ORIGINAL ARTICLE

Fibroids, Infertility and Laparoscopic Myomectomy

Pankaj Desai, Purvi Patel

Department of Obgyn, Medical College and S.S.G. Hospital, Baroda, India

ABSTRACT

Objective: To review the literature and summarize the available evidence about the relationship of fibroids with infertility and to review the role of laparoscopic myomectomy in infertility. **Materials and Methods:** Medline, PubMed, and Cochrane Databases were searched for articles published between 1980 and 2010. **Results:** Fertility outcomes are decreased in women with submucosal fibroids, and myomectomy is of value. Subserosal fibroids do not affect fertility outcomes, and removal may not confer benefit. Intramural fibroids appear to decrease fertility, but the results of therapy are unclear. Although pregnancy rates for women with leiomyomata, managed endoscopically, are similar to those after laparotomy, there is a risk of uterine rupture. The risk is essentially unknown. Finally, the risk of recurrence seems higher after laparoscopic myomectomy compared to laparotomy. **Conclusions:** Laparoscopic myomectomy, when performed by an experienced surgeon, can be considered a safe technique, with an extremely low failure rate and good results in terms of the outcome of pregnancy.

Key words: Fibroid, laparoscopic myomectomy, Infertility

INTRODUCTION

Uterine fibroids are the most common benign tumors occurring in women in the reproductive age group. The prevalence rates quoted in literature range from 20 – 50%, based on postmortem studies.[1] The prevalence varies with age, with an increase in the late reproductive period. Current trends suggest that there is a tendency to delay pregnancy to a later age when the incidence of fibroids is more. Indeed, uterine fibroids are detected in a small, but significant number of infertile women. If a causal relationship between fibroids and infertility can be established, treatment is indicated for enhancing fertility. However, the impact of fibroids on infertility is still controversial.

Laparoscopic myomectomy was described for the first time in 1979, exclusively for subserous fibroids.[2] In the beginning of 1990s, the procedure began to be used for intramural fibroids.[3-6] At present, Laparoscopic myomectomy, in infertile patients, is one of the common surgical procedures. Despite the obvious advantages of laparoscopic myomectomy, its role in treatment of infertility has been an issue of continuous debate.

This review attempts to summarize the available evidence regarding the association of fibroids with infertility and the role of laparoscopic myomectomy in infertility.

MATERIALS AND METHODS

Medline, PubMed, and Cochrane Databases were searched for articles published between 1980 and 2010, using the following search terms; fibroid, infertility, and laparoscopic myomectomy. We took into consideration both prospective and retrospective articles. We also selected cross-references, which we came across during the review search, if they were not included initially.

Address for correspondence:
Dr. Pankaj Desai,
Chief of Unit in Obgyn (VRS), Medical College and S.S. G. Hospital, Baroda, India.
E-mail: pankaj@drpankajdesai.com

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RESULTS

Association between fibroids and infertility

Fibroids are present in approximately 5-10% of the patients presenting with infertility; however, they are found to be the sole identified factor in only 1-2.4% of the infertile patients.[7-11] The study most commonly cited to give an epidemiological estimate of the impact of fibroids on infertility, is the review published by Buttram and Reiter.[12] The authors, in their 10 years of experience, found uterine fibroids to be the sole cause of infertility in only 2.4% of the cases. They concluded that fibroids alone are an infrequent cause of infertility. Verkauf[13] reported that only 1% of the 339 infertility laparotomies between 1981 and 1990 required myomectomy for otherwise unexplained infertility. It would be worthwhile to note that these data are generated from case series, which may not give the correct estimate of the prevalence of fibroids in the infertile population. Cross-sectional studies in a group of unselected patients undergoing transvaginal sonography may give more reliable information. However, this study design has been performed rarely[14-16] and infertility was unfortunately never assessed. It has been suggested that for establishing the association between fibroids and infertility, a case-control study would provide better quality evidence, where infertile women are cases, whereas, fertile women are controls. Although some authors advocate prospective controlled studies, it is unlikely that an easy answer will be found, due to considerable variations in location, size, and the number of fibroids, as also the presence of additional infertility factors and variation of surgical techniques.

