

Chapter 2

Uterine Fibroids and Effect on Fertility

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Introduction

Uterine myomas are benign noninvasive but proliferative swellings of the uterine muscle located either under the endometrium, intramurally, or under the peritoneal surface. They can be symptomatic provoking pain or can just be asymptomatic.

Arising from the smooth muscle cells of the uterus, fibroids may be single or multiple. Many times they cause symptoms such as meno- and metrorrhagias.

Big fibroids, due to their size, can compress any of the neighboring organs leading to urinary, digestive, or sexual problems and seem to have a fertility-diminishing effect. Especially when large fibroids are present or when the cavity of the uterus is distorted. Here, in fact, we have to put forward one major question—If women with myomas really suffer from decreased fertility? If we find a myoma or myomas in a woman seeking fertility treatment, can we

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conclude that there is a direct link between the myoma and the infertility and can we hope to improve fertility by removing the myoma?

Etiology and Microscopy

The etiology of fibroids shows a panorama of theories. Fibroids are composed primarily of smooth muscle cells. The uterus, stomach, and bladder are all organs made of smooth muscle. Smooth muscle cells are arranged so that the organ can stretch instead of being arranged in rigid units like the cells in the skeletal muscles in arms and legs that are designed to “pull” in a particular direction.

In women with fibroids, tissue from the endometrium typically looks normal under the microscope. Sometimes, however, over submucosal fibroids, there is an unusual type of uterine lining that does not have the normal glandular structures. The presence of this abnormality called aglandular functionalis (functional endometrium with no glands) in women having menstrual symptoms is sometimes a clinical clue for their doctors to look more closely for a submucosal fibroid [1]. A second pattern of endometrium termed chronic endometritis can also suggest that there may be a submucosal fibroid, although this pattern can also be associated with other problems such as retained products of conception and various infections of the uterus.

Pathophysiology

Myomas arise from genetic alternations in a single myometrial cell and thus often are described as clonal. Although estrogen may stimulate myoma development and growth, myomas also may grow when circulating estrogen levels are low, possibly because ovarian and adrenal androgens may be converted to estrogens by aromatase activity within myoma cells. Growth of myomas is clearly also regulated by

progesterone and a number of local growth factors. The genetic basis for myoma growth may relate primarily to these factors and their receptors.

Although most women with uterine myomas are asymptomatic, many may have significant symptoms including pelvic and abdominal pressure or pain and menstrual irregularities. Other symptoms of myomas may result from their pressure on adjacent organs such as the bladder (urinary frequency) or rectum (tenesmus). Once we move beyond hysterectomy as a one-size-fits-all solution to fibroids, distinctions in size, position, and appearance will likely be important for treating fibroids. After understanding these issues, we may be able to tell why some women have severe bleeding and other women with a similarly sized fibroid have no problem.

Genetic Origin

It is important to us as clinicians to be up to date with the genetic advances in regard to fibroids, as it will eventually guide the best methods of treatment in women desiring fertility. The genotype is the pattern of genes that you inherit, while the phenotype is the physical manifestation or end result of the genotype. For example, with eye color, brown is a dominant color and is represented by a “B.” Blue is a recessive trait and represented by a “b.” Therefore, a person can have “BB,” “bb,” or “Bb” as genotypes for eye color. Each person gets two copies of the gene, one originally from his or her mother and the other from his or her father. The dominant gene will always dominate. It has the power to trump a recessive trait. Although there are three different genotypes (BB, bb, or Bb), there are only two phenotypes: brown eyes and blue eyes. People with the “BB” or the “Bb” genotype have brown eyes because brown is the dominant trait. Only the people with the “bb” genotype have blue eyes.

We believe that fibroids are a common phenotype that represents many different underlying genotypes. In other

words, in my view fibroids can arise through multiple different pathways. In this case, “Bb” might represent two different genes that code for the estrogen receptor beta, which influences the action of estrogen on fibroid tissue. A “B” may make the fibroid more sensitive to this hormone and therefore more likely to grow. In addition, probably multiple genes influence fibroids, so that, in addition to “Bb,” we may also have “Pp” for progesterone receptors, “Ff” for fibrotic factors, and so on. This information would be most helpful in advance of treatment, so that the woman who carried a high risk of recurrent fibroids and have completed their family might even choose to have a hysterectomy because their chance of having an additional surgery was so high. We currently have some clinical information (based on physicians’ clinical experience with many patients) to predict prognosis for recurrence after abdominal myomectomy, but our clinical information for any other kind of treatment options is limited.

Finally, understanding the underlying genotype would open up important possibilities for the future. It may, for example, point to ways in which women can modify their risk of disease and lead to prevention of disease. If, for example, a major protein involved in body fat metabolism was found to be abnormally sensitive in women with fibroids, weight loss or preventing weight gain might be an effective strategy for decreasing the risk of fibroids. In this day and age, new therapies can be developed that are targeted to specific abnormalities. This is what happened with chronic myelogenous leukemia (CML) and Gleevec which combats this disease with minimal side effects.

Understanding which genes are involved in fibroids doesn’t automatically tell us why fibroids develop or how to control them. From our understanding of fibroid behavior, we could guess that genes involved in estrogen or progesterone production, metabolism, or action would be involved. Unfortunately, science is seldom that straightforward. Most guesses regarding these “candidate genes” turn out to be wrong, and many studies are usually required to find out how these genes lead to disease.

There are also small variations called polymorphisms in genes that may play a role in influencing the risk of fibroids. Both polymorphisms and mutations are changes in the sequence of genes, but the difference is in the degree of change. A mutation makes a major change in the gene that leads to a change in the protein the gene is coding for. It changes the amino acid from alanine to glycine, for example, or causes the protein to be prematurely cut off.

Finally, in the age of molecular genetics, we can look for genes involved in a disease, which is effectively looking for a needle in a haystack. This process is called a genome-wide scan. This is a common approach to finding genes in complex diseases such as diabetes, asthma, and heart disease. With a genome-wide scan, women who are sisters and both have fibroids (an affected sibling pair) are recruited to participate in the study. Their DNA is studied for common genes. If hundreds of women are studied, each region of every chromosome can be examined, and it can be determined which genes are shared by the sisters who share the fibroid phenotype but are different in many other respects. This approach often produces novel genes that were not previously thought to be involved in the disease process [2–5].

Philosophy of Myomas in Infertility

Ideally, to prove a relationship between fibroids and infertility, prospective randomized studies should be performed comparing women desiring pregnancy with and without myomas in order to compare pregnancy rates and possibly the time needed to achieve pregnancy. These studies are lacking. A comparison between pregnancy rates and undisturbed pregnancy outcomes of infertile women with and without myomas in whom other infertility factors have been excluded however clearly speaks for the benefit of myomectomies [6–8].

A publication of the Italian team that compares spontaneous conception in infertile women with and without myomas in whom andrological and tubal infertility factors have been

excluded [9], the authors found a significant difference ($P < 0.002$) in pregnancy rates between infertile women with and without myomas (11% vs. 25%). It is the only randomized prospective study to date, and if it is to be believed, infertile women with myomas have better pregnancy rates after myomectomy (42%) than infertile women without myomas (25%), who in turn have better pregnancy rates than infertile women with untreated myomas (11%).

