

Predisposing Factors for Fibroids and Outcome of Laparoscopic Myomectomy in Infertility

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ABSTRACT

Introduction: Fibroids are very common tumors affecting women for centuries, however surprising that no significant data is still available as to what could be the cause of fibroid? What could be the predisposing or risk factors? Does it has any impact on fertility? Outcomes of Laparoscopic myomectomy in infertility? **Setting:** Advanced Tertiary Gynecologic endoscopic unit. **Aims and Objectives:** 1) What are the predisposing factors to develop fibroids? 2) Do fibroids lead to infertility? 3) What are the indications for removal of fibroids in infertility? 4) Is laparoscopic surgery better than open surgery? 5) Is the risk of rupture uterus more after laparoscopic myomectomy? 6) What is the success in terms of pregnancy rate after myomectomy? 7) What are the chances of abortions with or without myomectomy? **Materials and Methods:** A retrospective research study was carried out on 2540 women at the National Institute of Laser and Endoscopic Surgery and Aakar IVF Centre, Mumbai, a referral centre in India. This study was done over a period of 14 years. Women varied in age from 23 to 51 years and infertility of at least more than three years. The woman had fibroids from one to seventeen in number and two centimeters to eighteen centimeters in size which were either submucous, intramural, serosal, cervical or broad ligament. The women requiring hysteroscopic myoma resection were excluded in this study and Laparoscopic myomectomy done in woman other than infertility are also excluded from the study. **Results:** During the course of our study we found that the diet, weight, hypertension, habits had a bearing on incidence of fibroid. In one of the most promising research fact we found that fibroids itself produce prolactin and due to three times high level of aromatase had higher level of estradiol locally compared to normal myometrium. This was detrimental to fertility. A mild elevation of blood levels of prolactin usually in the range of 40 – 60 ng/ml was noticed in nearly 42% of the cases. Fibroids with infertility as a major complaint along with excessive vaginal bleeding in 33%, pain abdomen and dysmenorrhea 10%, pressure symptoms in 3%, accidental finding of a large mass in 5% were the major indications for laparoscopic myomectomy. The pregnancy rate after removal of fibroids with active fertility treatment was 42 % and in donor oocyte IVF was 50%, abortion rate was 5%, 64% LSCS, 31% vaginal deliveries. There was no scar rupture in all pregnancies post laparoscopic myomectomy. **Conclusion:** Presence of fibroids in first degree female relative, predominantly red meat eating women, excess weight and high Blood pressure increased incidence of fibroids. Pregnancies & oral contraceptives decreased chances of fibroids. In infertile patient fibroids of significant size, multiple, had high local prolactin & aromatase level affecting fertility. Laparoscopic removal of fibroids increased pregnancy rate to 37.2% & 50% in donor oocyte IVF.

Key words: Fibroids, infertility, predisposing factors, laparoscopic myomectomy

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INTRODUCTION

Treatment innovations have been slow, perhaps because many women have an asymptomatic fibroids, myomas

are benign and mortality is very low.^[1] If hysterectomy was the treatment options given; some women choose to bear with the symptoms and stop seeking treatment.

It is surprising that for more than a century there is no major research on causes of Fibroids, actual impact on fertility and outcome of newer minimally invasive surgical techniques.

MATERIALS AND METHODS

In our retrospective research study over 14 years on 2540

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patients of fibroids managed at our Endoscopic Surgery and IVF Centre, a tertiary specialized centre, we analyzed factors contributing to the incidence of fibroids. The impact of fibroids on fertility and outcome of Laparoscopic myomectomy in 1788 indicated cases was studied. Those women who required hysteroscopic resection of myoma and Laparoscopic myomectomy for women with no fertility problems also were not included in this study.