The IVF model

In vitro fertilization (IVF) can be used as a tool to establish the association between fibroids and infertility. We reviewed 20 studies, which investigated the impact of fibroids on the outcome of IVF–ICSI (intra cytoplasmic sperm injection) cycles. The results from these studies[17-34] were not consistent. Pritts[35] documented a significant negative impact of submucosal fibroids on the pregnancy rate, but failed to observe any relevant impact of fibroids located at other sites. Donnez and Jadoul[8] had similar results. However, Benecke *et al*,[7] also reported a negative impact of intramural fibroids. An updated meta-analysis conducted by Somigliana *et al*,[34] concluded that myomas negatively affect the pregnancy rate. According to them, submucosal lesions appear to strongly interfere with the chance of pregnancy. The impact of intramural myomas is less dramatic, even though they are statistically significant. In general, these effects appear to be more relevant when considering the delivery rate rather than the clinical pregnancy rate. Conversely, subserosal lesions do not seem to play a role. The findings regarding intramural lesions have been conflicting. The two initial meta-analyses[8,35] failed to document a harmful effect. The Practice Committee of the American Society for Reproductive Medicine (2006)[10] recently supported this conclusion. On the contrary, the meta-analysis of Benecke *et al*,[7] and Somigliana *et al*. showed a lower pregnancy rate in women with intramural fibroids. It should be remembered that the results based on IVF studies evaluate the impact of fibroids on embryo implantation. Possible detrimental effects on tubal transport of oocytes and/or embryos are overcome by the technique. Also, recent findings suggest that the size of the fibroids is positively related to implantation failure, especially when the diameter of the lesion exceeds 4 cm.[19] The mean or median diameter of the fibroids included in IVF-based studies is usually less than 3 cm, since most of the IVF units recommend surgery for fibroids measuring more than 5 cm. This could undermine the actual effect of fibroids on fertility.

Approximately 50% of the women with infertility and myomas become pregnant after myomectomy. As epidemiological studies have not been able to provide unflinching evidence of the impact of fibroids on fertility, a large number of studies have been based on pregnancy rates after myomectomy.

Donnez and Jadoul[8] performed a literature review on both prospective and retrospective studies published between 1988 and 2001. The pregnancy rate in patients undergoing hysteroscopic and laparoscopic / abdominal myomectomy was 45 and 49%, respectively. More recent studies on a large series have confirmed these findings.[36-42]

Laparoscopic and laparotomic surgeries appear to have similar success rates,[39,43-46] but larger studies are warranted before drawing definite conclusions. Despite a large number of series reporting on the pregnancy rate after myomectomy, randomized studies are lacking. A cochrane review[46] on this issue failed to identify any randomized trial comparing surgery with expectant management. On reviewing the literature, we found only one comparative study[47] investigating the chances of pregnancy in women undergoing laparoscopic myomectomy and in a control group of unoperated patients (Bulletti *et al*.). Patients with causes of infertility other than fibroids were excluded. There were 106 women who underwent myomectomy and 106 who did not receive treatment. The patients were followed for nine months after allocation. A higher delivery rate was observed in the surgical group (42 versus 11%).

The impact of myomectomy on the outcome of IVF has also been studied. A recent comparative study[48] has provided evidence on the effectiveness of myomectomy prior to IVF (Bulletti *et al*,). Patients selected for the procedure, who were diagnosed with intramural-subserosal fibroids, with at least one lesion with a mean diameter of 5 cm, were informed about the pros and cons of myomectomy. The patients themselves decided whether to undergo surgery and were divided into two groups ($n = 84$ each) with similar characteristics. The cumulative delivery rate in women who did and did not undergo surgery was 25 and 12%, respectively.

Several hypotheses have been put forward to explain the mechanisms by which fibroids can lead to infertility. Fibroids can cause distortion and enlargement of the endometrial cavity by submucous and intramural leiomyomas, with an intracavitary component affect implantation.[49,50] Implantation failure may also be explained by focal endometrial vascular disturbances, endometrial inflammation, and secretion of vasoactive substances.[12,51] Leiomyomas may also cause dysfunctional uterine contractility and interfere with sperm and ovum transport.[12,52,53] Likewise, intramural leiomyomas may also obstruct the tubal ostia.

The location of the myomata may play an important role in determining infertility. Both large intramural and subserosal myomata are thought to interfere with conception and reduce the effectiveness of the assisted reproduction cycles,[54] whereas, pedunculated myomata are not believed to have detrimental effects on fertillity.[55] The size of the myomata may represent another important prognostic factor,[12,56] 5 cm in diameter being the size limit that appears to justify myomectomy. In several uncontrolled surgical trials, restoration of fertility after myomectomy has been reported, with pregnancy rates ranging between 44 and 62%.[55,57,58] The time to postmyomectomy conception is short with around 80% of pregnancies occurring during the first year following surgery. Therefore, myomectomy is a valuable approach for treating patients with leiomyomata and otherwise unexplained infertility.

