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Fertility and obstetric outcome after laparoscopic myomectomy of large myomata: a randomized comparison with abdominal myomectomy

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The purpose of this study was to compare, in infertile patients, the efficacy of laparoscopic myomectomy versus abdominal myomectomy, in restoring fertility and to evaluate the obstetric outcomes. Between January 1993 and January 1998, 131 patients of reproductive age, with anamnesis of infertility, underwent myomectomy because of the presence of at least one large myoma (diameter ≥5 cm). Patients were randomly selected for treatment by laparotomy (n = 65) or laparoscopy (n = 66). The two groups were homogeneous for number, size and position of large myomata. Significant differences were found in the post-operative outcome: febrile morbidity (>38°C) was more frequent in the abdominal than in the laparoscopic group (26.2 versus 12.1%; $P < 0.05$). Laparotomy caused a more pronounced haemoglobin drop (2.17 ± 1.57 versus 1.33 ± 1.23; $P < 0.001$); three patients received a blood transfusion after laparotomy and none after laparoscopy. The post-operative hospital stay was shorter in the laparoscopic group (142.80 ± 34.60 versus 75.61 ± 37.09 h; $P < 0.001$). No significant differences were found between the two groups as concerns pregnancy rate (55.9% after laparotomy, 53.6% after laparoscopy), abortion rate (12.1 versus 20%), preterm delivery (7.4 versus 5%) and the use of Caesarean section (77.8 versus 65%). No case of uterine rupture during pregnancy or labour was observed.

Key words: fertility/laparoscopy/laparotomy/large myoma/myomectomy

Introduction

It has been suggested that the presence of uterine myomata may cause infertility and recurrent pregnancy loss (Buttram and Reiter, 1981; Rosati *et al*., 1989). This hypothesis is confirmed by the evidence that 43% of women presenting uterine leiomyomata were found to have experienced a history of infertility for at least 2 years (Hasan *et al*., 1990). 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 assisted reproduction cycles (Stovall *et al*., 1998), whereas pedunculated myomata are not believed to have detrimental effects on fertility (Dubuisson *et al*., 1996). The size of the myomata may represent another important prognostic factor (Buttram and Reiter, 1981; Rosenfeld, 1986), 5 cm in diameter being the size limit which 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% (Berkeley *et al*., 1983; Gatti *et al*., 1989; Vercellini *et al*., 1992; Dubuisson and Chapron, 1996; Dubuisson *et al*., 1996). The time to postmyomectomy conception is short with ~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. Although abdominal myomectomy has been considered the surgical technique of choice, recent studies have demonstrated that laparoscopy can be used for the enucleation of myomata (Daniell and Gurley, 1991; Dubuisson *et al*., 1991, 1993; Nezhat *et al*., 1991, 1996). The advantages of the laparoscopic approach are well established, but laparoscopic myomectomy still needs to be adequately evaluated. Laparoscopic myomectomy, even for an experienced endoscopist, can be a difficult and troublesome procedure, especially for large myomata. The aim of this study was to compare the efficacy of the two surgical techniques. In particular, we intended to assess whether, even in the presence of large myomata, laparoscopic myomectomy is a feasible and safe procedure offering the same results as laparotomy in restoring fertility. To our knowledge, this is the first study that has randomly compared laparoscopic and abdominal myomectomy in relation to the post-operative recovery of fertility.

Materials and methods

Laparoscopic myomectomy has been performed in our Department since 1991. Every year about 100 patients (a total of 744 patients between 1991 and 1998) undergo this type of intervention utilizing laparoscopy or laparotomy and the majority of these patients suffers from infertility. This study involved 131 patients who underwent myomectomy between January 1993 and January 1998 due to the presence of at least one large uterine myoma (diameter ⩾5 cm). Cases presenting pedunculated myomata were excluded. Patients with a uterine size above the transverse umbilical line as well as those with more than three myomata >5 cm in diameter were also excluded from the present study. Diagnosis was performed by transvaginal and abdominal ultrasonography. Hysteroscopy was used when ultrasonography showed the probable involvement of the endometrium and was performed up to 6 months before the operation. All patients recruited were of reproductive age (range 21–42 years), with an

anamnesis of infertility (between 24 and 120 months; mean 43.69 ± 19.92). Infertility was primary in 87 cases (66.4%) and secondary in 44 cases (33.6%). In order to assess the presence of other infertility factors, patients were pre-operatively evaluated by ovulation studies, hysterosalpingography, a post-coital test and a spermocytogram.