Inclusion criteria

Indications of laparoscopic myomectomy for fertility enhancement

Our criteria for removal of fibroid in an infertile woman was

- (a) Multiple more than four fibroids of more than four centimeters in size.
- (b) Large fibroids more than five centimeters upto 18 cms in size with more than three years of infertility
- (c) Fibroid indenting the endometrial cavity.
- (d) Fibroid compressing the tubal ostia or distorting tubo ovarian anatomy.
- (e) Fibroids associated with raised prolactin levels.
- (f) Fibroids associated with increased vascularity and excessive bleeding.
- (g) Any non pedunculated fibroids of more than five cm in size in a patient to be taken up for IVF or ICSI [Figures 1 and 2].
- (h) Women with fibroids of more than five centimeters with history of more than one spontaneous abortion.
- (i) Fibroid affecting tubo-ovarian anatomy/multiple fibroids [Figures 3-5 and Table 1].

Surgical procedure

Patient's position

Woman is placed in modified lithotomy position as shown in Figure 6. Allen's stirrups are the ideal leg rests to have but in absence, 45 degree angle in padded leg holders was the option.

Unlike the popular belief, fibroids of any size do not have stalk blood supply. They have a "parasitic" blood supply, Myoma is completely surrounded by vascular layer that supplies the myoma and there is no so-called vascular

pedicles existing at the base of myoma.^[2]

After pneumoperitoneum is created 10mm trocar is inserted through umbilical incision (or two inches above umbilicus in uterus of more than 18-20 wks). We prefer five mm, short flower valve trocars at the three ancillary ports (two Ipsilateral port placement [Figure 11]).

A dilute vasopressin one ampoule (20 units) in 100ml. of normal saline is injected in the cleavage between fibroid capsule and uterine muscle Nezhat *et al.*^[3] [Figure 7]. Pitressin, is synthetic vasopressin decreases blood loss during myomectomy and in a prospective, randomized study, was as effective as mechanical closure of uterine and ovarian vessels.^[4,5]

We prefer a horizontal incision made with a monopolar or plasma kinetic spatula or hook of harmonic scalpel, adequate to remove the fibroid Figure 8. The midline vertical incision cuts multiple arcuate vessels and may be associated with greater blood loss.^[6] Transverse incisions parallel to the arcuate vessels may reduce bleeding by avoiding many of these vessels^[7] [Figure 8].

A myoma screw is put in left upper port to fix the fibroid and gently pull it as spatula dissects the surrounding tissue of the fibroid [Figure 9 a,b].

After removal fibroids are parked in appendicular area [Figure 10].

Some surgeons use scissors to cut the myometrium over the fibroids due to a belief that electrocautery may affect tissue healing. We don't agree with this and use pure cutting current or plasma kinetic spatula or harmonic hook set at a proper level, for last 15 years this has not increased any rupture uterus.

We have designed the "Ipsilateral technique of laparoscopic suturing", standing on the same left side of the patient Figure 11 which is comfortable. This method simulates the physiological movements while operating prevents fatigue and 6-7 sutures can be taken with a 100 cm suture length on curved needle.

The suture with curved on-needle is introduced through the left lower port by Reich and Clarke method. We commonly use polygalactin 910 no.1-0 for suturing the myometrium. Deep interrupted sutures in single layer are taken with distance of one centimeter in between to obliterate the myometrial bed completely [Figures 12 and 13]. This ensures proper haemostasis and also approximates the myometrial flaps.

Table 1: Details of women of laparoscopic myomectomy (788 cases)

Parameter	Our findings
Age (yrs)	23-51 (avg. 37.2)
Preoperative haemoglobin level (gm %)	9-13 (avg. 10.8)
Medical risk factors	250 (13.98%)
Single fibroid	465 (26%)
Multiple fibroids	1323 (73.99%)
Previous abdominal surgery	214 (11.94%)