Submucosal fibroids are associated with a 70% reduction in delivery rate. Intramural fibroids have a lesser effect and reduce the delivery rate by approximately 30%. By contrast, studies have demonstrated that subserosal fibroids do not negatively impact fertility.[59]

One study[12] suggested a link between infertility and the existence of menometrorragia associated with fibroids (50% for patients suffering from infertility compared to 15% of those without infertility). The likely explanations could be endometrial changes associated with fibroids, deformation of the uterine cavity, and vascular changes (ectasia of the submucosal venous plexus) associated with the presence of the myoma, which could play a part in infertility.

Laparoscopic myomectomy in infertility

In spite of its known advantages, laparoscopic myomectomy is still a debated operation, whose feasibility, indications, and risks are still matters of discussion. Indications: Universally accepted indications include the presence of a submucous or intramural fibroid that distorts the uterine cavity, fibroids greater than 3 cm, and multiple fibroids. Feasibility: The feasibility of laparoscopic myomectomy has been already shown with numerous clinical studies. The location and size of uterine fibroids are major determinants for making a decision about which surgical approach is the most feasible. A consensus gradually emerges that the maximal size must be 8-10 cm and the total number of fibroids should not exceed four.[60] Some authors' criteria for laparoscopic myomectomy are a single intramural or subserosal fibroid ≤15 cm or three or fewer fibroids of ≤5 cm,[61] whereas, others believe in an individual choice based on pathological findings and surgical skill.[62] It is prudent not to perform laparoscopic myomectomies with more than five to seven large myomas because in these cases, the procedure is excessively time-consuming and the surgeon can miss the smaller myomas after the uterus has been incised and repaired in too many places.

Risks

In an Italian multicentric trial, which is one of the largest series reported of laparoscopic myomectomy and the first focused on the complications, the authors[63] have observed that the probability of complications significantly rises with an increase in the number (more than three myomas) and with the intramural or the intraligamentous location of the myomas, whereas, the myoma size seems to particularly influence the risk of major complications.

Uterine rupture

One of the major concerns about myomectomy is the risk of uterine rupture during pregnancy or labor. Uterine rupture can occur following myomectomy at both laparoscopy and laparotomy. In a retrospective study, the rate of rupture observed at birth, after myomectomy, at laparotomy was 5.3%.[64] Whether laparoscopic myomectomy has an increased risk is questionable.

Regardless of the surgical approach, fear about the risk of uterine rupture certainly leads to a high rate of cesarean sections in pregnant patients, who previously underwent myomectomy. Although, conventionally, cesarean section is recommended if more than 50% of the myometrium has been disrupted, as it is that which is responsible for uterine integrity.[65]

Nine cases of uterine rupture after laparoscopic myomectomy have been reported so far.[66-70] However, these reports generally do not describe the incidence per number of procedures performed.[45] Authors cite breach of endometrial cavity, application of excessive tissue coagulation, difficulties in tissue approximation or use of unsuitable suture size with the risk of intramural hematomas, indentations, and uterine fistulas as the possible contributing factors. Laparotomic myomectomies allow multilayered suturing using suture materials of sufficient tensile strength, to optimally close the uterine defect following enucleation. Laparoscopic surgeons are trying to reduce this complication by changing over from single-layer to multilayer suturing techniques.[71] The underlying principle is that good approximation without hematoma formation is important in the healing of myomectomy wounds.[72] However, there are studies suggesting that uterine rupture following laparoscopic myomectomy is rare even when following single-layer myometrial closure. This data, although reassuring, is not conclusive, and there is a need for a randomized study to compare single-layer and multilayer suturing techniques. When postoperative infection is absent, uterine rupture is uncommon.[73,74] There have been reports of uterine ruptures following laparoscopic myomectomy in cases of removal of pedunculated or subserosal myomas using electrosurgery only.[66] It has been suggested to apply sutures or endoscopic loops in such cases.

Adhesions

Dubuisson *et al*,[75] found an adhesion rate of 35.6% on second-look laparoscopy, and this result is corroborated by other studies.[76,77] The rates are significantly low compared to those observed following laparotomy, which averaged an adhesion rate of almost 90% or above.[75] The incidence is highest with posterior uterine incisions and lower with fundal or anterior incisions.[45,78] The fact that the cumulative probability of conception after myomectomy was lower in the presence of a posterior myoma, an intramural myoma, and / or uterine suture, indirectly suggests the hypothesis that adhesions are responsible for lower postoperative fertility. Reduced fertility is secondary to the involvement of the adnexa in adhesions associated with scarring due to posterior myomectomy.