Patients were excluded if they presented concomitant alterations of tubal patency or other infertility factors, including male factors. We also excluded women with alterations of the uterine cavity such as septum or subseptum. Gonadotrophin-releasing hormone agonists (GnRHa) or other medical treatments were never prescribed before surgery.

All women signed an informed consent form and a surgical consent form to participate in this study.

Sixty-five patients underwent laparotomy (group 1, 49.6 %) and 66 laparoscopy (group 2, 50.4%) by means of random selection. Assignment to laparotomy or laparoscopy took place after the patients had consented to surgery. It was carried out the day before surgery by use of total random digits (Zar, 1984) unknown to the surgeons. All patients underwent general anaesthesia. All surgical procedures were performed by the same investigators (R.S. and S.V.). Both surgeons performed laparoscopic and abdominal myomectomy. For each patient, the total operating time, from skin incision to closure, was recorded. Laparoconversion was defined as the substitution of laparoscopy by laparotomy for intra-operative complications. Haemoglobin loss and the incidence of febrile morbidity (indicated by a temperature of ⩾38°C in two consecutive measurements ⩾6 h apart, excluding the first 24 h) were reported. The length of hospital stay, in term of hours of hospitalization after surgery, was noted. Before hospital discharge, patients had to tolerate a normal diet, be able to dress themselves, be fully mobile around the ward, be analgesic-free and be satisfied that they could manage at home. Information about subsequent fertility and obstetric outcome was obtained from hospital records, physicians and direct reports from the patients. Only patients with a follow-up period at least of 12 months were included in the study.

Patients were operated on by abdominal laparotomy or by laparoscopy according to the following techniques.

Abdominal laparotomy

A low transverse abdominal incision was made. A linear uterine incision, as small as possible, was made on the most prominent part of the leiomyoma. When possible, incisions were made on the anterior uterine wall and as many myomata as possible were removed through a single approach in order to minimize potential adhesion formation. Myomas situated on the posterior uterine wall were removed through a fundal hood incision to prevent adhesions between the uterus and the bowel.

After identification of the myoma capsule, enucleation was possible following the cleavage plane. The uterus was then sutured in one or two planes according to the depth and the size of the myomata. The myometrium was closed using interrupted absorbable sutures of Vycril 1/0 (Polyglactine; Ethicon, Rome, Italy) and the uterine serosa was closed with a continuous or separated suture of Vycril 2/0, 3/0. After washing the pelvis with saline solution, no absorbable adhesion barrier or saline dextrane macromolecular solutions were left in the peritoneal cavity.

Laparoscopy

In subjects undergoing laparoscopy, a pneumoperitoneum was obtained with carbon dioxide insufflation using a Veress needle. A standard umbilical incision was made to introduce the laparoscope which was connected to a camera for video monitoring.

Two suprapubic access routes (5 mm) were inserted lateral to the deep inferior epigastric arteries and slightly higher than usual. A third trocar (10 mm) was inserted in the midline. Uterine cannulation was always used in order to obtain optimal exposure of the myoma, in particular when it was in a posterior location. A methylene blue test was carried out to confirm tubal patency and to enable the endometrium to be identified during surgery in the case of deeply intramural myomata. An incision was made on the serosa overlying the myoma using a monopolar pointed knife. The incision was extended until it reached the capsule. The myometrium retracted as the incision was made, exposing the tumour. The myoma was enucleated by entering into the cleavage plane with claw forceps and scissors. Traction on the myoma with a countertraction on the uterus facilitated dissection. Vessels in the connective tissue bridges between the fibroid tissue and uterus were electrocoagulated with bipolar current before being cut.

The uterine wall was then sutured in one or two layers, according to the depth of the hysterotomy, with an interrupted or continuous suture of Vycril, 1/0, 2/0 (Polyglactine; Ethicon) using intracorporeal knots.