Figure 1: Large intramural fibroid



Figure 2: Multiple and large intramural fibroids



Figure 3: Left broad ligament fibroid

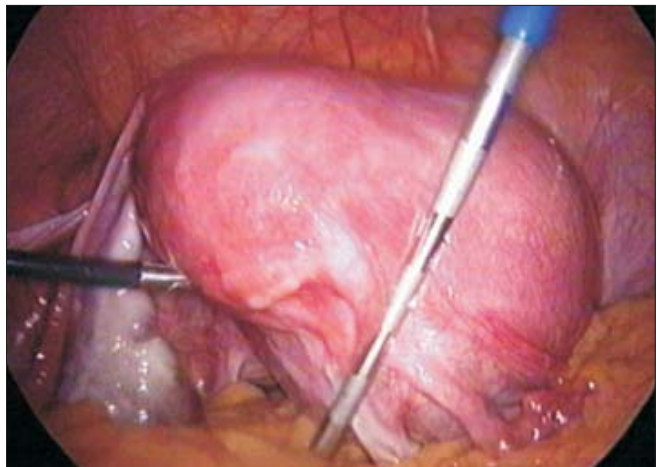


Figure 4: Fibroid distorting tuboovarian anatomy

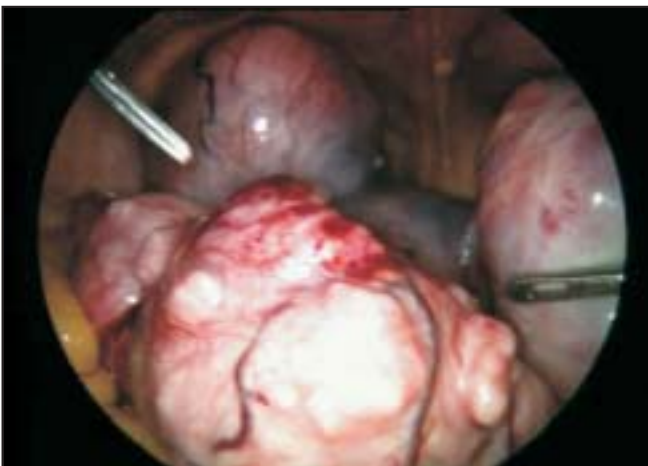


Figure 5: Multiple large fibroids



Figure 6: Patient's position – Modified lithotomy position with Allen's stirrups

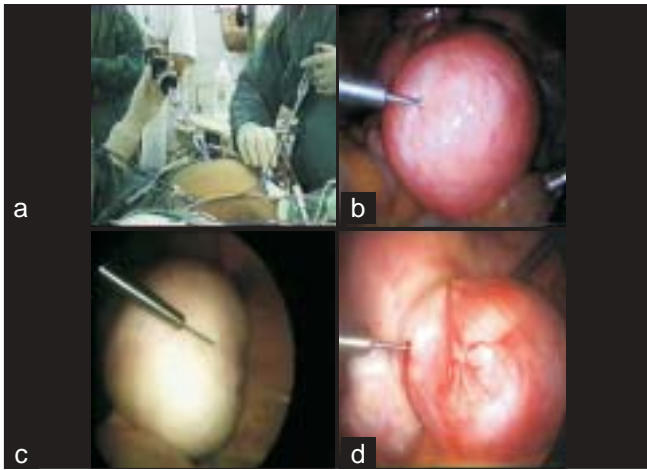


Figure 7 (a-d): Injecting vasopressin in the proper plane



Figure 8: Horizontal incision with spatula

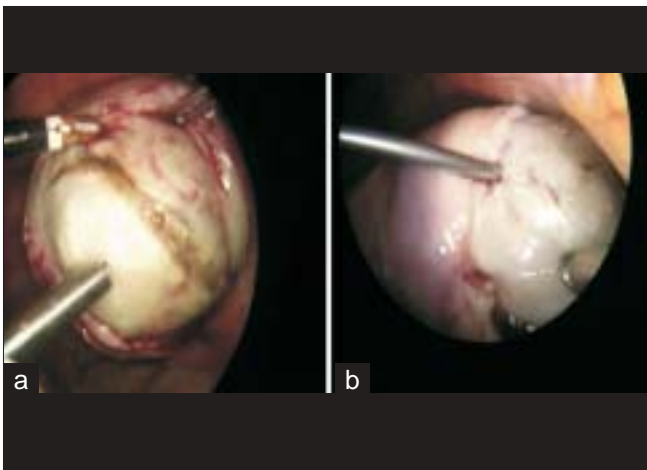


Figure 9 (a-b): Enucleation of fibroid from uterus

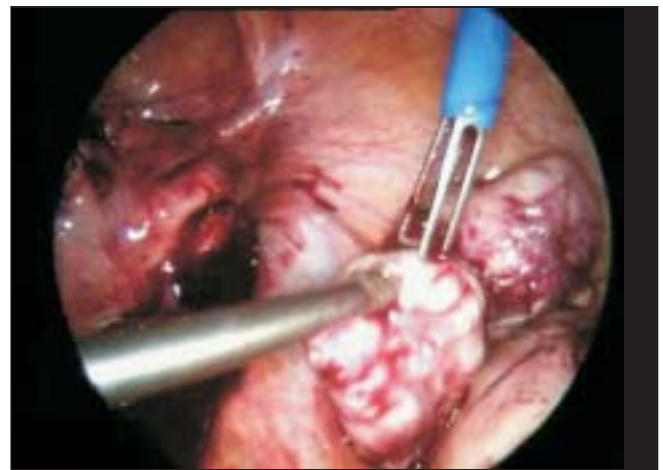


Figure 10: Parking separated fibroids near appendix



Figure 11: Ipsilateral port placement



Figure 12: Grasping and driving the needle through posterior wall