Different theories have been proposed to explain the effects of myomas on fertility. What are the mechanisms involved? It is generally accepted that the anatomical location of a fibroid as a submucous fibroid may impair fertility, but about the influence of intramural and subserosal fibroids in causing infertility, no consensus has ever been achieved. Myomas may distort the uterine cavity making it enlarged and elongated and altering its contour and surface area. Myomas may cause dysfunctional uterine contractility which may interfere with sperm migration, ovum transport, or nidation [10–12]. Myomas may also be associated with implantation failure or gestation discontinuation due to focal endometrial vascular disturbance, endometrial inflammation, secretion of vasoactive substances, or an enhanced endometrial androgen environment [11, 13].

In an era of evidence-based medicine, we need a clear analysis of the literature. Can we draw any conclusions from what has been published or do we need to consider new studies? Well, the following discussion gives a good overview of this situation.

Myomas and Fertility Outcome?

Let us first ask the essential question if myomas do affect implantation rates of the embryo and then ask, if these surgeries may be crucial for achieving pregnancy and for avoiding problems during pregnancy. Leiomyomas of the uterus are the most common solid pelvic tumors found in women and are estimated to occur in 20–50% of women with

increased frequency during the late reproductive years [14]. The incidence of myomas in infertile women without any obvious cause of infertility is estimated to be between 1 and 2.4% [11, 14, 15]. The relationship between leiomyomas and infertility remains a subject of debate. To address this issue, we have tried to evaluate the impact of myomas on fertility and pregnancy outcome in different conditions where myomas are implicated.

Implantation Rates

The Practice Committee of the American Society for Reproductive Medicine in collaboration with The Society of Reproductive Surgeons and American Society for Reproductive Medicine, Birmingham, Alabama, established some facts. The purpose of this educational bulletin is to examine the relationship between myomas and reproductive function and to review current methods for their management. Overall, evidence suggests that myomas are the primary cause of infertility in a relatively small proportion of women. Myomas that distort the uterine cavity and larger intramural myomas may have adverse effects on fertility.

It was established by J. Ben-Nagi et al. that women with submucous fibroids had significantly lower concentrations of glycodeilin and IL-10 in mid-luteal phase uterine flushings [16]. It was seen that the uterine cavities of women with submucous fibroids were producing decreasing amount of substances favorable to early pregnancy development hence explaining adverse reproductive outcomes [16]. While submucous myomas may certainly impair implantation rates, the question whether intramural or subserous myomas interfere with implantation remains unanswered.

While it is accepted that it is always better to operate on myomas that distort the endometrial cavity, the controversy arises in non-cavity-distorting myomas. When the implantation rates and pregnancy outcomes were compared between women with and without non-cavity-distorting myomas, in

2007 V.Y. Fujimoto et al. did not support myomectomy before ART in patients with asymptomatic fibroids that do not significantly distort the endometrial cavity [17]. We found that live birth rates were not affected by the presence of intramural myomas in IVF patients with a hysteroscopically normal uterine cavity. However, in 2010, a meta-analysis of 6087 IVF cycles by Sunkara et al. showed a significant decrease in the live birth and clinical pregnancy rates in women with non-cavity-distorting intramural fibroids compared with those without fibroids, following IVF treatment [18]. Concluding that the presence of non-cavity-distorting intramural fibroids is associated with adverse pregnancy outcomes in women undergoing IVF treatment.

In 2004 a case-control study revealed that patients with intramural fibroids >4.0 cm had lower pregnancy rates than patients with intramural fibroids ≤ 4.0 cm. Patients with subserosal or intramural fibroids <4 cm had IVF-ICSI outcomes (pregnancy, implantation, and abortion rates) similar to those of controls [19].

In 2002 Check et al. did a prospective case-control study comparing women with and without non-cavity-distorting fibroids and found that myomas smaller than 5 cm had lower implantation rates (13.6% vs. 20.2%), lower pregnancy rates (34.4% vs. 47.5%), and lower delivery rates (22.9% vs. 37.7%) [20]. Hart and colleagues studied a similar cohort of women undergoing IVF and found that pregnancy, implantation, and ongoing pregnancy rates were reduced significantly to 23.3, 11.9, and 15% compared with 34.1, 20.2, and 28.3%, respectively, in control groups. A higher frequency of uterine peristalsis during the mid-luteal phase was thought to be one of the causes of infertility associated with intramural-type fibroids.

Yan L et al. in 2014 in the study of one of the largest reported sample sizes—245 patients after ROC analysis—identified 2.85 cm as the cutoff value for largest single fibroid diameter (SFD) [21]. Patients with fibroids with SFD >2.85 cm tended to have significantly lower delivery rate (DR) compared with patients with lower diameter. These results are in part consistent [22–24]. When comparing patients with

fibroids with non-fibroid matched controls, only SFD larger than 2.85 cm showed a significant reduction in DR. The study does not claim that there is definitely a fertility benefit of myomectomy in patients whose fibroids meet the above criteria. It states that perhaps we may ignore the effect on IVF/ICSI outcomes of single IM fibroids smaller than 2.85 cm. Currently, it is impossible to achieve a consensus regarding the surgical treatment of IM fibroids that do not cause mass effect on the uterine cavity [25]. Removing IM fibroids between 2.85 and 5 cm to improve fertility remains a controversial area, but this study gives strength to the clinical consultation of infertile patients with fibroids regarding the need for surgical intervention.

In conclusion, there are various cutoff sizes of fibroids to guide the need for a myomectomy for reproductive enhancement ranging from 2.5 to 5 cm. Fibroid location, followed by size, is the most important factor determining the impact of fibroids on fertility. Surgery is indicated in cases of distortion of the endometrial cavity. Myomectomy should also be considered for patients with non-cavity-distorting fibroids based on the studies presented and for patients with unexplained unsuccessful IVF cycles after thorough evaluation of the patient and weighing the role of the fibroid as the cause for infertility.

Recurrent Pregnancy Loss

The data on association of RPL and myomas is controversial. In one study, the abortion rates in patients with and without fibroma were 71.4% and 34.9%, respectively, that indicates abortion rate is significantly higher in the presence of fibroids even after elimination of other factors ($P = 0.024$). In another large series, a miscarriage rate of 19% was reported in women following myomectomy compared to 41% for the same group of women prior to myomectomy. A review states that both submucosal and intramural fibroids were associated with an increased risk of spontaneous miscarriage [26].

While the Cochrane database review 2012 stated that there was no evidence of a significant effect of myomectomy on the miscarriage rate, the Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society of Reproductive Surgeons came to the conclusion—"In infertile women and those with recurrent pregnancy loss myomectomy should be considered only after a thorough evaluation has been completed."

Myomas During Pregnancy

The question is if intracapsular myomectomies with a correct adaption of wound edges by sutures and their resulting scars impair pregnancy outcome whether performed by laparotomy, laparoscopy, or hysteroscopy.