Removal of the myomata from the abdominal cavity was obtained with a manual laparoscopic morcellator (Wisap, Sauerlach, Germany) using a trocar, 15 or 20 mm in diameter, inserted through a suprapubic incision. After washing the pelvis with saline solution, no absorbable adhesion barrier or saline dextrane macromolecular solutions were left in the peritoneal cavity.

Statistical analysis

Each variable was examined with a descriptive analysis by computing frequency distributions, mean values, SD and percentages. The analysis of the differences between the two groups (laparoscopy and laparotomy) was performed using the following tests: the χ^2-test for the categorical variables, the Student's *t*-test and the Mann-Whitney non-parametric test for quantitative variables. $P < 0.05$ was considered to be statistically significant.

After the operations, the patients were followed for at least 12 months, recording the presence of pregnancies and relapses. In the event of a pregnancy, a survival analysis was performed using the Kaplan-Meier (1958) method. Pregnancy rates in the two groups (laparotomy and laparoscopy) were compared using the log rank test.

Results

From January 1993 to January 1998, surgery was performed on 131 patients: 65 women by laparotomy (49.6%) and 66 by laparoscopy (50.4%). The characteristics of these patients are given in Table I. No significant differences were found concerning the mean age and the infertility period.

All patients had at least one large myoma (⩾5 cm). A total of 145 large myomata were enucleated: 73 (50.3%) by laparotomy and 72 (49.7%) by laparoscopy. No significant differences were found between the two groups of patients concerning number, size and location of large myomata (Table I).

The operative time is slightly but not significantly lower in the group of patients who underwent abdominal myomectomy (Table II).

Three laparoconversions were performed (4.3%), due to difficulties of haemostasis and/or difficulties in suturing time. Figure 1 shows the mean distribution of the operating time; one case in group 1 and six cases in group 2 needed >150 min. No anaesthesiological complications were observed in either group. There were no intra-operative complications

Table I. Patient characteristics: number, size and location of large myomata

	Abdominal myomectomy	Laparoscopic myomectomy
No. of patients (%)	65 (49.6)	66 (50.4)
Age (years)[a]	33.97 ± 4.79	34.00 ± 4.11
Infertility period (months)[a]	45.32 ± 20.67	42.07 ± 19.17
Total no. of myomata[a]	2.75 ± 1.98	2.94 ± 1.53
No. of large myomata (%)	73 (50.3)	72 (49.7)
No. of large myomata[a]	1.12 ± 0.33	1.09 ± 0.29
Size of large myomata (cm)[a]	7.47 ± 2.60	7.07 ± 2.54
Location		
Subserosal (%)	19 (44.2)	24 (55.8)
Intramural (%)	54 (52.9)	48 (47.1)
Reaching uterine cavity (%)	5 (9.2)	2 (4.1)

[a]Values are expressed by mean ± SD.
There were no significant differences between the groups.

Table II. Comparison of the two surgical techniques: abdominal versus laparoscopic myomectomy

	Abdominal myomectomy	Laparoscopic myomectomy	*P*
Mean operative time (min)	88.85 ± 26.91	100.23 ± 38.34	NS
Post-operative outcome			
Average drop in Hb	2.17 ± 1.57	1.33 ± 1.23	<0.001
Transfusions (%)	3	0	ND
Fever (>38°C)	17 (26.2%)	8 (12.1%)	<0.05
Average hospital stay (h)	142.80 ± 34.60	75.61 ± 37.09	<0.001

NS = not significant; Hb = haemoglobin; ND = not determined.