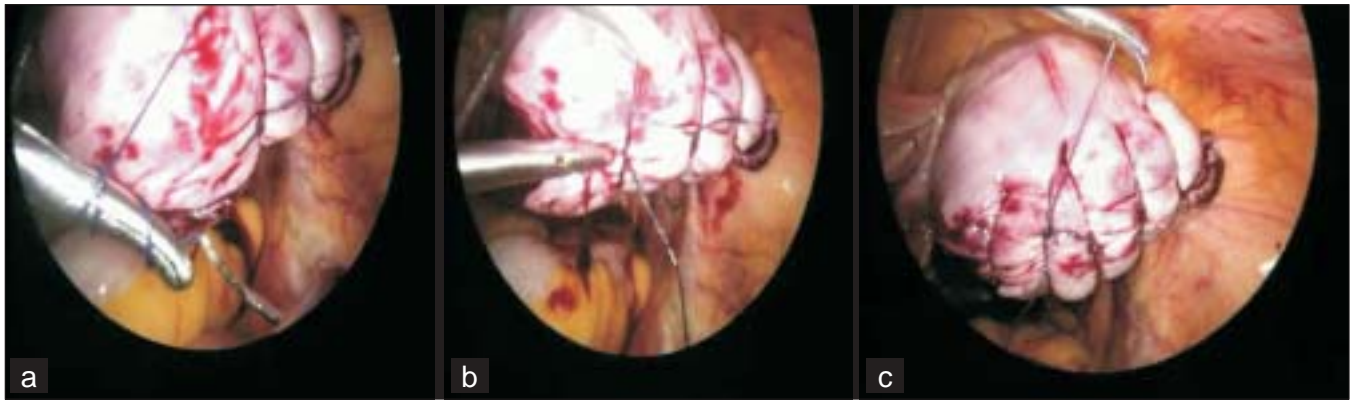


Figure 13: Intracorporeal ipsilateral suturing of incision on uterus

Intracorporeal suturing

After proper suturing a meticulous lavage is given and fibroids are removed by morcellation. We have found that in majority of cases suturing in single layer had no disadvantages over multiple layer suturing. In our experience, multiple layer suturing rather has associated risk of eversion of layers while suturing, which makes suturing difficult and adds to the risk of rupture due to improper approximation.

Paul *et al.*^[8] have also reported that single layer suturing, if done by a skilled laparoscopic surgeon, does not compromise the integrity of the subsequent scar. In cases of broad ligament fibroid, we prefer a posterior incision [Figure 14].