According to Li et al. and Vercellini et al., miscarriage rates are significantly reduced after myomectomy [27, 28]. Uterine scars are associated with a risk of vicious placental implantation (accreta, increta, percreta, praevia) and a risk of uterine rupture. In our different evaluations of abdominal and laparoscopic myomectomies in more than 2000 cases over 20 years as well as over 500 hysteroscopic myomectomies, only one uterine rupture occurred during labor which was well taken care of by the attending obstetrician [6]. In Seracchioli's randomized study comparing laparoscopic and abdominal myomectomies, no uterine rupture occurred [29]. There were no significant differences between the percentages of vaginal births (35% vs. 22%) and cesarean sections (65% vs. 78%).

Of the 145 pregnancies in Dubuisson's follow-up after laparoscopic myomectomy, 38 (26.2%) resulted in miscarriage, 58 in vaginal deliveries, and 42 in cesarean sections [30]. Dubuisson describes three uterine ruptures, all occurring before labor and one attributed to the laparoscopic myomectomy. A few case reports were found in the literature on uterine rupture after laparoscopic myomectomy [30–36].

However, they do not allow us to draw any conclusions on the relative risk compared with abdominal myomectomy. Moreover, we found no recent reports on the risk of uterine rupture after abdominal myomectomy.

Some obstetricians consider the presence of a uterine scar as an indication for cesarean section [33, 37], while other authors have never expressed the need [30, 38, 39].

Treatment Possibilities

Today, in general, broad spectrums of treatment possibilities are available and are best depicted in Fig. 2.1. In our estimation, particularly for infertile patients, hysteroscopic excision and the laparoscopic enucleation are still the leading technologies.

A recent study showed that the median serum AMH levels and median AFC per ovary were significantly lowered after uterine arterial embolization (UAE) compared to women

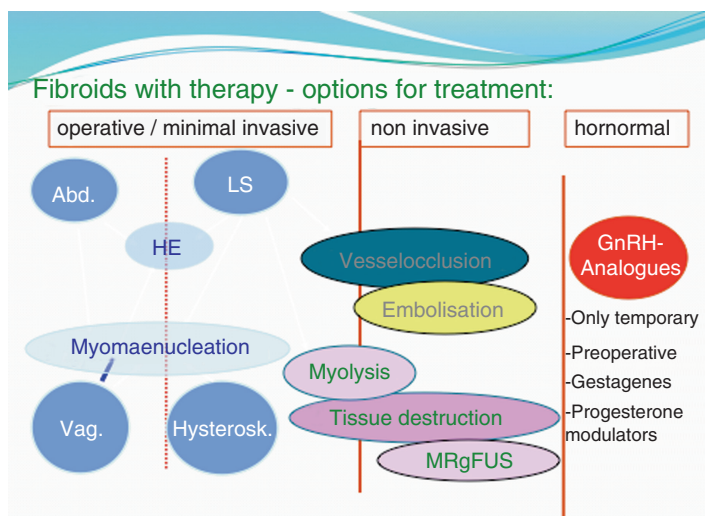


FIGURE 2.1 Treatment options for uterine fibroids

who had undergone laparoscopic myomectomy (LM) concluding that this could have an adverse impact on future response to fertility treatment and/or fecundity [40]. As the safety and effectiveness of UAE has not been established for women with myomas seeking to maintain or improve their fertility, it should not be recommended till further evidence is available.

Although studies claim that treatment of symptomatic uterine myomas with magnetic resonance-guided focused ultrasound (MgRfUS) improves both QOL and subsequent fertility, further evidence should be explored before its application in women of reproductive age [41].

Medical treatment for myomas does not improve infertility. Preoperative medical treatment with a GnRH agonist should be considered for women who are anemic and those who might be candidates for a less invasive procedure if the volume of their myoma(s) was moderately smaller the Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society of Reproductive Surgeons).

However, according to the specific needs and with future evidence-based medicine UAE, focused ultrasound applied under MRI and the medical treatment with the progesterone modulator ulipristal acetate (5 mg) might be considered [42]. It has recently gained importance in the treatment of menstrual disturbances due to submucosal and intramural fibroids.

Myomectomy and Fertility: Laparoscopic and Hysteroscopic Resection of Fibroids

General Aspects

Based on immunohistochemical findings, it is proposed to remove fibroids in women seeking pregnancy while respecting the pseudocapsule by neurofiber sparing in the incision

site. We published that this is of utmost importance for optimal muscular healing and myometrial function in future pregnancies. In fibroids detected under a size of 5–6 cm in diameter especially in young women wanting to achieve pregnancies, the myomectomy should be performed before the myoma reaches a size causing compression of the surrounding tissues and uterine distortion, which may result in the loss of regenerative potential [43].

It is good surgical and clinical practice to perform a hysteroscopy before advancing to the laparoscopic myomectomy. The advantage of the hysteroscopy is that, as this is a patient seeking fertility, endometrial pathology can be identified and corrected, and intracavity extension of the fibroid can be noted. A chromopertubation should be performed before proceeding to the myomectomy. It is advisable to use a uterine manipulator to stabilize the mobile uterus during a myomectomy.

A longitudinal incision is usually preferred on the uterus for a myomectomy, but if the myoma extends laterally, a horizontal incision is also acceptable. If the uterine cavity is entered during the procedure, it just has to be sutured additionally in a special layer. If the fibroid is posterior, there might be an increased risk of adhesion formation, and an anti-adhesive strategy needs to be adopted. The patient should always be informed that there might be a rare possibility to convert the surgery to a laparotomy.

The Practice Committee of the American Society for Reproductive Medicine in collaboration with The Society of Reproductive Surgeons concluded that myomectomy is a relatively safe surgical procedure associated with few serious complications. However, postoperative adhesions are common after abdominal myomectomy and pose a significant potential threat to subsequent fertility. Hence, a laparoscopic and/or hysteroscopic myomectomy should be preferred to an abdominal. However, each surgeon should determine his or her own criteria for laparoscopic myomectomy.

Post-surgery, the patient is usually advised to attempt pregnancy after 3 months to give adequate time for the uterine scar to heal.

Laparoscopic Stepwise Enucleation of an Intramural Fibroid and Uterine Reconstruction

Figures 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, and 2.8 give a detailed diagnostic and surgical description of myomectomy and surgical reconstruction of the uterine wall.

This stepwise description of laparoscopic myoma enucleation as an intracapsular approach with an adequate reconstruction of the uterine wall gives the patients a good start for further fertility results. The adaption of wound edges may be in 1, 2, or 3 layers depending of the situation. If the uterine cavity has been opened, an extra layer of sutures has to be applied. Conventional or barbed sutures are acceptable.