Pregnancy wastage after myomectomy

The risk of miscarriage does not appear to be increased in patients who have undergone myomectomy. On the contrary, several studies support the concept that the rate of pregnancy wastage significantly decreases after surgery. In a review of 1941 patients who underwent myomectomy, the spontaneous abortion rate improved from 41% prior to surgery to 19% following myomectomy.[12] Results from recent studies also confirm a strong benefit of the surgery.[37,41,79,80]

Recurrence

In a recent multicenter study,[81] the recurrence rate of leiomyomas was estimated to be 11.7, 36.1, 52.9, and 84.4%, respectively, after one, three, five, and eight years following laparoscopic myomectomy. However, the probability of a re-operation is 6.7% after five years, and 16% after eight years. Unlike laparotomy, laparoscopic myomectomy has the shortcoming of difficulty in diagnosing small fibroids deep in the myometrium by palpation of the uterine body, especially in cases of multiple fibroids, hence these may be missed. It has been reported that the recurrence rate of fibroids is higher in laparoscopic myomectomy as compared to laparotomy.[82]

Preoperative treatment with GnRH may increase difficulties in identifying and dissecting the cleavage plane between the fibroid and its pseudocapsule. According to Dubuisson,[83] GnRH analogs are one of the preoperative factors that are found to be independently related to the risk of conversion, and, moreover, there is a possibility of missing these fibroids because of their shrinkage after therapy, leading to a higher risk of recurrence in GnRH analog-treated patients.[84]

Other complications

Major intraoperative and postoperative complications associated with laparoscopic myomectomy include bladder, bowel, and ureteral injury, intraoperative and postoperative hemorrhage requiring transfusion, and unintended conversion to hysterectomy, fistula, thrombosis, and embolism.[85] However, the complication rates of laparoscopic myomectomy have been decreasing over time. In a multicenter study[63] of 2050 women who underwent laparoscopic myomectomy, the most serious complications were hemorrhage (0.68%), postoperative hematoma (0.48%), bowel injury (0.04%), and emergency hysterectomy (0.09%). These figures suggest that laparoscopic myomectomy is safe in the hands of skilled laparoscopic surgeons.

Laparoscopic myomectomy versus total abdominal myomectomy

We found five randomized controlled trials (RCTs) comparing laparoscopic versus abdominal myomectomy, with regard to peri- and postoperative outcomes.[43,84,86-88]

These studies concluded that there was no significant difference in the length of surgery, blood loss, or postoperative complications (fever) between laparoscopic and abdominal myomectomy.[86] Women having laparoscopic myomectomy reported a lower intensity of postoperative pain (unlabeled scale), required less analgesia, and had a shorter recovery time than women having abdominal myomectomy by laparotomy. Two days after surgery, a significantly smaller proportion of women (15%) required analgesia with laparoscopic myomectomy than with abdominal myomectomy (85%), and by day 15 more women had fully recovered after laparoscopic myomectomy (90%) with laparoscopic as against (5%) abdominal myomectomy. Another RCT[43] found a significantly greater reduction in hemoglobin with abdominal rather than with laparoscopic myomectomy (1.33 g / dL with laparoscopic *v* 2.17 g / dL with abdominal myomectomy; $p < 0.001$), a lesser incidence of postoperative fever (12%) with laparoscopic *v* (26%) abdominal myomectomy, and a shorter hospital stay (75.6 hours with laparoscopic myomectomy *v* 142.8 hours with abdominal myomectomy). The RCT comparing minilaparotomy with laparoscopic myomectomy found that laparoscopic myomectomy significantly reduced the mean decline in hemoglobin, duration of ileus, time to hospital discharge, pain intensity six hours after surgery, and the percentage of women requesting analgesics, as compared to minilaparotomy.[88]

As regards the pregnancy rate following myomectomy, the RCT found no significant difference in pregnancy rate after surgery between laparoscopic and abdominal myomectomy (53.6% with laparoscopic *v* 55.9% with abdominal myomectomy). One RCT comparing the recurrence rate found no significant difference between laparoscopic and abdominal myomectomy in recurrence of fibroids at 3.3 years (27% with laparoscopic *v* 23% with abdominal myomectomy).[84]

CONCLUSIONS

Although epidemiological studies have been inconclusive in establishing a relationship between fibroids and infertility, clinical evidence supports the view that fibroids interfere with fertility.

A laparoscopic approach is more advantageous than laparotomy, but laparoscopic suturing is more demanding. Its advantages over open myomectomy include reduced postoperative pain, shorter hospitalization, quicker recovery, and reduced febrile morbidity and blood loss. It may also reduce the risk of postoperative adhesion formation. There are now large numbers of pregnancies following laparoscopic myomectomy and the risk of uterine rupture in future pregnancies seems to be very low, with a good surgical technique. It can be concluded that laparoscopic myomectomy, when performed by an experienced surgeon, can be considered a safe technique with an extremely low failure rate and good results in terms of pregnancy outcome.

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