The ureters are always lateral and their course is altered. Most of the broad ligament fibroids might not require the suturing of the bed or dead space, as they do not involve a bulk of the myometrial tissue. Drainage in such cases is always posterior. We would emphasize here that if an anterior incision is made, then the exudates or blood may get collected in the leaves of the broad ligament. In cases of multiple fibroids it is always prudent to remove the fibroids from the most prominent area. Limiting the number of uterine incisions can reduce adhesions on the uterine serosa.^[9] However distant myomas extracted through the tunnel created within the myometrium make haemostatic defects and difficulty to control bleeding.^[10]

Morcellation is done with a 10 mm or 15 mm morcellator. We normally prefer a reusable morcellator—Rotocut's morcellator, [Figure 15 a,b] (Karl Storz, Gmbh Germany).

The left lower port is the preferred port wherein the five mm incision is widened to 10-15 mm, morcellation is always under vision. Long pieces of fibroids morcellated are seen



Figure 14: Broad ligament fibroid

in the tray [Figure 16].

In cases of very large fibroid the author prefers to use a 10 mm myoma screw from the right sided port introduced higher than normal. Figure 17 In the absence or malfunction of morcellator, if the woman is sexually active, colpotomy is a “poor man’s morcellator”. Colpotomy is performed by a spatula or hook incising over the protruding CCL Colpo Chirurgie Lausane trocar in the posterior fornix. Fibroids are fed from above to the claw forceps in the vagina. The stretchability of the vagina is remarkable and hence even the large fibroid can be removed. The wound is closed from below using polyglactin No. 1 or 1-0. An intraperitoneal drain, usually 16 G Ryle’s tube is placed through the right port, reduces postoperative pyrexia and adhesion formation.

Out of 2540 women with fibroid, only 1788 needed myomectomy which we essentially did laparoscopically excluding hysteroscopic myoma resection. In nearly

28.3% surgery was not needed, since the fibroid was not contributing to infertility.

Women were advised to plan conception two months after surgery. The average operating time of laparoscopic myomectomy varied from 32 minutes to 255 minutes

depending on the number and size of the fibroids [Table 2].

In our study we had a pregnancy rate after laparoscopic myomectomy of 42% with active fertility management including IUI, IVF – ICSI. Surprisingly the highest pregnancy rate was 50% in the group of donor oocyte

Table 2: Comparison of different parameters of laparoscopic myomectomy between Trivedi *et al.* and Dubuisson *et al.*

Laparoscopic myomectomy (details)	Trivedi <i>et al.</i> (2009)	Dubuisson <i>et al.</i> (1996)
Average duration	102 +42 min (32-255 min)	130 + 56.1 (range 30-300)
Average blood loss	90 ml (20- 900 ml)	-
Average haemoglobin drop	0.9+1.48 (range- 0-5gm/dl)	1.4+1.18 (range 0-6gm/dl)
Average no. of myomas removed per woman	2.85 + 1.9 (range-1-17)	2.05 +1.5 (range -1-10)
Maximum no. removed in one woman	17	-
Size of the myomas	5.7 + 3.18 cm (range- 1-18 cm)	5.3 +2.2 cm (range-1-12 cm)
Maximum size removed	18 cm	12 cm
Average duration of hospital stay	26 + 6.34 hours (Range 16 – 96 hours)	-
Morcellator port site hernia (15mm)	3/1788 (0.17%)	-