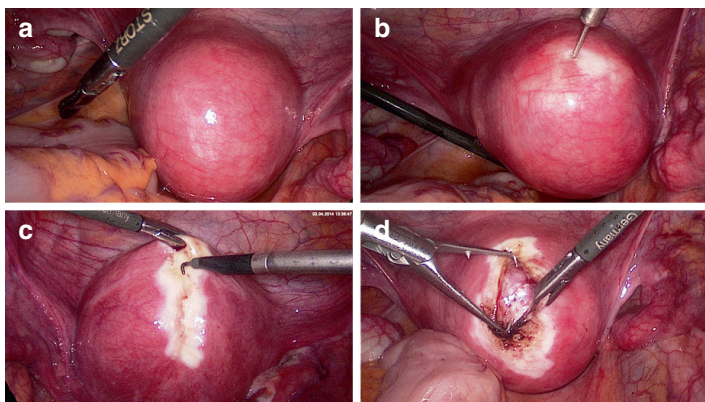


FIGURE 2.2 Laparoscopic myoma enucleation. **(a)** Situs of a fundal/anterior wall fibroid. **(b)** Prophylactic hemostasis with 1:100 diluted vasopressin solution (Gylpressin) in separate wells. The injection intends to separate the pseudocapsule from the fibroid and reduces bleedings. **(c)** Bipolar superficial coagulation of the longitudinal incision strip and opening of the uterine wall with the monopolar hook or needle till the fibroid surface. **(d)** Grasping of the fibroid and beginning of the enucleation. The pseudocapsule remains within the uterine wall and is pushed off bluntly

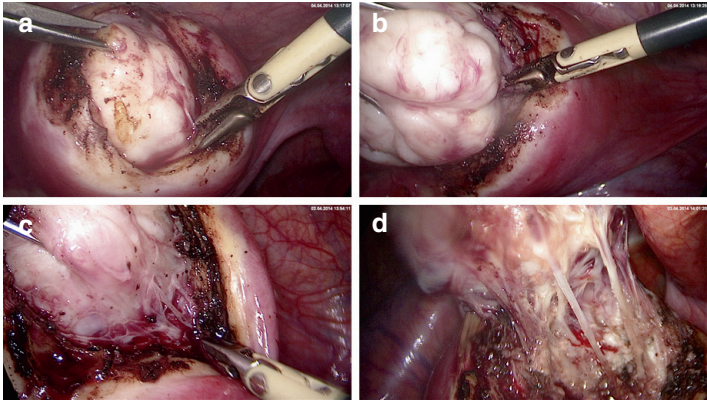


FIGURE 2.3 Laparoscopic myoma enucleation. **(a)** Traction of the fibroid with a tenaculum and blunt delineation from the capsule. **(b)** Focal bipolar coagulation of basic vessels. **(c)** Continuous enucleation of the fibroid under traction and specific coagulation of capsule fibers containing vessels. **(d)** Magnification of remaining capsule fibers to be coagulated and cut

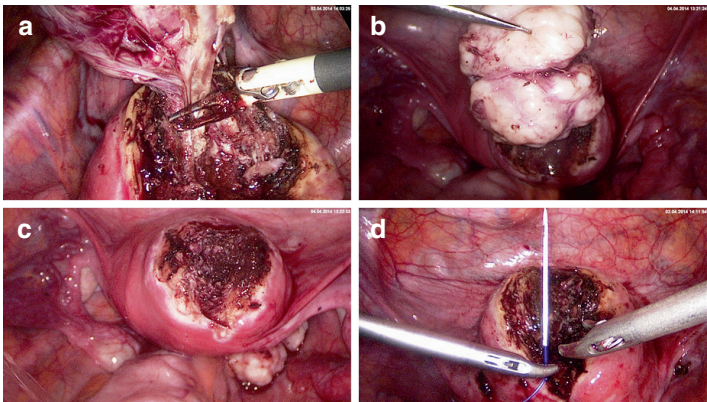


FIGURE 2.4 Laparoscopic myoma enucleation. **(a)** Final coagulation of the capsule vessels. **(b)** Double belly fibroid after complete enucleation. **(c)** Minimal coagulation of bleeding vessels under suction and irrigation. **(d)** Approximation of wound edges with either straight or round sharp needle and a monofilar late resorbable suture

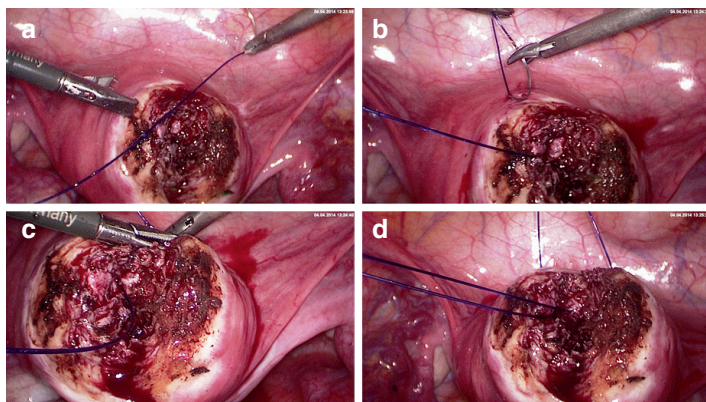
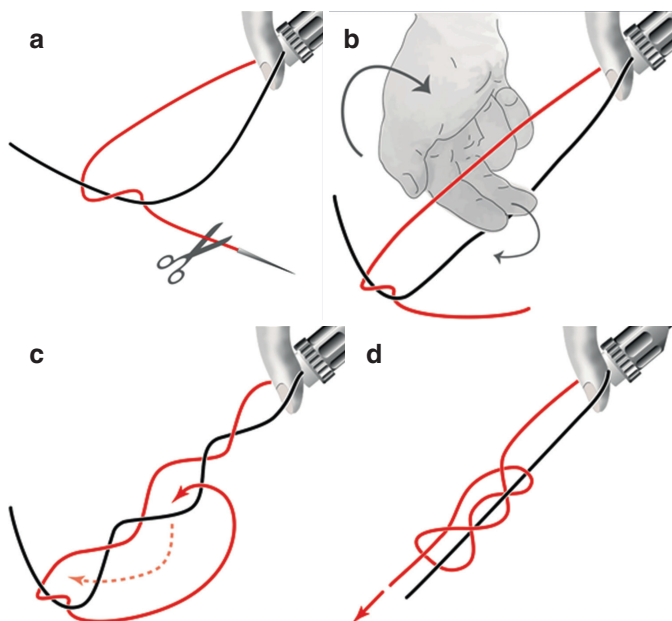


FIGURE 2.5 Laparoscopic myoma enucleation. **(a)** Advantage of round needle stitch. The wound angle is elevated safely and completely by elevating it with a Manhes forceps. Deeper layers of the myometrium can be grasped more easily using a round needle. **(b)** Needle exit and simplified regrasping with the right needle holder. **(c)** Final stitch to invert the knot. **(d)** Extirpation of the needle and completing the extracorporeal knot and preparing to push down the extracorporeal knot



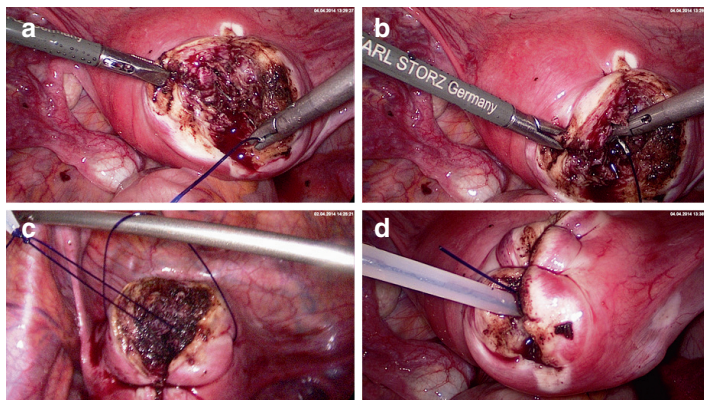


FIGURE 2.7 Laparoscopic myoma enucleation. **(a)** Second single stitch starting as deep as possible in the uterine wound. **(b)** Exiting of the needle on the left wound margin (just next to the Manhes forceps). **(c)** Completing of the stitch and preparation of the extracorporeal von Leffern knot. The needle holder elevates the thread to avoid tearing of the uterine wall while pulling through the monofilar thread (PDS). **(d)** Pushing down the extracorporeal performed knot with a plastic pushrod in the depth of the wound to dump the knot minimizing the external suture part



