The presumed etiology stems from discordancy between the arterial supply to and the venous and lymphatic drainage from leiomyomas. Resolution of ascites and hydrothorax follows hysterectomy.

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FUTURE RESEARCH IN FIBROIDS

Prof Pratap Kumar
Dept of Obstetrics & Gynecology
Kasturba Medical College
Manipal University
Manipal 576104 (Karnataka)

Fibroids are the most common tumors of women during their reproductive life and they are found in one out of every four women. Majority of symptomatic uterine fibroids are currently treated by surgical interventions (myomectomy or hysterectomy) or radiological treatments (uterine artery embolization or focused ultrasound surgery).

One of the areas of the future research may be on the Selective progesterone receptor modulation. Recent biochemical studies have suggested that progesterone and its receptors enhance proliferative activity in fibroids and this has, therefore, raised the possibility that anti-progestational agents and progesterone receptor modulators could be useful in the medical management of fibroids The first progesterone receptor antagonist, mifepristone (RU-486), emerged on the clinical horizon 25 years ago and since then hundreds of steroidal as well as non-steroidal compounds displaying progesterone antagonist (PA) or mixed agonist/antagonist activity have been synthesized. Ulipristal acetate (UA) also known as CDB-2914 belongs to this group of compounds collectively known as selective progesterone receptor modulators (SPRMs). It reversibly blocks the progesterone receptor in its target tissues (uterus, cervix, ovaries, hypothalamus) and acts as a potent, orally active anti-progestational agent. UA downregulates the expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and their receptors in cultured fibroid cells.This can result

in the suppression of neovascularization, cell proliferation and survival. UA also increases the expression of matrix metalloprotei nases and decreases the expression of tissue inhibitor of metalloproteinases and collagens in cultured fibroid cells. This can reduce the collagen deposition in the extracellular spaces of fibroids, impairing tissue integrity. UA and other SPRMs have been shown to modulate the ratio of progesterone receptor isoforms (PR-A and PR-B) in the cultured leiomyoma cells.

There are several factors considered for the development of fibroids like infections in the uterus, hormonal, metabolic, dietary, stress, and environmental factors. Infection-related oncogenesis may be connected injury or inflammation. This causes increased in the extracellular matrix, cell proliferation, and decreased apoptosis, leading to abnormal tissue repair [1]. Studies have shown that there is an upregulation of extracellular matrix proteins that is consistently seen in gene profiling studies of fibroids compared with normal myometrium. There is a possibility that the luteinizing hormone (LH) shares a receptor with human chorionic gonadotropin, and this LH would stimulate fibroid growth. Metabolic factors like diabetes, polycystic ovaries, and hypertension have been examined.

Genetics

Genetic factors differ by race or ethnicity may help identify subgroups that are at highest risk and allow for the targeting of therapies for specific subpopulations may be thought of in the future. Research in this area should include gene and environmental interactions, such as lifestyle and diet. Researchers should provide an opportunity for increased research in the area of genotypes, gene mutations, gene/environment interactions, epigenetic modifications, or other biomarkers that differ by race or ethnic group that may account for differences in the incidence, natural history, and treatment response (including rate of growth and symptom patterns) of disease among these group.

Research can focus on understanding the basic genetic mechanisms of the disease, so that physicians can predict disease severity and have a better understanding of when intervention is appropriate. Learning more about molecular genomics would also support the development of alternative therapies for women who are at risk of developing symptomatic fibroids, with the goal of preventing fibroid development.Researchers could examine fibroid tissue samples for gene mutations that affect size,number, or locations of the fibroids; researchers could also look for biomarkers in serum samples, as these samples are much easier to collect. Fibroids are connected to chromosomal abnormalities in some. Major abnormalities in the chromosomes are seen the chromosomes 6, 7, 12 and 14. This has led to a belief that the disruptions or dysregulations of high-mobility group (HMG) protein gene family, HMGIC and HMGIY,genes contribute to the development of these tumors. Genes such as *RAD51L1* act as translocation partners to *HMGIC* and lead to disruption of gene structure leading to the pathogenesis of uterine fibroids. Molecular analysis is the future to understand that the cytogenetics provides a broad perspective on uterine fibroid formation[2].