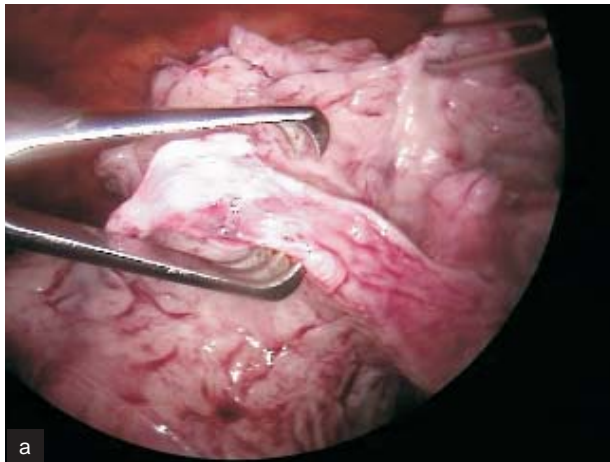


Figure 15 (a-b): Morcellation of fibroid with rotocut morcellator



Figure 16: Tray full of morcellated pieces of fibroid

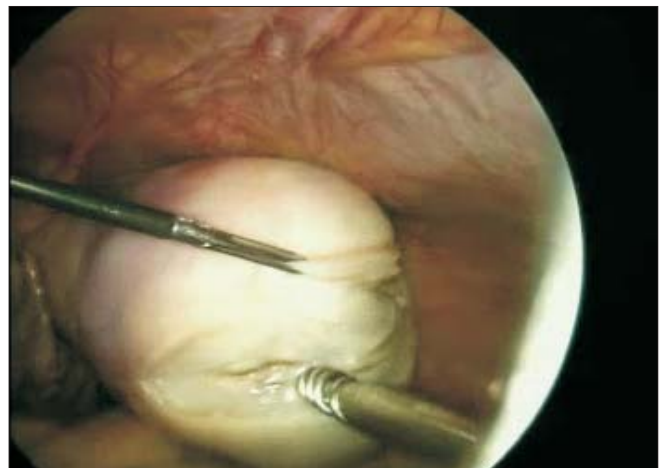


Figure 17: 10 mm Myoma screw for very large fibroid enucleation

IVF or ICSI. Out of the total number of pregnancies we had 64% caesarian section, 31% vaginal delivery and 5% abortions. There was no uterine scar rupture noticed or reported so far in our study. We had to convert less than 1% of our cases to laparotomy mainly because of poor case selection or history of previous open surgery coexisting with extensive endometriosis. In 22 cases of laparoscopic myomectomy, women needed blood transfusion because of either primarily border line low hemoglobin or in few cases due to excess blood loss.

DISCUSSION

Predisposing factors of fibroid obtained in our study were

1. If a first-degree female relative 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.^[11]
2. Age at 45 to 50 years of age, fibroids was 20 times more than women between 25 to 30 years of age (6.2 per thousand vs 0.3 per thousand).^[12]
3. A red meat eating women has three times higher chances of having fibroids compared to women having a vegetarian diet or mainly fish eating women.^[13]
4. For every 10 kg rise in weight of patient there is 18% increase in incidence of fibroids.^[14]
5. For every 10 mm rise in diastolic blood pressure there is 10% increase in incidence of fibroids. Hypertensive women in later years had 24% chances to be having fibroids and the degree of fibroids were proportionate to the severity of the hypertension.^[15]
6. A women who had a habit of smoking cigarettes, beedi's etc they had less incidence of fibroids this was probably due to associated lower levels of estrogen.^[16,17]
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.^[18]
8. The growth rate of fibroids we noticed was average 1.25 cm in 2.5 years.^[19] Even sometimes a fast-growing fibroid didn't mean that it was sarcomatous.
9. Parity reduced the risk of fibroids three to five fold, showed more specifically in the later age as the incidence of fibroids are higher in later age.^[20]
10. The recurrence rate of fibroids after removal is from 25 to 62% by the end of 5 years follow-up, in nearly 10 to 20% needed a second surgery within one to ten years.^[21]
11. The tissue prolactin level was high in the fibroid tissue acts as a stimulator of the proliferation of Leiomyoma cells by the mitogen activated protein kinase cascade.^[22] This was suppressed by anti-prolactin antibodies and also progesterone showed suppressive effect.^[23-26]
12. Fibroids express three times high aromatase levels than surrounding myometrium, increases active estradiol promoting growth of fibroids. Aromatase mRNA was detectable in 91% of myomas 75% at two cm from the myoma and not detectable in disease-free myometrium of the uterus.^[27-32] A situation of local hyperprolactinemia and local hyperestrogenemia leading to infertility and abortions. Uterine Leiomyoma is even reported in 27% of infertile women^[33] and 50% of women with unexplained infertility became pregnant after myomectomy.
13. Myomas of less than five centimeters 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.^[34,35] The spontaneous abortion rate was 41% in cases of myomas of significant size, this reduced to 19% after myomectomy.^[36-38] Patients of fibroids with pregnancy had increased incidence of bleeding in the first trimester premature rupture of membranes, breech presentation placental abruption prolonged labor higher caesarean section rate. The estimation of premature labor was 15 to 20%, intrauterine growth restrictions in 10% and malpresentations in 20%.^[39-41]
14. The risk of malignant transformation in myomas: Literature suggests Leiomyosarcoma incidence from 0.23% in premenopausal women to 2% in postmenopausal women.^[42] The incidence of Leiomyosarcoma is 0.67 per 1,00,000 women per year.^[43]