FIGURE 2.6 Performance of the extracorporeal “von Leffern” knot. **(a)** Pulling out the suture, removing the needle, half hitch. **(b)** Holding the knot with the left hand and reaching over with the right hand. **(c)** Grasping the short end from below and leading it back, exiting before the half hitch. **(d)** Turning back the knot. Holding the straight suture and tightening the knot

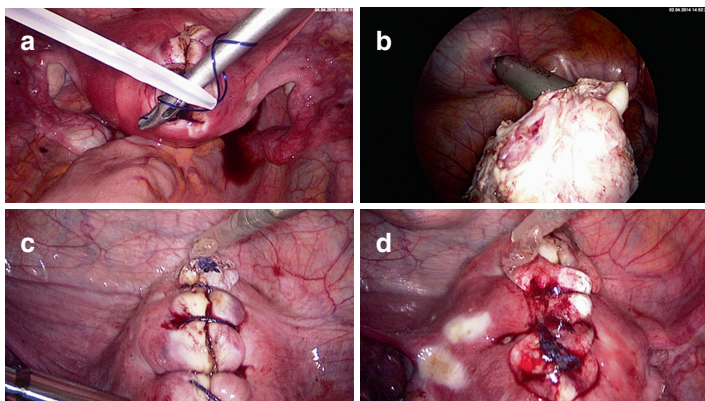


FIGURE 2.8 Laparoscopic myoma enucleation. (a) Intracorporeal safety knot of the performed extracorporeal knot. (b) Morcellation of the fibroid with the Rotocut morcellator (Storz) in an apple peeling manner. (c) Final situs showing the extracorporeal sutures to adapt the uterine wound edges. (d) Application of Hyalobarrier (Nordic Pharma) for adhesion prevention

Hysteroscopic Myoma Enucleation Has to Be Performed According to the Depth of Infiltration into the Myometrium

Submucous myomas may cause serious implantation problems and raise the frequency of abortions. The best time of surgery is the early phase in the cycle without bleeding. Saline infusion sonography best reveals the fibroid enucleation level and helps to plan the correct surgery which sometimes needs to be combined with a laparoscopic approach [8].

Differentiation of Fibroids and Focal Endometriosis to Adenomatoid Tumors

Focal adenomyosis may create a lot of pain and has to be resected if the patient is below the childbearing age or wants to conceive sooner or later, although hysterectomy best

solves the dysmenorrhea of these patients. But, this is of course not an option in infertile women. Focal adenomyosis is of mesothelial origin and affects the epididymis, testis, tunica albuginea, ejaculatory duct, prostate, and spermatic cord in men and uterus, ovary, and fallopian tubes in women. Cases have been reported of adenomatoid tumors located in the heart, pleura, liver, and adrenals [44–47]. Multifocal or multicentric appearance is exceptional [48, 49].

The excision of these lesions is much more difficult than any myomectomy as there is no myoma capsule. Adenomatoid tumors also resemble fibroids without a capsule, sometimes after GnRH analogue treatments. They can also be mistaken for lymphangiomas, metastatic adenocarcinoma, and metastasis of other origin.

These tumors form circumscribed tubercular solid masses. A recognizable separating layer or capsule enclosing the lesion is missing, as the tumors are densely adherent to the surrounding tissue. These circumstances make intraoperative preparation difficult and inhibit the definite macroscopic exclusion of a malignant event. Sixty percent of the uterine adenomatoid tumors are subserosal or at least in the external region of the myometrium. As described in our cases, most frequently they are situated in the fundus or in the posterior wall of the uterus [44–46, 50, 51]. The following two case reports reflect the complexity of the problem.

Case 1

A 26-year-old Caucasian woman, nulliparous, was transferred for surgery with a recurring symptomatic ovarian cyst. During the gynecological examination, in addition to an unsuspecting-looking cyst on the left ovary, a 2.1 cm diameter well-circumscribed uterine mass located in the posterior wall of the fundus, 1.2 cm from the serosal surface, was recorded as a fibroid (Fig. 2.9). This known tumor had been seen by an ultrasound scan 1 year earlier measuring 1 cm in diameter. The patient had a medical history of three laparoscopic surgeries for the enucleation of relapsing functional ovarian cysts with no evidence of endometriosis.

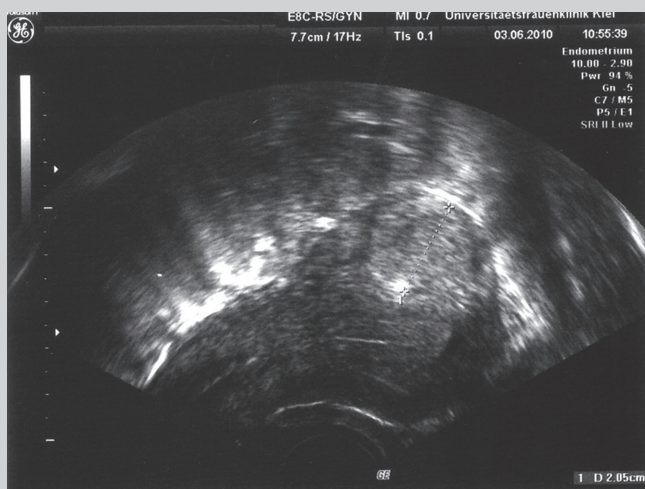


FIGURE 2.9 Preoperative transvaginal ultrasound scan showing the typical misleading sonographic picture of a fibroid (Case 1)

The patient required a fourth laparoscopy to treat the symptomatic ovarian cyst. Because of the growth of the tumor on the posterior wall, the age of the patient, and possible problems in future family planning, it was decided to simultaneously excise the suspected myoma. At laparoscopy, the ovarian cyst was enucleated, and the presumed fibroid was resected. Excision of the tumor was difficult as it was smoother than a typical myoma and more difficult to grasp with forceps. The tumor was enucleated with a special instrument which we also use to remove myomas. The usual enucleation performed in fibroid surgery was not possible as there was no capsule separating nodule from the myometrium, and the tumor seemed to grow into the orthotope myometric tissue (Fig. 2.10a). After removal of the nodule and the surrounding myometrial layer, the uterine wall was reconstructed in a

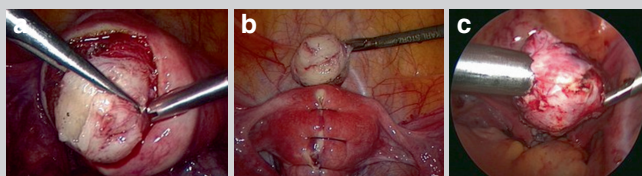


FIGURE 2.10 (a) Intraoperative sight of the adenomatoid tumor connected to the surrounding myometrium (Case 1). (b) Reconstruction of the uterine wall after excision of the tumor (Case 1). (c) Removing the adenomatoid tumor by morcellation (Case 2)

single layer with reversed and inverted single stitches (Fig. 2.10b). The tumor was removed after intra-abdominal morcellation (Fig. 2.10c).