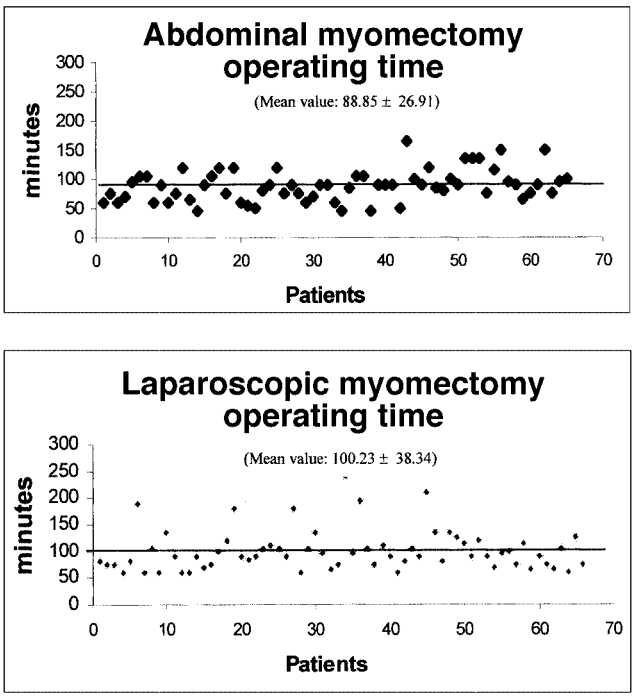

Figure 1. Operating times of the two different surgical techniques. Horizontal lines represent median.

Table III. Obstetric outcome after abdominal or laparoscopic myomectomy

	Abdominal myomectomy	Laparoscopic myomectomy
Pregnancy rate (%)	33/59 (55.9)	30/56 (53.6)
Abortion rate (%)	4 (12.1)	6 (20)
Ongoing pregnancy	2	3
Ectopic pregnancy	0	1
Deliveries	27	20
Preterm deliveries (%)	2 (7.4)	1 (5)
Vaginal deliveries (%)	6 (22.2)	7 (35)
Caesarean sections (%)	21 (77.8)	13 (65)
Uterine rupture	0	0

There were no significant differences between the groups.

during laparotomies. There was only one case of subcutaneous diffused emphysema in the laparoscopic group. The average drop in haemoglobin was significantly higher in group1 (Table II). Three cases of blood transfusions were reported after laparotomy and none after laparoscopy. All patients underwent antibiotic prophylaxis (ampicillin 2 g i.m.). Antibiotic therapy was carried out post-operatively only in cases of febrile morbidity (>38°C). Seventeen patients in group 1 (26.2%) and eight patients in group 2 (12.1%) ($P < 0.05$) needed antibiotic therapy.

The post-operative hospital stay was significantly longer after abdominal myomectomy (Table II).

Fertility after myomectomy

After the waiting period of 6 months necessary for uterine scar reparation, all patients were followed up for almost one year (mean: 32.4 ± 18.5 months, group 1; 30.6 ± 16.9 months, group 2), to evaluate their pregnancy rate. Six patients in group 1 and seven in group 2 were lost from our study for evaluation of future fertility. Inasmuch as both techniques were used in cases of laparoconversion ($n = 3$), they were not included in the statistical analysis of fertility. Fifty-nine patients in group 1 and 56 patients in group 2 tried to become pregnant after surgery (Table III).

Pregnancy outcome was not significantly different between patients suffering from primary or secondary infertility in both groups.

Fertility after abdominal myomectomy

The pregnancy rate and the obstetric outcome of the two different groups are shown in Table III. In group 1 there were 27 deliveries. Vaginal delivery occurred in six women (22.2 %), while 21 (77.8 %) underwent Caesarean section. Fourteen Caesarean sections were carried out between the 38th and 39th week of gestation due to patient history of a uterine scar (five of these had undergone a previous Caesarean section). Moreover, two cases of pre-term delivery (at 34 and 35 weeks) and five cases of fetal distress during labour required Caesarean section.

Laparoscopic myomectomy

In group 2 there were 20 deliveries. Normal vaginal delivery occurred in seven women (35%), while 13 women (65%)