Specific risks of laparoscopic myomectomy

1. Surgery and anesthesia is longer judicious monitoring and good anesthesia avoids morbidity.
2. Major risk imagined is the future rupture of the uterus in pregnancy in antenatal period or during labor.^[44-49] This is due to the popular belief, rather misconception, that laparoscopic suturing is inferior to an open surgery.
3. Excessive bleeding, but use of dilute vasopressin and right plane of dissection, decreases the blood loss. GnRh analogues offer significant benefit, only in severely anaemic patients, in whom immediate surgery is avoided. We do not advocate prophylactic suturing of both uterine vessels to reduce bleeding in a patient keen for conception. This increases risk of ureteric

injury and bleeding can occur due to collateral blood supply.

4. Conversion to laparotomy: In our study we had 0.75% (14 cases) of conversion to a Laparotomy, mainly due to inappropriate patient selection. The risk of conversion is nearly three times more, when the sizes of the fibroid are more than eleven centimeters, or are anterior in location. Dubuisson *et al.*^[44] reported a three times higher conversion rate when fibroids measured more than eight centimeters or located anteriorly. Conversion to a Laparotomy is actually a prudent judgment on the part of the surgeon.
5. Post operative adhesions: After laparoscopic myomectomy, chances of adhesions are much lesser than that of an open surgery. Adhesion barriers are thought to prevent or significantly reduce the incidence of formation of postoperative adhesions^[50] their actual benefit is still a matter of debate.

Technical complications of laparoscopic myomectomy and prevention

Breakage of myoma screw (nine cases) happened while pulling the myoma with the screw out of the uterus. One should ensure that removal of the broken piece is always done before the conclusion of the procedure, taking care of not slipping suddenly when it can get lost in the peritoneal cavity

Laparoscopic myomectomy if judiciously employed in properly selected cases definitely offers significant advantages over an abdominal myomectomy, but the surgeon should be well trained and skilled in the procedure. The advantages: short hospital stay, faster recovery, less post operative pain, decreased thrombo-embolic phenomenon.^[51] The maximum number and size of fibroids removed laparoscopically can not be generalized as it is dependent on surgeon's skill, skill of endosuturing, operation theatre setup and assisting team.

The true contraindication of laparoscopic myomectomy is any medical condition which can worsen with abdominal distention and trendelenburg position for prolonged period. The relative contraindication may be diffuse leiomyomata.

In a series reported by Seiner *et al.*,^[52] 65 pregnancies were achieved in 54 women with no case of uterine rupture. In another study by Dubuisson *et al.*,^[53] The estimated risk of uterine rupture has been reported to be 1.0 % (95% CI 0.0-5.5).