Case 2

A 19-year-old *nulligravida* presented with pain in the lower abdomen for the last 6 months, dyspareunia and pain in the back. Transvaginal ultrasound revealed a well-circumscribed 5 cm mass in the fundus of the uterus. No additional lesions were noted in the pelvis. The patient underwent an uneventful laparoscopic procedure with excision of the tumor and reconstruction of the uterus wall.

The postoperative recovery was in each case unremarkable, and the patients were discharged 2 days after surgery free of pain. The follow-up period was without pathological findings.

Histological tissue was available from both original tumor specimens. Routine histological studies were performed according to the usual procedures: 4 μ m thick sections of formaldehyde-fixed, paraffin-embedded tissue were stained with hematoxylin and eosin (H&E) for the light microscopic histological examination. Immunohistochemistry was performed using the

following antibodies: calretinin for staining cells of mesothelial origin and CD34 for marking endothelial cells; KI-67 was used as a proliferation marker [47, 52].

Macroscopically, both tumors showed a white-gray, nodular, non-capsulated surface. The histological examination showed smooth muscle cells of normal myometrium and in between the myometrium tumor elements consisted of slit-like, tubular, cystic, or cribriform anastomosing gland-like spaces reminiscent of vascular structures (Fig. 2.11a, b). The lining cells were columnar, cuboidal to flat with bland cytologic features and mitotic activity. The angiomatoid spaces were lined by a single layer of flattened cells with oval or round nuclei, divided by fine connective tissue septa rich in blood vessels with a slight lymphocytic infiltration. The spaces contained cells with slightly eosinophilic cytoplasm and prominent cytoplasmic vacuoles that mimic signet ring cells. The pseudoglandular spaces were surrounded by hyperplastic smooth muscle with a sprinkling of stromal lymphocytes. Nuclei were usually small with inconspicuous nucleoli. Neither atypical nuclei, mitoses, nor necrosis was found.

Immunohistochemical techniques showed a strong staining of tumor cells with calretinin but no staining with CD34 (Fig. 2.11c, d). However, CD34 marked the endothelial cells and the surrounding orthotopic lymphovascular vessels (Fig. 2.11e, f). The Ki-67 index of the tumor cells was <1% (Fig. 2.11g).

Adenomatoid tumors occur most commonly during the reproductive years. Nevertheless, they are rare, benign neoplasms, occurring in about 1% of pathologically examined hysterectomies and are mostly incidental findings [45, 53]. In the majority of the known case reports, the diagnosis is made only after pathological examination of other suspected tumor origins. As in our case, most of the adenomatoid tumors remain asymptomatic. Adenomatoid tumors of the uterus can be either subserosal or intramural and can involve the subendometrial myometrium. Due to their anatomical

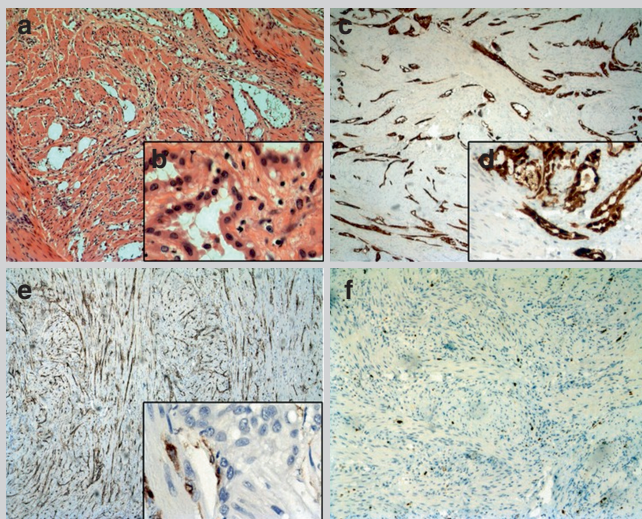


FIGURE 2.11 **(H&E)** (a) low magnification ($\times 25$) of the uterine adenomatoid tumor showing the typical tubular-glandular growth pattern and surrounding small muscle cells. (b) The lining cells in typical cuboidal growth pattern with unsuspicious nuclei at high magnification ($\times 400$). **(Calretinin)** (c), showing the strongly positive immunohistochemical calretinin staining of the tumor tissue ($\times 25$). (d) positive-stained tumor cells at high magnification ($\times 400$). **(CD34)** immunohistochemical CD34 staining (e, f) showing no positive staining of the tumor cells but the surrounding lymphovascular endothelial cells in low and high magnification ($\times 25$ and $\times 400$). **(Ki-67)** immunohistochemical Ki-67 staining ($\times 10$) showing no enhanced mitotic activity of the tumor tissue (g)

localization, the most common symptoms are pain and menorrhagia or symptoms associated with adenomyosis uteri. Many cases of incidental diagnosis do not show any clinical symptoms at all [45, 46, 52, 54–56]. In females, adenomatoid tumors are mostly situated in the fallopian tubes and the uterus and less frequently in the ovaries or the periovarial tissue. In males, they occur in the epididymitis, tunica albuginea, and testicular parenchyma. Very

seldom, adenomatoid tumors are seen in extragenital regions, e.g., the adrenal gland, omentum majus, or liver. Accordingly, the clinical symptoms are similar to those caused by other benign space-consuming lesions in these regions. There is no evidence of recurrence, malignant transformation, or metastasis [46].

In the majority of cases, preoperative detailed differential diagnostics are the exception as adenomatoid tumors are found incidentally. Despite the well-established microscopic features that distinguish adenomatoid tumors from all other entities, preliminary clinical examination, ultrasound, or MRI cannot differentiate adenomatoid tumors from their differential diagnosis [52, 56, 57].

The dissimilarity to uterine fibroids, the most frequent misdiagnosis of uterine adenomatoid tumors, is seen in the intraoperative complexity of the separation between tumor and myometrium. Mitsumori et al. report two cases of adenomatoid tumors of the uterus that also imitated leiomyoma and were only diagnosed postoperatively [57]. Histologically, fibroids have their own capsule of connective tissue. This is missing in adenomatoid tumors [49], and it is, therefore, necessary to include a layer of unaffected myometrium when operating adenomatoid tumors. Nevertheless, laparoscopic surgery for the treatment of adenomatoid tumors is feasible and recommended. In contrast to adenomyosis uteri, there is no histological infiltration of endometrial glands and stroma into the myometrial tissue. Adenomyosis uteri in its primary and disseminated forms infiltrate the entire myometrial wall. A more disseminated spreading of adenomatoid tumor has been reported in women with immunosuppression [58].