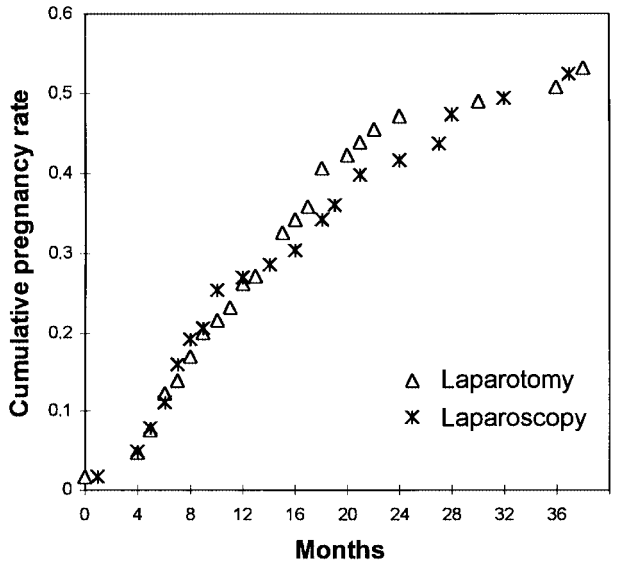

Figure 2. Cumulative pregnancy rate after abdominal or laparoscopic myomectomy. No significant difference between the two groups was found.

required Caesarean section. Eight were decided upon due to patient history of a uterine scar (three of these had undergone a previous Caesarean section). One case of pre-term delivery (at 36 weeks) and four cases of fetal distress required Caesarean section.

Survival analysis was performed using the Kaplan-Meier method (Kaplan and Meier, 1958). The cumulative spontaneous pregnancy rate (not considering the first 6 months after the operation) was 26.22% for the abdominal group and 26.98% for the laparoscopic group at 1 year, 47.07 and 41.75% at 2 years and 50.72 and 49.26% at 3 years respectively The log rank test was used for comparing the pregnancy rate in the two groups; no significant differences were found (Figure 2).

Myoma recurrence

During the follow-up period, patients underwent clinical examination and pelvic ultrasonography every 6 months. Reappearance of myomata occurred in 12 patients in each group (20.3% in group 1, 21.4% in group 2).

Considering only myomata having a size of $\geqslant$5 cm, the recurrence rate was 6.7% ($n = 4$) after laparotomy and 1.8% ($n = 1$) after laparoscopy. Four patients in group 1 underwent a second operation (three myomectomies and one hysterectomy) but none in group 2.

Discussion

Several hypotheses have proposed a causal relationship between uterine leiomyomata and infertility. Myomas may interfere with sperm migration and embryo transport by modifying the normal uterine contractility (Iosif and Akerlund, 1983; Jacobson and Enzer, 1986) and, if reaching the uterine cavity, may be responsible for vascular changes influencing endometrial trophism and consequently embryo implantation (Farrer-Brown *et al*., 1970; Hunt and Wallach, 1974; Wallach and Vu, 1995, Garcia and Turek, 1984).

In addition, myomata have been associated with an increase in abortion and preterm labour (Deligdish and Lowenthal, 1970; Vollenhover *et al*., 1990). Recently, the effects of myomata on the ability to achieve pregnancy were evaluated in IVF cycles (Seracchioli *et al*., 1997; Stovall *et al*., 1998). In patients who had undergone prior myomectomies, the implantation rate and the pregnancy rate were slightly but not significantly higher than in patients having myomata. Statistical significance was achieved when myomata deformed the uterine cavity. Moreover, when the number and size of myomata increase, better results were obtained if the myomata were removed before the IVF cycle (Seracchioli *et al*., 1997). Therefore, the presence of large myomata now represents an indication for surgery in patients without other causes of infertility. The size of the myoma is an important prognostic factor of fertility. We have considered only large myomata measuring $\geqslant$5 cm. This limit was chosen in accordance with recent publications (Rosenfield, 1986; Dubuisson and Chapron, 1996). Many studies have suggested that pedunculated myomata are probably not responsible for infertility, so they were not considered in this trial.

The primary reason for performing myomectomy in patients of reproductive age is the preservation of the uterus for the purpose of child-bearing. Therefore, when surgery is required, the question arises as to which technique is best indicated, laparotomy or laparoscopy.

Many authors are in agreement with the choice of the laparoscopic approach, when it is possible, considering its advantages when compared with traditional abdominal surgery, but laparoscopic myomectomy is still a controversial operation. To the best of our knowledge, only one prospective randomized trial comparing laparoscopic and abdominal myomectomy has been published in order to evaluate benefits in the post-operative period (Mais *et al*., 1996). The conclusion from that trial was that laparoscopic myomectomy may offer the benefits of less post-operative pain and shorter recovery time but no data about subsequent fertility were reported.