Dubuisson *et al.*^[4] reported a scar rupture from a three cm

posterior wall fibroid removed and sutured properly by him. The author has observed an interesting fact relevant to uterine scar rupture post myomectomy namely when a lower segment caesarean section is done the round ligaments are very close to the lower segment incision even at full term suggesting that the stretchable part of the uterus is usually above the round ligament and posterior wall, hence whenever there is a large or multiple fibroids removed from this area an elective caesarean section is strongly recommended at 36–37 weeks or unexplained pain in abdomen with tachycardia suggesting an impending rupture.

An interesting detail from the world fibroid registry has clearly pointed out that the uterine scar rupture after open myomectomy is grossly under reported or missed.^[54,55] Further the International registry of fibroid also firmly quotes that chances of laparoscopic myomectomy scar to rupture in the hands of expert is less than a lower segment caesarean section scar rupture and far less than a classical caesarean section scar rupture.^[56]

Breakthrough in histopathology of fibroids

In histopathology we had one Endometrial stromal tumor, one Desmoid, one Primary uterine malignancy thought to be Fibroid. Kempson and co-workers^[57-61] for four decades^[62,63] evaluated whether the cells show smooth muscle or endometrial stromal differentiation. Architectural features, such as fascicular alignment of the tumor cells and the presence of thick walled vascularity, favor with a smooth muscle tumor. The vessels in endometrial stromal tumor are mainly thin-walled capillaries in arching pattern. In difficult cases, immunohistochemical staining with this Desmin, CD-10, and caldesmon may aid in determining whether the cells are of smooth muscles or endometrial stromal origin^[64]. In endometrial stromal tumors infiltration of myometrium or vessels indicates malignant behavior^[65]. In smooth muscle tumors, despite of infiltrating pattern the clinical course may be benign. Fibroids without any features of malignancy, such as coagulative necrosis, significant atypia or increased mitotic index (MI), yet they do metastasize. There can be nodes in lung, lymph nodes yet relatively non aggressive.^[66-69]

Unusual differentiation of so called fibroids

Epitheloid (clear cell)/Myxoid differentiation with M.I. equal or more than 5mf/10 HPF prognosis is poor irrespective of absent tumor necrosis or cytological atypia.^[70,71]

Molecular markers of prognosis immunostaining for

Ki-67 can be useful for differentiation of Leiomyosarcoma (50%) from Leiomyoma (8%).^[72-75]

Leiomyosarcoma are isolated lesions and not originating from fibroids, an Austrian multi-institutional study of 71 cases of Leiomyosarcoma accumulated over ten years revealed that none arise from any myoma, which may mean that Leiomyosarcoma is primarily a tumor on its own thought to be myoma at some stage which may be myth than reality.^[76]

CONCLUSIONS

In a retrospective study of 2540 cases fibroids over 14 years we could find certain factors predisposing occurrence of fibroids: first degree female relative having fibroid, diet, weight, age, hypertension increases but oral contraceptives, parity reduces chances.

A major breakthrough revealed fibroids having higher levels of aromatase converting estrogens to estradiol and high prolactin were detrimental to pregnancy. Laparoscopic removal of significant size fibroids increased pregnancy rate both spontaneous, or on infertility ~ ART treatment specially even in donor oocyte program.

Laparoscopic myomectomy in properly selected cases has significant advantages in the hands of well trained and skilled surgeon. The pregnancy rates after removal of fibroids laparoscopically in infertility and ART was higher with less abortion rate. Also the unnecessary feared uterine scar rupture after the laparoscopic myomectomy is disproved in the hands of expert.

In our study we had a pregnancy rate after laparoscopic myomectomy of 42% with active fertility management including IUI, IVF – ICSI. Surprisingly the highest pregnancy rate was 50% in the group of donor oocyte IVF or ICSI. There was no uterine scar rupture noticed or reported so far in our study. We had to convert more than 1% of our cases to laparotomy.

Finally what looks like Fibroids can be Leiomyoma, Endometrial stromal tumor, Epithelioid, Myxoid, Leiomyosarcoma or rarely desmoid tumor.

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