The term adenomatoid tumor was first presented by Golden and Ash in 1945 based on its histological appearance [48–50]. Mesonephric, mullerian, endothelial, and mesothelial origins have been discussed. Extensive research has been needed to prove that adenomatoid tumors have their origin in the uterine wall

and are of mesothelial origin [44–46, 54, 59, 60]. All affected organs have a common embryological origin, that is, a celomic thickening, and are influenced by different steroid hormones, which support the mesothelium concept. Nevertheless, the pathogenesis remains uncertain, as the superficial location suggests a peritoneal origin, whereas the mesothelium part could in the same way originate from the muscle. In contrast, fibroids are of mesenchymal origin. These results have however led to an immunohistological differentiation distinguishing adenomatoid tumors from other morphological entities. The corresponding immunohistological markers are CD34, calretinin, and Ki-67. Other markers are HMBE1, other cytokeratins, EMA, WT1, and vimentin [48, 60].

There have been different attempts to classify adenomatoid tumors. They can be macroscopically separated into *small solid* tumors measuring 0.2–3.5 cm and *large cystic* tumors measuring 7–10 cm [46]. The small solid tumors, if recognized preoperatively by ultrasound or MRI, are similar to fibroids. However, the large cystic tumors resemble cystic-degenerated fibroids, cystic adenomyosis, congenital uterine cysts such as mesonephric or paramesonephric cysts, lymphangiomas, cervical ovula nabothi, or echinococcus cysts. Lee et al. described three different histological growth patterns of adenomatoid tumors: (a) *plexiform*, (b) *tubular*, and (c) *canalicular* although most tumors show more than one pattern [51]. Quigley and Hart differentiated adenomatoid tumors of the uterus into four different types according to their microscopic features: (a) *angiomatoid*, (b) *adenoid*, (c) *solid*, and (d) *cystic*. Many of the tumors show two or more patterns, with one pattern predominating [61].

Even though adenomatoid tumors are benign, non-metastasizing, and nonrecurring, the preoperative and intraoperative differential diagnosis has to consider more threatening possibilities: lymphangioma, metastatic adenocarcinoma, and metastasis of other origins. For this reason, all specimens need to be analyzed histologically.

Intraoperative frozen section could be of use in protecting women of reproductive age from an unnecessary hysterectomy due to the misleading picture an adenomatoid tumor can present. Nevertheless, as adenomatoid tumors are usually encountered during the reproductive age and can be treated by similar surgical techniques used for the enucleation of fibroids, laparoscopic surgery is the gold standard.

Morcellation of Fibroids and the Threat of Sarcomas

This topic has only minor concern for myomectomy and infertility. However, **endometrial stromal sarcoma (ESS)** accounts for approximately 20% of all uterine sarcomas and commonly affects premenopausal age women. All other sarcomas appear beyond the reproductive age and are not an issue within this chapter. Nucci [62] describes that on macroscopic examination, LG-ESS generally forms multiple soft, poorly defined, attached nodules within the endometrium and myometrium which tend to have a tan to yellow color. It is difficult to make reliable pre-operative diagnoses by way of imaging modalities and endometrial sampling. Consequently, surgical procedures are often incorrectly carried out for a presumed fibroid, polyp, or adenomyosis. The hysterectomy with bilateral oophorectomy is the initial surgical procedure for early stages of LG-ESS; however in young women ovarian preservation may be a possibility. Clinical course of LG-ESS is favorable due to its high response to progesterone therapy. Patients with low-grade ESS have a 90% 5-year disease-free survival (DFS) rate for stage (I/II); this 5-year outlook drops to 50% if high stage (III/IV), and recurrence is possible 10–20 years after the primary diagnosis [63]. However, morcellation of ESS can cause negative consequences. Park et al. [64] analyzed the surgical outcomes of 50 women with (Low Grade Endometrial Stromal Sarcoma) LG-ESS diagnosis (27 cases without morcellation and 23 cases with morcellation). The results showed that abdominopelvic recurrence was significantly higher in the group where morcellation was applied than

in the group without morcellation. In addition, the 5-year DFS rates were 84% in the group where morcellation was not used and 55% for the group where morcellation was used. [64].

In a study over a period of 12 years in our department, seven uterine sarcomas within 2297 patients with fibroid surgery were detected. In six patients the preoperative evaluation clarified the possibility of malignancy, and the patient was operated by open abdominal surgery in the usual radical way. Only one patient with low-grade endometrial stromal sarcoma (LG-ESS) was preoperatively diagnosed by ultrasound (US) and endometrial sampling as having symptomatic uterine fibroids; however, when this patient underwent laparoscopic supracervical hysterectomy, postoperative histopathological examination detected ESS. Thus, the incident of ESS among women who underwent benign uterine fibroid surgery is 1/2297 (0.043%). Other publications results: Graebe et al. (2005) identified three ESS cases among 1361 patients who had uterine fibroids surgery (0.22%); Bojar et al. (2015) reported four ESS cases of ESS among 10,119 LASH procedures (0.037%); and Kto et al. (2016) reported two cases of ESS among 10,119 hysterectomies (0.019%) [65–67]. The risk of ESS seems to be low, but morcellation can negatively impact the patient's prospects. The risk of morcellation of uterine sarcoma is low; however, it has negative affect on recurrence and survival rate of the disease and should be avoided if there is any risk of malignancy especially in infertility surgery.

Discussion

Recurrence Rates

Even with the best, at this moment, surgical intracapsular excision of fibroids gives no guarantee of a nonrecurrence at another sight. Myomas do reoccur and we do not yet know the causing factors. One of our patients had five laparoscopic myomectomies in a span of 16 years. She then conceived and delivered two healthy children; finally, by the age of 43, she had reoccurring symptomatic fibroids. We performed a subtotal laparoscopic hysterectomy (SLH). At this occasion we

even found some small retrocervical implants that histologically proved to be myomatosis. Hence, it is always safe to explain this to the patient preoperatively. It was observed that women with a single fibroid tended to experience a lower rate of cumulative recurrence after myomectomy.

Fertility Outcome: Our Experience

Of the 392 patients who underwent laparoscopic surgery for fertility in our department, in 129 cases (32%) the indication for surgery was myomas. Of these 129 patients, in 56 cases (14.3%) myomas were the only indication with infertility lasting more than 3 years. In 44 cases (11.2%), myomas appeared along with other factors: in 20 cases (5.1%) with other genital abnormalities, in 18 cases (4.6%) with tubal pathology, in 3 cases (0.8%) with endometriosis, and in 3 cases (0.8%) with ovarian cysts [68].

Location of Myoma

The different locations of myomas are clearly visible in (Fig. 2.12). The location of fibroids was evaluated as diffuse (this group comprised of all partly intramurally and partly subserously located myomas), submucous, intramural, and subserous. Primarily a deep, diffuse myomatosis with partly subserous and partly intramural location of fibroids was found in 60% of patients, submucous fibroids in 16%, and subserous fibroids in 13%.

In 122 patients a laparoscopic myoma enucleation was performed. In 61% of patients, the myomas were situated subserous-intramural, in 18% submucous, in 13% subserous,

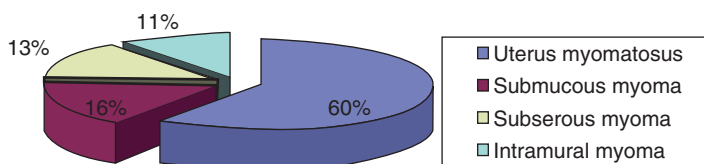


FIGURE 2.12 Localization of myomas in the 392 patients

and in 8% intramural. In 33 patients adhesiolysis was necessary prior to the myomectomy.