Potential research would be on one of the stem cell evaluation and therapy.Tissue-specific (or somatic) stem cells constitute a subset of cells residing in normal adult tissues. By undergoing asymmetric division, they retain their ability to self-renew while producing daughter cells that go on to differentiate and play a role in tissue regeneration and repair. The human uterus consists primarily of endometrium and myometrium (the smooth muscle layer) that rapidly enlarges through its tremendous regenerative and remodeling capacity to accommodate the developing fetus. Such uterine enlargement and remodeling can take place repeatedly and cyclically over the course of a woman's reproductive life. These unique properties of the uterus suggest the existence of endometrial and myometrial stem cell systems. In addition, like somatic cells, tumor stem cells or tumor-initiating cells, a subset of cells within a tumor, retain the ability to reconstitute tumors. Uterine smooth muscle cells are thought to be the origin of leiomyomas that are the most common type of gynecologic tumor. Recent work has

identified, isolated, and characterized putative stem/progenitor cells in the myometrium and in leiomyomas[3].

Despite numerous publications on Somatic stem cells (SSCs), it was not until 2007 that scientific evidence based on the use of 5-bromo-2'-deoxyuridine (BrdU) and side population (SP) methods in murine and human myometrium were first published. Recently, it has been reported that SP cells are present in human leiomyomas; however, to date the pathogenesis of this benign tumor remains unclear. Besides many genetic/epigenetic alterations, changes to steroid hormones and growth factors may also be associated with the impaired function, proliferation, and differentiation of a subset of putative SSCs in human myometrium[4].These findings open up new possibilities for understanding the origin of this benign tumor and help to develop new nonsurgical approaches for their management.

Human UFs and their adjacent myometrium were analyzed for expression of estrogen receptor (ER)-á, progesterone receptor (PR)-A, and PR-B, as well as members of the steroid receptor coactivator (SRC) family. Immortalized human uterine fibroid (human uterine leiomyoma [HuLM]) cells were treated with 1,25(OH)2D3 and assayed for the expression and localization of the aforementioned receptors and SRCs using Western blot, immunohistochemistry, immunofluorescence, and immunoprecipitation assays.It was observed that there was an inverse correlation between the up-regulated ER-á, PR-A, and PR-B and expression of VDR in UFs. Treatment with 1,25(OH)2D3 significantly decreased levels of ER-á, PR-A, and PR-B, as well as SRCs in HuLM cells ($P < .05$). In contrast, 1,25(OH)2D3 self-induced its own VDR, which resulted in an induction of VDR-retinoid X receptor-á complex in HuLM cells. Together, these results suggest that 1,25(OH)2D3 functions as an antagonist of sex steroid hormone receptors in HuLM cells. Hence the study showed that 1,25(OH)2D3 functions as a potent antiestrogenic/antiprogesteronic agent that may have utility as a novel therapeutic option for Uterine fibroids[5].

Conclusion

In fibroids the newer concept the selective progesterone reception modulators are the concepts which seem logical for the efficient treatment of the same at the moment. However, several other parameters and the etiological factors like genetic factor seem an important role in the development of fibroids in a woman.If the molecular basis for fibroid development and of myometrial proliferation is understood,additional nonsurgical therapeutic interventions may be forthcoming. Current clinical needsare stated to a) include an effective prevention strategy if possible b) improve earlydetection; c) slow the growth of fibroids; d) determine the mechanisms of infertility due tofibroids; e) develop better treatment modalities; f) reduce recurrences after treatment.

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The Federation of Obstetric and Gynecological Society of India (FOGSI)
Model Residency, 605, Bapurao Jagtap Marg, Jacob Circle, Mahalaxmi East, Mumbai 400 011, India
Ph: 32954564 / 23021648 / 23021654 / 23021343 Email: fogsi2007@gmail.com