In our study, we performed a randomized comparison between abdominal and laparoscopic myomectomy with the aim of verifying the real efficacy of the laparoscopic approach.

From the technical point of view, operative and post-operative complications were fewer in the laparoscopic group. The mean average haemoglobin drop was significantly lower after laparoscopy ($P < 0.001$). Improved haemostasis was probably the result of the greater visual capacity which endoscopy allows.

Transient episodes of febrile morbidity were significantly more frequent ($P < 0.05$) after laparotomy, confirming the fact that laparoscopy seems to be a less invasive technique. Moreover, our data confirm the conclusions reported by recent studies (Mais *et al*., 1996; Stringer *et al*., 1997) which report a significantly shorter mean hospital stay after laparoscopic myomectomy when compared with classical abdominal myomectomy. Uniform procedures for hospital discharge were adopted in both groups and the length of the hospital stay was similar to that reported by other European Hospitals (Acién and Quereda, 1996; Dubuisson *et al*., 1996; Darai *et al*., 1997).

Operating time is the only of the laparoscopic technique.

The difference between the two groups was not significant, but appeared to be larger (89 versus 100 min). Considering the distribution of operating times (Figure 1), only one case in the group undergoing laparotomy needed >150 min due to difficulties in haemostasis, whereas six patients in the laparoscopic group needed >150 min. Three of these were laparoconversions; in the other three cases, the suturing was particularly time-consuming as a result of the simultaneous presence of very large, deep and difficult-to-reach myomata. These data may support the hypothesis that operating time for laparoscopic myomectomy is more difficult to schedule depending on different steps: myoma location, suture, morcellation.

Concerning fertility restoration after myomectomy, several studies report results obtained after laparotomy. In a recent trial (Vercellini *et al*., 1992), data collected from 13 published series of myomectomies, all of which were performed to correct infertility were summarized. Approximately 55% of the infertile women who underwent surgery achieved pregnancy. Our data about the fertility rate after laparotomy (55.9%) are very similar to those reported by other authors. Moreover, the pregnancy rate obtained after laparoscopy (53.6%) is not significantly different from that obtained in the abdominal group and it was similar to the data reported by other authors after laparoscopic myomectomy (Dubuisson *et al*., 1996; Darai *et al*., 1997; Nezhat *et al*., 1999).

Pregnancy outcome confirmed the validity of the laparoscopic approach. No significant differences were found between the two groups in terms of abortion rate, delivery rate and pre-term labour rate. In particular, we were concerned about the quality of the uterine scar after laparoscopy inasmuch as three cases of uterine dehiscence were reported in the literature (Harris, 1992; Dubuisson *et al*., 1995; Friedman *et al*., 1996). In our trial, the absence of any cases of uterine rupture (in either group) demonstrates the reliability of the laparoscopic technique. The very high Caesarean section rate, both after laparotomy and laparoscopy, is difficult to comment on because none of these pregnancies was followed by our Department and information about the obstetric outcome was obtained indirectly. Nevertheless, the presence of a large uterine scar (sometimes associated with a previous Caesarean section), the duration of infertility and the age of the patient may all have been factors involved in the decision for the surgical approach.

Another point of debate is the recurrence of myomata after myomectomy. Some authors think that laparoscopic myomectomy tends to be less complete when dealing with multiple fibroids (Daniell and Gurley, 1991).

The reappearance of myomata during the follow-up period was similar in the two groups (22.3% in group 1; 21.4% in group 2) and, considering only large myomata, the recurrence rates were 6.7% (laparotomy) and 1.8% (laparoscopy) respectively. Even if we cannot draw any firm conclusions because of the low number of cases reported, our data support the hypothesis that the laparoscopic approach may be as effective as the laparotomic one. Other randomized studies will be required to confirm the data obtained in our trial.

In conclusion, this study demonstrates that laparoscopic myomectomy may give the same results as laparotomic myomectomy in terms of restoring fertility and pregnancy outcome, and has well-known advantages, including a shorter hospital stay and improved post-operative outcome. In our opinion, laparoscopic myomectomy is no longer a controversial operation and can be performed in a great number of cases even in the presence of very large myomata.

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