Figure 2.13 shows the additional surgical procedures performed on the 392 patients who underwent laparoscopic surgery for infertility in 2008/2009. Pregnancy rates clearly increased after surgery (Fig. 2.14).

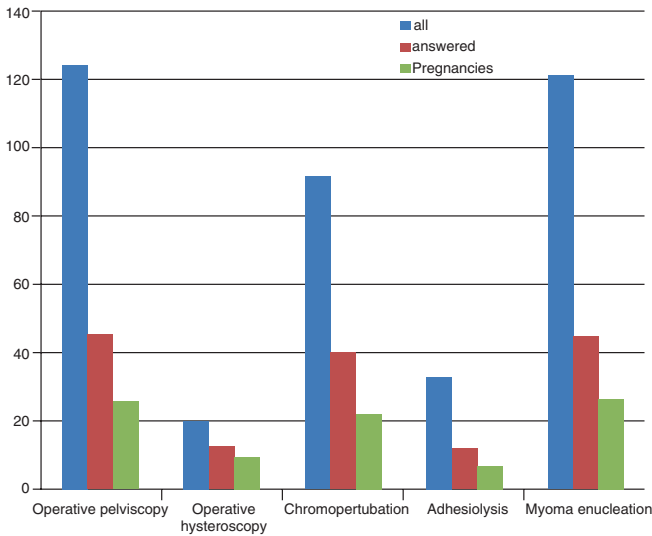


FIGURE 2.13 Laparoscopic surgical procedures performed for infertility according to groups A, B, and C

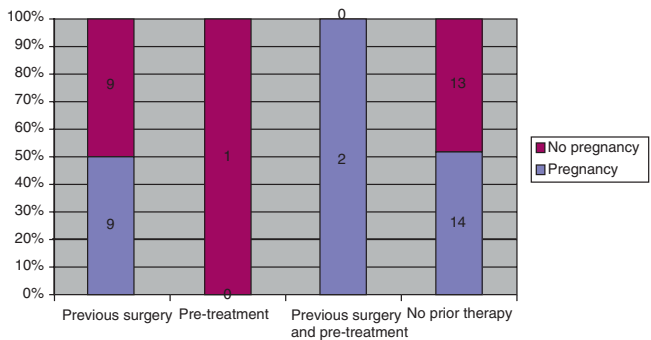


FIGURE 2.14 Influence of surgery and pretreatment on pregnancy rates of patients with myomas

Pregnancies and Deliveries

The average age of the evaluated patients was 34.6 years. Different pregnancy rates resulted depending on the localization of the fibroids. The resection of intramural-subserous fibroids resulted in a good pregnancy and delivery rate, and the highest pregnancy rate was achieved after submucous fibroid resection (Figs. 2.15 and 2.16). The lowest pregnancy rate was achieved after intramural fibroid resection.

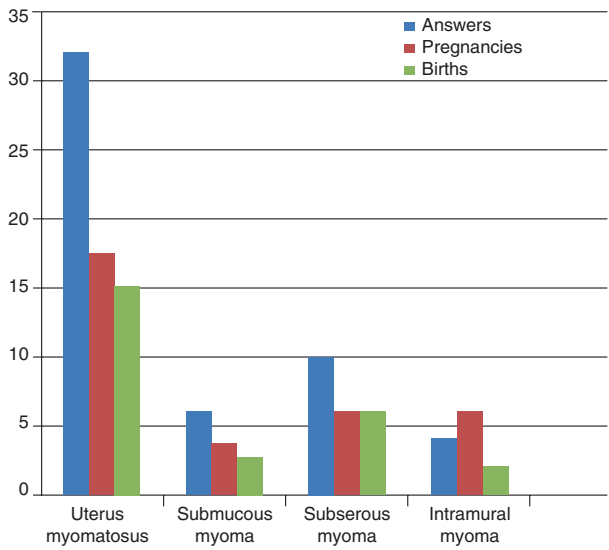


FIGURE 2.15 Number of pregnancies and deliveries according to localization of myoma with display of answers

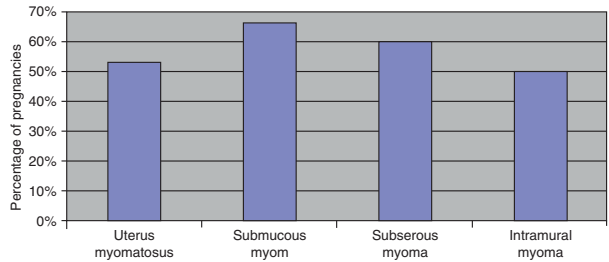


FIGURE 2.16 Number of pregnancies according to myoma localization

Mode of Delivery

Eleven of the 129 myomectomy patients underwent a cesarean section. Of these 129 patients, only 25 suffered from myomas alone; all others had multiple morbidities. The 14 pregnancies (56%) which resulted in this group of 25 led to 12 deliveries (48%), 5 (42%) of which were spontaneous and 7 (58%) cesarean sections. In the group of patients who underwent myomectomy for infertility, we had a pregnancy rate of 53% ($n = 17$) and a delivery rate of 47% ($n = 15$).

Complications

Four complications occurred in the group of myomectomy patients at or after delivery: genital descent after delivery, placenta accreta, one uterine rupture with cesarean section, and one emergency cesarean section due to imminent asphyxia of the baby.

Two of these appear to be normal intrapartum complication, while the placenta accreta and the uterine rupture may be seen in connection with the myomectomy. The size of the enucleated fibroid was 12 cm, but it could have occurred after a laparotomy myomectomy as well.

Conclusions

The role of uterine fibroids in infertility remains unknown. A causal relationship between fibroids and infertility has not been definitively demonstrated. Ideally, a comparison of pregnancy rates should be made between women with known fibroids and women post myomectomy. Such prospective studies have not been conducted, so our knowledge of the relationship between infertility and myomas results from indirect studies. The IVF/ET evaluations indicate that pregnancy rates only decrease when myomas are submucosal. However, only study comparing infertile women without tubal and andrological infertility factors, with and without myomas before and after myomectomy, seems to suggest that

the presence of myomas decreases pregnancy rates, while their removal increases pregnancy rates.

The favorable pregnancy rates obtained after myomectomy lead us to believe that myomas influence fertility. Surprisingly, the global pregnancy rates are the same after hysteroscopic, laparoscopic, and abdominal myomectomy. However, we have no control groups of women who did not undergo surgery.

So the question remains: do myomas influence fertility? Every situation has to be judged separately, and efforts must be made to develop the best technique, that is, to say, the technique with the least risk of impairing fertility or causing complications during pregnancy. Although more fundamental research should be carried out to detect the mechanisms of infertility and understand the genetic basis for fibroid development and the molecular and hormonal mechanisms of myometrial proliferation, it is clear that intramural myomas may complicate pregnancies and healthy child delivery [69]. Myomectomies at cesarean sections have led to dramatic complications, and it is not advisable to be performed at that time [70].

A better understanding of the genetic basis of fibroid development in the future may show possibilities for the development of an effective prevention strategy in genetically predisposed individuals and provide strategies to slow the growth of myomas.

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